Pharmacotherapy

23

Mirko Petrovic, Danijela Gnjidic, Eline Tommelein, and Koen Boussery

Abstract

The number of octogenarians is growing which results in increasing number of people with multimorbidity. Multimorbidity creates polypharmacy, which, consequently, is the most consistent predictor of inappropriate prescribing and drug-related problems (DRPs) in older people. In this chapter, the main characteristics of polypharmacy and the risks for DRPs, with focus on prescribing cascade and drug interactions, are described. Subsequently, steps to be considered during prescribing for older persons, methods for detecting DRPs and optimisation of polypharmacy are elaborated on. This chapter provides insights on assessment of pharmacotherapy in older patients, detection of potential DRPs, optimal solutions for the detected problems and tailoring pharmacotherapy to the profile, the needs and the goals of care in older patients.

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M. Petrovic (✉)
Department of Internal Medicine (Geriatrics), Faculty of Medicine and Health Sciences, Belgium, Ghent University, Ghent, Belgium
e-mail: mirko.petrovic@ugent.be

D. Gnjidic
Faculty of Pharmacy and Charles Perkins Centre, University of Sydney, NSW, Australia
e-mail: danijela.gnjidic@sydney.edu.au

E. Tommelein
Department of Bioanalysis, Pharmaceutical Care Unit, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium
e-mail: eline.tommelein@ugent.be

K. Boussery
Department of Bioanalysis, Pharmaceutical Care Unit, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium
e-mail: koen.boussery@ugent.be

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Learning Objectives

By the end of the chapter, the reader will be able to
- Assess pharmacotherapy in older patients
- Detect potential DRPs
- Derive the optimal solutions for the detected problems
- Tailor pharmacotherapy for the individual older patients

23.1 Polypharmacy

23.1.1 Definition and Prevalence

Polypharmacy is usually defined as the concurrent use of multiple medications. There is a high variability in the exact number of medications that is used as a threshold for polypharmacy, but a threshold of five and more has shown to be useful in identifying those patients that may benefit from an assessment of the potential inappropriateness of their polypharmacy (Gnjidic et al. 2012a). Polypharmacy is increasingly common and the prevalence varies according to the setting and population studied. Up to 40% of people aged 65 years and older in the community setting take five or more drugs (Kantor et al. 2015). In particular, exposure to central nervous system (CNS) polypharmacy is common and has increased over the last decade among adults over 75 years of age reaching more than 35% (Maust et al. 2017). Polypharmacy is more common in older frail compared to robust adults. In community-dwelling older men, polypharmacy was reported in 65% of frail men compared to 27% of robust men (Gnjidic et al. 2012b). Over the last 20 years, measures for polypharmacy have moved from merely counting medications to the use of instruments that assess medication burden and that focus on the optimisation of rational prescribing in older people. Explicit and implicit instruments, such as the Beers Criteria, Screening Tool of Older Persons' Prescriptions and Screening Tool to Alert doctors to Right Treatment (STOPP/START) criteria and Medication Appropriateness Index (MAI), can be used to identify high-risk medications that are no longer appropriate. The prevalence of potentially inappropriate medication use defined using STOPP criteria was 51% across six European hospitals (Gallagher et al. 2011). Polypharmacy in older people can also be assessed using tools that consider pharmacological principles (i.e. dose response, cumulative effects) and target specific medications such as those with clinically significant anticholinergic effects and sedative effects (i.e. Anticholinergic Drug Score, Anticholinergic Risk Scale, Drug Burden Index) (Kouladjian et al. 2014). However, comparing medication burden exposure using these tools is challenging, for example, because of a lack of consensus on what medications exactly constitute 'anticholinergic medication'. This is illustrated by the fact that the prevalence of anticholinergic medication use in the literature ranges from 18% to 23%, depending on the tool used (Kashyap et al. 2014).

