World Health Organization

Medication Safety in Polypharmacy

MEDICATION WITHOUT HARM
Global Patient Safety Challenge

Technical Report

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Contents

Abbreviations

ACE	angiotensin-converting enzyme
ADR	adverse drug reaction
ARB	angiotensin II receptor blocker
BP	blood pressure
COPD	chronic obstructive pulmonary disease
eGFR	estimated glomerular filtration rate
NNH	number needed to harm
NNT	number needed to treat
NSAID	non-steroidal anti-inflammatory drug
OTC	over-the-counter
PESTEL	political, economic, social, technological, environmental and legal
PIM	potentially inappropriate medication
RLS	reporting and learning systems
SWOT	strengths, weaknesses, opportunities and threats
UHC	universal health coverage
WHO	World Health Organization

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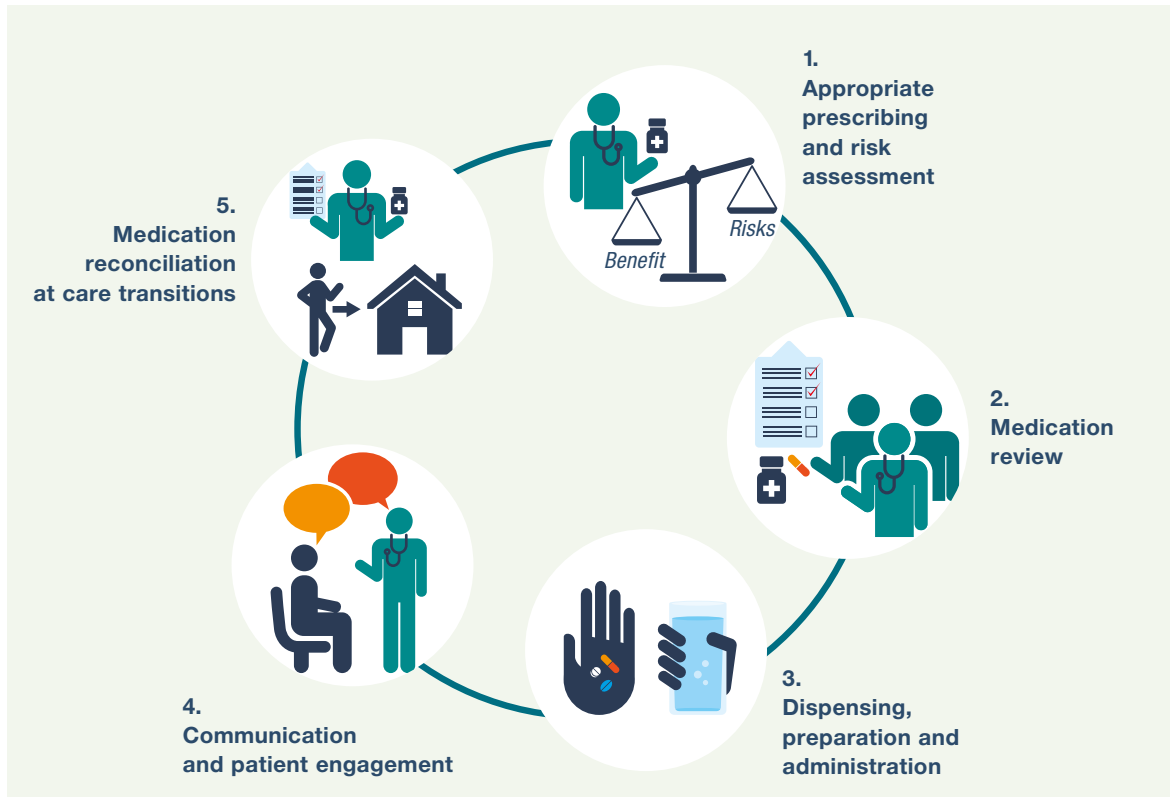
In this scenario the key steps that should have been followed to ensure medication safety in the inpatient setting include:

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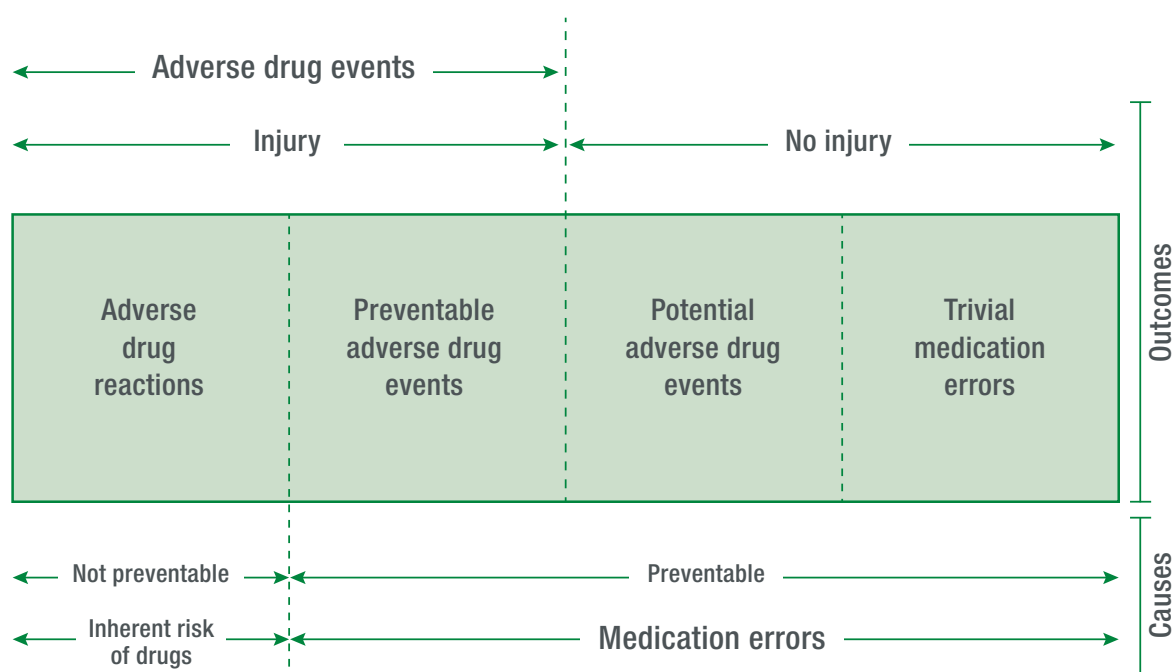
Source: Reproduced, with the permission of the publisher, from Otero and Schmitt *(6)*.

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

Executive summary:
medication safety in polypharmacy

Ensuring medication safety in polypharmacy is one of the key challenges for medication safety today. Due to the traditional focus of both medical research and health care delivery models on single-disease interventions, there has been a notable lack of evidence-based solutions. Conventionally polypharmacy has been perceived as an overuse of medicines, whereas it may be more useful to perceive in terms of appropriateness, as there are many cases where the concurrent use of multiple medicines may be deemed necessary and beneficial. Globally the prevalence of polypharmacy is set to rise as the population ages and more people suffer from multiple long-term conditions. Countries should therefore prioritize raising awareness of the problems associated with inappropriate polypharmacy and the need to address this issue.

All stakeholders have a vital role to play in driving change for the management of polypharmacy. Polypharmacy management involves multifaceted decision-making and necessitates the combined knowledge of physicians, nurses, pharmacists and other health care professionals, including the systematic involvement, engagement and empowerment of patients. Thus it is important to implement interventions, such as medication reviews, whenever possible in collaboration with the patient and/or the caregiver. Good communication and accurate sharing of information is essential and can be facilitated by the use of patient-held medication records. Furthermore, a redesign of care processes and/or services may be necessary to help medical practitioners manage workload related to polypharmacy in order to improve medication safety.

In complex health care setting with many competing priorities, it is useful to outline the safety, clinical and economic implications for appropriate polypharmacy management. It can also be helpful to develop an implementation plan which applies change management and implementation theories and tools. The four domains in the strategic framework of the third WHO Global Patient Safety Challenge: *Medication Without Harm* can assist in providing a guiding structure to create a medication safety strategy addressing polypharmacy.

Introduction

This technical report does not attempt to cover the entire scope of polypharmacy, but merely aims to introduce polypharmacy as a concept, and examine some approaches for the appropriate management of polypharmacy, which are crucial for ensuring greater medication safety.

1.1 Polypharmacy

Despite the increasing prevalence of polypharmacy, the term continues to lack a clear universal definition. A recent systematic review of the definitions of polypharmacy showed that the term was most commonly applied to situations where patients took five or more medications, and this numerical definition was used by 46.4% of the studies evaluated *(7)*. Furthermore, there are inconsistencies with the use regarding duration of therapy and whether to include over-the-counter (OTC), and traditional and complementary medicines in the definition or not. However, with the aim of reducing medication-related harm, it is important to verify to the fullest extent possible all the medications that the patient is taking, including all OTC, and traditional and complementary medicines.

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. This includes over-the-counter, prescription and/or traditional and complementary medicines used by a patient (see Annex 1).

While polypharmacy is often defined as routinely taking a minimum of five medicines, it is being more frequently suggested that the emphasis should be on evidenced-based practice *(7)*. The goal should be to reduce inappropriate polypharmacy (irrational prescribing of too many medicines) and to ensure appropriate polypharmacy (rational prescribing of multiple medicines based on best available evidence and considering individual patient factors and context) *(7–11)*. Therefore, appropriate polypharmacy should be considered at every point of initiation of a new treatment for the patient, and when the patient moves across different health care settings.

Appropriate polypharmacy is present, when (a) all medicines are prescribed for the purpose of achieving specific therapeutic objectives that have been agreed with the patient; (b) therapeutic objectives are actually being achieved or there is a reasonable chance they will be achieved in the future; (c) medication therapy has been optimized to minimize the risk of adverse drug reactions (ADRs); and (d) the patient is motivated and able to take all medicines as intended *(12)*.

Inappropriate polypharmacy is present, when one or more medicines are prescribed that are not or no longer needed, either because: (a) there is no evidence based indication, the indication has expired or the dose is unnecessarily high; (b) one or more medicines fail to achieve the therapeutic objectives they are intended to achieve; (c) one, or the combination of several medicines cause ADRs, or put the patient at a high risk of ADRs or because (d) the patient is not willing or able to take one or more medicines as intended *(12)*.

