World Health Organization

Medication Safety in High-risk Situations

MEDICATION WITHOUT HARM
Global Patient Safety Challenge

Technical Report

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Contents

Abbreviations

ACE	angiotensin-converting enzyme
ADR	adverse drug reaction
aPTT	activated partial thromboplastin time
DOAC	direct-acting oral anticoagulant
INR	international normalized ratio
LASA	look-alike, sound-alike
LMWH	low molecular weight heparin
NOAC	newer oral anticoagulant
NSAID	non-steroidal anti-inflammatory drug
STOPP	screening tool for older people's prescriptions
UHC	universal health coverage
UFH	unfractionated heparin
WHO	World Health Organization

Preface

Health care interventions are intended to benefit patients, but they can also cause harm. The complex combination of processes, technologies and human interactions that constitutes the modern health care delivery system can bring significant benefits. However, it also involves an inevitable risk of patient harm that can – and too often does – result in actual harm. A weak safety and quality culture, flawed processes of care and disinterested leadership teams weaken the ability of health care systems and organizations to ensure the provision of safe health care. Every year, a significant number of patients are harmed or die because of unsafe health care, resulting in a high public health burden worldwide.

Most of this harm is preventable. Adverse events are now estimated to be the 14th leading cause of morbidity and mortality in the world, putting patient harm in the same league as tuberculosis and malaria *(1)*. The most important challenge in the field of patient safety (see Annex 1) is how to prevent harm, particularly avoidable harm, to patients during their care.

Patient safety is one of the most important components of health care delivery which is essential to achieve universal health coverage (UHC), and moving towards the UN Sustainable Development Goals (SDGs). Extending health care coverage must mean extending safe care, as unsafe care increase costs, reduces efficiency, and directly compromises health outcomes and patient perceptions. It is estimated that over half of all medicines are prescribed, dispensed or sold inappropriately, with many of these leading to preventable harm *(2)*. Given that medicines are the most common therapeutic intervention, ensuring safe medication use and having the processes in place to improve medication safety (see Annex 1) should be considered of central importance to countries working towards achieving UHC.

The Global Patient Safety Challenges of the World Health Organization (WHO) shine a light on a particular patient safety issue that poses a significant risk to health. Front-line interventions are then developed and, through partnership with Member States, are disseminated and implemented in countries. Each Challenge has so far focused on an area that represents a major and significant risk to patient health and safety (see Annex 1). In 2005, the Organization, working in partnership with the (then) World Alliance for Patient Safety, launched the first Global Patient Safety Challenge: *Clean Care Is Safer Care (3)*, followed a few years later by the second Challenge: *Safe Surgery Saves Lives (4)*. Both Challenges aimed to gain worldwide commitment and spark action to reduce health care-associated infection and the risks associated with surgery, respectively.

Recognizing the scale of avoidable harm linked with unsafe medication practices and medication errors, WHO launched its third Global Patient Safety Challenge: *Medication Without Harm* in March 2017, with the goal of reducing severe, avoidable medication-related harm by 50% over the next five years, globally *(5)*.

This Challenge follows the same philosophy as the previous Challenges, namely that errors are not inevitable, but are very often provoked by weak health systems, and so the challenge is to reduce their frequency and impact by tackling some of the inherent weaknesses in the system.

As part of the Challenge, WHO has asked countries and key stakeholders to prioritize three areas for strong commitment, early action and effective management to protect patients from harm while maximizing the benefit from medication, namely:

- medication safety in high-risk situations
- medication safety in polypharmacy
- medication safety in transitions of care.

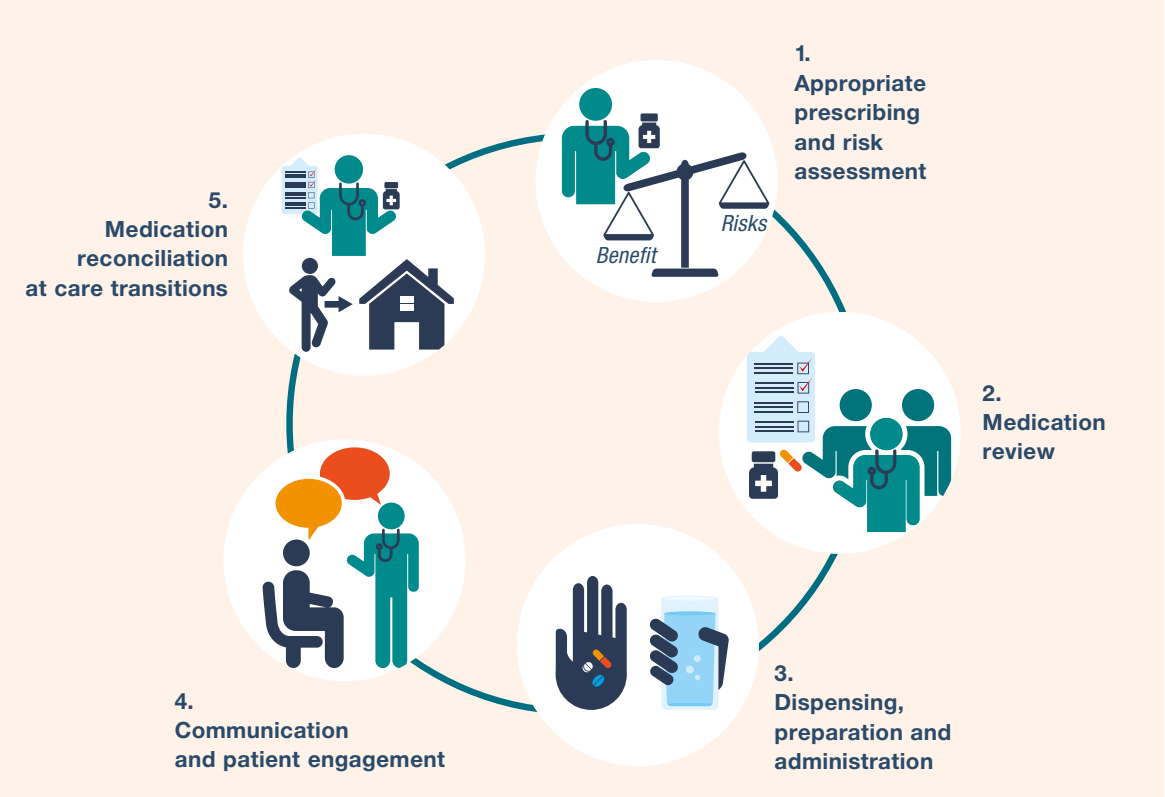
Consider the following case scenario describing a medication error (see Annex 1) involving these three areas.

Medication error: case scenario

Mrs Poly, a 65-year-old woman, came to the outpatient clinic complaining of abdominal pain and dark stools. She had a heart attack five years ago. At her previous visit three weeks ago she was complaining of muscle pain, which she developed while working on her farm. She was given a non-steroidal anti-inflammatory drug (NSAID), diclofenac. Her other medications included aspirin, and three medicines for her heart condition (simvastatin, a medicine to reduce her serum cholesterol; enalapril, an angiotensin-converting enzyme (ACE) inhibitor; and atenolol, a beta blocker). She was admitted to hospital as she developed symptoms of blood loss (such as fatigue and dark stools). She was provisionally diagnosed as having a bleeding peptic ulcer due to her NSAID, and her doctor discontinued diclofenac and prescribed omeprazole, a proton pump inhibitor. Following her discharge, her son collected her prescribed medicines from the pharmacy. Among the medicines, he noticed that omeprazole had been started and that all her previous medicines had been dispensed, including the NSAID. As his mother was slightly confused and could not remember exactly what the doctor had said, the son advised his mother that she should take all the medications that had been supplied. After a week, her abdominal pain continued and her son took her to the hospital. The clinic confirmed that the NSAID, which should have been discontinued (deprescribed), had been continued by mistake. This time Mrs Poly was given a medication list when she left the hospital which included all the medications she needed to take and was advised about which medications had been discontinued and why.

The events leading to the error in this scenario and how these could have been prevented are reflected in Figure 1, and the text below.

Figure 1. Key steps for ensuring medication safety



In this scenario the key steps that should have been followed to ensure medication safety in the inpatient setting include:

1. Appropriate prescribing and risk assessment

Medication safety should start with appropriate prescribing and a thorough risk–benefit analysis of each medicine is often the first step. In this case scenario, prophylactic aspirin and NSAID without a gastroprotective agent left Mrs Poly at an increased risk of gastrointestinal bleeding. NSAIDs can also increase the risk of cardiovascular events, which is of particular concern, as she had had a myocardial infarction (heart attack) five years ago. This is a good example of a high-risk situation requiring health care professionals to prescribe responsibly after analysing the risks and benefits.

2. Medication review

A comprehensive medication review (see Annex 1) is a multidisciplinary activity whereby the risks and benefits of each medicine are considered with the patient and decisions made about future therapy. It optimizes the use of medicines for each individual patient. Multiple morbidities usually require treatment with multiple medications, a situation described as polypharmacy (see Annex 1). Polypharmacy can put the patient at risk of adverse drug events (see Annex 1) and drug interactions when not used appropriately. In this case, there should have been a review of medications, particularly as Mrs Poly was prescribed aspirin and diclofenac together. The haemodynamic changes following blood loss should have also prompted temporary stopping the ACE inhibitor before restarting once the episode of blood loss has been resolved.

