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ESSENTIALS The use of pharmacological agents is often a central component of medical therapy for older people. Medications can relieve symp- toms, improve function, and prevent illness, but they also have the capacity to inflict great harm. Older people are at particular risk of such harms as a result of impaired homeostatic reserve, of al- tered drug metabolism, the presence of multimorbidity and conse- quent polypharmacy, which increases both exposure to potentially harmful agents and the chance of drug–drug interactions. The therapeutic priorities for older, frail people may differ when com- pared to younger, robust patients; limited life expectancy means that attempts to prolong life may become relatively less important than the relief of symptoms and avoidance of side effects and medi- cation burden. Prescribing in younger patients, especially those with single dis- eases, is strongly influenced by evidence collected from randomized controlled trials, reflected in disease-specific guidelines. This ap- proach is much less useful in older patients, when combining guide- lines can lead to contradictory advice in those with multimorbidity, and simply summing the prescribing recommendations from mul- tiple single disease guidelines leads to high medication burdens. Adverse drug events are a major source of ill-health, and unthinking adherence to disease-based guidelines is unlikely to provide overall benefit to older people's health, function, or quality of life. The aim of prescribing for older people is to ensure that prescribing is neither avoided, nor is needlessly excessive, but is appropriate. Appropriate prescribing requires that: • all medicines are prescribed for the purpose of achieving specific therapeutic objectives that have been agreed with the patient • therapeutic objectives are actually being achieved, or there is a reasonable chance they will be achieved in the future • therapy has been optimized to minimize the risk of adverse drug events • the patient is motivated and able to take all medicines as intended The principal risk factors for inappropriate prescribing are polypharmacy related to complex multimorbidity and exposure to multiple prescribers. Tools such as the Screening Tool of Older People's Prescriptions/Screening Tool to Alert to Right Treatment criteria can help with identifying and managing inappropriate pre- scribing. Two complementary Cochrane systematic reviews have shown that deprescribing is beneficial in older people. Introduction The use of pharmacological agents is often a central component of medical therapy for older people. Although medications have an important role to play in the relief of symptoms, the

improve- ment of function, and the prevention of future illness, such agents also have the capacity to inflict great harm. Older people are at particular risk of such harms—as a result of impaired homeo- static reserve, of altered drug metabolism, and the presence of multimorbidity and consequent polypharmacy—increasing both exposure to potentially harmful agents and the chance of drug– drug interactions. The therapeutic priorities for older, frail people may differ when compared to younger, robust patients; limited life expectancy means that attempts to prolong life may become rela- tively less important than the relief of symptoms and avoidance of side effects and medication burden. This chapter addresses these issues that make prescribing in older people challenging, discusses the important emerging healthcare hazard of polypharmacy, but also offers advice on key principles of prescribing, deprescribing, and decision-making to ensure appropriate medication use for older people. Pharmacokinetics and pharmacodynamics in old age The physiological changes seen with ageing impact both the me- tabolism and mechanism of action of drugs. This is particularly salient as multimorbidity in older people is often accompanied by polypharmacy. Despite the advances in drug design, computational pharmacology, and modelling, the current state of knowledge is still a very long way away from understanding the rate, extent, and mechanisms of multidirectional drug–drug, drug–food, and drug–disease interactions in whole-system biology applicable to older people. Furthermore, inter-racial differences in the response 6.7 Drugs and prescribing in the older patient Miles Witham, Jacob George, and Denis O'Mahony