Polypharmacy has been described as a significant public health challenge *(13)*. It increases the likelihood of adverse effects, with a significant impact on health outcomes and expenditure on health care resources *(14–16)*. Although co-prescribing multiple medicines increases the risk of adverse events, it is important to note that assigning a numeric threshold to define polypharmacy is not always useful. There are cases where polypharmacy is necessary and beneficial, such as the secondary prevention of myocardial infarction, which requires the use of four different classes of medications (a beta blocker, a statin, an antiplatelet agent and an ACE inhibitor) *(8, 12)*. Appropriate polypharmacy recognizes that patients can benefit from multiple medications if the patients' clinical conditions, comorbidities, allergy profiles, the potential drug–drug and drug–disease interactions are considered, and the medicines are prescribed based on the best available evidence *(17)*. Thus, it is critical to distinguish appropriate polypharmacy from inappropriate polypharmacy *(12)*.

The most vulnerable patient groups to the risks of polypharmacy are susceptible to events such as drug–drug interactions, higher risk of falls, ADRs, cognitive impairment, non-adherence and poor nutritional status *(18–20)*. Vulnerable patient groups often include older patients above the age of 65 years and patients who are living in care homes *(19–21)*.

1.2 Prevalence of polypharmacy

Polypharmacy is a major and growing public health issue occurring within all health care settings worldwide *(8, 13)*. The issue is well described in literature from countries in North America *(10, 18)*, Europe *(8, 22)* and the Western Pacific *(23)*, with more data becoming available from other countries in recent years. Additional information from selected countries is available in Annex 2, illustrating that polypharmacy is a global problem. However, variation in the structure of health care delivery and data collection systems, compounded by the different operational definitions of polypharmacy, makes country comparison difficult.

Multimorbidity is defined as 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 (see Annex 1).

While its true magnitude is not known, the prevalence of polypharmacy is expected to rise due to a multitude of factors *(8)*. First, the global population faces a demographic shift with the proportion of older population

groups on the rise. It has been estimated that the global population aged over 65 years will double from 8% in 2010 to 16% in 2050 (24). In 2015, approximately 5% of the population in OECD countries were aged 80 years and above, this percentage is expected to rise more than double by 2050 (25). Second, epidemiological data indicates that multimorbidity increases markedly with age. In a Scottish study, multimorbidity was prevalent in 81.5% of individuals aged 85 years and over, with a mean number of 3.62 morbidities (26). Ornstein et al. found that the most prevalent chronic conditions in primary care were hypertension (33.5%), hyperlipidemia (33.0%), and depression (18.7%) (27). The presence of multiple morbidities is associated with multiple symptoms, impairments and disabilities. Multimorbidity may result in a combined negative effect on physical and mental health, and can have a major impact on a person's quality of life, limiting daily activities and reducing mobility (28, 29). The need to take multiple medications can be just as problematic, resulting in frequent health care contacts and an increase in the likelihood of medication-related harm (30). Furthermore, it imposes a large economic burden due to patients' complexity of health care needs and frequent interaction with health services, which may be fragmented, ineffective and incomplete (31).

Despite extensive advances in pharmacotherapy, the availability of clinical guidelines for older adults with multiple morbidities is limited (28). Prescribing is largely based on evidence-based guidance for single diseases, which does not generally take into account multimorbidity (21, 28, 32). Consequently, patients are often prescribed several medicines recommended by a number of specialists using disease-specific guidelines which in combination makes the management of any single disease challenging and may even lead to patient harm (21, 26).

1.3 Economic impact of polypharmacy

Advancing the responsible use of medicines: applying levers for change identified several opportunities to reduce health care spending through more responsible use of medicines worldwide. The authors estimated that mismanaged polypharmacy contributed to 4% of the world's total avoidable costs due to suboptimal medicine use. A total of US$ 18 billion, 0.3% of the global total health expenditure could be avoided by appropriate polypharmacy management. Some of the specific recommendations outlined in the report included (33):

- investment in medical audits targeting older patients with multiple medications;
- support for a greater role of pharmacists in medication management and in collaboration with health care professionals for review of therapeutic plans;
- identification of high-risk patients and preparation of targeted medicine management plans for this group; and
- to establish a system for blame-free reporting of medication errors.

The objectives of polypharmacy management should be comprehensive, addressing such issues as improved health outcomes for the patient and population, greater patient engagement in therapeutic decision-making and cost-effectiveness of health care systems and resources. This comprehensive approach – embracing care, health and cost – has been termed the "triple aim" strategy, and it is designed to guide health system performance optimization (34). The term has been built upon to become a "quadruple aim" upon recognizing that staff wellbeing is essential to ensure good care for the public (35).

Improved safety and quality leading to economic benefits
In a randomized control trial by Gillespie et al. clinical pharmacists performed comprehensive medication reviews (see Annex 1) of older hospitalized patients. Patients that received

a medication review experienced 16% fewer hospital visits and 47% fewer visits to the emergency department within a 12-month follow-up period, compared to those with usual care. In addition, medication-related readmissions were reduced by 80%. After factoring in the intervention costs, the comprehensive medication reviews were found to lower the total hospital-based health care cost per patient by US$ 230. The conclusion presumed that the addition of clinical pharmacists to health care teams on a wider scale could result in even greater health care cost reductions and reducing morbidity *(36)*.

1.4 Other factors influencing appropriate polypharmacy

Social determinants of health and lifestyles

A proactive approach to sustainable and appropriate medication regimens should target lifestyles as part of the health management process. It is recognized that an unhealthy lifestyle can contribute to multimorbidity, requiring treatment with multiple medications *(37)*. Unhealthy lifestyle factors should be discussed with patients when considering alternatives to medication. The WHO *Active ageing: a policy framework* identified three important economic factors for active ageing: income, work and social protection *(38)*. Individuals with low incomes may be restricted in their choice of healthy ageing options as healthy foods, health care and housing may be less affordable and accessible, and are thus at higher risk of ill health and disability *(39)*, which can be exacerbated for patients with polypharmacy.

Non-adherence

Non-adherence to prescribed medication is a major challenge in polypharmacy, particularly among older persons and/or in patients with multimorbidity. Older patients who receive treatment for several chronic health conditions simultaneously present both pharmacological and medication adherence (see Annex 1) risks *(40)*. A systematic review of older patients with polypharmacy found a correlation between medication non-adherence and the number of medicines being taken *(41)*.

This section outlines the case for managing polypharmacy at the point of initiation of treatment, when prescribing, when adding a new medication to a patient's list of medications, during a medication review, or during a medication reconciliation (see Annex 1) when a patient moves across care settings.

2.1 Medication-related harm in polypharmacy

Studies conducted in many countries have estimated the rate of medication errors both in hospitals and in general practice *(42–45)*. One study by Avery et al. found that over a 12-month period, patients receiving five or more medications had a prescribing or monitoring error rate of 30.1%, while in those receiving 10 or more medications the error rate was 47%, demonstrating that the error rate increased with the number of medicines prescribed *(42)*. Another study conducted across eight countries found that the incidence of patient-reported errors increased with the number of medications that were taken *(43)*.

Reporting of medication incidents such as medication errors and ADRs associated with polypharmacy could provide useful information to improve patient safety *(46)*. Polypharmacy may have harmful implications for patients such as an increased risk of medication errors, drug–drug interactions, suboptimal patient adherence and reduced quality of life *(8, 47, 48)*. Health care professionals together with patients and caregivers play a crucial role in reporting medication-related events *(46, 49)*.

Learning from medication incidents is vital for the implementation of preventive strategies and interventions in order to reduce risk and prevent harm from occurring again *(46)*.

Polypharmacy at transitions of care

When patients move across care settings, medication reconciliation is an important issue that needs to be addressed. A systematic review of hospital based medication reconciliation practices showed a consistent reduction in medication discrepancies (see Annex 1), potential adverse effects and adverse drug events after medication reconciliation, with the most success seen in high-risk patient populations such as polypharmacy patients *(50)*. Discrepancies in medication orders are common, and they increase with the number of medications prescribed *(51)*. A study of post-discharge patients found that almost one fifth of currently used prescription medicines had not been recorded during hospitalization and that less than half of the medications used had been registered in the patients' discharge letter. This illustrates the challenge that health care professionals encounter at transitions of care (see Annex 1), as polypharmacy in combination with an insufficient knowledge of the patients' medication history is an important contributor to prescribing errors, which can potentially result in adverse drug events *(52)*.

Polypharmacy in care homes

Residents of care homes may be at higher risk of complications from polypharmacy and inappropriate prescribing *(21)*. Findings suggest that up to 40% of prescriptions for nursing

home residents may be inappropriate or suboptimal *(53)*. Barber et al. found that the average care home resident in England was taking eight medications a day and over two thirds of these residents had one or more medication errors *(54)*. Inappropriate prescribing contributes toward the medication burden and exacerbates the problem of inappropriate polypharmacy. This is particularly evident with regards to the widespread prescribing of antipsychotic medications in patients with dementia in nursing and residential homes *(55)*.

Non-prescribed medications
In addition to prescribed medications, many patients self-medicate by purchasing OTC medicines. OTC medicines, such as NSAIDs for pain and some medications for allergies and coughs, may interact with their prescribed medications and have the potential to cause harm. In some cases, patients may also be sharing prescription medicine with other individuals *(8, 56)*. Therefore it is important to carefully ask patients about the use of all types of medicines or remedies *(8)*.

Traditional and complementary medicines
The use of herbal medicines is widespread and often taken in combination with conventional medicines to treat diseases *(49, 57, 58)*. Health care providers should ask their patients if they use traditional and complementary medicines or remedies and include these products in the medication review, as these will contribute to the polypharmacy burden *(8)*. Alongside drug–drug interactions, herb–drug interactions should be considered, as they can cause a considerable patient safety risk *(49, 59, 60)*. Further high-quality research is needed to identify interactions of herbal medicines *(60)*.

2.2 Medication review in polypharmacy

> **Medication review** is 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 (see Annex 1).