3. Dispensing, preparation and administration

This is a high-risk situation as the medication (diclofenac) has the potential to cause harm. However, this medication was continued after discharge when the patient transitioned from hospital to home. Dispensing this medicine and its administration caused serious harm to Mrs Poly. Dispensing this medicine and its administration caused significant harm to Mrs Poly.

4. Communication and patient engagement

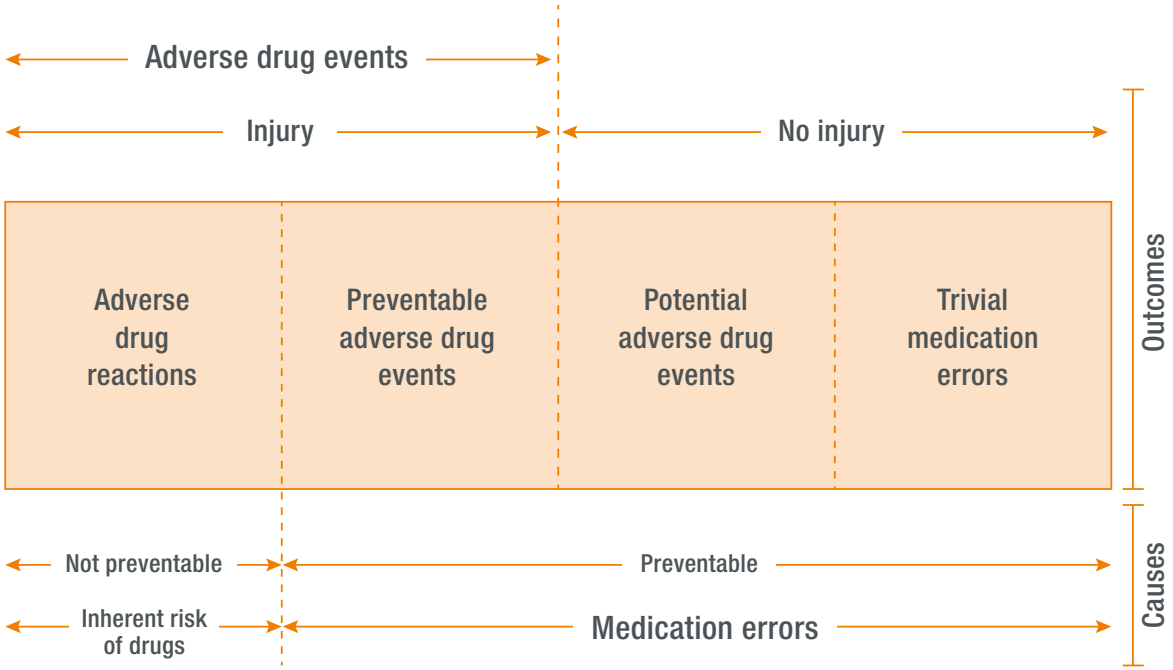
Proper communication between health care providers and patients, and amongst health care providers, is important in preventing errors. When Mrs Poly was severely ill due to gastric bleeding, the NSAID was discontinued. However, the decision to discontinue the medicine was not adequately communicated either to the other health care professionals (including the nurse or the pharmacist) or to Mrs Poly. Initial presenting symptoms due to adverse effects could have been identified earlier if she had been warned about the risks.

5. Medication reconciliation at care transitions

Medication reconciliation is the formal process in which health care professionals partner with patients to ensure accurate and complete medication information transfer at interfaces of care. Diclofenac, the NSAID that can cause gastrointestinal bleeding and increase the risk of cardiotoxicity and had led to this hospital admission, was discontinued, and this information should have been communicated at the time of discharge (in the form of a medication list or patient-held medication record). This would have helped her and her caregivers in determining what the newly added and discontinued medications needed to be.

Medication-related harm is harm caused to a patient due to failure in any of the various steps of the medication use process or due to adverse drug reactions (see Annex 1 for glossary). The relationship and overlap between medication errors and adverse drug events is shown in Figure 2.

Figure 2. Relationship between medication errors and adverse drug events



Source: Reproduced, with the permission of the publisher, from Otero and Schmitt *(6)*.

WHO is presenting a set of three technical reports – *Medication safety in high-risk situations*, *Medication safety in polypharmacy*, and *Medication safety in transitions of care* – to facilitate early priority actions and planning by countries and key stakeholders to address each of these areas. The technical reports are intended for all interested parties, particularly to inform national health policy-makers and encourage appropriate action by ministries of health, health care administrators and regulators, organizations, professionals, patients, families and caregivers, and all who aim to improve health care and patient safety.

This report – *Medication safety in high-risk situations* – outlines the problem, current situation and key strategies to reduce medication-related harm in high-risk situations. It should be considered along with the companion technical reports on *Medication safety in polypharmacy* and *Medication safety in transitions of care*.

Executive summary: medication safety in high-risk situations

High-risk situations are important because they are more often associated with significant harm due to unsafe medication practices or medication errors. There are three main factors contributing to high-risk situations: medication, provider and patient, and systems factors (work environment).

- **Medication factors** include the use of high-risk (high-alert) medications, often medicines with a low therapeutic index (a low ratio of the maximally tolerated dose of a medication to the minimal curative or effective dose). The development of local high-risk (high-alert) medication lists that are regularly updated help health care professionals focus on particular risks in their own workplace. This report seeks to highlight some of the medications which have been identified globally as being high-risk (high-alert). However, such lists need to be developed locally to reflect the medications most commonly associated with medication error and adverse drug events in different countries and health care settings. Merely creating a high-risk (high-alert) medication list is of little use without associated risk reduction strategies.
- **Provider and patient factors** may be related to the health care professional providing patient care or the patient being treated. Poor prescribing practices by health care professionals include overprescribing, underprescribing and misprescribing. However, errors may occur at any stage of the medication process, including dispensing and administration.
- **Systems factors (work environment)** include the setting (such as hospitals) and high-risk situations within those settings (e.g. risks associated with perioperative or neonatal care).

Medication errors are often caused by a combination of medication, provider and patient, and systems factors; therefore, a range of sustainable strategies of proven efficacy should be developed and implemented in conjunction.

These strategies form part of a systems approach to reduce the risk of medication errors, supported by a strong safety and reporting culture, alongside education and feedback.

Each country participating in the third WHO Global Patient Safety Challenge: *Medication Without Harm* needs to clearly define its own objectives for improving medication safety by convening a group of experts, including for instance physicians, pharmacists, patient representatives, regulators and health system leaders; to select a small number of high-risk (high-alert) medications and high-risk situations for action that are applicable to their situation and achievable within the resources available.

1 Introduction

High-risk situations, in the context of medication safety, relate to those circumstances which are associated with a significant risk of medication-related harm. The inherent risks of certain medications, unsafe medication use processes and difficulty in complying with safe medication practices in certain clinical scenarios (such as in the case of emergencies) are just some examples of high-risk situations. These may result in an adverse drug reaction (ADR) or a medication error, which are often preventable.

High-risk situations warrant special mechanisms to prevent medication errors, and when they do occur, should include means of identifying and intercepting them before they result in harm to the patient.

Some high-risk situations may require improvements in various steps of the medication use process. Situations arising from look-alike, sound-alike (LASA) naming, packaging and labelling of some medications, could be prevented by ensuring that these are checked thoroughly during prescription, transcription, procurement, storage and dispensing. Medications with an increased risk of harm, such as concentrated electrolyte solutions, can be stored in a controlled environment to prevent the inadvertent administration of undiluted solutions.

It has been suggested that there are three broad factors that influence medication safety in high-risk situations *(7)*. These are:

- medication factors
- provider and patient factors
- systems factors.

Unsafe medication practices and medication errors may be triggered by one or more of these factors acting alone or in combination, increasing the risk of harm to patients. The following sections consider each of these factors in turn.

2 Medication factors

High-risk (high-alert) medications are drugs that bear a heightened risk of causing significant patient harm when they are used in error. Although mistakes may or may not be more common with these medications, the consequences of an error are clearly more devastating to patients (see Annex 1).

Studies have shown that there is a burden of harm associated with ADRs. In one study, it was estimated that ADRs are related to 6.5% of hospital admissions *(8)*. In practice many medication errors may not result in harm and although every medicine has risks during use, medication-related harm can be reduced with appropriate prescribing, responsible use, and by implementing strategies that minimize risks. Medications associated with a high risk of ADRs are traditionally classified under two categories: (a) those with a high risk of type A (for "augmented") reactions, normally a dose-related "augmentation" of the known pharmacological effects of the medication; and (b) those with a high risk of type B (for "bizarre") reactions, sometimes termed "idiosyncratic", for which the effect is often unpredictable (and sometimes allergic in nature) and not related to the known pharmacological properties of the medication. It has been proposed that there could be more classification schemes and categories for classifying ADRs *(9)*. Digoxin toxicity would be classified as a type A reaction while anaphylaxis (see Annex 1) caused by the penicillin group of antibiotics is an example of a type B reaction *(10)*. However, some medications may be associated with a significant risk of both type A and type B reactions (e.g. the antiarrhythmic agent, amiodarone).