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who have had previous gastro- intestinal surgery or require tube feeding via naso-jejunal or per-cutaneous endoscopic gastrostomy feeding. Older patients are also more likely to have peripheral oedema and therefore transdermal and subcutaneous routes of drug de- livery may also be impaired. The presence of intestinal wall oedema in congestive cardiac failure or hypoalbuminemia may reduce ab- sorption of oral medications (e.g. furosemide). The route of delivery of any drug is therefore a particularly important consideration to make when prescribing for older people. Distribution The key factor that alters drug distribution in older people is in- creased fat in proportion to muscle mass. This therefore increases the volume of distribution (Vd) of lipophilic drugs in relation to body weight while hydrophilic drugs (gentamicin, digoxin, ethanol) have lower Vd and therefore higher plasma concentra- tions, making them more liable to cause toxicity at conventional doses. Despite this, the t½ of hydrophilic drugs is often unchanged as renal/hepatic clearance is often reduced concomitantly. Lipophilic drugs (e.g. haloperidol, amitriptyline, or diazepam) are sequestered in fatty tissue and released at a slow rate, particu- larly after repeated administration. In starvation or other catabolic states, the rate of release of these drugs may accelerate as fat is used as an energy source. Protein binding of drugs is also altered in frail, older people due to the commonly observed reduction in albumin (which is respon- sible for binding of acidic drugs). Therefore free unbound drug levels of acidic drugs such as warfarin, digoxin, and lorazepam tend to be higher in older, frailer patients. α-1 acid glycoprotein (A1AG), which binds to basic drugs, is often increased in illnesses. This would, in theory, have the effect of lowering free drug concen- trations of basic drugs such as diazepam and morphine. However, the consequence of these changes is not fully understood as the ef- fects of protein binding on free drug concentrations are also de- pendent on hepatic and renal clearance. Metabolism Drugs are mainly metabolized in the liver via phase I (oxidation, hydrolysis, reduction) and phase II reactions such as glucuronida tion (which increases water solubility), acetylation and sulphation (which reduce toxicity). The rate of first pass metabolism is thought to decrease with age. The ability of the liver, via first pass metabolism, to extract drugs from the circulation as well as the rate of hepatic blood flow are the major determinants of hepatic drug clearance. Drugs that have high extraction ratios such as propranolol, nifedipine, and pethidine have a higher risk of toxic effects. Nonsteroidal anti-inflammatory (NSAIDs) and opiates are particularly liable to result in toxicity in older people due to a combination of decreased hepatic metabolism and reduced renal excretion. Polypharmacy may lead to cytochrome P450 (CypP450) inter- actions between inducer and inhibitor drugs, which may lead to complex drug–drug and drug–food interactions. Excretion Ageing is associated with reduced renal blood flow, tubular secre- tion, and renal mass. The reduction in muscle mass in older frail people also has an impact on the reliability of serum creatinine as a measure of renal function in older people; alternatives that may be of use include measurement of cystatin C. Current recommenda- tions for drugs mainly excreted via the kidneys are for estimated glomerular filtration rate using the Modified Diet in Renal Disease (MDRD) calculation. The Cockcroft and Gault formula used to calculate creatinine clearance may underestimate renal function in older people compared to eGFR calculated by CKD-EPI and MDRD equations. Excretion of water-soluble drugs such as di- goxin, lithium, and NSAIDs are disproportionately affected by a

 reduction in renal function and therefore more liable to accumu- late to toxic levels when renal function is reduced. Pharmacodynamics The action of a drug on its intended and unintended targets results in its efficacy and/or adverse effects. Impaired homeostasis and the presence of multiple chronic diseases, coupled with changes in re-ceptor binding or affinity may either augment or blunt the effect of a drug in older people. An