23.1.2 Clinical Consequences of Polypharmacy

While polypharmacy might lead to positive outcomes for some older people with multimorbidity (see also Chapter 6), there is strong evidence that it is associated with increased risks of adverse events. Evidence from systematic review of observational studies suggests that polypharmacy is linked to a range of clinically relevant outcomes including drug–drug interactions (DDI), medication non-adherence, inappropriate prescribing, adverse drug events (ADEs), adverse drug reactions (ADRs), hospitalisation, falls, functional decline and mortality (Fried et al. 2014). Among older people, polypharmacy is often considered to be among the most important risk factors for ADRs (Hilmer et al. 2009). Therefore, rational withdrawal of medications may be the appropriate clinical decision and may result in significant clinical and functional benefits in some older people with polypharmacy. Evidence also suggests that polypharmacy is linked with frailty in older people (Gnjidic et al. 2012b; Saum et al. 2017). Frailty is commonly defined as a multifactorial syndrome that is associated with functional impairment and increased susceptibility to disease, disability and mortality in older people. Among community-dwelling older men, increasing medication load is associated with transitioning from the pre-frail to frail status and subsequent death (Jamsen et al. 2016). Each additional drug was associated with a 22% higher risk of death in men who were initially defined as robust. However, it remains unclear how causality fits into this relation. An important issue to take into account when discussing clinical consequences of polypharmacy is that there is a need for more research into the relevance of polypharmacy thresholds within the clinical context of the patient. For example, a post hoc analysis of the apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial showed that patients with atrial fibrillation treated with apixaban had consistently lower major bleeding rates compared to warfarin treatment, but the magnitude of benefit decreased with the increasing polypharmacy exposure (Focks et al. 2016).

As this clearly demonstrates that it is essential to consider polypharmacy within the context of multimorbidity, and that this consideration should guide clinical practice. National Institute for Health and Care Excellence (NICE) guidelines provide excellent recommendations for management of polypharmacy among people with multimorbidity (Farmer et al. 2016).

23.1.3 Strategies to Reduce Inappropriate Polypharmacy

Recent efforts have been focused towards providing an evidence base on medication withdrawal or deprescribing. Deprescribing can be referred to as a process of withdrawing inappropriate medications, supervised by a healthcare professional with the goal of managing polypharmacy and improving patient outcomes (Reeve et al. 2015). To date, the success of deprescribing interventions to reduce the medication burden is mixed. The reported effects of deprescribing on clinical outcomes are inconsistent and vary by setting and by the nature of the intervention that is

evaluated. A Cochrane review of interventions aiming to improve the use of appropriate polypharmacy found beneficial effects in reducing inappropriate prescribing and medication-related problems. However, no benefits were observed in terms of clinical outcomes (Patterson et al. 2014). A structured, multidisciplinary approach including medication reconciliation, medication review conducted by a pharmacist or use of assessment tools to identify medications known to increase the risk of adverse events may minimise potentially inappropriate prescribing (PIP) and improve patient-centred and clinical outcomes. Moreover, an integrated approach taking into account patient perspectives may result in more successful deprescribing interventions.

23.2 Drug-Related Problems

23.2.1 Definition

DRPs are defined as events or circumstances that interfere with a patient experiencing the optimal outcome of medical care (Hepler et al. 1990). *Inappropriate prescribing*, on its turn, is defined as prescribing in which risks outweigh benefits or as the prescribing of medications that have no clear evidence-based indication, carry a high risk of adverse side effects or are not cost-effective (Gallagher et al. 2007) (Table 23.1). The risk factors associated with DRPs include polypharmacy, multimorbidity, poor functional status, depression and impaired renal function (Tommelein et al. 2015). Research on prevalence of DRPs is mainly focused on potentially inappropriate prescribing or on DRPs leading to hospital admissions. It was estimated that around 5–10% of hospital admissions were due to DRPs, of which 50% are avoidable (Al Hamid et al. 2014; Nivya et al. 2015). A systematic review showed that pharmacotherapy can be optimised in at least 20% of older community-dwelling patients (Maust et al. 2017). Additionally, the consequences of DRPs comprise a reduced quality of life and an increased social and economic burden through increased morbidity and mortality.