Medication reviews are widely used to address inappropriate polypharmacy globally and are also recommended by many polypharmacy guidance documents, see Annex 3. It provides a structured evaluation that can be used to prevent harm, optimize treatments and improve outcomes by optimizing the use of medicines for each individual patient *(8, 61)*. Medication reviews in polypharmacy should take into account the effectiveness and the risk–benefit ratio of the medication treatment options, and examine these criteria for the specific patient group in which the medication is being used. Where possible medication reviews should be performed in collaboration with the patient or their caregiver *(8, 13)*.

The main purpose of medication reviews is to improve the appropriateness of medications, reduce harm and improve outcomes. Therefore, it is essential to reassure that the review is not viewed merely as a mechanism to reduce or stop medications.

A systematic review and meta-analysis indicated that pharmacist-led medication reviews led to a reduction in hospital admissions *(62)*. In addition, medication reviews may have an effect on the reduction of medication-related problems *(63, 64)*. For example, a study by Schnipper et al. found that medication reviews reduced the number of preventable adverse drug events 30 days after patient discharge *(64)*. One Cochrane review found that medication reviews may have a preventive effect on reducing the number of emergency department contacts, however it did not reduce mortality or hospital readmissions.

The reducing effect on emergency department visits was more significant in high-risk groups (such as older persons or patients with multiple medications) (65). The general consensus is that more evidence is necessary to determine the effect of medication reviews due to the heterogeneity of the studies and limitations in follow-up time (62, 66, 67).

Assessing risks and benefits

To facilitate the medication review, prescribers need practical tools and information to help with decision-making on the safety and effectiveness of medicines and the appropriateness of initiating or continuing long term medications (11). One useful measure which helps prescribers to understand the probable clinical efficacy of a medicine is the number needed to treat (NNT). The NNT can be defined as the average number of patients who require to be treated over a time period for one patient to benefit compared with a control; it can also be expressed as the reciprocal of the absolute risk reduction (61). The ideal NNT, being one, signifies that every patient improves on the outcome with the treatment. The higher the NNT, the less effective the treatment is in terms of the trial outcome and timescale. The NNT is only a statistical estimate of the average benefit of treatment, usually calculated based on clinical trials. It is rarely possible to know precisely the likely benefit for a particular patient. However, NNT still remains a universal concept to assess the efficacy of medicine. Several tables and further information are available on NNT, which can support prescribers in decision making and aid discussions with patients regarding the potential benefits of their treatment (61, 68–71).

Similarly to NNT, another measure used in decision making is the Number Needed to Harm (NNH). The NNH is the average number of people taking a medication over a time period in order for one adverse event to occur (61). This concept is not as widely used as the NNT. Combined with NNT, the overall benefit to risk ratio (NNT/NNH) should be considered for individual patients during the decision making process. In polypharmacy this ratio may vary considerably between patients (61). For several commonly used medications, there are some NNT and NNH estimates available (61, 71).

Ideally, such information on risks and benefits is made accessible and comprehensible for the public, in order to include patients in the decision-making process. For example, a Scottish polypharmacy guidance tool helps health care professionals work in partnership with patients. This resource is available as a combined mobile application and website that outlines the process for initiation and the review of treatments (72).

Medication review process in polypharmacy

The review process should include engagement with the patient. The perspective of the patient on managing and taking multiple medications should be assessed, as well as the patient's goal of care. The intentions of the patient would need to be aligned with the prescribers' view of improving outcomes and treatment goals (8). The information and changes derived from the medication review should be made available to other health care professionals, especially as the patient moves across different care settings, in order to enable collaboration in appropriate polypharmacy management. An example of a step-by-step method to conduct a medication review while using a patient-centered approach is elaborated in Table 1. Annex 4 outlines how this process can be further applied to selected clinical scenarios.

Table 1. Step-by-step approach to conducting a patient-centred medication review

Aims	1.	What matters to the patient	*Review diagnoses and identify therapeutic objectives with respect to:* • Understanding of goals of medication therapy • Management of existing health problems • Prevention of future health problems
Need	2.	Identify essential medications	*Identify essential medications (not to be stopped without specialist advice) such as:* • Medications that have essential replacement functions (e.g. thyroxine) • Medications to prevent rapid symptomatic decline (e.g. medications for Parkinson's disease)
	3.	Does the patient take unnecessary medications?	*Identify and review the (continued) need for medications:* • With temporary indications • With higher-than-usual maintenance doses • With limited benefit in general for the indication they are used for • With limited benefit for the particular patient under review
Effectiveness	4.	Are therapeutic objectives being achieved?	*Identify the need for adding/intensifying medication therapy in order to achieve therapeutic objectives:* • To achieve symptom control • To achieve biochemical/clinical targets • To prevent disease progression/exacerbation
Safety	5.	Does the patient have/ is at risk of adverse drug reactions? Does the patient know what to do if they are ill?	*Identify patient safety risks by checking for:* • Drug–disease interactions • Drug–drug interactions • Robustness of monitoring mechanisms for high-risk medications • Risk of accidental overdosing *Identify adverse drug effects by checking for:* • Specific symptoms/laboratory markers (e.g. hypokalaemia) • Cumulative adverse drug effects • Medications that may be used to treat adverse drug reactions caused by other medications
Costs	6.	Is therapy cost-effective?	*Identify unnecessarily costly medication by:* • Considering more cost-effective alternatives (but balance against effectiveness, safety, convenience)
Patient-centeredness	7.	Is the patient willing and able to take medication as intended?	*Does the patient understand the outcomes of the review?* • Does the patient understand why they need to take their medication? • Consider teach-back technique[a] to ensure full understanding *Ensure medication changes are tailored to patient preferences:* • Is the medication in a form the patient can take? • Is the dosing schedule convenient? • Consider what assistance the patient might have and when this is available • Is the patient able to take medicines as intended? *Agree and communicate plan:* • Discuss with the patient therapeutic objectives and treatment priorities • Decide with the patient what medicines have an effect of sufficient magnitude to consider continuation or discontinuation • Inform relevant health care and social care change in treatments across care transitions

Method to confirm that the information provided is being understood by getting people to 'teach-back' what has been discussed and what instruction has been given *(73)*.

Source: Adapted, with permission of the publisher, from Scottish Government Polypharmacy Model of Care Group *(61)*.

Deprescribing is the process of tapering, stopping, discontinuing, or withdrawing drugs, with the goal of managing polypharmacy and improving outcomes (see Annex 1).

Considerations for cessation of medication should be a part of all medication reviews, and the process of "deprescribing" should be as robust as that of prescribing. The process encompasses minimization of the medication load in terms of dosage, number of tablets taken and frequency of administration times *(23, 74)*. Supporting tools such as STOPP/START criteria can be useful in deprescribing and improving appropriate prescribing *(72, 75)*. Examples of prescribing indicator sets which can be used to identify inappropriate polypharmacy and appropriateness of prescribing are available *(8, 76)*. There are also algorithms available that could improve medication therapy by deprescribing, which have been shown to be feasible *(77)*. Hence it is important to undertake medication reviews with a holistic approach, as medications may need to be started or stopped, both to prevent harm from some medications and to prevent health deterioration *(8)*.

3 Implementing polypharmacy initiatives

In order to address inappropriate polypharmacy multiple programmes have been implemented, particularly in high-income countries (78, 79). To illustrate the international initiatives, several polypharmacy guidance documents from different countries are listed in Annex 3.

3.1 Implementing sustainable programmes to address polypharmacy

In the context of the third WHO Global Patient Safety Challenge: *Medication Without Harm*, countries are urged to take early priority action to protect patients from harm arising from polypharmacy by implementing programmes which help to reduce inappropriate polypharmacy that are sustainable and can be delivered across the country. For the implementation of national, subnational or local polypharmacy guidance and new polypharmacy practices, it may be relevant to apply change management principles and theory-based implementation strategies.

Tools and theories to support the implementation process include Kotter's *eight step process for leading change*; political, economic, social, technological, environmental and legal (PESTEL); and strengths, weaknesses, opportunities and threats (SWOT) (11). A recent case study applied Kotter's *Eight step process for leading change* and normalization process theory to assess successful polypharmacy management activities in Europe, and provided advice that can be applied across the entire health system to address the management of polypharmacy (22). PESTEL and SWOT exercises enable organizations to evaluate issues that need to be addressed to ensure that barriers to implementation are removed and enablers are optimized (11). To support wider implementation of medication reviews in selected populations, an economic analysis tool has been developed to help countries assess the potential economic benefits of introducing and undertaking medication reviews in polypharmacy (80).

In addition to change management tools, some key factors that need to be considered are described in the following. Existing health care delivery models for polypharmacy should be reassessed to ensure the pharmacist plays a key role within a multidisciplinary team alongside physicians and nurses (33). Medication reviews performed by health care professionals would need to be incorporated in the design of clinical pathways in the management of patients with multimorbidity to facilitate workflow (81). Transfer of information across transitions of care is important to the management of appropriate polypharmacy, because it ensures medications that were reviewed and stopped are not restarted without proper justification.

Addressing organizational culture and multidisciplinary working

The organizational dynamics within health care systems can be complex and include

the values, beliefs and assumptions held by those within an organization *(33)*. Cultural factors can facilitate or hinder the implementation of innovative practices in managing polypharmacy. Failure to account for organizational culture is one of the main reasons mentioned when evaluating why planned initiatives fail to overcome barriers *(82)*. Not only should the culture of the health system as a whole be considered, but also the cultural norms within given professions *(83, 84)*. The results from a European Delphi study support that "prior to implementation of polypharmacy management, the culture of an organization should be assessed for both strengths and potential barriers to implementation" *(11)*. As with change management and systems thinking, there are multiple tools and frameworks available to help decision-makers identify the characteristics of the organizational culture and to make appropriate modifications, in parallel with a safety culture assessment *(85)*.

Various studies have identified the necessity and benefits of multidisciplinary collaboration when addressing polypharmacy *(10, 22)*. Policy-makers would need to consider addressing the legislative and contractual barriers that are in place if appropriate polypharmacy is to be applied across the health care system. Political commitment is required to ensure that dedicated resources are allocated to the development of new systems to address polypharmacy, but more importantly to strengthen the existing health care system. Political support is important to promote multidisciplinary team work *(11)*. For example, *Medicines Optimisation Quality Framework of Northern Ireland* recommends medicines optimization (see Annex 1) activities to be delivered by multidisciplinary teams *(86)*.

3.2 Programmes on appropriate polypharmacy

To assist countries in understanding the hurdles and benefits of investing in programmes addressing polypharmacy, this report presents some programmes below.