example of this would be the use of anti- cholinergic agents in older men with benign prostatic hypertrophy, which may as a side effect cause urinary retention. There are no hard and fast rules that allow for the prediction of altered pharma- codynamics when prescribing in older people. The following are examples of changes that occur during ageing that have clinical im- plications on drug action: • Increased sensitivity to benzodiazepines, tricyclic antidepressants, anticholinergics due to increased volume of distribution and pro- longed half-life. • Reduced β-adrenergic receptor mass and sensitivity, therefore reducing catecholamine responsiveness as well as effectiveness of β-blocker therapy. • Reduced intravascular volume leading to exaggerated hypoten- sive effect of antihypertensive agents. • Increased vitamin K-dependent factors (II, VII, IX, X) inhibition by warfarin in older people, despite no age-related differences in pharmacokinetics of warfarin. Suggested mechanisms include increased intrinsic sensitivity of vitamin K to warfarin in older people and the relative deficiency of vitamin K in older people. The mechanism of action for most of these pharmacodynamic adverse effects is unknown. However, the prescriber should ex- ercise increased caution when prescribing drugs in older people that have a narrow therapeutic index (e.g. theophylline, warfarin, lithium, digoxin, aminoglycoside antibiotics) as fragile compensa- tory homeostatic mechanisms may be quickly overwhelmed due to other seemingly unrelated factors such as pre-existing condi- tions. The advice in prescribing for older people has always been to gradually up-titrate to effect—‘start low and go slow’ as discussed next. There is however a concern that this strategy may result in underdosing and a lack of therapeutic effect and therefore regular review for efficacy as well as side effects is warranted. Pharmacology of drug withdrawal The practice of regular medication review is becoming increasingly important. Polypharmacy is a major cause of illness, as is discussed next in more detail. Patients often accumulate new medications with every admission to hospital and in many instances, courses of treatment intended for a limited time or as a trial end up as chronic repeat prescriptions, increasing the potential for adverse drug events and drug–drug interactions. Medications are also often commenced to treat the side effects of an existing treatment, rather than switching to another agent (e.g. diuretics prescribed for ankle oedema secondary to a dihydropyridine calcium channel blocker). Abrupt withdrawal and rebound effects are often exaggerated in older people due to reduced homeostatic responsiveness and pre- existing disease (e.g. abrupt β-blocker withdrawal and increased frequency of angina). Drug withdrawal may be beneficial—oral hypoglycaemic agents are often linked with hypoglycaemia in older people who have re- duced oral intake. A study of nursing home residents in Sweden showed that the withdrawal of oral hypoglycaemic agents in older patients with tight glycemic control is safe and reduced the risk of hypoglycaemic attacks. Discussions surrounding issues such as long-term benefits of therapy versus quality of life, end-of-life planning, adherence to therapy, and patient preference ought to occur when consid- eration of additional therapy for older people is made. Once a decision is made to reduce therapy, tapering down doses and stopping one medication at a time is ideal, mirroring the ‘start low and go slow’ approach when starting new medications. Long- term use of medications such as benzodiazepines can result in physiological tolerance and dependence. Therefore, monitoring of withdrawal symptoms for central nervous system agents in particular, is crucial. Balancing benefits and harms of prescribing What are the aims of prescribing for older people? The central aim of prescribing for older people is to ensure that prescribing is neither avoided nor is needlessly excessive, but is ap- propriate. Appropriate prescribing requires that: • all medicines are prescribed for the purpose of achieving specific therapeutic objectives that have been agreed with the patient • therapeutic objectives are actually being achieved or there is a reasonable chance they will be achieved in the future • therapy has been optimized to minimize the risk of adverse drug events • the patient is motivated

and able to take all medicines as intended A hallmark of older people is heterogeneity, not only of physiology and function, but also of health beliefs and expectations. No two older people are the same, and it is critical that this heterogeneity is embraced when making prescribing decisions. Before rational prescribing decisions can be made, clinicians need to be clear about the aims of prescribing for an individual older person. For some older people who are in robust health with good phys- ical function, the aim desired by both patient and clinician may be prevention of future illness—and the approach to prescribing may be similar to that adopted in younger patients. However, for many older people, life expectancy may be limited, and the burden of side effects relative to benefit may not be favourable—either due to a lack of benefit, perceived or actual excessive risk or side effects, or a reluctance to add to an already large burden of medicaliza- tion. Still others may not place a high priority on preventing future disease onset, but would still value interventions that forestall de- compensation of existing illnesses, such as heart failure or chronic obstructive pulmonary disease. Clinicians are not adept at antici- pating patients' perceptions, for example, of their quality of life, hence asking patients and carers about their views and wishes is essential. Therefore the approach to prescribing might vary—multiple medications for disease prevention together with medications to relieve multiple symptoms may be desirable in the first instance,