23.2.2 Why Are Older Patients More at Risk for DRPs

Different factors can explain the high incidence of DRPs in older people compared to their younger counterparts (van den Bemt et al. 2000; Hajjar et al. 2003; Field et al. 2001, 2004; Lund et al. 2010; Steinman et al. 2006; Page et al. 2010). First, older people often have multiple diseases and are consequently treated with many drugs. This increases the risk for both DDI and drug–disease interactions (DDisI). Second, changes in pharmacokinetics (Table 23.2) and pharmacodynamics make older people, and particularly those with frailty, more vulnerable to DRPs, also because of reduced resilience. Pharmacodynamic changes in older age, however scarcely evidenced, include alterations in the end-organ responsiveness to drugs and reduced homeostatic mechanisms that results in usually increased sensitivity to several classes of drugs, such as anticoagulants, cardiovascular and psychotropic drugs

Table 23.1 Overview of different types of DRPs (Spinewine et al. 2007, Mallet et al. 2007)

	Some examples
Inappropriate prescribing	
Overuse	
Therapy for an indication which is no (longer) present Combination therapy where monotherapy is sufficient Pharmacotherapy for treatment of side effects of other drugs ('prescribing cascade')	Antidepressants in case of a normal grief reaction; antibiotics in case of a common cold
Underuse	
Not treating present medical condition Omission of prophylactic therapy	No anticoagulation in case of atrial fibrillation; no osteoporosis prophylaxis during long-term corticosteroid treatment
Misuse	
Wrong choice of drug (formulation) *Drug with better effectiveness or with lower risk available* – *Functional capacity of the patient does not allow use of the drug* – *Suboptimal formulation* Dosing problem – *Dose too high or too low* – *Suboptimal dosing scheme* Presence of or higher risk for adverse drug events – *Adverse drug events (type 1 or 2)* – *Contra-indicated drug ('Drug–Disease Interaction' (DDisI))* – *Interaction with other drug ('Drug–Drug Interaction' (DDI))* – *Interaction with food*	First instead of second generation antihistamines with less sedating effects; a screw cap container instead of an easy opening blister in patients with osteoarthritis; tablets prescribed in case of swallowing difficulties; doses not adjusted to impaired renal function; myopathy due to statins, benzodiazepines in case of increased risk of falls; concomitant use of psychotropic drugs; vitamin K-rich food (i.e. leafy greens) with warfarin
Inappropriate dispensing	
Wrong drug dispensed Insufficient or inadequate information provided during drug dispensing Overlooking of practical problems (opening package, swallowing problems, etc.)	Not offering a practical advice for inhalation devices
Inappropriate patient behaviour	
Not following user instructions Medication non-adherence	Patient is intentionally non-adherent to diuretics because of social inconvenience
Inappropriate monitoring and reporting	
Insufficient or no follow-up of medication adherence Insufficient or no follow-up of lab values or clinical effect after start of some drugs Not discussing or reporting side effect with/to the treating physician	Thyroid function tests not timely evaluated; never asking about constipation in patients on opioid analgesics

(Klotz et al. 1975, Wang 2005). Third, older people are often treated by multiple prescribing physicians. Therefore, it can be difficult to keep an overview of the different drugs prescribed in terms of indications, duration of therapy, monitoring of adverse reactions and follow-up of the effectiveness of the drugs for the different medical problems. Fourth, decreased capability to handle medications can lead to decreased adherence and inappropriate drug therapy.

Table 23.2 Differences in pharmacokinetics in older vs. younger adults

Pharmacokinetic changes
Absorption
– Decreased active transport decreases bioavailability for some drugs – Possibility of reduced hepatic metabolism in older age: Reduced first-pass metabolism (reduced liver mass and blood flow) increases bioavailability of some drugs—necessitates initiation at lower doses with extended administration intervals (Page et al. 2010, Kinirons et al. 1997)
Distribution
– Decreased body water increases serum concentration of water-soluble drugs (Klotz et al. 1975) – Increased body fat prolongs half-life of fat-soluble drugs
Metabolism
– Possibility of reduced hepatic metabolism in older age: hepatic disease or reduced hepatic volume and blood flow results in reduced oxidative metabolism (reduced metabolism through CYP450) and higher steady-state concentrations of some drugs (Page et al. 2010, Kinirons et al. 1997)
Excretion
– Decreased cardiac output results in less perfusion of kidneys and liver, which reduces elimination of high extraction ratio drugs – Reduced kidney function reduces elimination of renally excreted drugs or metabolites (Kwan et al. 2014)