OPtimising thERapy to prevent Avoidable hospital admissions in the Multimorbid elderly (OPERAM), aims to optimize existing pharmacological and non-pharmacological therapies to reduce avoidable hospital admissions, particularly among older patients with multimorbidity in Europe. The goal of the study is to assess the impact of a structured medication review with a software intervention, obtain and compare intervention studies to find what is most effective and safe in order to determine the best and most cost–effective measures for preventing avoidable hospital admissions. Initiated in 2015, this study is ongoing until year 2020 *(87, 88)*.

Polypharmacy in chronic diseases: Reduction of Inappropriate Medication and Adverse drug events in older populations by electronic Decision Support (PRIMA-eDS), aims to provide physicians with the best evidence regarding medication therapy for older patients with multimorbidity through an electronic decision support tool. The electronic decision support tool comprises of an indication check, recommendations based on guidelines, systematic reviews, drug interaction database, renal dosing database, adverse effect database and the European list of inappropriate medications for older people *(89)*. The practicability and relevance of the tool was evaluated through a randomized clinical trial to test if discontinuing inappropriate medications could improve patient outcomes, such as reduction of hospitalization or death; and the patient data entry was found to be too time-consuming. Recent findings provide more insight in the future development of the tool and the potential risk groups *(90, 91)*.

Stimulating Innovation Management of Polypharmacy and Adherence in The Elderly (SIMPATHY) project intends to stimulate, promote and support innovation across the European Union in the management of appropriate polypharmacy and medication adherence in older patients *(78)*. This project aims to contribute to developing efficient and sustainable health care systems. Through

stakeholder engagement, studies were undertaken in a range of different health care environments, including European Innovation Partnership on Active and Healthy Ageing reference sites. The studies provide a framework and politico-economic basis for a European Union-wide benchmarking survey of strategies being employed for polypharmacy and non-adherence management. Innovative multidisciplinary models were developed to support patients with long-term conditions using the professional expertise of pharmacists and physicians to reduce inappropriate polypharmacy and promote innovation in health care workforce development *(11)*. A set of contextualized change management approaches and tools was developed to help politicians, regulators, health service providers, and other stakeholders to advance current practice by implementing organizational change, thereby improving the management of patients on polypharmacy *(11, 80)*.

In addition to creating a European knowledge-sharing network on polypharmacy and adherence management, the targeted dissemination of these validated findings may support policy development, implementation of strategic organizational development and the exchange of best practices *(11)*. There is still room for improvement, as polypharmacy management is currently not widely addressed within most EU countries *(22)*. This programme has generated information on which benchmarks can be applied for regional and national progress measurements, a definitive guidance on the role of key stakeholders and guidelines on how to initiate and manage the change process *(11)*.

Health systems approach to polypharmacy

4

Initiatives to address polypharmacy can be complex and require strong leadership and management. Identifying a lead organization and allocating responsibility could facilitate the implementation of polypharmacy management initiatives at the regional or national level. Organizational leadership is vital in driving change to achieve effective polypharmacy management *(11)*. The need to address polypharmacy is universal, but the challenge of leading change goes to the heart of the policies and culture of organizations, requiring the active involvement of policy-makers, health care professionals and managers, as well as patients, families and caregivers *(61)*. Often the window of opportunity to ensure that change is implemented is small, with three components being crucial: problem recognition, generation of policy proposals, and a supportive political environment, to create a momentum for a change in public policy *(92)*. Countries may wish to consider using existing infrastructure such as pharmacovigilance centres (see Annex 1) and patient safety incident reporting and learning systems (RLS) to collect reports as well as to disseminate learning from harm occurring from polypharmacy and drug interactions *(46, 49)*.

The irrational use of medicines is a global issue. A WHO report, *The World Medicines Situation*, estimated in 2004 that half of all medicines are inappropriately prescribed, dispensed or sold. Furthermore, half of all patients fail to take their medicine as prescribed. This can be harmful to patients, leads to ineffective therapies and waste of resources, generating an unnecessary burden for the patient as well as the whole society. Inappropriate polypharmacy is a common example of irrational use of medicines. To address the challenge at the system level, effective policies such as supportive incentive structures, education and management, clear clinical guidance and appropriate training are considered far-reaching *(93)*.

When deciding how to address polypharmacy, any solution needs to achieve the aforementioned "quadruple aim", so that quality of prescribing and outcomes from medication are improved whilst delivering an economically sustainable solution that will promote patient engagement across the health care system without compromising the work life of health care professionals *(35)*. In many countries polypharmacy management may not be widely addressed, which makes it important to establish change management strategies to support implementation at a national scale *(22)*. An initial step would be to undertake a benchmarking survey so that countries can assess their current status with regard to polypharmacy. Business operation tools such as PESTEL and SWOT analysis have been used for polypharmacy programmes, and are helpful in identifying barriers and issues that countries would need to address in order to improve polypharmacy management *(11)*.

In order to attain medication safety in polypharmacy management, a strategy could be developed using the strategic framework of the third WHO Global Patient Safety Challenge: *Medication Without Harm*. The key domains to be addressed as part of this framework include patients and the public, medicines, health care professionals, and systems and practices of medication. The four domains and the cross-cutting theme of monitoring and evaluation are elaborated in the following sections, addressing a health system approach for implementing polypharmacy programmes under the umbrella of the Challenge.

4.1 Patients and the public

The role of patients in delivering appropriate polypharmacy

Raising patient awareness about the problems of polypharmacy and non-adherence is important, as patients can play a key role in the prevention and early detection of inappropriate polypharmacy (*11, 21*). Patients should be seen as shared decision-makers on the use of medication, and health care professionals need to support patients, families and caregivers in order to enable them to undertake this role (*8*). Patients should be encouraged and supported to disclose all the medications they are taking, including OTC and traditional and complementary medicines, especially if they are suffering from multiple conditions and are being treated with polypharmacy (*94*). Health literacy, social norms and cultural factors would need to be taken into account when considering the role of patients, and designing materials for patient education (*95, 96*).

Patient tools and materials can support the engagement and empowerment of patients, families and caregivers in playing an active role in health care. Such resource materials may include:

- Patient-held medication list or patient-held medication record, sometimes called medication passport (either paper or electronic), can help to optimize patients'

medicines. The use of these tools has received positive feedback from patients (*97*). Such lists, provided that they are up-to-date, can also be helpful at care transitions (*98*).

- Patient resource materials that enable patients to understand how to make decisions regarding management of their health conditions and their medications are available (*99, 100*). An example of a tailormade tool is the *Medicine Sick Day Rules card,* which explains to patients which medicines should be temporarily stopped during dehydration due to an illness (*101*). Different organizations, including WHO, have developed materials that include simple questions to encourage patients to be active participants in their therapeutic decision-making (*102–104*). For example, the *5 Moments for Medication Safety* focuses on five 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 tool aims to engage and empower patients to be involved in their own care in a more proactive way and feel responsible for it, encourage their curiosity about the medications they are taking, empower them to communicate openly with their health professionals and be involved in shared decision-making (*104*).

Technology could improve both patient experience and medication adherence. Furthermore, it has potential to enable patients to be active participants in medication reviews. However, more research is required to evaluate strategies for integrating such tools into clinical practice and to ensure they meet their potential in improving patient outcomes and creating value for all users (*105, 106*).

Prioritizing patients for medication reviews in polypharmacy

Due to limited resources in most health care systems, patients who may benefit from medication reviews need to be prioritized. There are many factors that could increase the likelihood of predisposing a patient to harm

from medication. Research has shown that patients on multiple medications have a higher risk of medication-related harm, due to harm from occurrences such as drug–drug interactions, falls and adverse events (*8, 48*).

Any methods for identifying patients at risk due to polypharmacy need to be considered in the clinical context. Even in resource-limited settings with inadequate health information databases, the following criteria can be applied to identify situations where a medication review may prove beneficial:
- residents in a care home setting (*12, 21*)
- patients on high-risk (high-alert) medications (see Annex 1) (*12*)
- patients taking 10 or more medicines (*12, 21, 107*)
- patients with two or more co-morbidities (*12*)
- patients with frailty (*12, 77, 20*)
- patients with dementia (*12, 108*)
- palliative care situations (*8, 12*)

4.2 Health care professionals

Health care professionals and policy-makers can take a leadership role in raising awareness among peers regarding the role of medication review in reducing the harm associated with inappropriate polypharmacy (*11*).

Development of multidisciplinary workforce through changes in undergraduate, postgraduate, and continuing professional development has been identified as a key area to address polypharmacy (*22*). Educational curricula for health care professionals, including physicians, pharmacists and nurses, should include safe medication management to develop necessary competencies and skills for addressing risks associated with polypharmacy (*109*). To help support education of health care professionals, a set of clinical case studies are presented in Annex 4.

Existing guidelines that incorporate key steps for patient-centered medication review should be shared to ensure the dissemination of best practices, including the importance of sharing the information about the outcomes of the medication review in polypharmacy with relevant health care professionals. Establishing support networks to enable health care professionals in sharing scientific and practical information on polypharmacy may assist in that regard. There are several special interest groups focusing on appropriate polypharmacy available internationally (*110–112*).

Health care professionals working in multidisciplinary teams deliver optimum outcomes for patients. They need to be aware of human factors that may affect their performance and the performance of others (*113*). Knowledge of human factors can be further useful in communication with patients and in shared decision-making in polypharmacy (*109*).

A study from Hawaii revealed that many older persons were uncertain about the information about their medications and did not exhibit confidence on understanding the ADRs associated with use of multiple medications (*114*). This emphasizes the need for interventions that are aimed at enhancing the provider–patient interaction about polypharmacy and medication reviews. Safety culture should be addressed to enable health care professionals and patients to discuss issues of polypharmacy, so that patients feel that it is safe and acceptable to ask questions (*95*). For example, *Choosing Wisely* campaign focuses on promoting dialogue between health care professionals and patients; with the aim to reduce utilization of inappropriate tests and medical treatment, empower patients to ask questions, and help patients to choose evidence-based care (*115*).