 but perhaps an approach characterized by removal of medications and minimization of intervention in the second instance. The first and most important step in appropriate prescribing for older people is therefore to ascertain their expectations, beliefs, and pref- erences for healthcare intervention. Evidence and guidelines Prescribing in younger patients, especially those with single dis- eases, is strongly influenced by evidence collected from random- ized controlled trials, reflected in disease-specific guidelines. This approach is much less useful in older patients for several reasons. Firstly, most clinical trial evidence is collected in relatively young patients, often with few comorbidities and taking few other medi- cations. Ageism—both overt by using upper age limits in trial proto- cols, and covert, via unnecessarily rigid inclusion and exclusion criteria—remains a significant barrier to providing trial evidence that is applicable to older people, although some progress has been made in recent years. Harms of medications are often poorly re- ported. Although trial evidence may be applicable to some older people, it is a mistake to assume that the balance of risk and benefit in older people is necessarily the same as that seen in trials involving younger people. Older people are usually at higher absolute risk of adverse disease outcomes, hence the absolute benefit of an interven- tion may be greater. However, limited life expectancy may not pro- vide sufficient opportunity for these benefits to be realized. Furthermore, impaired homeostatic reserve, and interactions with other medications mean that the risk of adverse drug events may be correspondingly higher—and in some cases this may out- weigh any benefits. Thus trial evidence garnered in younger pa- tients must be interpreted with caution in informing prescribing decisions in older people, and the more dissimilar the older person is to the trial population, the less useful the trial results are likely to be. Lastly, most clinical guidelines are focused on single diseases, but older people suffer from multimorbidity and hence single dis- ease guidelines may be unhelpful. Combining some guidelines leads to contradictory advice in patients with multimorbidity, and simply summing the prescribing recommendations from mul- tiple single disease guidelines leads to high medication burdens. Anticholinergic burden is a particularly important example of this; many medications have anticholinergic side effects (including some antidepressants, antipsychotics, antimuscarinics, but also drugs such as ranitidine). Following individual guidelines can easily re- sult in a high cumulative anticholinergic burden, which is associ-

ated with an increased risk of falls, cognitive decline, and mortality. The combination of limited life expectancy and multimorbidity also leads to uncertainty as to whether a given medication intervention can change the attributable risk of a given condition in frail, multimorbid patients. A lack of time for an intervention to have an effect (e.g. on death) is one aspect of this uncertainty, but the other issue is whether a reduction in death attributable to a given condition (e.g. heart failure) is simply replaced by a different risk (e.g. death from dementia) with no overall gain in life expectancy. To answer this uncertainty requires data from trials in frail patients with multimorbidity, but such trial data are lacking, as just discussed. It cannot be assumed that benefits seen in more robust patients with single diseases will translate into benefits for frail, multimorbid patients.
Common prescribing risks in older people Although medication side effects can affect any physiological system, there are certain manifestations of harm that are particularly common in older people, and provide a framework for practice. Such effects may be idiosyncratic (comparatively rare in older people), due to off-target effects (effects on physiological systems other than that intended), or on-target (adverse effects as a direct consequence of the intended physiological effect of the drug). An example of the first would be a rash due to antibiotics; an off-target example would be falls due to the central nervous system effect of antimuscarinic medications used for overactive bladder, and an on-target effect would be bleeding due to anticoagulants. Table 6.7.1 outlines some key medication side effects seen in older people.
Table 6.7.1 Selected examples of common harms from medications in older people Clinical problem Medication classes Falls Opioids Benzodiazepines Neuroleptics Antidepressants H1 blockers Hypoglycaemic agents Drugs with anticholinergic effects Anticholinesterase inhibitors Antihypertensives Digoxin Delirium Opioids Benzodiazepines Neuroleptics Antidepressants Drugs with anticholinergic effects Hypoglycaemic agents Steroids Gastrointestinal bleeding NSAIDs Steroids SSRIs Levo-dopa Anticoagulants Impaired renal function ACEi/ARB Aldosterone antagonists Diuretics Aminoglycoside antibiotics Trimethoprim Proton pump inhibitors Electrolyte disturbance ACEi/ARB Aldosterone antagonists Diuretics Trimethoprim Proton pump inhibitors Laxatives Theophylline β-2 agonists Constipation Opiates Drugs with anticholinergic side effects Oral iron Calcium channel blockers Worsening of
heart failure Steroids NSAIDs Tricyclic antidepressants Nondihydropyridine calcium channel blockers Thiazolidinediones ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; SSRI, selective serotonin uptake inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs.

 Principles of prescribing in older people The following principles can help to ensure that prescribing in older people maximizes effectiveness, minimizes risk, and meets the needs and wishes of the patient: • Make the patient central to the decision-making process and align prescribing goals with those of the patient. • Start low, go slow. Start with the lowest possible dose of medi- cation, give adequate time for the medication to work, and in- crease doses in small increments. If side effects occur, reduce the dose to the previous step. Similarly, when stopping medications, reduce the dose gradually to avoid withdrawal effects; this is of particular importance where rebound physiological effect may occur (e.g. with β-blockers, benzodiazepines, antidepressants, or proton pump inhibitors). • Review prescribing and prescribing goals regularly. In particular, new symptoms or illnesses, changes in physical function, or life expectancy should prompt review as patient priorities, risks and benefits may all change. • If a medication is no longer indicated, stop it. An example of this is the inappropriate long-term use of proton pump inhibi- tors; many older people take these medications for years despite having no