CYP450 = cytochrome P450

23.2.3 Focus on the Prescribing Cascade

The 'prescribing cascade' begins when an ADR is misinterpreted as a new medical condition for which another drug is then prescribed, and the patient is placed at risk of developing additional adverse effects relating to this potentially unnecessary treatment (Rochon et al. 1997) (Table 23.3). In case of polypharmacy, it sometimes becomes difficult to recognise which medications were prescribed to treat underlying disease rather than drug-related adverse effects. To prevent the prescribing cascade, physicians should therefore always consider any new sign and symptom as a possible consequence of current drug treatment. Timely recognising and managing prescribing cascades requires detailed history, including the timing of new symptom onset in relation to drug initiation or modification.

23.2.4 Focus on Drug–Drug Interactions

DDI occur when there is a modification of the effect of a drug when it is administered together with another drug. Drug interactions may present as increased efficacy, lack of efficacy or increased toxicity. In a recent observational study on potentially inappropriate prescribing (PIP) in older community-dwelling patients with polypharmacy, it was observed that 51% of 1016 included patients had at least one interaction with specific relevance for this population (Tommelein et al. 2016a). Most DDI are either pharmacodynamic (i.e. two drugs have additive or antagonistic effects) or pharmacokinetic (i.e. one drug affects the other's absorption, distribution,

Table 23.3 Examples of frequent prescribing cascades

Initial therapy (=Drug 1)	Side effect for Drug 1	Therapy for side effect (=Drug 2)	Side effect from drug 2	Therapy for side effect (=Drug 3)
Metoclopramide	Parkinsonism	Levodopa	Confusion and behavioural disturbances	Sedative or atypical antipsychotic
Levofloxacin	Delirium	Antipsychotic		
Calcium channel antagonist Gabapentin	Oedema	Loop diuretic		
Lithium	Tremor	Beta blocking agent	Depression	Antidepressant
ACE inhibitors	Cough	Cough suppressants		
NSAID	Hypertension	Antihypertensives		
NSAID	Heartburn	PPI	Low vitamin B_{12}	B_{12} supplement
Donepezil	Urinary incontinence	Oxybutynin	Dry eyes or constipation	Artificial tears/ laxatives
Tricyclic antidepressant	Decreased cognition	Donepezil		
Thiazide diuretics	Hyperuricaemia	Treatment for gout		

ACE angiotensin-converting enzyme, *NSAID* non-steroid anti-inflammatory drug, *PPI* proton pump inhibitor

metabolism, or excretion) in nature. Sometimes, it is however not possible to avoid an interaction, e.g. the combination of calcium for osteoporosis prophylaxis and levothyroxine for hypothyroidism. Then, its impact should be minimised by modifying the dose, way, or sequence of the drug administration. In this specific example, intake can be kept 6 h apart. It is important to anticipate the onset and maximum effect and monitor the patient at all times (Björkman et al. 2002, Ogu et al. 2000, Lynch et al. 2007, Marengoni et al. 2008). Authors of the recently developed Ghent Older People's Prescriptions community Pharmacy Screening (GheOP^{3}S) tool to detect potentially inappropriate prescribing in community-dwelling older patients established a list of DDI with specific relevance for older patients (Tommelein et al. 2016b). They considered a DDI having specific relevance for this population when it was often associated with an unplanned hospital admission. Table 23.4 presents the interactions that have shown the highest prevalence in observational research studies (Tommelein et al. 2016a).