4.3 Medicines

Polypharmacy and drug interactions
Patients with polypharmacy might be subject to drug–drug, drug–food, drug–disease or herb–drug interactions (*116*). Detection of drug interactions should be included

in the monitoring process of long-term and latent effects of medications as part of post-marketing surveillance (*49*). Such information is pivotal for health care professionals prescribing or reviewing medication lists to ensure safe use of medicines. Drug interaction and contraindication databases and various computer systems are increasingly available in hospitals and general practice. However, technology systems may not flag all relevant potential harm (*8*, *117*), or they may conversely lead to numerous reminders, creating an information overload for health care professionals and over-riding of reminders inappropriately (*118*). While there is a huge potential in computer-based systems to prevent medication-related harm (for example, by helping to detect contraindications, interactions or potentially inappropriate choice of medicine), they should not replace health care professionals' own clinical judgement (*117*).

Medication management and adherence
In polypharmacy it is important to find innovative solutions to improve medication adherence and develop strategies to ensure that the right medicine is taken at the right time. Patients may be supported case-by-case based on their individual needs and concerns by helping them understand the importance of taking their medicines (i.e. through further information and discussion) and/or overcoming practical problems associated with nonadherence faced by the patient (i.e. through practical changes in the medication regimen or type of formulation). Multi-compartment medication compliance devices, also known as pill dispensers or dose administration aids, are used to aid patients in their medication management (*119*). However, it may not be a suitable solution for all patients and medicines, for example, due to individual patient factors, the specific type of medication formulation, or the risk of improper handling and storage. Furthermore, such devices do not necessarily provide sufficient dosing information. Patient-centred interventions such as memory aids, mobile applications, labels with pictograms, reminder applications, large print

labels and information sheets can also be utilized (*120*). Digital health tools, such as smart pill boxes and mHealth solutions, are approaches likely to be increasingly adopted in the future (*121*).

4.4 Systems and practices of medication

A system has been defined as "an operating mechanism where the sub-parts work jointly towards achieving an outcome, and the success of the system is dependent upon this collaboration". In the field of patient safety and medication safety, these sub-parts include patients, different levels of health care organizations, policy-makers and regulators (*122*). It is important that all stakeholders understand and agree on the outcomes to be achieved to ensure successful collaboration. In the case of polypharmacy management, the goal of a systems approach is the optimal and sustainable use of medicines in patients with multimorbidity and supporting them to live active and healthy lives. It is important that countries also consider a system wide approach at all levels within their organizations. For example, the National adaptation of the *WHO Model List of Essential Medicines* (*123*) has been proven to improve rational use of medicines, as demonstrated in China, however it had limited effect on polypharmacy (*124*).

When designing systems and delivery of a programme, the importance of patients and the public as key stakeholders in the implementation of policy should be considered. Involving patients in the design and delivery of a programme will help to ensure effective implementation and the sustainability of measures to address medication safety in appropriate polypharmacy (*125*, *126*). Patients, families and caregivers should be given the opportunity to be involved in the decision-making process during medication reviews as it helps to improve and optimize the clinical outcomes of the treatment. Guidance for medicines optimization focuses on patient engagement and improving

the patients' understanding on medicines so they are able to make decisions such as the choices of prevention and healthy living (*127*).

Some areas to address during systems design and programme delivery include the following:

- Appropriate polypharmacy should be addressed at the point of initiation of new medicines for treatment plans, during medication review and at care transitions.
- The adoption of a systems approach prevents an overly narrow view of a particular problem. For example, development of an essential medicines list may help countries put in place national schemes to address the appropriateness of medicine use.
- Carrying out reviews to ensure appropriateness of medication should be integrated into care pathways for patients with multiple morbidities. Reviews of appropriate polypharmacy should be built into systems and practices, and learning should be incorporated from existing initiatives that are working to bring appropriate polypharmacy programmes to scale.
- The development of change management strategies will be useful for implementation across health care systems.
- Monitoring systems can be used to capture data regarding admissions following medication-related harm so that improvement can be measured and feedback and learning can take place, when patients are admitted to hospital or attend primary care.

4.5 Monitoring and evaluation

As discussed earlier, there is no single agreed definition of polypharmacy. The term polypharmacy does not by its nature imply whether it is appropriate to prescribe several medications or not, although it is often assumed to be the same as being inappropriate (*8*). The distinction between inappropriate and appropriate polypharmacy is highly dependent on the patient and therapy rather than the number of medications used (*17, 128*).

Existing published literature addresses the issue of measurement of polypharmacy as a standalone domain or as part of an overall medication safety measurement. Using a Delphi method of analysis, Rankin et al. developed a set of key outcome measures identifying 16 of these as outcomes that are measurable. The highest ranked outcomes of this study are serious ADRs, medication appropriateness, medication regime complexity and medication-related side effects (*129*).

Several countries have developed inappropriate polypharmacy indicators that are related to either the number of medications used, medications used for older persons, or to specific medication combinations (*61, 130–133*). A systematic review of indicators relevant to polypharmacy appropriateness identified a set of 12 core indicators for monitoring polypharmacy, which included ADRs, contraindications, drug–drug interactions, and conduction of medication reviews (*134*). Countries can adopt or adapt a set of these indicators based on the context, priorities and resources available. Polypharmacy indicators could be a part of existing RLS for medication safety. Existing measures should be drawn upon to support the learning process.

For hospitals or health systems that have initiated implementation of a medication safety measurement programme and may have limited resources, the following indicator "Percentage of patients on polypharmacy" derived from *Polypharmacy and medicines optimization: Making it safe and sound* (*8*), could be a useful start.

Indicator	Percentage of patients on polypharmacy
Numerator	Total number of patients on polypharmacy
	Inclusion criteria:
	All patients with 10 or more regular medicines (for example, medicines taken every day or every week)
	OR
	Patients receiving between four and nine regular medicines who also:
	• have at least one prescribing issue that meets the criteria for potentially inappropriate prescribing;
	• have evidence of being at risk of a well-recognized potential drug–drug interaction or a clinical contraindication;
	• have evidence from clinical records of difficulties with taking medicines, including problems with adherence;
	• have no or only one major diagnosis recorded in the clinical record (it might be expected that large numbers of medicines are unlikely to be justified in patients without multiple clinical conditions); or
	• are receiving end-of-life or palliative care (where this has been explicitly recognized).
Denominator	Total number of eligible patients in the target group

The polypharmacy indicators could assist the development of models to predict adverse outcomes in relation to certain clinical scenarios, such as with specific therapeutic classes, and in certain specific patient populations. Prior to implementation of interventions to reduce medication-related harm a baseline assessment should be considered to monitor progress.

Points of consideration for countries

5

The key points of consideration are summarized as follows:

- Policies for regular, holistic medication reviews for patients taking multiple medications.
- Addressing appropriate polypharmacy at the point of medicines initiation, during medication review and at care transitions.
- Safety culture enabling health care professionals and patients to discuss issues of polypharmacy and make patients to feel safe in asking questions.
- Policies and implementation plans that support appropriate polypharmacy management at scale, and promote effective multidisciplinary team work by removing barriers.
- Sharing of information about the outcomes of medication reviews in polypharmacy with health care professionals.
- A people-centered approach while reviewing medication with patients and their caregivers.
- Addressing lifestyle issues during medication review process.
- Use of appropriate technologies to reduce medication-related harm, improve patient experience and medication adherence.
- Reporting of medication incidents, for example, occurrence of an adverse drug reaction, hospitalization, or primary health centre attendance due to medication-related symptoms.

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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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Annex 2. Global prevalence of polypharmacy

Country/region	Study population	Definition of polypharmacy	Statistics	Reference
Worldwide (including United States of America, Australia, Italy, Netherlands and more)	Residents in long-term care facilities (n=20 studies included all residents, n=19 included residents ≥ 65 years), mean age ranged 61.7–86.0 years	Definitions varied widely and were most commonly described as 5 (n=11), 9 (n=13) or 10 (n=11) or more medications	A systematic review of 44 studies assessing medication use in long-term care facilities reported a 38.1–91.2% prevalence of polypharmacy, where polypharmacy was defined as ≥5 medications. When defined as ≥ 9 medications, the prevalence ranged from 12.8–74.4% and 10.6–65.0% when considered as ≥ 10 medications	Jokanovic N, Tan EC, Dooley MJ, Kirkpatrick CM, Bell JS. Prevalence and factors associated with polypharmacy in long-term care facilities: a systematic review. J Am Med Dir Assoc. 2015;16(6):535.e1–12. https://doi.org/10.1016/j.jamda.2015.03.003 https://www.ncbi.nlm.nih.gov/pubmed/25869992
7 European Union (EU) countries (Czech Republic, England, Finland, France, Germany, Italy and Netherlands) and 1 non-EU country (Israel)	4,023 nursing home residents in 57 facilities, mean age of 83.5 years	Non-polypharmacy (0–4 medications), polypharmacy (5–9 medications) and excessive polypharmacy (≥10 medications)	Cross-sectional analysis of residents found that 49.7% experienced polypharmacy and 24.3% experienced excessive polypharmacy	Onder G, Liperoti R, Fialova D, Topinkova E, Tosato M, Danese P et al. Polypharmacy in nursing home in Europe: results from the SHELTER study. J Gerontol A Biol Sci Med Sci. 2012;67(6):698–704. https://doi.org/10.1093/gerona/glr233 https://www.ncbi.nlm.nih.gov/pubmed/22219520