Type A reactions are common, often predictable and are generally associated with medications which have a low therapeutic index (the ratio of the maximally tolerated dose of a medicine to the minimal curative or effective dose), which is associated with a steep dose–response curve *(9, 10)*. This means that even small increases in the concentration of the medication at its site of action (e.g. due to a drug interaction, medication error or concomitant clinical condition) may cause a significant increase in its effect, sometimes resulting in harm. Thus, even doses of the medication within the recommended range may produce ADRs in some individuals, due to variation in their response to medicines and as the safe dose range may be narrow.

Type B reactions are less common than type A reactions and have a higher mortality rate. Examples of type B reactions include skin rashes (sometimes severe) which can occur with certain antibiotics and other immunological reactions. Some of the serious ADRs associated with type B reactions are severe anaphylaxis and malignant hyperthermia *(9, 10)*. In the absence of sensitive and specific biomarkers, such reactions are often difficult to predict, so prevention of future type B reactions usually requires obtaining a comprehensive medication and medication-allergy history, and the establishment of systems to prevent

subsequent inadvertent re-administration of the suspected medication. Since predicting these ADRs is difficult, the objective could be to have systems in place to recognize the reactions and manage in a timely, proper manner when required.

2.1 Medications frequently classified as high-risk (high-alert)

Many medicines may have a high risk of harm when used in error or taken inappropriately. The specific medications contained in lists of high-risk (high-alert) medications may differ between countries because of variation in preferences of specific agents within a class, as well as variations in care settings and disease epidemiology. Nevertheless, there is generally good concordance between the classes of medications in reports from several countries, and a selected list is shown in Table 1. It has been observed that these therapeutic groups can be easily recalled using the mnemonic "A PINCH" (which is not representing the order of severity of potential harm they can cause), first proposed by the New South Wales Clinical Excellence Commission *(11)*. Many of the therapeutic groups listed in A PINCH have been identified as high-risk (high-alert) by various entities globally *(12–18)*. It is important to note that while Table 1 includes examples of the medications frequently classified as high-risk (high-alert), there are several other medications which have been implicated less frequently. In addition, some authors have separately identified high-risk (high-alert) medications most likely to be associated with harm in acute care settings, community settings and long-term care settings *(14)*.

Table 1. Some high-risk (high-alert) medications associated with harm when used in error

High risk medicine group	Examples of medicines
A: Anti-infective	Amphotericin Aminoglycosides
P: Potassium and other electrolytes	Injections of potassium, magnesium, calcium, hypertonic sodium chloride
I: Insulin	All insulins
N: Narcotics (opioids) and other sedatives	Hydromorphone, oxycodone, morphine Fentanyl, alfentanil, remifentanil and analgesic patches Benzodiazepines, for example, diazepam, midazolam Thiopentone, propofol and other short term anaesthetics
C: Chemotherapeutic agents	Vincristine Methotrexate Etoposide Azathioprine
H: Heparin and anticoagulants	Warfarin Enoxaparin Rivaroxaban, dabigatran, apixaban
Other	High-risk medicines identified at local health district/facility/unit level which do not fit the above categories

Source: Reproduced, with the permission of the publisher, from State of New South Wales (NSW Ministry of Health) *(11)*.

A recent systematic review of the prevalence and incidence of prescribing errors with high-risk (high-alert) medications in hospitals included nine studies published between 2008 and 2014 *(19)*. It showed that the prevalence of prescribing errors was highly variable, perhaps because of different definitions of both prescribing errors and high-risk (high-alert) medications, and could be extremely high (ranging from 0.24 to 89.6 errors per 100 prescriptions). It is of concern that the three highest prevalence rates in this systematic review were observed in studies in children, with a child's weight not recorded or incorrectly recorded being the most common error. The commonest type of prescribing error identified by the systematic review was dosage error. Other common prescribing errors of high-risk (high-alert) medications included incorrect date of prescription and omissions of required medications. It was also noted that despite safe prescribing policies being in place, they were often not strictly followed. Thus, it is evident that high-risk (high-alert) medications pose a major clinical challenge for prescribers.

It is important to highlight that errors can also occur in any of the other steps of the medication use process (e.g. storage, preparation, dispensing, administration or monitoring). These will be discussed later in this report.

Adverse drug events during hospitalization in Dutch hospitals demonstrated no visible improvements in preventable adverse events related to medication over the four years after a national programme *Prevent Harm, Work Safely* was launched in 2008, with the aim of reducing the number of preventable adverse events by 50%. The intervention targeted two aspects related to medication; medication reconciliation at hospital admission and discharge, and high-risk (high-alert) medication *(20)*. A Dutch study by Damen et al. found that adverse drug events related to chemo-therapeutic agents and anticoagulants were the commonest. In this study, anticoagulant-related events accounted for a substantial proportion of preventable adverse drug events *(21)*. However, management of anticoagulation is complex and requires good coordination and communication within the health care team for safe and effective medication practice.

A recent review identified narcotic agents (particularly opioids) as the high-risk (high-alert) medications most often associated with prescribing errors in the hospital setting *(19)*. Another recent survey of adverse drug events during hospitalization cited chemotherapeutic and anticoagulants as the two main medication types responsible for medication-related adverse events *(21)*. Thus, in any intervention plan, it would be appropriate to focus attention on those high-risk (high-alert) medications that are associated with the greatest likelihood of producing serious harm in specified settings. Most of these interventions do not require sophisticated monitoring facilities and could be widely adopted globally to minimize risk associated with the administration of high-risk (high-alert) medications.

The medication safety information and interventions given below are not exhaustive but have been suggested by different international bodies to minimize medication-related harm from high-risk (high-alert) medications.

Anti-infective agents

Aminoglycosides *(11)* (e.g. amikacin, gentamicin, streptomycin and tobramycin) and the glycopeptide antibiotic, vancomycin *(17)*, may cause damage to hearing or the kidneys in a dose-related, type A adverse drug reaction. Individuals at particular risk are those with pre-existing renal impairment, older persons, obese individuals, patients with cystic fibrosis, neonates and children, particularly when high doses are administered. Since the major route of excretion of these medications is by filtration through the kidney, any nephrotoxicity caused by the medications can further reduce their renal clearance, resulting in a vicious cycle of increasing renal damage and reduced excretion of the offending agent *(22)*.

Rapid intravenous infusion of vancomycin increases the risk of anaphylactic-like reactions, so particular care should be exercised during intravenous infusion, especially during any loading infusion *(23)*.

Amphotericin B is used in the treatment of severe fungal infections and is available in several formulations. Lipid-based forms of the medication appear to have less severe toxicity, but the conventional form of the medication may be inadvertently substituted at an inappropriate dose, risking possible severe cardiotoxicity, including cardiorespiratory arrest *(24, 25)*.

Potassium and other salts or electrolytes for intravenous injection

Potassium is a vital component for normal cellular function, and deficiency of potassium in the blood (hypokalaemia) may need to be corrected rapidly by administering intravenous potassium (usually the chloride salt in dilute form) to avoid serious sequelae, including cardiac arrest. It has been observed that concentrated potassium chloride, in place of the diluted solution, is occasionally administered in error, sometimes resulting in fatal outcomes due to severe hyperkalaemia *(12, 26)*. There have been many incidents where health care professionals have mistaken potassium chloride concentrate solution for sodium chloride (normal saline) solution when reconstituting a medication for injection, or in other cases, intravenous infusions of potassium chloride have been prepared incorrectly *(27, 28)*.

Harm can also occur as a result of administration of other electrolytes, including potassium phosphate, magnesium and calcium salts and hypertonic sodium chloride *(11, 16, 18)*. Administration errors of hypertonic sodium chloride can have fatal outcomes *(26)*.

Insulins

Various publications identify insulin as a high-risk (high-alert) medication *(11–18)*. The complexity of dosing, variety of available products and pharmacology of the medicine, all contribute to the potential for error and insulin-related harm *(15)*. Two common errors that have been identified in association with insulin administration are (a) use of non-insulin syringes, which are marked in millilitres and not in insulin units, to administer the dose; and (b) use of abbreviations such as “U” or “IU” for units, which when added to the prescription for the intended dose may cause it to be misread (e.g. “10U” misread as “100”) *(29)*. The introduction of new formulations (including high-strength) requires prescribers to become familiar with various preparations to avoid error.

Narcotics and sedatives

Narcotics and sedatives can cause significant harm when used in error *(11–18)*. Type A reactions associated with opioid medications (e.g. buprenorphine, diamorphine, dipipanone, fentanyl, hydromorphone, meptazinol, methadone, morphine, oxycodone, papaveretum, tramadol and pethidine) include nausea, vomiting, constipation and in severe cases respiratory depression or respiratory arrest which may result in death. The availability of a wide range of alternative opioids (some short-acting and others long-acting) make the possibility of an error more likely, as health care professionals may not be familiar with different preparations. Health care professionals should therefore check that the intended dose of the specific opioid is safe for the individual receiving it, and an awareness of the previous opioid dose is vital in ensuring the safe use of these medications *(30)*.