evidence of oesophagitis, active peptic ulceration, or symptoms. Proton pump inhibitor use has been associated with multiple potential harms including increased risks of osteopor- osis, enteric infections, pneumonia, hyponatraemia, hypomag- nesaemia, and microscopic colitis. • Use single medications for multiple benefits. For example, if a patient has angina and heart failure, use a β-blocker as a first-line agent, as this will have symptomatic benefit for the angina as well as improving symptoms and prognosis for heart failure. • Avoid treating drug side effects with another medication. An ex- ample here is the aforementioned case of ankle oedema caused by dihydropyridine calcium channel blockers. This common side effect is often treated with diuretic therapy, rather than by stop- ping the offending drug; the consequence is often intravascular volume depletion, orthostatic hypotension, falls, and worsening renal function. • Consider nonpharmacological interventions before adding to medication burden. Such interventions may be at least as ef- ficacious, and may carry considerably less risk. For instance, physiotherapy to improve quadriceps strength is a powerful (and underused) way to improve both pain and function in knee osteoarthritis. A concept that is useful in managing multimorbidity for some older people is to identify the ‘dominant condition’; that is, the illness that impacts overwhelmingly on a patient’s function and quality of life. Examples include advanced dementia, where severe cognitive impairment has an impact far in excess of virtually any other comorbidity, or severe heart failure. Although this concept can help to clarify the thoughts of both the patient and prescriber, it is sometimes difficult to identify a dominant condition, or to disen- tangle which illnesses are causing which symptoms. In such cases, a multifaceted approach to management is essential. In addition, it is worthwhile to try to select interventions that are least disruptive to the lives of older people. This might mean using once-daily formulations (which may make supervised administration easier), selecting therapies requiring less moni- toring such as blood tests, or scheduling treatments so that side effects do not interfere with daily life (e.g. timing of diuretic doses). Appropriate and inappropriate prescribing in older people Potentially inappropriate prescribing encompasses the three inter-related areas of misprescribing, overprescribing, and under prescribing. Misprescribing occurs when drugs are introduced that heighten the risk of an adverse drug event. Increased adverse drug event risk may be the result of incorrect dose, incorrect frequency, of inappropriate or suboptimal mode of drug delivery or inappro- priate duration of drug therapy. Misprescribing also includes the introduction of drugs that increase the risk of adverse drug–drug or drug–disease interaction to an unacceptable level. Overprescribing refers to drug therapy that has no clear indication but is neverthe- less continued without any valid clinical reason. Underprescribing is the omission of appropriate pharmacotherapy for irrational or ageist reasons, resulting in heightened risk to the patient, for example, the omission of long-term anticoagulant therapy in an older patient with chronic atrial fibrillation and concurrent risk factors for stroke. Potentially inappropriate prescribing also refers to the use of a drug that: • has the wrong indication • has no indication • has a high risk of an adverse drug event (i.e. adverse drug–drug or drug–disease interactions) • is unnecessarily expensive • is prescribed for too short or too long a time period The principal risk factors for inappropriate prescribing are polypharmacy and exposure to multiple prescribers. Complex multimorbidity is the principal driver of polypharmacy; indeed, major polypharmacy (i.e. 10 or more daily prescription drugs), may be viewed as the potentially inappropriate prescribing response to complex multimorbidity that results in heightened risk of ad- verse drug–drug and drug–disease interactions. This increased risk of iatrogenic morbidity is now the focus of deprescribing interventions, particularly in frailer multimorbid older people with limited prognosis. Tools such as the Screening Tool of Older People’s Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) criteria can potentially help

with identifying and managing inappropriate prescribing. Potentially inappropriate medications and potential prescribing omissions occur frequently in older people in all clinical settings. Recent studies using both STOPP/START criteria and Beers cri- teria for the detection of both types of events show that poten- tially inappropriate prescribing is commonplace in primary care, hospital care and particularly in extended nursing care settings (Table 6.7.2). While the literature is generally consistent on the high prevalence of potentially inappropriate medications and potential prescribing omissions in older people, it is less clear how best to attenuate their occurrence. This uncertainty about how to tackle potentially in- appropriate medications may, in part, arise from the lack of clear association between potentially inappropriate medications that are defined by Beers criteria and occurrence of adverse drug events in