Country/ region	Study population	Definition of polypharmacy	Statistics	Reference
Australia	1,608 Australians aged ≥50 years	Use of 5 or more medications of any type in the previous 24 hours	The cross-sectional postal survey reported 43.3% of respondents using 5 or more medicines in the previous 24 hours	Morgan TK, Williamson M, Pirotta M, Stewart K, Myers SP, Barnes J. A national census of medicines use: a 24-hour snapshot of Australians aged 50 years and older. Med J Aust. 2012;196(1):50–53. https://doi.org/10.5694/mja11.10698 https://www.ncbi.nlm.nih.gov/pubmed/22256935
Brazil	142 patients aged ≥60 years in primary health care setting	Use of 4 or more medications per day. Prevalence of potentially inappropriate medication (PIM, see Annex 1) as determined by Beers criteria (a medication list for PIM use in older adults updated by the American Geriatric Society)	The prospective survey determined that PIM usage was 34.5%, with polypharmacy (PR = 2.36; 95% CI 1.79–3.11) and use of medications prescribed by a doctor (PR = 2.52; 95% CI 1.12–5.69), found to have a strong association	Oliveira MG, Amorim WW, de Jesus SR, Rodrigues VA, Passos LC. Factors associated with potentially inappropriate medication use by the elderly in the Brazilian primary care setting. Int J Clin Pharm. 2012;34(4):626–32. https://doi.org/10.1007/s11096-012-9656-9 https://www.ncbi.nlm.nih.gov/pubmed/22692715
Chile	250 hospitalized patients aged ≥ 65 years in one hospital	Prevalence of PIM as determined by Beers criteria (a medication list for PIM use in older adults updated by the American Geriatric Society) and STOPP criteria	The observational study confirmed an association between PIM prescribing and polypharmacy according to both criteria. Using Beers criteria, prescribed PIMs identified: one PIM 32%, two PIMs 20% and more than two PIMs 48%. According to STOPP criteria, prescribed PIM identified: one PIM 41%, two PIMs 51% and more than two PIMs 8%	Arellano C, Saldivia G, Cordova P, Fernandez P, Morales F, Lopez M et al. Using two tools to identify potentially inappropriate medications (PIM) in elderly patients in Southern Chile. Arch Gerontol Geriatr. 2016;67:139–44. https://doi.org/10.1016/j.archger.2016.08.001 https://www.ncbi.nlm.nih.gov/pubmed/27504710

Country/region	Study population	Definition of polypharmacy	Statistics	Reference
China	717 community-dwelling adults ≥60 years	The concomitant use of 5 or more medications	The cross-sectional analysis found that the prevalence of polypharmacy was 11.5% in rural residents and 17.5% in urban residents	Yang M, Lu J, Hao Q, Luo L, Dong B. Does residing in urban or rural areas affect the incidence of polypharmacy among older adults in western China? Arch Gerontol Geriatr. 2015;60(2):328–33. https://doi.org/10.1016/j.archger.2014.11.004 https://www.ncbi.nlm.nih.gov/pubmed/25440757
India	814 hospitalized patients aged ≥60 years in two hospitals	Polypharmacy (5–9 medications) and high-level polypharmacy (≥10 medications)	The prospective surveillance study reported 45.0% and 45.5% of patients to experience polypharmacy and high-level polypharmacy respectively	Harugeri A, Joseph J, Parthasarathi G, Ramesh M, Guido S. Prescribing patterns and predictors of high-level polypharmacy in the elderly population: A prospective surveillance study from two teaching hospitals in India. Am J Geriatr Pharmacother. 2010;8(3):271–80. https://doi.org/10.1016/j.amjopharm.2010.06.004 https://www.ncbi.nlm.nih.gov/pubmed/20624616
New Zealand	444,827 patients evaluated in 2005 and 603,670 patients in 2013, aged ≥65 years	Polypharmacy (use of 5–9 medications) and hyperpolypharmacy (use of ≥10 medications) by an individual, dispensed concurrently for a period of ≥90 days	The cross-sectional analysis of population-level dispensing data found that the prevalence of polypharmacy and hyperpolypharmacy increased from 23.4% and 1.3% in 2005 to 29.5% and 2.1% in 2013 respectively	Nishtala PS, Salahudeen MS. Temporal trends in polypharmacy and hyperpolypharmacy in older New Zealanders over a 9-Year Period: 2005–2013. Gerontology. 2015; 61(3):195–202. https://doi.org/10.1159/000368191 https://www.ncbi.nlm.nih.gov/pubmed/25428287
Nigeria	220 older persons ≥65 years attending general outpatients clinic of a rural hospital	Polypharmacy was not explicitly stated but inferred Prevalence of PIM as determined by Beers criteria (a medication list for PIM use in older adults updated by the American Geriatric Society)	The prospective cross-sectional study of patients reported 29.5% patients had 5 medications or more prescribed. The prevalence of patients with at least one PIM was 25.5%	Fadare JO, Agboola SM, Opeke OA, Alabi RA. Prescription pattern and prevalence of potentially inappropriate medications among elderly patients in a Nigerian rural tertiary hospital. Ther Clin Risk Manag. 2013;9:115–20. https://doi.org/10.2147/TCRM.S40120 https://www.ncbi.nlm.nih.gov/pubmed/23516122

Country/region	Study population	Definition of polypharmacy	Statistics	Reference
Saudi Arabia and the United Kingdom of Great Britain and Northern Ireland	300 hospitalized patients ≥18 years admitted with cardiovascular disease and/or diabetes mellitus in two hospitals (n=150 Saudi Arabia, n=15 United Kingdom)	The use of 5 or more medications	The retrospective medical record review found that polypharmacy was the major risk factor associated with medication-related problems. It was reported to be 40.9% and 50.9% of patients in Saudi Arabia and the United Kingdom respectively	Al Hamid A, Aslanpour Z, Aljadhey H, Ghaleb M. Hospitalisation Resulting from Medicine-Related Problems in Adult Patients with Cardiovascular Diseases and Diabetes in the United Kingdom and Saudi Arabia. Int J Environ Res Public Health. 2016;13(5):479. https://dx.doi.org/10.3390%2Fijerph13050479 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4881104/
Singapore	454 nursing home residents across three nursing homes ≥65 years, mean age 80 years	The use of 5 or more medications, including routine and as required orders. Inappropriate medication use was determined by Beers criteria for PIM	The retrospective case note review found that 58.6% and 70% of residents experienced polypharmacy and inappropriate medication use respectively	Mamun K, Lien CT, Goh-Tan CY, Ang WS. Polypharmacy and inappropriate medication use in Singapore nursing homes. Ann Acad Med Singapore. 2004;33(1):49–52. https://www.ncbi.nlm.nih.gov/pubmed/15008562

Annex 3. Internationally available guidance on appropriate polypharmacy management

No.	Country	Guidance document details
1	Australia	Guidelines for Residential Medication Management Review (RMMR) and Quality Use of Medicines (QUM) services. Deakin: Pharmaceutical Society of Australia; 2011 (https://web.archive.org/web/20180430113735/https://www.psa.org.au/download/practice-guidelines/rmmr-and-qum-services.pdf, accessed 22 March 2019).
2	Australia	Guiding principles for medication management in residential aged care facilities. Canberra: Department of Health and Aging; 2012 (http://www.health.gov.au/internet/main/publishing.nsf/Content/guide-med-mgmt-aged-care, accessed 22 March 2019).
3	Brazil	Cartilha para a promoçao do uso racional de medicamentos. Brasília: Ministério da Saúde; 2015 (http://bvsms.saude.gov.br/bvs/publicacoes/cartilha_promocao_uso_racional_medicamentos.pdf, accessed 22 March 2019).
4	Brazil	Caderneta de saúde da pessoa idosa, 3a ediçao. Brasília: Ministério Da Saúde; 2016 (http://portalarquivos2.saude.gov.br/images/pdf/2017/julho/03/Caderneta-do-Idoso.pdf, accessed 22 March 2019).
5	Canada	Deprescribing guidelines and algorithms [website]. Ottawa (ON): Canadian Deprescribing Network; 2019 (http://deprescribing.org/resources/deprescribing-guidelines-algorithms/, accessed 22 March 2019).
6	England, United Kingdom	Duerden M, Avery T, Payne R. Polypharmacy and medicines optimisation: making it safe and sound. London: The King's Fund; 2013 (http://www.kingsfund.org.uk/sites/files/kf/field/field_publication_file/polypharmacy-and-medicines-optimisation-kingsfund-nov13.pdf, accessed 22 March 2019).
7	England, United Kingdom	Multimorbidity and polypharmacy. London: National Institute for Health and Care Excellence; 2019 (https://www.nice.org.uk/advice/ktt18; accessed 22 March 2019).
8	Germany	Bergert FW, Braun M, Ehrenthal K, Feßler J, Gross J, Hüttner U et al. Recommendations for treating adult and geriatric patients on multimedication. Int J Clin Pharmacol Ther. 2014;52 Suppl 1:1–64. https://doi.org/10.5414/CPP52S001 https://www.ncbi.nlm.nih.gov/pubmed/25310921
9	Germany	Hausärztliche Leitlinie Multimedikation. Köln: PMV forschungsgruppe; 2016 (http://www.pmvforschungsgruppe.de/pdf/03_publikationen/multimedikation_ll.pdf, accessed 22 March 2019).
10	Japan	高齢者の安全な薬物療法ガイドライン. Tokyo: Japan Geriatrics Society; 2015 (https://www.jpn-geriat-soc.or.jp/info/topics/pdf/20170808_01.pdf, accessed 22 March 2019).