Some opioid medications are also administered transdermally (across the skin), especially for cancer pain, and patients or caregivers should be educated about how to use them correctly.

Opioids and sedatives are widely used in paediatric anaesthesia, and a recent study found that these agents were the two most common causes of medication errors. Over 80% of reported medication errors in this study, reached the patient and over half of these errors caused patient harm *(31)*.

Chemotherapeutic and immunosuppressive agents

The increasing availability of a wide range of orally active anticancer medications, allied to their generally low therapeutic indices, means that errors in the dose, frequency, or duration of treatment can be a cause of harm. The United Kingdom National Patient Safety Agency has advised that the prescribing and use of oral cytotoxic medications should be carried out to the same standard as parenteral anticancer therapy and should be monitored in the same way *(32)*.

The alkylating agent etoposide is available in two different intravenous formulations, the etoposide base and the etoposide phosphate salt, with 100 milligrams of the etoposide base being equivalent to 113.6 milligrams of etoposide phosphate. This can lead to dosing errors if these differences are not taken into account *(33)*.

Vincristine is used to treat certain leukaemia, lymphomas, and some solid tumours, such as breast and lung cancer. Vincristine injections are intended for intravenous administration only and inadvertent intrathecal administration has caused severe ascending radiculomyelo-encephalopathy, which is almost always fatal *(11)*.

Although the folic acid antagonist methotrexate is used as an anticancer agent, it is also used in the treatment of rheumatoid arthritis and other autoimmune conditions due its immunosuppressive properties. In the treatment of autoimmune conditions, it is often administered as a weekly rather than daily dose which can lead to errors and significant harm *(11, 12, 13, 34)*. Errors in prescription or dispensing of excessive doses of methotrexate have resulted in bone marrow suppression, pulmonary complications and, in some cases, even death.

Heparins and oral anticoagulants

Anticoagulants are high-risk (high-alert) medications *(11–18)*, widely used both in inpatient and outpatient settings.

Unfractionated heparin (UFH) is still used parenterally in high-risk situations, either by intravenous infusion or subcutaneously, with monitoring of the blood using the activated partial thromboplastin time (aPTT). It has been shown that there is a non-linear relationship between the dose of UFH infused and the aPTT. This means that disproportionate adjustments in dose are required depending on the aPTT if underdosing or overdosing is to be avoided. It has been observed that overdosing is associated with an increased risk of haemorrhage *(35)*. Heparin was also shown to be the most common medication associated with prescription errors in a Brazilian study *(36)*.

In many clinical circumstances, UFH has been replaced by low molecular weight heparins (LMWH), which are typically administered subcutaneously *(35)*. They are predominantly excreted unchanged in the urine and the safe and effective dose is determined by the patient's weight and renal function. Underdosing risks inefficacy while overdosing may increase the risk of haemorrhage *(37)*.

Orally active vitamin K antagonists, including warfarin, phenindione, acenocoumarol (nicoumalone) and phenprocoumon, are widely used throughout the world in the treatment and prevention of thrombosis, particularly in the prevention of thromboembolic stroke in individuals with (valvular and non-valvular) atrial fibrillation. The main type A reaction of all of these agents is haemorrhage. Due to the low therapeutic index of these agents, and the wide inter-individual pharmacokinetic and pharmacodynamic variability caused by genetic and environmental influences, these medications should be monitored throughout treatment using the international normalized ratio (INR) *(38)*.

A study in the community revealed that monitoring errors (when a prescribed medication is not monitored in the way that would be considered acceptable in routine general practice) involved warfarin in nine out of 11 severe medication errors. The most

common error was failure to monitor or document the INR for a considerable period (sometimes for more than two years) in patients receiving long-term anticoagulant therapy *(39)*.

In the United Kingdom, warfarin (which still accounts for almost all of the use of vitamin K antagonists) was reported 10 years ago as one of the medications most commonly associated with medication errors leading to severe harm including death *(38)*. The same report noted that in secondary care, it was one of the 10 medications most frequently related to dispensing errors. Bleeding in association with oral anticoagulants is also one of the most frequent causes of hospital admission, particularly in older people *(40)*. This is probably in part related to their increased sensitivity to warfarin, and increased frequency of concomitant conditions leading to unstable anticoagulation (e.g. heart failure and drug interactions). The risk of bleeding in association with anticoagulant use is highest early in therapy during anticoagulant induction and stabilization as the appropriate dose for a particular individual is often not known early in the course of treatment. In addition, the low therapeutic index means that even small increases in the dose may cause a significantly increased risk, particularly if there is a potential underlying bleeding site not yet identified.

Newer oral anticoagulants (NOACs), also known as direct-acting oral anticoagulants (DOACs), including apixaban, dabigatran, edoxaban and rivaroxaban, are agents acting directly on clotting factor II or X. The main type A reaction is haemorrhage. In a recent study in the United States of America, almost 18% of all oral anticoagulant-related medication errors involved NOACs. The commonest error associated with all oral anticoagulant therapy was the omission of a dose *(41)*.

2.2 Other medications occassionally considered as being high-risk (high-alert)

Non-steroidal anti-inflammatory drugs used for pain associated with inflammation can be high-risk (high-alert) medications in certain circumstances. Type A reactions include gastrointestinal effects (e.g. ulceration) and cardiotoxicity (including exacerbation of heart failure, worsening of hypertension and myocardial infarction due to increased thrombotic risk). NSAIDs may also rarely precipitate renal failure *(42)*. Those at particular risk of such events are patients already at higher risk of gastrointestinal, renal or cardiovascular morbidity (including older persons).

Paracetamol (acetaminophen) is one of the most widely used over-the-counter medicines and has been responsible for a high rate of medication errors in children, including several instances of dose-related liver failure *(43)*.

Lithium salts are used in the treatment of a range of psychiatric disorders, including the treatment and prevention of mania, bipolar disorder and recurrent depression. They have a narrow therapeutic index, so should ideally only be given when serum lithium concentrations can be regularly monitored (*44*).

Type A reactions of lithium include gastrointestinal and central nervous system disturbances, and cardiac conduction disturbances. Lithium is largely eliminated unchanged by the kidney, and has the potential to interfere with kidney and thyroid function, so these functions should be monitored prior to starting treatment, and regularly thereafter. Special consideration is required for women of childbearing age, so a pregnancy test should also be performed if relevant *(44, 45)*.

Allergies to medications can cause high-risk situations when used in error, while medications causing allergic reactions are not necessary considered as high-risk (high-alert) medications. One example of this is allergy to

antibiotics with beta-lactams (especially penicillins) predominating. The most severe allergic reaction to penicillin, anaphylaxis, was estimated to cause 500 –1000 fatalities in the United States of America each year *(46)*. Unfortunately, individuals who have previously experienced a rapid-onset allergic reaction in relation to a medicine may be given the same agent again, sometimes with fatal outcome. Several other groups of medications (e.g. diuretics, cardiac glycosides and neuroleptics) may be considered to be high-risk (high-alert), particularly in certain patient groups. Thus, these agents are included in the Screening Tool of Older Person's Prescriptions (STOPP) criteria *(47)*.

2.3 Strategies to reduce harm from high-risk (high-alert) medications

Standardization

Standardization and systematization of processes and documentation (including naming, packaging and labelling) are important in reducing harm from high-risk (high-alert) medications *(48, 49)*. To support the implementation of Australia's national medication safety standard, the Australian Commission on Safety and Quality in Health Care developed a *National medication management plan*, *National recommendations for user-applied labelling of injectable medications, fluids and lines*, and a *National tall man lettering list (50)*. The tall man lettering approach is discussed in further detail by U and Cohen *(51)*.

Prescribing errors decreased upon introduction of a standardized inpatient medication prescription chart in Queensland *(52)*, and then across Australia *(53)*. The Australian National Inpatient Medication Chart and support materials are accompanied by standardized national terminology, abbreviations and symbols to be used in the prescribing and administering of medications in Australian hospitals *(54)*.

A similar approach was adopted in the development of a national inpatient prescription chart in Wales in 2004 *(55)* that has now been endorsed by the Royal College of Physicians as an example of good practice *(56)*. Several standards for the design of paper-based hospital inpatient prescription charts outlined by the Academy of Medical Royal Colleges will also be applicable to electronic prescribing when they become available in a particular region, state or country *(57)*. In conjunction with chart standardization, standards for prescribing can be agreed at national level *(58)*.

A study by Rozich et al. found that when patterns of care are widely divergent, clinical outcomes may be suboptimal and safety may be jeopardized *(59)*. Standardization of processes can reduce the risk of error. The authors demonstrated that standardization of a sliding scale protocol for insulin was associated with better outcomes in hospital inpatients. Donaldson found that weaknesses or deficiencies in communication, safety culture, operational practices, protocols and training, and packaging and design of medications and equipment, all contributed to episodes when vincristine sulphate was inadvertently administered intrathecally with fatal consequences *(60)*. This particular problem has since been successfully addressed by standardization of practices, indicating that it is possible to eliminate certain medication errors by using effective strategies.

