INTRODUCTION — Optimizing drug therapy is an essential part of caring for an older person. The process of prescribing a medication is complex and includes: deciding that a drug is indicated, choosing the best drug, determining a dose and schedule appropriate for the patient's physiologic status, monitoring for effectiveness and toxicity, educating the patient about expected side effects, and indications for seeking consultation.

Avoidable adverse drug events (ADEs) are the serious consequences of inappropriate drug prescribing. The possibility of an ADE should always be borne in mind when evaluating an older adult individual; any new symptom should be considered drug-related until proven otherwise.

Prescribing for older patients presents unique challenges. Premarketing drug trials often exclude geriatric patients and approved doses may not be appropriate for older adults [1]. Many medications need to be used with special caution because of age-related changes in pharmacokinetics (ie, absorption, distribution, metabolism, and excretion) and pharmacodynamics (the physiologic effects of the drug).

Particular care must be taken in determining drug doses when prescribing for older adults. An increased volume of distribution may result from the proportional increase in body fat relative to skeletal muscle with aging. Decreased drug clearance may result from the natural decline in renal function with age, even in the absence of renal disease [2]. Larger drug storage reservoirs and decreased clearance prolong drug half-lives and lead to increased plasma drug concentrations in older people.

As examples, the volume of distribution for diazepam is increased, and the clearance rate for lithium is reduced, in older adults. The same dose of either medication would lead to higher plasma concentrations in an older, compared with younger, patient. Also, from the pharmacodynamic perspective, increasing age may result in an increased sensitivity to the effects of certain drugs, including benzodiazepines [3-6] and opioids [7].

Hepatic function also declines with advancing age, and age-related changes in hepatic function may account for significant variability in drug metabolism among older adults [8]. Especially when polypharmacy is a factor, decreasing hepatic function may lead to adverse drug reactions (ADRs).

A stepwise approach to optimized prescribing of drug therapy for older adults will be reviewed here. Drug treatments for specific conditions in the older population are discussed separately.

MEDICATION USE BY OLDER ADULTS — Medications (prescription, over-the-counter, and herbal preparations) are widely used by older adults.
Prescription medications — A survey in the United States of a representative sampling of 2206 community-dwelling adults (aged 62 through 85 years) was conducted by in-home interviews and use of medication logs between 2010 and 2011 [9]. At least one prescription medication was used by 87 percent. Five or more prescription medications were used by 36 percent, and 38 percent used over-the-counter medications.

In a sample of Medicare beneficiaries discharged from an acute hospitalization to a skilled nursing facility, patients were prescribed an average of 14 medications, including over one-third with side effects that could exacerbate underlying geriatric syndromes [10].

Herbal and dietary supplements — Use of herbal or dietary supplements (eg, ginseng, ginkgo biloba extract, and glucosamine) by older adults has been increasing, from 14 percent in 1998 [11] to 63 percent in 2010 [9]. One study in over 3000 ambulatory adults 75 years of age or older in four states in the United States found that almost three-quarters used at least one prescription drug and one dietary supplement [12]. Often, clinicians do not question patients about use of herbal medicines and patients do not routinely volunteer this information. In one United States survey, three-quarters of respondents aged 18 years and older reported that they did not inform their clinician that they were using unconventional medications [13].

Herbal medicines may interact with prescribed drug therapies and lead to adverse events, underscoring the importance of routinely questioning patients about the use of unconventional therapies. Examples of herbal-drug therapy interactions include ginkgo biloba extract taken with warfarin, causing an increased risk of bleeding, and St. John's wort taken with serotonin-reuptake inhibitors, increasing the risk of serotonin syndrome in older adults [14]. A study of the use of 22 supplements in a survey of 369 patients aged 60 to 99 years found potential interactions between supplements and medications for 10 of the 22 supplements surveyed [15]. (See "Overview of herbal medicine and dietary supplements", section on 'Herb-drug interactions'.)

Many older adults receive their information about herbal products from the internet. Eighty percent of 338 retail web sites identified in a search of the eight most widely used herbal supplements (ginkgo biloba, St. John's wort, echinacea, ginseng, garlic, saw palmetto, kava, and valerian root) made at least one health claim suggesting that the therapy could treat, prevent, or even cure specific conditions [16].