No.	Country	
11	Netherlands	Handreiking: Geriatrisch assessment door de specialist ouderengeneeskunde. Utrecht: Verenso; 2014 (https://www.verenso.nl/_asset/_public/Praktijkvoering_handreikingen/VER-003-29-handrGeriatrischAssesement-v4.pdf, accessed 22 March 2019).
12	Netherlands	De richtlijn: Comprehensive geriatric assessment. Utrecht: Nederlandse Vereniging voor Klinische Geriatrie; 2012 (https://richtlijnendatabase.nl/gerelateerde_documenten/f/669/Publieksversie%20richtlijn%20CGA.pdf, accessed 22 March 2019).
13	Netherlands	Multidisciplinaire richtlijn polyfarmacie bij ouderen. Utrecht: Nederlands Huisartsen Genootschap; 2012 (https://www.nhg.org/sites/default/files/content/nhg_org/uploads/polyfarmacie_bij_ouderen.pdf, accessed 22 March 2019).
14	New Zealand	Bpacnz. Polypharmacy in primary care: managing a clinical conundrum. BPJ.2014; 64 (https://bpac.org.nz/BPJ/2014/October/docs/BPJ64-polypharmacy.pdf, accessed 22 March 2019).
15	Scotland, United Kingdom	NHSGGC mindful prescribing strategy: polypharmacy. Glasgow: NHS Greater Glasgow and Clyde; 2012 (http://www.ggcprescribing.org.uk/media/uploads/prescribing_resources/mindful_prescribing_strategy_-_1212.pdf, accessed 22 March 2019).
16	Scotland, United Kingdom	Scottish Government Polypharmacy Model of Care Group. Polypharmacy guidance: realistic prescribing, 3rd edition. Edinburgh: Scottish Government Model of Care Polypharmacy Working Group; 2018 (https://www.therapeutics.scot.nhs.uk/wp-content/uploads/2018/04/Polypharmacy-Guidance-2018.pdf, accessed 22 March 2019).
17	Sweden	Olämpliga listan–om okloka läkemedel för äldre. Stockholm: Koll på läkemedel; 2011 (https://www.kollpalakemedel.se/wp-content/uploads/2014/04/olaempliga_listan-20121219.pdf, accessed 22 March 2019).
18	Sweden	Läkemedelsgenomgångar för äldre ordinerade fem eller fler läkemedel. Stockholm: Socialstyrelsen; 2013 (https://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/19019/2013-3-18.pdf, accessed 22 March 2019).
19	Sweden	Läkemedelsbehandling av de mest sjuka äldre. Västerås: Regionala läkemedelsrådet i Uppsala - Örebro och läkemedelskommittén region Jönköpings län; 2018 (https://regionvastmanland.se/globalassets/vardgivare-och-sammarbetspartners/lakemedel/baslakemedel/aldrelathund-2018.pdf, accessed 22 March 2019).
20	United States of America	Guiding principles for the care of older adults with multimorbidity: an approach for clinicians. J Am Geriatr Soc. 2012;60(10):E1–25. https://doi.org/10.1111/j.1532-5415.2012.04188.x https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4450364/
21	United States of America	Pellegrino AN, Martin MT, Tilton JJ, Touchette DR. Medication therapy management services: definitions and outcomes. Drugs. 2009;69(4):393–406. https://doi.org/10.2165/00003495-200969040-00001 https://www.ncbi.nlm.nih.gov/pubmed/19323584
22	Wales, United Kingdom	Polypharmacy: guidance for prescribing. Llandough: All Wales Medicines Strategy Group; 2014 (http://www.awmsg.org/docs/awmsg/medman/Polypharmacy%20-%20Guidance%20for%20Prescribing.pdf, accessed 22 March 2019).

Annex 4. Case studies

The following case studies have been adapted from Polypharmacy guidance: realistic prescribing[1]

Case 1: Frailty without overt multimorbidity

Case summary

Patient details
- 69-year-old man

Current medical history
- Fractured neck of femur 2 years ago
- Dementia – mixed Alzheimer's disease / alcohol abuse
- Falls frequently
- Ex-smoker

Results
- Blood pressure (BP) 120/84 mmHg
- Estimated glomerular filtration rate (eGFR) > 60ml/min

Current medication (stable since admission)
- Trazodone 150 mg at night
- Thiamine 50 mg three times daily
- Bendroflumethiazide 2.5 mg once daily
- Tramadol 50 mg four times daily
- Cetirizine 10 mg once daily
- Amisulpride 100 mg twice daily
- Emollient cream (as required)
- Fusidic acid 2% and betamethasone 0.1% cream topically twice daily

Current function
69 year old man has been a care home resident for two years. He is a long-term heavy alcohol user in the past and developed dementia exacerbated by alcohol-related brain damage. A fall at home led to a fractured hip. Post-surgery he was very confused and distressed. When settled, he was unable to manage at home post-fracture and transferred to a care home. At the time of admission the patient lacked capacity, but showed indication towards recovery and put weight on initially. He has exhibited a slow decline in function since.

Assistance of two caregivers is required for transfer to chair. The patient falls frequently as he attempts to move unaided. Conversation is confused and occasional verbal aggression is apparent. He also has poor short term memory, prompting is required to ensure that he eats and drinks. He spends most of the day sleeping in his chair and sleeps well at night. Over the last 12 months he has developed shortness of breath and swollen ankles.

Most recent consultations
Communication may be difficult due to cognitive impairment. If there is an adult with welfare powers (power of attorney or guardian) involve them. Family if still in touch may also help. Three consultations in the last six months, one concerning chest infection, another for review following fall, and most recently due to leg oedema.

1. Scottish Government Polypharmacy Model of Care Group. Polypharmacy guidance: Realistic prescribing, 3rd edition. Edinburgh: Scottish Government; 2018 (https://www.therapeutics.scot.nhs.uk/wp-content/uploads/2018/09/Polypharmacy-Guidance-2018.pdf, accessed 15 April 2019).

Applying the 7 steps

Checks	Medication-related risks/problems identified
1. What matters to the patient • Review diagnoses and identify therapeutic objectives	**Priorities may include:** • Reduce shortness of breath • Improve ability to self-manage and interact socially • Reduce ankle swelling • Reduce sedation **Prevention:** • Reduce risk of falls/fractures
2. Need • Identify essential medications (not to be stopped without specialist advice)	• None

3. (Continued) need for medications
• Identify and review the (continued) need for medications
	• Thiamine – may be redundant if well-nourished in care home
	• Bendroflumethiazide – no longer hypertensive, potential for withdrawal
	• Tramadol – indication unclear (may have been started after surgery)
	• Central nervous system (CNS) medication (trazodone, amisulpiride) – indication unclear
	  – Consider withdrawal if not agitated
	• Cetirizine/topical emollient cream
	  – Required for itch? Clarify the cause (i.e. dermatological versus CNS problem or adverse drug reaction). If dermatological problem, follow non-pharmacological measures e.g. pay attention to washing powder, use natural fabrics, reduce use of perfumed products etc., and ensure proper use of emollients regularly and in sufficient quantity)
	• Antimicrobial cream (fusidic acid/betamethasone cream) – use should be limited to short term (e.g. one week)

4. Therapeutic objectives achieved? • Identify the need for adding/intensifying medication therapy in order to achieve therapeutic objectives	• Ankle swelling and shortness of breath: consider presence of left ventricular systolic dysfunction. Consider thorough cardiac investigation. If present effective treatments such as ACEI/Angiotensin II receptor blocker (ARB), beta blocker can be prescribed • Reduce risk of falls/fractures: – Falls risk mainly associated with sedative medications. Fracture risk modification with osteoporosis prevention could be considered. Decision to treat needs to be balanced against expected efficacy (see NNT) and ability to comply with treatment. Dental health needs to be considered if moving to active treatment with bisphosphonates, unlikely to have time to benefit if life expectancy is estimated to be < 1 year

Checks	Medication-related risks/problems identified

5. Safety
• Identify patient safety risks
• Identify adverse drug effects
	Actual adverse drug events:
	• Oversedation
	Adverse drug event risk:
	• Risk of cardiovascular events:
	  – Antipsychotics carry a markedly elevated risk of cardiovascular events in dementia
	• Risk of cognitive deterioration:
	  – Amisulpride, cetirizine and tramadol
	• Risk of falls/fractures:
	  – Amisulpride, trazodone (sedative), cetirizine
	• Risk of serotonin syndrome:
	  – Tramadol and trazodone
	• Risk of steroid adverse effects (topical and systemic):
	  – High dose topical corticosteroid
	• Risk of acute kidney injury:
	  – Bendroflumethiazide would need to be stopped if patient is dehydrated
	  – In case of care home resident with managed medications, ensure staff have clear information on prescriptions to withhold if dehydrated

6. Costs • Identify unnecessary costly medication therapy	• Opportunities for cost minimization (e.g. generic substitution) should be explored • Ensure prescribing is in keeping with current formulary recommendations (see Annex 1)

7. Patient centeredness
• Does the patient understand the outcomes of the review?
• Ensure medication therapy changes are tailored to patient preferences
• Agree and communicate plan
	• Reduce risk of falls/fractures:
	  – Reduce trazodone and amisulpiride to reduce sedation and falls risk
	  – Decision to start bisphosphonate: balance ability to take versus expected benefit
	• Patient cooperation:
	  – Involve the patient where possible. If deemed to lack capacity, discuss with relevant others e.g. welfare guardian, power of attorney, or nearest relative if one exists. Even if adult lacks capacity, still ensure adult's views are sought and thorough documentation takes place

SUMMARY: KEY CONCEPTS IN THIS CASE
• Low number of conditions and medications but still high potential for medication-related illness
• Ongoing review of medication commenced for symptomatic relief
• Apparent low level of multimorbidity but potential for undiagnosed treatable conditions
• Oversedation is a major risk to quality of life, morbidity (falls) and mortality

Case 2: Acute Pain and Depression with Asthma

Case summary

Patient details
• 57 year old woman

Current medical history

• Back pain	• Depression last two years since losing job after break-up of marriage
• Asthma since childhood	

Results

- BP 150/80 mmHg
- Urea and electrolytes all within normal range
- Peak Flow Rate 300 (predicted 390)
- Respiratory rate 22 per minute

Lifestyle

- Smokes 5–10 cigarettes per day

Current medication

• Lansoprazole 30 mg once daily	• Beclomethasone inhaler 100 micrograms 2 puffs twice daily
• Gabapentin 600 mg three times daily	• Mirtazapine 30 mg every night
• Tramadol 50 mg –100 mg every 4–6 hours	• Zopiclone 7.5 mg 1 every night
• Salbutamol inhaler 100 micrograms two puffs as required	

Current function

The patient has been suffering from pain and complaining of drowsiness and weight gain. She has suffered from low mood for the last two years and has tried multiple antidepressants. The patient can be difficult to engage depending on mood, but has sought advice today as she is finding the pain unbearable and received letter for a medication review.

Most recent consultations

Most recent consultations have been for pain and management. Prior to that consultations were concerning low mood and poor sleep after break up of marriage. The patient has also complained about increased breathlessness and ordered salbutamol inhaler each month.