Assessing safety risks of products

The National Patient Safety Agency of the United Kingdom has recommended that all health organizations develop a purchasing for safety policy for medication safety *(61)*. Products can be assessed using a risk score approach such as the medication error potential assessment (MEPA), which reflects a product's suitability for use based upon a wide range of factors (e.g. clarity of labelling, packaging, and availability of patient information). A pharmaceutical quality risk assessment tool has been made available for this purpose *(62)*.

There is some evidence that barcoding of medications might reduce medication and administration errors *(63)*, and an implementation plan using the GS1 global standard is available *(64)*.

Medication errors and adverse drug reactions may also be associated with substandard and falsified medical products. Further information is available from WHO *(65)*.

Reporting and learning systems and pharmacovigilance centres

A strong safety culture is one where errors are anticipated and watched for, where risks are proactively assessed and managed, and where health care professionals feel comfortable and confident to discuss and report errors and near misses (see Annex 1) and learn from them. Details of two initiatives to support reporting and learning – the WHO *Minimal Information Model for Patient Safety* and *the Conceptual Framework for the International Classification for Patient Safety* – can be found on the WHO website *(66)*. Tools are available to assess, develop and improve organizational safety culture *(67–69)*.

Although the primary role of regional and national pharmacovigilance centres (see Annex 1) is to optimize the reporting and detection of suspected adverse drug reactions, it has been shown that they can also detect, identify, analyse, and classify medication errors and carry out root cause analysis to investigate causality *(70)*.

Patient Safety Reporting and Learning System have been implemented at a national level in Spain, and England and Wales *(71, 72)*. The reporting system may encompass all types of incidents related to patient safety and be designed to respond to the context unique needs identified by the stakeholders *(71)*.

Use of multiple strategies

Due to the complexity of systems in health, the Institute for Safe Medication Practices has highlighted that a single strategy for addressing the risks associated with each high-risk (high-alert) medication in the acute care setting is rarely sufficient *(73)*.

The following measures may therefore be considered:

- Several risk reduction strategies may be used together.
- Strategies may be chosen that influence as many steps of the medication management system as possible.
- “High-leverage” risk reduction strategies, such as forcing functions (see Annex 1) and standardization, may be bundled together with “low-leverage” strategies, such as staff education and passive information dissemination (Table 2).
- Strategies that have been implemented successfully, proven effective and recommended by experts, should be used.
- The strategies that are chosen should be sustainable.

Table 2. Key strategies for medication safety

Key strategies	Description
Failure mode effects analysis (FMEA) and self-assessments	Proactively identify risks and how they can be minimized
Error-proof designing (forcing functions and fail-safes)	Build in safeguards to prevent or respond to failure
Limit access or use	Use constraints (e.g. restriction of access or requirement for special conditions or authorization)
Maximize access to information	Use active means to provide necessary information when critical tasks are being performed
Constraints and barriers	Use special equipment or work environment conditions to prevent hazard from reaching patient
Standardize	Create clinically sound, uniform models of care or products to reduce variation and complexity
Simplify	Reduce number of steps in the process of handoffs (handovers) without eliminating crucial redundancies
Centralize error-prone processes	Transfer to external site to reduce distraction of staff with expertise, with appropriate quality control checks
Preparation to respond to errors	Have antidotes, reversal agents or remedial measures readily available and ensure staff are appropriately trained to manage an identified error

Source: Adapted, with the permission of the publisher, from Institute for Safe Medication Practices *(73)*.

2.4 Potential actions to reduce medication-related harm due to medication factors in high-risk situations

The following guidance is not comprehensive, but constitutes advice given by a range of authorities worldwide. They may be adapted to suit local contexts depending on their applicability. Valuable resources for further information are listed in Annex 2.

Anti-infective agents

Aminoglycosides (74)

- Aminoglycoside doses (e.g. gentamicin) should be calculated taking into account the patient's weight and renal function (e.g. using a nomogram). Adjustments can then be made according to serum gentamicin concentrations.

Vancomycin (75)

- Monographs to improve the safe use of intravenous vancomycin and other commonly used antibiotics are available at the reference website, providing information for home and community care, and how various antibiotics should be prepared, stored and administered

Amphotericin B (24, 76)

- Potential local interventions include segregating storage areas in the fridge for different formulations of amphotericin (lipid-based and non-lipid based), and use of cautionary labels or warning signs to remind staff about the differences.

Potassium and other salts or electrolytes for intravenous injection *(26, 28, 77, 78)*

- In critical areas where high concentrations and doses of potassium chloride are necessary, a risk assessment should be performed to determine whether it is appropriate to keep the ampoules as a stock item in the critical areas. If required as a stock item, a protocol for safe storage, preparation and use should be developed.
- In the general ward, need for potassium chloride ampoules (and other concentrated potassium salts) should be assessed and stock may be removed if not necessary. Replacement with premixed solutions could also be considered.
- The storage of potassium chloride ampoules and premixed solutions should be assessed periodically to ensure they are stored separately and are readily identifiable from preparations with similar packaging.

Insulins *(79, 80)*

- Abbreviations, unclear instructions and ambiguous doses should be avoided. Insulin syringes and well titrated doses should be used. Moreover, prescribing by "brand name" and device could reduce error.
- When storing insulin, consider physically separating insulin from vaccines or LASA products, or store vaccines in a separate fridge if possible.
- Engagement of patients and caregivers is strongly encouraged. They should be educated to identify symptoms of hyperglycemia and hypoglycemia, and encouraged to take immediate corrective measures or seek advice when needed. Patients and caregivers should also be empowered to seek clarification at any time and to ensure there is a clear understanding of their signs, symptoms and treatment, insulin use in relation to meals and illness, and the differences between the different types of insulins.

Narcotics and sedatives *(13, 81–84)*

- The correct product in the correct dose should be selected, particularly with morphine and diamorphine as they carry an increased risk of adverse events at high doses.
- To minimize the risks in neonatal units, staff should ensure that protocols relating to the preparation and administration of intravenous morphine for neonates are clear and easy to follow. For example, steps may be outlined separately in a checklist format. In addition, the use of prefilled syringes from a central intravenous additive service and smart pumps could be considered.
- Guidance on counselling patients and caregivers on the safe use of opioid patches is available.
- *Navigating opioids for chronic pain* is a tool that provides guidance on different opioid options based on morphine equivalence to compare the relative potency of these different medications.
- *Opioid pain medicines information for patients and families* provides guidance and information for patients to consider when prescribed an opioid medicine.

Chemotherapeutic and immunosuppressive agents *(32)*

- Processes should be in place to avoid administering the wrong medication, dose, route, concentration, duration or frequency. The prescribing and use of oral chemotherapeutic medications should be carried out to the same standard as parenteral anticancer therapy and should be monitored in the same way.

Heparins and oral anticoagulants

Unfractionated heparin (UFH) *(35)*

- All patients should have a baseline aPTT performed before initiation of therapy.
- Platelet counts should also be measured just before therapy with UFH, and regular monitoring of platelet counts may be required if UFH is administered for longer than four days.

Low molecular weight heparin (LMWH) *(37, 85, 86)*

- The weight of the patient is used to calculate

the treatment dose required of LMWH. The medication chart (when in use) and clinical record should have the weight of the patient accurately recorded. At the beginning of therapy, patients should be weighed and, during treatment, where applicable.

- When prescribing treatment doses of LMWH, renal function should be taken into account. Initiation of the first dose should not be delayed by renal function tests but every effort should be made to base subsequent dosing on these results.
- Dose calculation tools are available for different LMWH products, specific clinical indications and varying body weights.
- Rationalizing the variety of LMWH products used within an organization has been used as a means to reduce errors.

Vitamin K antagonists (e.g. warfarin) *(87)*

- Prior to commencing anticoagulation, a risk assessment should be undertaken and documented, and repeated on an annual basis.
- Prescribers should discuss the risks, benefits and implications of long-term warfarin treatment with newly diagnosed patients. This discussion should be documented and decision aids used where possible.
- The baseline prothrombin time (or INR) should be determined.
- The appropriate (rapid or slow) induction should be used. This should reduce the likelihood of ineffective or excessive anticoagulation and some can also be used to predict the likely long-term daily doses of warfarin.
- INR should be measured regularly, particularly during the induction period.
- Computer dosing software could be used when available.
- Anticoagulant treatment booklets may be issued to all patients; these booklets could include advice for patients on anticoagulant treatment, an alert card to be carried by the patient at all times, and a section for recording INR results and dosage information.
- There should be reliable follow-up systems in primary care to ensure that patients on warfarin are reviewed regularly and not lost to follow-up.