576 Section 6 Old age medicine large scale studies in the last decade. In contrast, there is a clear association between STOPP criteria-defined potentially inappro- priate medications and adverse clinical outcomes, such as adverse drug events, or decline in physical function in older people who are hospitalized with acute illness. STOPP criteria have been used as an intervention in prospective randomized clinical trials in older people with interesting results. STOPP/START criteria when applied at a single time point to the medication lists of hospitalized acutely ill older people resulted in highly significant improvement in medication appropriate- ness at discharge. The application of STOPP/START criteria also improved underutilization of medication to a highly significant degree at discharge. Importantly, the marked improvements in medication appropriateness and underutilization were maintained at 6 months' follow-up in the intervention population compared to control patients who experienced no significant change throughout the study from randomization to end of follow-up. The number of patients needed to 'treat' with STOPP/START criteria to produce improvement in medication appropriateness (measured using the Medication Appropriateness Index) was just 3 (absolute risk reduc- tion in inappropriate medication was 35.7%); the number of pa- tients needed to treat (NNT) to produce a reduction in underuse of appropriate medication was 5. In another trial involving 359 older residents of a long-term care facility in Israel, application of the STOPP/START criteria at baseline, at 6 and 12 months was compared to standard pharma- ceutical care. Patients in the intervention group experienced significantly lower numbers of daily prescription medicines, sig- nificantly lower monthly prescription costs, and significantly fewer falls compared to control patients. A further trial involving acutely ill hospitalized older people evaluated the effect of STOPP criteria recommendations made by a specialist inpatient geriatric consultation team to attending physicians to discontinue potentially inappropriate medications in addition to the standard geriatric assessment and advice. Control patients received standard geriatric assessment and advice only. The intervention group had twice as many patients with reduction of potentially inappropriate medications at discharge (39.7%) as the control group (19.3%). A fourth trial examined the effect of a single application of STOPP/START criteria to medication lists within 48 hours of hospital admission on incident adverse drug reactions during the index hospitalization in unselected older people with acute un- selected acute illness. Patients under the care of specialist teams, other than Geriatric Medicine, Clinical Pharmacology, Palliative Medicine, and Oncology were eligible for randomization. The re- sults showed a highly significant reduction in incident adverse drugs reactions in the intervention group (12.5%) compared to the control group (23.9%); the absolute risk reduction of 11.4% meant that the number of patients needed to treat to prevent one older patient experiencing a nontrivial incident adverse drug reaction was 9. In the same study, the median monthly medication cost was significantly lower in the intervention group compared to the control group. In contrast to the randomized controlled trial

evidence sup- porting the clinical relevance of STOPP/START criteria, there is no current trial evidence showing that application of Beers criteria as a clinical intervention results in better clinical outcomes. Other tools (e.g. the Fit fOR The Aged (FORTA) tool) are also being developed and are currently being evaluated in trials. Deprescribing in older people Deprescribing can be defined as 'the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values, and preferences'. A review of 31 studies of drug withdrawal in patients aged 65 years and over concluded that antihypertensive, psychotropic and benzodiazepine medications could be withdrawn safely in 20–100% of cases. An Australian study of older patients taking antihypertensive medica- tion demonstrated that over one-third of patients had normal blood pressure one year after discontinuation of antihypertensive therapy. Another study involving community-based patients on long-term benzodiazepines showed that an education programme provided and sustained by community pharmacists led to a reduction in benzodiazepine use of over three-quarters without serious with- drawal problems. Importantly, results in those aged over 80 years and those taking ≥10 daily drugs were no worse than other groups. In two recent complementary Cochrane systematic reviews, deprescribing has been shown to be beneficial in older people. Among frailer older people, deprescribing appeared to be most effective when there was a combination of physician medication review and a proactive palliative approach to pharmacotherapy involving collaboration with patients, their relatives, and primary care physicians. In one study in Israel, applying an algorithm for proactive deprescribing in nursing home residents led to two- thirds of patients taking three drugs per patient less without pa- tient detriment. In the same study, one-year mortality and acute hospitalization rates in intervention patients was approximately half those of control patients. A structured approach to deprescribing has been described as follows:

1. Full medication reconciliation (i.e. determine all drugs taken by the patient and why).
2. Estimate overall drug-related risk in the patient.
3. Consider each drug as a possible candidate for exclusion on the basis of: (a) Valid indication (b) Being prescribed to counteract the adverse effects of another drug (prescribing cascade) Table 6.7.2 Prevalence of potentially inappropriate medications and potential prescribing omissions in various clinical settings Primary care Hospital Nursing home Potentially inappropriate medication prevalence (STOPP criteria, version 1) 21% 34–50% 60–70% Potentially inappropriate medication prevalence (Beers criteria, version 3) 13–18% 25–32% 37–53.4% Potential prescribing omission prevalence (START criteria, version 1) 22.7% 57.9% 70%

 (c) Actual/potential harm of a drug exceeding actual/potential benefit (d) Loss of efficacy or symptoms completely resolved (e) Likelihood to yield benefit during the patient's estimated re- maining lifespan (f) Overall medication burden 4) Prioritization of drugs to remove from the patient's prescription. 5) Proceed with and monitor structured drug discontinuation programme, removing one drug at a time and observing for overall improvement or worsening of the patient's condition. Other interventions for improving prescribing in older people There are several other ways of improving the overall quality of prescribing in older people. These include:

1. Comprehensive geriatric assessment (CGA), which includes structured scrutiny of older patients' medications, their mode of delivery and acceptability, and adherence.
2. Structured pharmacist review of medication with feedback to prescribers. This can occur as an opportunistic review (level 0), can be limited to a technical review to remove unused items or switch to more cost-effective items (level 1), a review of medi- cations and conditions with patient notes (level 2), or a full re- view with both notes and the patient present (level 3). Given the complexity of prescribing in older people, level 3 reviews are to be preferred.
3. Clinical decision support software systems with automated screening for adverse drug–drug and drug–disease interactions.
4. Medication adherence interventions. The evidence base to support the overall clinical relevance of comprehensive geriatric assessment is now very strong indeed (see Chapter 6.4). Two recent systematic reviews of the efficacy of comprehensive geriatric assessment in the acute hospital setting concluded that it significantly reduces mortality, nursing home re- quirement, functional dependency, and re-admission. The positive impact of pharmacist delivered medication review is stronger when it is delivered in the context of multidisciplinary team working. Computerized physician order entry and clinical decision support system approaches to prescribing optimization have been in exist- ence for approximately 20 years with varying efficacy when applied to older patients. The impact of various interventions to improve medication ad- herence in older people has been evaluated by meta-analysis and systematic review. Several interventions such as medication review, written and verbal patient education, drug regime simplification, drug administration aids, patient-friendly packaging and label- ling, medication reminders, home visits, and follow-up have been shown to significantly improve medication adherence. However, the impact of these adherence-promoting interventions on positive health outcomes and health service utilization is unclear. Conclusion Safe and effective prescribing in older people requires both ex- pert knowledge of drug effects, side effects, and interactions, but also in-depth knowledge about a patient's multimorbidity, life ex- pectancy, and their therapeutic agenda. Adverse drug events are a major source of ill- health, and unthinking adherence to disease- based guidelines is unlikely to provide overall benefit to older people's health, function, or quality of life. Careful consideration of the aims of new prescribing, a cautious approach to uptitration of medication, use of nonpharmacological alternatives, regular re- view, and deprescribing form the basis of a safe and effective ap- proach to prescribing in older people. The use of appropriateness tools such as the STOPP/START criteria can help to improve the quality of prescribing for older people, and the use of such tools along with comprehensive assessment, decision support software and the expert input of pharmacy staff can help prescribers to navi- gate the often difficult passage between overtreatment and thera- peutic nihilism. FURTHER READING Alldred DP, et al. (2013). Interventions to optimise prescribing for older people in care homes. Cochrane Database Syst Rev, 2, CD009095. Dumbreck S, et al. (2015). Drug–disease and drug–drug inter- actions: systematic examination of recommendations in 12 UK national clinical guidelines. BMJ, 350, h949. Ellis G, et al. (2011). Comprehensive geriatric assessment for older adults admitted to hospital. Cochrane Database Syst Rev, 7, CD006211. Frankenthal D, et al. (2014). Intervention with the screening tool of older persons potentially inappropriate prescriptions/screening tool to alert doctors to right treatment criteria in elderly residents of a chronic geriatric facility: a randomized clinical

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