Applying the 7 steps

Checks	Medication-related risks/problems identified
1. What matters to the patient • Review diagnoses and identify therapeutic objectives	**Priorities may include** • Manage the pain • Manage asthma through the use of preventative treatments. • Minimise medication-related harm dependence: – Zopiclone, tramadol and gabapentin • Help patient quit smoking: impact on asthma
2. Need • Identify essential medications (not to be stopped without specialist advice)	• Medicines for symptomatic deterioration of asthma • Cause of back pain may need thorough investigation
3. (Continued) need for medications • Identify and review the (continued) need for medications	• Review the need for ongoing proton pump inhibitor: if still needed, aim for dose reduction (maintenance dose of lansoprazole is 15 mg/day) • Patient examined and breathlessness due to asthma: check use of preventative treatment inhaler technique • Review of pain management: trial dose reduction of gabapentin as there is no existing complaint for nerve pain, reduce this gradually and consider alternatives • Confirm daily intake of tramadol: if the patient is taking regularly, consider switching to an extended-release formulation to improve compliance and manage pain better Ensure the daily limit is not exceeded (maximum dose of tramadol is 400 mg/day) • Trial dose reduction of zopiclone • Discuss depression and review treatment: consider other support that might be needed (e.g. non-pharmacological interventions)

4. Effectiveness
• Identify the need for adding/intensifying medication therapy in order to achieve therapeutic objectives
	• Pain symptoms: consider reviewing treatment to manage pain more appropriately. Discuss about the realistic expectations with the patient
	• Reduce one treatment at a time: consider need for on-going zopiclone, tramadol and gabapentin
	• Consider options for smoking cessation
	• Ensure adequate treatment plan for asthma:
	  – Review use of salbutamol and beclomethasone
	  – Step-up or step-down treatment as required

5. Safety
• Identify patient safety risks
• Identify adverse drug effects
	• Adverse effects of long-term zopiclone use:
	  – Avoid prolonged use due to risk of dependence, falls etc.
	  – Also consider the interaction with tramadol
	• Avoid long-term use of gabapentin, reduce dose gradually
	• Assess for the risk of accidental overdose
	• Check that patient is aware of safety advice e.g. what medication to stop if at risk of dehydration

6. Costs • Identify unnecessary costly medication therapy	• Opportunities for cost minimization (e.g. generic substitution) should be explored • Ensure prescribing in keeping with current formulary recommendations

Checks	Medication-related risks/problems identified
7. Patient centeredness • Does the patient understand the outcomes of the review? • Ensure medication therapy changes are tailored to patient preferences • Agree and communicate plan	• Patient may need support with inhaler and inhaler technique if continuing treatment • Discuss with patient other strategies to help manage pain • Reduce medication one at a time to build patient's confidence. This will ensure that any changes in symptoms as a result of a medication change can easily be attributable to one medication

SUMMARY: KEY CONCEPTS IN THIS CASE

1. Low number of conditions and medications but still high potential for drug dependence

2. Ongoing medication review needed for those for symptomatic relief for pain and for sleep

3. Patient education on the benefit of preventive medication for asthma

Case 3: Multimorbidity without frailty

Case summary

Patient details
- 58 year old woman

Current medical history
- Type 2 diabetes (diagnosed 5 years ago)
- Coronary heart disease (non-ST elevation myocardial infarction 1 year ago)
- Hypertension
- Atrial fibrillation
- Chronic obstructive pulmonary disease (COPD)
- Chronic back pain
- Depression (2 episodes)
- Hypothyroidism

Results
- HbA1c 86 mmol/mol (10%)
- BP 150/85 mmHg
- Body mass index 35 kg/m^2
- Spirometry shows mild airway obstruction
- No urinary protein detected
- eGFR 55 ml/min

Lifestyle
- Smoks 10–15 cigarettes per day
- alcohol: 20 units per week

Current medication
- Aspirin 75 mg once daily
- Metformin 1 g three times daily
- Gliclazide 80 mg twice daily
- Pioglitazone 30 mg once daily
- Salbutamol inhaler as required
- Beclomethasone inhaler 100 micrograms twice daily
- Levothyroxine liquid 100 micrograms once daily
- Citalopram 20 mg once daily
- Bendroflumethiazide 2.5 mg once daily
- Lisinopril 30 mg once daily
- Amlodipine 10 mg once daily
- Atenolol 50 mg once daily
- Furosemide 40 mg once daily
- Gabapentin 400 mg three times daily
- Codeine/paracetamole 8/500 mg 2 tablets up to four times daily
- Diclofenac 50 mg up to three times daily
- Omeprazole 40 mg once daily

Current function

Receptionist in local garage works 6 half days per week. She lives with her husband (out of work long-term) and provides support to her elderly mother who lives alone and has early dementia.

Two previous acute admissions to hospital. Flu-like illness led to exacerbation of COPD two years ago. Chest pain 12 months ago, found to be in atrial fibrillation on admission and troponin positive. Angiogram showed widespread coronary artery disease but not severe enough to warrant revascularisation. Echocardiography showed normal left ventricular systolic function. On dual aspirin and clopidogrel for 1 year, recently moved to aspirin monotherapy.

Most recent consultations

Ongoing problems with ankle swelling. Back pain difficult to manage and resistant to several strategies. Occasional heart palpitations and persistent indigestion with heartburn. Long-term financial worries and increasing caregiver strain.

"I had a heart attack about a year ago and really worried about that happening again. I don't know what my mother and husband would do if I got too ill to work or look after her".

Applying the 7 steps

Checks	Medication-related risks/problems identified
1. What matters to the patient • Review diagnoses and identify therapeutic objectives	**Priorities may include:** • Reduce shortness of breath • Guidance to manage her medications safely, independently • Reduce ankle swelling • Assess the effect and necessity of her medications • Discuss and create a medication management plan with the patient **Possible therapeutic targets:** • Secondary prevention of cardiovascular events (including stroke prevention in atrial fibrillation) • Rate control in atrial fibrillation • Management of chronic kidney disease • Management of COPD • Pain control • Management of depression • Weight reduction • Management of indigestion with heartburn
2. Need • Identify essential medications (ones that are not to be stopped without expert advice)	• Levothyroxine to treat hypothyroidism • Atenolol is needed for rate control in atrial fibrillation As a beta-blocker, will aggravate asthma/COPD, the patient will need another medication for rate control, e.g. verapamil • Antidiabetic medications to control symptomatic diabetes mellitus
3. (Continued) need for medications • Identify and review the (continued) need for medications	• Pain management: is the gabapentin for neuropathic pain (from diabetes mellitus) or mechanical back pain. Monitor use of codeine/paracetamol, consider switching to paracetamol only • Duration of antidepressant • High dose omeprazole: active peptic ulcer or oesophagitis? Check symptoms are of gastric origin rather than angina; may require endoscopy or trial without NSAID?

4. Effectiveness
• Identify the need for adding/intensifying medication therapy in order to achieve therapeutic objectives
	• Secondary prevention of coronary events:
	  – Patient is relatively young and active so potentially a long time to obtain benefit
	  – Not on statin despite high cardiovascular risk (check if omission or due to side effects. If side effects, consider alternative statin)
	  – Check BP control, lipid control and lifestyle
	• Stroke prevention in atrial fibrillation:
	  – CHA2DS2-VASc score = 4 (stroke risk 4.8% per year) – consider replacing aspirin with anticoagulant
	  – Rate control in atrial fibrillation: check heart rate
	• Management of COPD:
	  – Discuss symptom control with patient – MRC Breathlessness Score
	  – Ensure managing inhalers and that these are prescribed in keeping with current formulary guidelines

Checks	Medication-related risks/problems identified

	• Pain control:
	  – Discuss symptom control
	  – Gabapentin indicated for neuropathic pain. Consider withdrawal if not effective or misprescribed for mechanical back pain
	  – Review efficacy of NSAID in view of the risks of treatment
	• Management of depression: discuss symptom control with patient
	• Control of hypothyroidism: ensure recent thyroid function results are available
	• Management of chronic kidney disease: within normal range (no proteinuria) but requires regular monitoring
	• Diabetic control
	  – Check if experiencing any diabetic symptoms (e.g. thirst, polyuria)
	  – HbA1C remains high despite on three antidiabetic medication therapies, discuss adherence and HbA1C target

5. Safety
• Identify patient safety risks
• Identify adverse medication effects
	Actual adverse drug reactions:
	• Ankle swelling – due to amlodipine or pioglitazone?
	
	Risk of adverse drug reactions:
	• Risk of gastrointestinal bleeding: NSAID, citalopram and aspirin (or anticoagulant if changed in step 3)
	• Risk of acute kidney injury:
	  – Chronic kidney disease (eGFR 55mL/min) and on NSAID, consider stopping
	  – Co-prescribed diuretic, ACEI/ARB and NSAID ('triple whammy')
	  – Co-prescribed thiazide and loop diuretic. Duplication of therapy, discontinue one
	  – Consider more frequent monitoring of urea and electrolytes
	  – Check the patient is aware of safety advice e.g. what medication to stop if at risk of dehydration
	• Risk of cardiovascular disease/cardiac events:
	  – Ischaemic heart disease and on NSAID (diclofenac), ibuprofen and naproxen are preferred
	  – Pioglitazone (ankle swelling and ischaemic heart disease)
	• Risk of arrhythmia: QTc prolongation: omeprazole, citalopram and gabapentin

6. Costs • Identify unnecessary costly medication therapy	• Opportunities for cost minimization (e.g. generic substitution) should be explored • Ensure prescribing in keeping with current formulary recommendations • Levothyroxine: consider changing from liquid to tablet form

Checks	Medication-related risks/problems identified

7. Patient centeredness
• Does the patient understand the outcomes of the review?
• Ensure medication therapy changes are tailored to patient preferences
• Agree and communicate plan
	• Secondary cardiovascular disease prevention: consider how to prioritise discussion (and allocate time for this in consultation)
	• Most effective interventions requires: stopping smoking followed by anticoagulant for atrial fibrillation, BP control, addition of statin medication therapy, weight reduction and HbA1C control
	• Offer and support smoking cessation, diet and exercise
	• COPD management:
	  – Check patient's inhaler technique and adherence
	  – Adjust dose/formulation, if necessary
	• Patient cooperation:
	  – Ensure patient understands rational for medication
	Prevention: promote non-pharmacological strategies
	• Check the patient's willingness to make lifestyle changes (smoking, diet, exercise)
	• Social support: impact of stress

SUMMARY: KEY CONCEPTS IN THIS CASE

1. A high number of medications is likely to be needed and effective. A high number of medications on its own is not an indicator of problematic prescribing, but rather a high-risk patient requiring more support

2. Long medication lists make it harder to identify problems without a focused medication review

3. Potential to usefully detect and treat conditions (in this case atrial fibrillation)

4. Potential for high risk medication combinations particularly in patients on multiple medications

5. Need for direct advice to patient on medication, e.g. regarding dehydration

6. Link with non-pharmacological management

7. A longer than standard consultation to ensure that there is time to cover the patient concerns and issues and focus on medication

8. Need for multi-disciplinary approach to address patient's health conditions and future treatment

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