Newer oral anticoagulants /direct oral anticoagulants *(88)*

- When prescribing a NOAC an in-depth knowledge of its pharmacology and clinical use is needed. Prior to prescribing, conducting a risk–benefit assessment should be considered. Careful patient selection and monitoring ensures the best outcomes.
- Before prescribing a NOAC creatinine clearance should be calculated (e.g. using the Cockcroft Gault equation and ideal body weight) and documented.
- If renal function is impaired, excessive anticoagulation and drug accumulation can occur. Renal function should be monitored at least annually. Monitoring frequency may be increased to every three or six months due to declining renal function or dehydration, and amongst older persons. These factors should be communicated through all transitions of care (see Annex 1) to ensure proper monitoring.
- NOACs have fewer drug interactions than warfarin; however, many clinically significant interactions exist. Individual patient bleeding risks should be considered and specialist advice could be sought, as these are often complex situations.
- Counselling of patients and caregivers could include communicating the discharge information from hospital care, promoting regular and adequate follow-up and explaining how to recognize and respond to bleeding, and to seek medical attention immediately if bleeding is suspected.

Other medications

Non-steroidal anti-inflammatory drugs *(42)*

In the United Kingdom, the National Institute for Health and Care Excellence has proposed the following options for local implementation concerning NSAIDs:

- Review the appropriateness of NSAID prescribing widely and on a routine basis, especially in people who are at higher risk of

gastrointestinal, renal and cardiovascular morbidity and mortality (e.g. older people).

- If an NSAID is needed, use ibuprofen (1200 milligrams a day or less) or naproxen (1000 milligrams a day or less). Use the lowest effective dose and the shortest duration of treatment necessary to control symptoms.
- Consider co-prescribing proton pump inhibitors with NSAIDs, especially when used in those with risk of gastric bleeding or when used for long-term treatment of osteoarthritis, rheumatoid arthritis and lower back pain.

Paracetamol (acetaminophen) (43)

- To reduce dosing errors of paediatric liquid paracetamol (acetaminophen), extra attention should be paid to the dosing instructions, use of the correct measuring device, concentration of the paracetamol preparation to be administered, and whether or not paracetamol is included as an ingredient in other combination medication preparations.

Lithium (89)

- Patients prescribed lithium should be monitored in accordance with local guidance.
- There should be reliable systems in place such as an electronic alert, to ensure blood test results are communicated between laboratories and prescribers.
- At the start of lithium therapy and throughout treatment, patients may be given a record book to track serum lithium levels and other relevant clinical tests, and appropriate, continuing verbal and written information.
- Prescribers and pharmacists should check that blood tests are monitored regularly and if it is safe to issue a repeat prescription or dispense the prescribed lithium.
- Mechanisms to identify and deal with medications that might adversely interact with lithium therapy are very helpful.

Antibiotic allergy (56, 90–92)

- Information regarding previous adverse drug reactions should be elicited, documented and considered prior to prescribing, dispensing and administering a medication, including topical medications. Documentation of allergy history should be in a location where it can easily be reviewed by the prescriber (Figure 4).
- Advice on the diagnosis and treatment of antibiotic allergies is available, including from the National Institute for Health and Care Excellence and Australasian Society of Clinical Immunology and Allergy.

Figure 4. Example of medication allergies and sensitivities section of a paper-based inpatient prescription chart

DRUG ALLERGIES & SENSITIVITIES	NONE KNOWN	YES
	SIGNED	DATE.....
	NAME	
Drug / Allergen:		Description of Reaction:
This section must usually be completed prior to administration of any medicine. Refer to local policies for further guidance.		

Source: Reproduced, with the permission of the publisher, from Royal College of Physicians *(56)*.

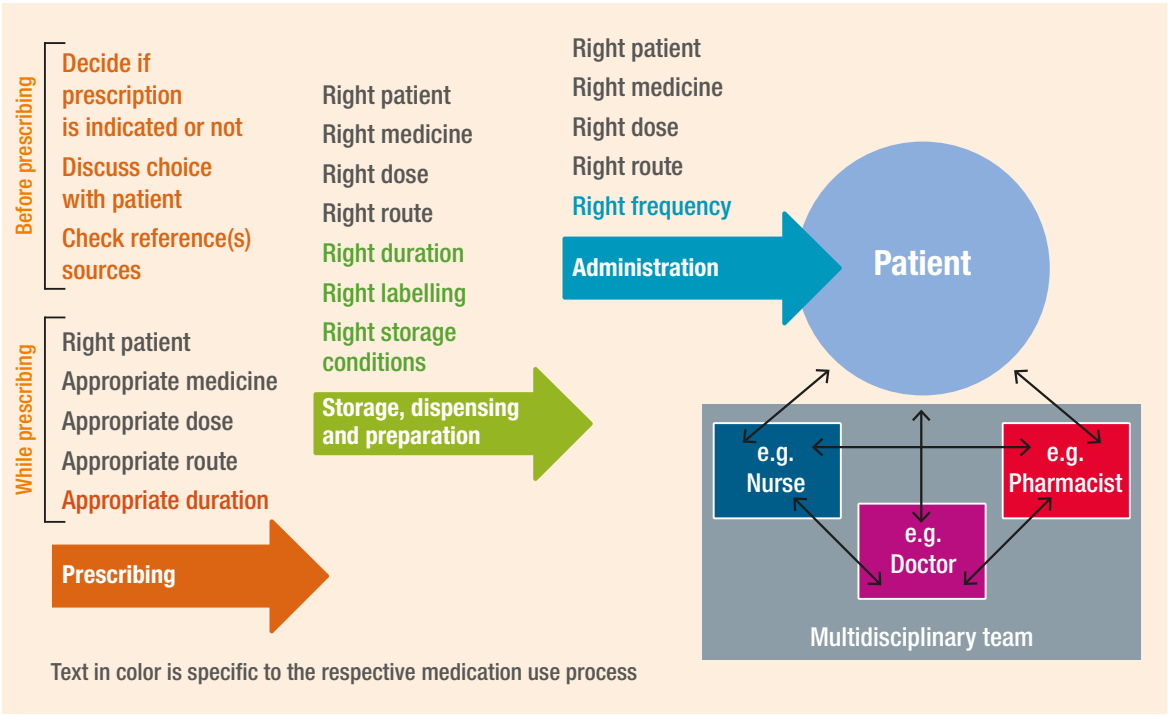
3 Provider and patient factors

Provider and patient factors influencing medication safety can relate to either the health care professional providing care or to the patient being treated.

3.1 Health care professionals

Even the most dedicated health care professional is fallible and can make errors *(93)*. The act of prescribing, dispensing and administering a medicine is complex, normally involving several health care professionals, with the patient necessarily being a part of, and in the centre of, what should be a "prescribing partnership" (Figure 5). Patients should expect that the health care professionals responsible for their care will communicate directly with them as well as with each other *(94)*. In broad terms, the prescribing process involves the prescriber in deciding whether any particular medication or combination of medications is indicated. Whenever feasible, the expected benefits and possible risks should be discussed with the patient, following which the appropriate dose and duration of the chosen medication should be prescribed, dispensed and then administered to the correct patient.

Figure 5. The prescribing partnership



Source: Adapted, with the permission of the publisher, from Routledge *(94)*.

Errors most commonly occur during the administration step of the medication use process, but can occur at any time, including: storage, prescription, preparation, dispensing and monitoring *(95)*.

Poor prescribing has been described to take three forms *(96)*:

- **Overprescribing** occurs when a medication is prescribed whose risk of harm exceeds its likely benefit (overall or relative to another medication) in a particular individual. Thus, every prescription requires the exercise of good prescribing skills to assess individual risk–benefit.
- **Underprescribing** occurs when a medication is not prescribed whose likely benefit greatly exceeds the risk of harm. The acquisition of sound therapeutic knowledge and skills by the prescriber is the key to minimizing this risk.
- **Misprescribing** occurs when either the wrong medication is prescribed or the wrong dose, route, frequency or duration of administration is chosen. It may occur as part of a medication error.

All of these forms of potentially inappropriate prescribing can contribute to an unfavourable risk–benefit ratio, and reduce, or even negate, the benefits of these medications to the patient. Poor medication adherence (see Annex 1) may also result in failure to benefit from the prescribed medication. However, avoidance of harm is only one aspect of appropriate prescribing. It is important that the right medicine reaches the right patient. In addition, significant health care costs can be avoided by using medicines more appropriately, thus achieving better and more cost-effective health care. These aspects of care are highlighted in two informative WHO publications. The first – *The pursuit of the responsible use of medicines: sharing and learning from country experiences* – highlights examples of how certain countries have positively addressed specific important areas of prescribing *(97)*.

The second – *Guide to good prescribing: a practical manual* – is a learning resource which uses case scenarios to outline the principles of selection of first-line medications, followed by a step-by-step overview of the process of rational treatment *(98)*.

Several studies indicate that training, experience and practice help to reduce prescribing errors by hospital doctors *(99, 100)*. However, there is no room for error during prescribing and thus it is important to train future doctors in the science of prudent prescribing, as rightly highlighted by Woods *(101)*. This is so that prescribers are competent to provide accurate and appropriate prescriptions upon graduation. This approach may also be adopted in relation to non-medical prescribers in countries where it is applicable.