Table 23.4 DDI of specific relevance in older patients and alternative therapeutic options

VKA + antiplatelet drugs (esp. ASA), not prescribed by cardiologist	1st Check if combination is appropriate (artificial valve, up to 3 months after acute coronary syndrome and for rheumatic mitral valve stenosis) 2nd When combination is not appropriate: stop ASA and monitor INR

(continued)

Table 23.4 (continued)

VKA + oral NSAIDs	1st Consider need for NSAID. If possible: paracetamol or stronger non-NSAID is safer choice 2nd If NSAID is unavoidable, prefer low dose ibuprofen 3rd Always add gastroprotection (most evidence for PPI in standard dose) 4th Also keep in mind to closely monitor renal function or blood pressure depending on present diagnoses
VKA + TMP/SMX	1st Preferably switch to other antibiotic based on indication 2nd If combination is unavoidable: monitor INR
RAAS-inhibitor + potassium sparing diuretic/potassium supplements/potassium containing drugs[a]	1st Preferably change to non-potassium sparing diuretic/switch to non-potassium containing drug equivalent 2nd If combination is unavoidable: monitor renal function and serum potassium 3rd Always inform patient about symptoms of hyperkalaemia
RAAS-inhibitor + TMP/SMX	1st Preferably switch to other antibiotic based on indication 2nd If combination is unavoidable: monitor renal function and potassium level
RAAS-inhibitor + oral NSAID	1st Consider need for NSAID. If possible: paracetamol or stronger non-NSAID is safer choice. 2nd If NSAID is unavoidable: monitor renal function, blood pressure and serum potassium
Oral NSAID + oral corticosteroids	1st Consider need for NSAID. If possible: paracetamol or stronger non-NSAID is safer choice 2nd If NSAID is unavoidable, prefer low dose ibuprofen 3rd Always add gastroprotection (most evidence for PPI in standard dose) 4th Also keep in mind to closely monitor renal function or blood pressure depending on present diagnoses
Oral NSAID + diuretic	1st Consider need for NSAID. If possible: paracetamol or stronger non-NSAID is safer choice 2nd If NSAID is unavoidable: monitor renal function, blood pressure and serum potassium
Oral NSAID + SSRI/SNRI	1st Consider need for NSAID. If possible: paracetamol or stronger non-NSAID is safer choice 2nd If NSAID is unavoidable, prefer low dose ibuprofen 3rd Always add gastroprotection (most evidence for PPI in standard dose) 4th Also keep in mind to closely monitor renal function or blood pressure depending on present diagnoses

Table 23.4 (continued)

Oral NSAID + antiplatelet drugs	1st Consider need for NSAID. If possible: paracetamol or stronger non-NSAID is safer choice 2nd If NSAID is unavoidable, prefer low dose ibuprofen 3rd Always add gastroprotection (most evidence for PPI in standard dose) 4th Also keep in mind to closely monitor renal function or blood pressure depending on present diagnoses
Oral antidiabetics/insulin + (non-)selective β-blocker	1st Consider need for beta-blocker + check glycaemic control 2nd Always change to cardio selective beta-blocker (also relevant for eye drops) 3rd Inform patient about possible changes in awareness of hypoglycaemia
Ca^{2+} + quinolones/tetracyclines	1st Use Ca^{2+} min 2 h after quinolone/tetracycline or take quinolone/tetracycline 6 h after intake of Ca^{2+} 2nd If not possible: Stop calcium
Ca^{2+} + levothyroxine	1st Use Ca^{2+} min 2 h after levothyroxine drug or take levothyroxine 6 h after intake of Ca^{2+} 2nd If not possible: Stop calcium
Bisphosphonate + Ca^{2+}, Mg^{2+}, Zn^{2+}, Fe^{2+}, Al^{3+}	1st Use complexing agent min 2 h after bisphosphonate 2nd If not possible: Switch to equivalent drug without complexing activity
Any combination of anticholinergic drug	1st Replace 1 or more of the drugs by an equivalent with less or without anticholinergic activity 2nd Always advise patients to report anticholinergic side effects

ASA acetylsalicylic acid, *NSAID* non-steroidal anti-inflammatory drug, *TMP/SMX* trimethoprim/sulphamethoxazole, *CCB* calcium channel blocker, *RAAS-inhibitor* renin-angiotensin-aldosterone system inhibitors, *SNRI* selective serotonin norepinephrine reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor, *VKA* vitamin K antagonist

[a]Some drugs contain considerable potassium amounts: Glucosamine in potassium salt (up to 300 mg/tablet), oral nutritional supplements (up to 200 mg/unit) (Recommended Daily Dose: 3000 mg/day for ≥60-year-old patients)

[b]Some supplements contain considerable vitamin K amounts: oral nutritional supplements (up to 13 μg/unit) (Recommended Daily Dose: 50–70 μg/day for ≥60-year-old patients)

23.3 Detecting Drug-Related Problems and Optimising Polypharmacy

23.3.1 Definition

A first step in detection of potential DRPs is *medication reconciliation*, defined as 'a process of obtaining and verifying a complete and accurate list of all patient's current medications – including the name, dosage, frequency and route' (Agency for Healthcare Research and Quality U.S. Department of Health and Human Services 2012, https://www.ahrq.gov/sites/default/files/publications/files/match.pdf). Medication reconciliation

could also be the first step of a clinical medication review. Strategies to optimise drug use include *medication review* defined as 'a structured, critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimising the impact of medicines, minimising the number of medication related problems and reducing waste' (NHS Cumbria Medicines Management Team 2013, http://www.cumbria.nhs.uk/ProfessionalZone/MedicinesManagement/Guidelines/MedicationReview-PracticeGuide2011.pdf); *criteria to avoid use of inappropriate medications* (which are discussed more in detail here below); *computer based prescribing systems* and *comprehensive geriatric assessment* (CGA) and management. Most of the available evidence is focused on a single intervention targeting either clinical or pharmacological factors causing DRPs. However, when these approaches were combined, for example, in studies assessing the efficacy of an intervention based on experienced pharmacists performing medication review in the context of a multidisciplinary team, positive effects on patient's health-related outcomes were found. Integration of skills from different healthcare professionals is therefore necessary to address medical complexity of older people. The challenge for future research is to integrate valuable information obtained by existing methods in a complete and global approach targeting all potential factors involved in the onset of DRPs (Onder et al. 2013) (Boxes 23.1 and 23.2).

Box 23.1 Multistep Assessment of Pharmacotherapy

Screening: Detection of subjects at risk of drug-related problems (DRP)

Strategies to prevent DRPs:

- Medication review: 1. identification of all the medications that the patient is taking; 2. drug scheme is screened for DRPs; 3. possible solutions to the DRPs are then discussed with the treating physician and, if possible, with the patient him/herself
- Criteria to avoid use of inappropriate medications
- Computer-based prescribing systems
- Comprehensive geriatric assessment and management (Onder et al. 2013)

Box 23.2 List of Items that Need to Be Checked

- Indication
- Right choice
- Dosage
- Directions
- Drug–drug interactions
- Drug–disease interactions
- Duration
- Adverse drug reactions (Somers et al. 2012)

23.3.2 Prescribing Rules in Older People

When prescribing a drug, there are a number of points to take into account (Box 23.3). Prescribe only where necessary, and consider benefits versus risks. Involve the patient in decisions about their care and respect patient autonomy. Note the patient's age, medical history (especially of any hepatic or renal dysfunction) and any concurrent medication. Think about dosage carefully; manufacturers' recommended doses are based on population studies and assume 'one dose fits all'. However, there are genetic differences (Engen et al. 2006). New drugs are often marketed at the highest therapeutic level to demonstrate effectiveness in large numbers of patients but companies are not required to provide data on lowest effective dose.

Box 23.3 Aspects to Be Taken into Consideration Before Prescribing New Medication

- *Primum non nocere*—First, do no harm.
- *Multimorbidity* and/or frailty.
- Prescribing within limits of competence.
- Evidence-based prescribing.
- Interaction with other drugs.
- Concordance, tolerability and formulation.
- Adverse effects.
- Checking dosages.
- Using prescribing formularies.
- Keeping up to date and following clinical guidelines, where available, from the National Institute for Health and Care Excellence (NICE) or Scottish Intercollegiate Guidelines Network (SIGN).
- Using electronic systems where available that can enhance the safety of prescribing.
- Responsible delegation of prescribing administration and dispensing (General Medical Council 2013, http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp).