Health care professionals are also involved in ensuring safe storage, preparation, dispensing, administration and monitoring of medications. These different steps of the medication use process are no longer the sole domain of any single health care professional group. However, it is vital that there is good communication between different groups of health care professionals. Interprofessional educational initiatives may help health care professionals to learn to work better together in multidisciplinary teams to promote patient safety. Certainly communication problems within and between health care professionals, and between them and their patients, are often major factors predisposing to prescribing errors *(100)*, as well as other errors involving dispensing and administration.

Resource-limited settings are often characterized by a lack of electronic support systems for prescribing or dispensing, overcrowding of patients, staff shortages and inadequate monitoring. In such circumstances poor prescribing practices, such as the use of error-prone abbreviations, increase the risk of medication errors.

Different health care professionals may elicit different information about a patient's medication history. The optimal medication histories are often achieved through proper training of workforce and use of appropriate tools. In one study in an emergency department, physicians omitted medicines or doses more often in comparison with their pharmacist colleagues, probably because the latter used a structured form to collect the information *(102)*. Differences in obtaining a medication history may also occur between specialties within a single health care profession. In one study, hospitalized patients, over 65 years of age, being treated by internal physicians were more likely to receive neuroleptic agents for long-term hypnotic use than those treated by geriatricians *(103)*.

3.2 Patients

It is well known that adverse drug events occur most often at the extremes of life (in the very young and in older people). In older people, it is the group of frail patients who are likely to be receiving several medications concomitantly, adding to the risk of adverse drug events. In addition, the harm of some of these medication combinations may sometimes be synergistic and be greater than the sum of the risks of harm of the individual agents. In neonates (particularly premature neonates), elimination routes through the kidney or liver may not be fully developed *(104)*. In children as well as in older persons, the impact of any resulting harm may be much more serious. The very young and those of old age are also less likely to tolerate adverse drug reactions, either because their homeostatic mechanisms are not yet fully developed (e.g. in the young, especially neonates and infants) or may have deteriorated (e.g. in older people). Therefore it is likely that outcomes involving high-risk (high-alert) medications will be more severe in these groups.

Medication errors in children, where doses may have to be calculated in relation to body weight or age, are a source of major concern.

Prescribing errors resulting from miscalculations have been reported in a paediatric intensive care setting *(105)*. In the *PRACtICe* study in primary care, the risk of medication errors was greater in those below the age of 15 years and in those aged over 64 years *(40)*.

Age also appears to be a major predictor of the risk of medication errors among older people. In a study of more than 1400 adult inpatients, 26% of whom experienced at least one clinically significant medication error; age and the number of prescribed medications were the two major predictors of the risk of experiencing a medication error *(106)*. Sears et al. showed that self-reported medication errors were more likely in females than males *(107)*.

Polypharmacy

The number of prescribed medications was the second major factor predicting risk of experiencing a medication error in adult inpatients *(106)*. The risk of medication (prescribing or monitoring) errors in the *PRACtICe* study was related to the number of unique medication items prescribed, reinforcing the important contribution of polypharmacy to the increased risk of harm *(40)*.

Multimorbidity

Multimorbidity (see Annex 1) is becoming more prevalent as life expectancy increases in many countries around the world. A meta-analysis that included 75 studies from primary care demonstrated that mental-physical multimorbidity was associated with an increased risk for "active patient safety incidents" and prescribing errors *(108)*.

High-risk medical conditions

Certain medical conditions predispose patients to an increased risk of adverse drug reactions, particularly renal or hepatic dysfunction and cardiac failure (where both kidney and liver can be compromised together). In part this is because the liver and kidney are the two main organs involved in the metabolism and excretion of medications from the body, so

if the normal doses of a certain medication are used during liver or kidney failure, dose-related ADRs (type A reactions) may occur. Hepatic and renal diseases are often also chronic conditions in which polypharmacy is common, and this can predispose patients to drug–drug interactions or drug–disease interactions. Other conditions that predispose people to a high risk of medication-related harm include pregnancy and poor hydration status *(98)*.

Medication errors may lead to significant harm in patients with renal disease. In a study of 200 renal transplant recipients, clinically significant medication errors (defined as those that contribute to hospital admission) were associated with more post-transplant readmissions, significantly higher costs for those readmissions, overall length of stay, and risk of graft failure *(109)*.

In a study of 50 people with liver disease (in this case cirrhosis), 27 (54%) had one or more discrepancies between what the patient reported they were taking and their medical record. These discrepancies were more common in older patients, those who were on five or more conventional medications, or those having a low to medium adherence ranking. Concordance between the two lists was lowest for respiratory medicines (0%), and complementary and alternative medicines (14.5%) *(110)*.

3.3 Strategies to reduce medication errors related to provider and patient factors

Health care professionals

James Reason has noted that there should be a systems approach to counter the effects of human fallibility. This approach concentrates on the conditions under which people work and endeavours to build the defences required to avert errors or limit their effects *(93)*. The Clinical Human Factors Group has identified four major themes – design, teamwork, incident investigations, and working in the real world – that are important components of a resilient systems approach to safety, and these can be usefully applied to medication safety *(111)*.

Education

The importance of safe medication practice should be conveyed at an early stage in training of health care professionals, and embedded in training curricula. WHO has developed a set of evaluation tools designed to complement the WHO *Patient safety curriculum guide for medical schools*, published in 2009 *(112)*. Within the first two years of its circulation, the guide had been implemented in curricula around the world. A multiprofessional version of the guide was subsequently produced in 2011 for students of dentistry, medicine, midwifery, nursing and pharmacy *(113)*.

As more groups of health care professionals are embracing the role of prescribers, they should be made aware of the importance of establishing an accurate medication history, covering both prescribed (conventional and/or traditional and complementary medicines) and non-prescribed medications (including self-prescribed, over-the-counter, food supplements, and traditional and complementary medicines). Similarly, a history of allergy to any previous medication should be elicited. Interprofessional education in this area can be used to improve communication within different professional teams.

Core prescribing competencies are relevant to all the prescribing health care professionals who are faced with addressing the increasing burden of complex polypharmacy among people with multimorbidity *(114)*. Several studies have shown that training using the WHO *Guide to good prescribing (98)* was associated with increased prescribing competency in a wide range of settings *(115)*. In the United Kingdom, a prescribing safety assessment has to be passed to ensure that all new medical prescribers, whether trained in the United Kingdom or elsewhere, meet a similar basic prescribing standard before they begin clinical practice *(116)*.

Prescribing, dispensing, administration and monitoring of medicines should be the subject of audit and clinical review by health care professionals, and consideration may be given to those using resources emphasizing medication safety as part of clinical revalidation or relicensing.

Medication reconciliation

Prescribing errors often occur at transitions of care. Pharmacy-led medication reconciliation on hospital admission may also have economic benefits *(117)*.

Patients

Many of the patient factors discussed earlier (e.g. age, multimorbidity) are relatively static. Patients should be supported by an effective prescribing team working in close partnership to ensure they are aware of the purpose of all medications taken, their likely benefits and potential risks (*94*). Useful aide-memoire tools for patients are available, such as *5 questions to ask about your medications when you see your doctor, nurse, or pharmacist (118)* and *5 Moments for Medication Safety (119)*:

The *5 Moments for Medication Safety* is a patient engagement tool developed to support implementation of the third WHO Global Patient Safety Challenge: *Medication Without Harm.* It focuses on 5 key moments in the medication use process, where action by the patient, family member or caregiver can greatly reduce the risk of harm associated with the use of medications. The five moments are: starting a medication, taking my medication, adding a medication, reviewing my medication and stopping my medication. Each moment, in turn, includes 5 critical questions, some of them being self-reflective for the patient and some requiring support from a health professional to be answered and reflected upon correctly (*119*). Application of the *5 Moments for Medication Safety* tool may vary depending on the country or local context and specific setting. It may be applied in targeted population groups (for example, older people, children, pregnant and breastfeeding women) or in targeted patient groups (for example, patients with chronic conditions, cancer or mental health conditions).

It is important to highlight that principles of co-production of resources and partnership with patients and caregivers should be applied in relation to developing systems for all the guidance for high-risk (high-alert) medications discussed earlier. Medication Safety, Standard 4, developed by the Australian Commission on Safety and Quality in Health Care states that the patient should be provided with patient-specific medication information that includes treatment options, benefits and associated risks *(50)*. The format of the information provided should meet the needs of patients and caregivers while being easily understandable. Finally, the medication plan should be discussed with the patient and the patient should agree to follow that plan, with the emphasis on joint decision-making.

Limited language proficiency, lower levels of education and misperceptions of illness severity are more likely to lead to patients having reduced knowledge regarding their prescribed medications *(120)*. It is also important to recognize the particular needs of people with intellectual disabilities, including (but not only) in the hospital *(121)*. Caregivers also have an important role and can make similar errors to those made by professionals *(122)*.

Systems factors (work environment)

4

4.1 Systems factors influencing medication safety

The external environment is an important determinant of the risk of medication errors. Prescribing error rates reported in two large studies were higher in hospitalized patients *(100)* than in the community *(39)*. Damen et al. highlighted the particular concern that adverse drug events during hospitalization remain common despite concerted attempts to reduce them. They also showed that anticoagulant-related adverse events still occurred during hospitalization, despite mostly being preventable, since they were often related to dosage errors *(39)*.