23.3.3 Criteria to Avoid Use of Inappropriate Medications

A systematic review by Kaufmann C et al. identified 46 tools to assess appropriateness of prescribing which were published between 1991 and 2013 (Kaufmann et al. 2014). Since the publication of that review in 2014 until now, the updates of some of these tools have been published in addition to several new tools (Tommelein et al. 2016b; O'Mahony et al. 2015, American Geriatrics Society Beers Criteria Update Expert Panel 2015; Renom Guiteras et al. 2015). These tools are categorised as explicit (criterion-based) or implicit (judgement-based) tools.

23.3.3.1 Explicit Tools

Explicit tools or criteria used with prescribing data only or with clinical data are often used to detect inappropriate prescribing. The medication-to-avoid criteria have been the most often used. They are based on lists of potentially inappropriate medications (PIMs), i.e. medications that should be avoided in older people because the risks outweigh the benefits (Spinewine et al. 2007). Various explicit tools are available, although only the Beers criteria and the STOPP/START criteria have been evaluated for predictive validity. Beers criteria, last updated in 2015, identify a list of 53 PIMs or medication classes divided into three categories: PIMs to avoid independent of co-morbidities, PIMs to avoid in older people with certain diseases and syndromes, and medications to be used with caution (Beers et al. 1991, the American Geriatrics Society Beers Criteria Update Expert Panel 2012).

The STOPP criteria for screening PIMs, as well as the START criteria for the detection of potential prescribing omissions of indicated, potentially beneficial drugs medications, updated in 2015, are organised according to physiological systems and include both PIP (80 criteria) and omission of potentially beneficial pharmacotherapy (34 criteria) (Gallagher et al. 2008, O'Mahony et al. 2015). Explicit criteria can be applied with little or no clinical judgement but do not address individual differences between patients. The fact that prevalence of PIMs detected with these criteria has not been consistently associated with poor outcomes in older people might indicate the general limitations of all drug-oriented geriatric prescription tools. Given the fact that older people are a heterogeneous group with regard to drug response, PIM might be needed and well tolerated in some, while others might experience harmful side effects. Accordingly, general lists of drugs to be avoided might classify appropriate drugs as inappropriate. However, based on analysis of the international classification of diseases and consequently the presence of a strong indication, the use of medications in such circumstances cannot explain the high rates of inappropriate medication administration. With regard to their relevance in everyday practice, these criteria generally neither address co-morbidities frequently found in older patients, nor do they take into consideration patient's preferences or previous treatments. Although use of explicit criteria should demonstrate an impact on patient-related outcomes in order to be clinically relevant, no criteria so far have demonstrated their impact on the incidence of ADEs. Explicit criteria have limited transferability between countries due to variations in national prescribing patterns and drug availability. Also, they should be regularly updated in accordance with growing clinical evidence (Spinewine et al. 2007).

23.3.3.2 Implicit Tools

Implicit tools take into account clinical information of the individual patient to judge appropriateness of prescribing. The MAI represents a comprehensive and validated implicit tool (Hanlon et al. 1992). It is a judgement-based process measure of prescribing appropriateness that assesses ten elements of prescribing: indication, effectiveness, dose, correct directions, practical directions, DDI, DDisI, duplication, duration and cost. These elements are assessed based on clinical judgement rather than on objective measures, and the ratings generate a weighted score that serves as a summary measure of prescribing appropriateness. Recently, an adapted version has been published in which the original MAI was changed to cover more

aspects of drug therapy and to reduce the number of questions by grouping certain aspects (Somers et al. 2012). Implicit criteria are time-consuming and more dependent on the user. No single ideal tool exists so far. The choice of a tool may depend on the purpose of use and availability of data. Implementation of such a tool requires that the tool should not only be well designed and comprehensive but also still practical in everyday practice. Integration of assessment tools in electronic decision support systems could be a promising approach. These tools are useful for identifying potentially inappropriate prescribing, although they cannot substitute good clinical decision when treating older patients.

23.3.4 Comprehensive Geriatric Assessment

One of the main challenges regarding therapeutic goals setting in older patients is to assess whether the expected benefits of treatment are superior to the risks in a population with decreased life expectancy and decreased tolerance to stress (Vander Walde et al. 2016). In accordance with the differences in life expectancy, CGA and assessment of multimorbidity is assumed to discriminate between three groups of patients, i.e. fit, unfit and frail (Stauder 2012; Balducci et al. 2000) (Box 23.4) (see also Chapter 26).

Box 23.4 Fit vs. Frail Patients.
Fit patients are functionally independent patients without medically relevant comorbidity (consider full therapy in order to achieve outcomes similar to that of younger patients).
Unfit patients represent the group in between with minor dependencies in instrumental activities of daily living (IADL) and/or one or two comorbidities in the absence of a geriatric syndrome or dependence in activities of daily living (ADL) (consider adapted/tailored therapy including deprescribing).
Frail patients are identified by the presence of at least one of the following: multiple comorbidities, the presence of one or more geriatric syndromes, or dependence in ADL. Most patients aged ≥ 85 years are attributed to this group (consider deprescribing and symptom palliation).

23.4 Clinical Example of 'Good Prescribing' in a Geriatric Patient

Mrs. Van Dyck is 87-year-old widow living in a nursing home. She suffers from Alzheimer-type dementia (Mini Mental State Examination Score, 15/30), depression, type 2 diabetes mellitus, hypertension, atrial fibrillation, osteoarthritis and osteoporosis and history of falls. She is currently on the following drugs: donepezil (10 mg, once daily), paroxetine (20 mg, once daily), metformin (850 mg, twice daily), diltiazem (300 mg, once daily), simvastatin (40 mg, once daily), warfarin (dose depending on international normalised ratio[INR]values), calcium/vitamin D

(1000 mg/880 international units (IU), once daily), alendronic acid (70 mg, once/week), lorazepam (2,5 mg, once daily).

Her blood pressure is 165/88 mmHg and her last HbA1c was 7.3% (56 mmol/mol).

23.4.1 Consider Withdrawal

Lorazepam: Gradual withdrawal should be considered because of risk of prolonged sedation, confusion, disturbed balance and consequent risk of falls.

Paroxetine: Continuation should be re-evaluated. To prevent relapse and recurrence in case of major depression, an antidepressant should be given for at least 6 months after a good initial response is seen. However, the effects of the treatment on, functional, cognitive and social outcomes in addition to the effects on co-morbidities, malnutrition and falls should be considered.

Alendronic acid: Cessation may be considered if the use has continued for 5 years or more because there is a limited benefit to continue the therapy further than 5 years.

Simvastatin: Cessation may be considered given a limited life expectancy of the patient and the balance between drug indication vs. adverse effects.

Metformin: Dose reduction or cessation may be considered since a somewhat higher goal for glycaemic control may be more appropriate for this patient. In older adults with diabetes with very complex/poor health (in this case a patient with Alzheimer-type dementia, living in a nursing home), a HbA1c < 8.5% (69 mmol/mol) is a reasonable treatment goal (American Diabetes Association 2017, http://care.diabetesjournals.org/content/diacare/suppl/2016/12/15/40.Supplement_1.DC1/DC_40_S1_final.pdf). This is in accordance with the finding that lower HbA1c levels are associated with increased hypoglycaemic events without accruing meaningful benefit (it should however be noted that in healthy older adults <7.5% (58 mmol/mol) is regarded as a reasonable treatment goal).

Donepezil: Cessation should be considered given the advanced state of dementia and the fact the patient has already been placed into a nursing home.

23.4.2 Consider Continuation After Reassessment

Calcium and vitamin D supplementation: Continuation should be considered given its safe profile and positive effects on osteoporosis and falls. However, if food intake is sufficient, cessation might be considered.

Warfarin: Continuation is recommended with the target INR between 2.0 and 2.5 for optimal stroke prevention, although the benefit/risk ratio (particularly increased risk of falls and bleeding risk associated with suboptimal INR control) should be repeatedly reassessed.

Diltiazem: Drug continuation may be recommended if needed for blood pressure and rate control. At the same time, a tight blood pressure control and bradycardia (<50 bpm) may be problematic given the high risk for falls.

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