The environment in hospitals can contribute to error-provoking conditions. The clinical ward may be busy or understaffed, contributing to inadequate supervision or failure to remember to check important information. Interruptions during critical processes (e.g. administration of medicines) can also occur, which can have significant implications for patient safety *(123)*. Tiredness and the need to multitask when busy or flustered can also contribute to error. Problems may be compounded by poor chart design *(100)*.

Even within the hospital environment, certain specialties seem to be associated with particular risk of medication administration error. In a prospective observational study, anaesthesia-trained staff observed randomly selected operations at a large tertiary care academic medical centre and identified a rate of medication errors and/or adverse drug events of 5.3% *(124)*. Administration errors are a particular problem in the anaesthesia setting. In a prospective incident monitoring study conducted at a large tertiary hospital in China, the frequency of administration error was 1.1% based on total forms returned. The largest categories of error were omissions, incorrect doses and substitutions. Significantly more respondents who had not been able to have sufficient rest reported inattention as a contributing factor to error than those who were sufficiently rested *(125)*.

It is important to note that most prescribing occurs in primary rather than secondary care. A WHO monograph, *Medication errors: technical series on safer primary care*, has highlighted the scale of this problem and proposes measures to address the issue. This monograph additionally outlines the particular issues related to prescribing in children in the community and in elderly care homes *(126)*.

4.2 Strategies to reduce medication errors related to systems factors

Workflow interruptions, noise and busy working environments can be distracting when prescribing, dispensing, preparing and/or administering medication. Tabards have been worn to reduce interruptions during prescribing or administering medications, but the evidence for their value is mixed *(127)*.

Preparing and administering intravenous medications is particularly error prone.

Checking at each stage markedly reduces the probability of error. In the study by McDowell et al. errors were found most likely to occur in the reconstitution step. The provision of pre-prepared injections removes the need for reconstitution and may reduce the overall error rate significantly *(128)*.

The issue of chart design has been discussed earlier and there is evidence that such standardization reduced prescribing errors in Australia *(52, 53)*. Electronic prescribing may reduce the rate of prescribing errors *(129, 130)* and, in one study, completely eliminated illegible prescriptions *(130)*. However, the transition to electronic prescribing is difficult in resource-limited settings, partly because of the acquisition and maintenance costs, and hence paper-based systems are still widely used.

Because prescribing each medication requires a risk–benefit assessment for each patient, it is important that prescribers have access to high-quality prescribing advice (e.g. from an authoritative formulary) at the time of prescribing. Prescribing assessment tools can also be helpful. Building on the original Beers Criteria (for potentially inappropriate medication use in older adults), the STOPP criteria have been developed to highlight potentially inappropriate medications (see Annex 1), and the Screening Tool to Alert Doctors to Right Treatment (START) criteria to highlight potentially beneficial treatments in older people *(47, 131, 132)*. Version 2 of this approach now contains 114 criteria to improve medication appropriateness, and there is emerging evidence that appropriate prescribing can reduce the incidence of falls in older residents of nursing homes *(133)*.

A set of 41 prescribing appropriateness criteria was developed for older people in Australia using the RAND/UCLA appropriateness method. The criteria could assist in improving patient care in a variety of settings by identifying medication problems related to common medical conditions and frequently used medications *(134)*.

Tables or software giving information on drug–drug interactions, and interactions with traditional and complementary medication are also helpful, particularly in situations where polypharmacy is common. These tools can assist health care professionals to better address problems related to complex polypharmacy and reduce risk to patients.

Implications for countries

5

Each country participating in the third WHO Global Patient Safety Challenge: *Medication Without Harm* is urged to take early priority action to improve medication safety in high-risk situations and reduce harm by *(5)*:

- identifying its objectives by convening a group of technical experts, physicians, nurses, pharmacists, patients, regulators, and health system leaders to select and prioritize a small number of high-risk (high-alert) medications and high-risk situations for action that are applicable to their situation and achievable with the resources available;
- developing a plan to achieve those objectives, including the processes, systems, patient involvement and education and training of health care professionals needed to deliver them;
- developing a range of sustainable strategies of proven efficacy to address each of the priority areas in medication safety identified by the country, as medication errors are often caused by a combination of medication, provider and patient, and systems factors;
- developing a strong safety culture within health care;
- promoting and supporting the establishment of systems for reporting medication errors at national and institutional level.

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Annex 1. Glossary

Term	Definition and source used in glossary (see separate glossary references below)
Adverse drug event	Any injury resulting from medical interventions related to a drug. This includes both adverse drug reactions in which no error occurred and complications resulting from medication errors *(1)*
Adverse drug reaction	A response to a drug which is noxious and unintended and that occurs at doses used in humans for prophylaxis, diagnosis or therapy of diseases, or for the modification of physiological function *(2)*. These are often classified as two types: Type A and Type B *(3)* *Type A adverse drug reaction* An augmented pharmacologically predictable reaction which is dose dependent. It is generally associated with high morbidity and low mortality *(4)* *Type B adverse drug reaction* A bizarre reaction which is unpredictable pharmacologically and is independent of dose. It is generally associated with low morbidity and high mortality *(4)*
Anaphylaxis	A severe, life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potentially life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes *(5)*
Best possible medication history	A medication history obtained by a clinician which includes a thorough history of all regular medication use (prescribed and non-prescribed), using a number of different sources of information *(6)*
Deprescribing	The process of tapering, stopping, discontinuing, or withdrawing drugs, with the goal of managing polypharmacy and improving outcomes *(7)*
Essential medicines	Essential medicines are those that satisfy the priority health care needs of the population *(8)*
Forcing function	An aspect of a design that prevents the user from taking an action without consciously considering information relevant to that action. It forces conscious attention upon something ("bringing to consciousness") and thus deliberately disrupts the efficient or automatized performance of a task *(9)*
Formulary	A list of medicines, usually by their generic names, and indications for their use. A formulary is intended to include a sufficient range of medicines to enable medical practitioners, dentists and, as appropriate, other practitioners to prescribe all medically appropriate treatment for all reasonably common illnesses *(10)*

Term	Definition and source used in glossary (see separate glossary references below)
High-risk (high-alert) medications	Drugs that bear a heightened risk of causing significant patient harm when they are used in error. Although mistakes may or may not be more common with these medications, the consequences of an error are clearly more devastating to patients *(11)*
Medication adherence	The degree to which use of medication by the patient corresponds with the prescribed regimen *(12)*
Medication discrepancy	Any difference between the medication use history and the admission medication orders *(13)*. Discrepancies may be intentional, undocumented intentional or unintentional discrepancies *(6)*
Medication error	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 *(14)*
Medication reconciliation	The formal process in which health care professionals partner with patients to ensure accurate and complete medication information transfer at interfaces of care *(6)*
Medication-related harm	Patient harm related to medication. It includes preventable adverse drug events (e.g. due to a medication error or accidental or intentional misuse) and non-preventable adverse drug events (e.g. an adverse drug reaction)
Medication review	A structured evaluation of patient's medicines with the aim of optimizing medicines use and improving health outcomes. This entails detecting drug related problems and recommending interventions *(15)*
Medication safety	Freedom from accidental injury during the course of medication use; activities to avoid, prevent, or correct adverse drug events which may result from the use of medications *(16)*
Medication use process	The multistep process in the use of medications by or for patients, including: prescribing, ordering, storage, dispensing, preparation, administration and/or monitoring
Medicines optimization	Ensuring that the right patients get the right choice of medicine, at the right time. By focusing on patients and their experiences, the goal is to help patients to (a) improve their outcomes; (b) take their medicines correctly; (c) avoid taking unnecessary medicines; (d) reduce wastage of medicines; and (e) improve medicines safety *(17)*
Multimorbidity	The presence of two or more long-term health conditions, which can include (a) defined physical and mental health conditions such as diabetes or schizophrenia; (b) ongoing conditions such as learning disability; (c) symptom complexes such as frailty or chronic pain; (d) sensory impairment such as sight or hearing loss; and (e) alcohol and substance misuse *(18)*
Near miss	An incident that did not reach the patient *(19)*
Patient safety	The absence of preventable harm to a patient and reduction of risk of unnecessary harm associated with health care to an acceptable minimum. An acceptable minimum refers to the collective notions of given current knowledge, resources available and the context in which care was delivered weighed against the risk of non-treatment or other treatment *(20)*
Pharma-covigilance	Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem *(2)*

Term	Definition and source used in glossary (see separate glossary references below)
Polypharmacy	Polypharmacy is the concurrent use of multiple medications. Although there is no standard definition, polypharmacy is often defined as the routine use of five or more medications *(21)*. This includes over-the-counter, prescription and/or traditional and complementary medicines used by a patient
Potentially inappropriate medications	Medications with ineffectiveness or high risk–benefit ratio for a particular individual or group of individuals *(22)*
Safety	The reduction of risk of unnecessary harm to an acceptable minimum *(19)*
Side effect	A known effect, other than that primarily intended, related to the pharmacological properties of a medication *(19)*
Transitions of care	The various points where a patient moves to, or returns from, a particular physical location or makes contact with a health care professional for the purposes of receiving health care *(23)*

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