QUALITY MEASURES OF DRUG PRESCRIBING — Multiple factors contribute to the appropriateness and overall quality of drug prescribing. These include avoidance of inappropriate medications, appropriate use of indicated medications, monitoring for side effects and drug levels, avoidance of drug-drug interactions, and involvement of the patient and integration of patient values [17].

Measures of the quality of prescribing often focus on one or some of these factors, but rarely on all. Furthermore, the predictive value of these measures of "quality of prescribing" in determining important long-term outcomes of care have not been determined. Approaches to decrease inappropriate prescribing in older adults include educational interventions, computerized order entry and decision support, multidisciplinary team care led by physicians, clinical pharmacists, and combinations of these approaches. Available data for these interventions generally show significant improvements in inappropriate prescribing but mixed results for health outcomes or costs [17,18]. A 2016 systematic review of eight studies of different prescribing interventions in long-term care homes (medication review, case conferences, staff education, clinical decision support technology, and/or some combination of these) showed no effect of the interventions on hospital admissions, adverse drug events (ADEs), and mortality [18]. The studies that evaluated medication-related problems, appropriate prescribing, or cost of medication showed some evidence that interventions helped the
recognition and solving of medication problems. A previous 2008 systematic review of 10 studies of computerized physician order entry with clinical decision support showed a mixed effect on reduction in ADEs, with five studies that showed a statistically significant reduction in ADEs, four that showed nonsignificant decrease, and one study that showed no impact on rate of ADEs [19].

POLYPHARMACY — Polypharmacy is defined simply as the use of multiple medications by a patient. The precise minimum number of medications used to define "polypharmacy" is variable, but generally ranges from 5 to 10 [20]. While polypharmacy most commonly refers to prescribed medications, it is important to also consider the number of over-the-counter and herbal/supplements used.

The issue of polypharmacy is of particular concern in older people who, compared with younger individuals, tend to have more disease conditions for which therapies are prescribed. It has been estimated that 20 percent of Medicare beneficiaries have five or more chronic conditions and 50 percent receive five or more medications [21]. Among ambulatory older adults with cancer, 84 percent were receiving five or more and 43 percent were receiving 10 or more medications, in one study [22].

The use of greater numbers of drug therapies has been independently associated with an increased risk for an adverse drug event (ADE), irrespective of age [23], and increased risk of hospital admission [24,25]. However, it is difficult to eliminate the impact of confounding factors in considering the relationship between polypharmacy and a variety of outcomes in observational studies [26].

There are multiple reasons why older adults are especially impacted by polypharmacy:

- Older individuals are at greater risk for ADEs due to metabolic changes and decreased drug clearance associated with aging; this risk is compounded by increasing numbers of drugs used.

- Polypharmacy increases the potential for drug-drug interactions and for prescription of potentially inappropriate medications [27].

- Polypharmacy was an independent risk factor for hip fractures in older adults in one case-control study, although the number of drugs may have been an indicator of higher likelihood of exposure to specific types of drugs associated with falls (eg, central nervous system [CNS]-active drugs) [28].

- Polypharmacy increases the possibility of "prescribing cascades" [29]. A prescribing cascade develops when an ADE is misinterpreted as a new medical condition and additional drug therapy is then prescribed to treat this medical condition. (See 'Prescribing cascades' below.)

- Use of multiple medications can lead to problems with adherence in older adults, especially if compounded by visual or cognitive impairment. A 2017 systematic review of observational studies suggested that drug regimen complexity is associated with medication nonadherence [24].

A balance is required between over- and under-prescribing. Multiple medications are often required to manage clinically complex older adults. Clinicians are often challenged with the need to match the complex needs of their older patients with those of disease-specific clinical practice guidelines. For a hypothetical older female patient with chronic obstructive pulmonary disease, type 2 diabetes, osteoporosis, hypertension, and osteoarthritis, clinical practice guidelines would recommend prescribing 12 medications for this individual [30].

A more systematic approach is required to guide the tailoring of medication regimens to the needs of
individuals. One important principle is to match the medication regimen to the patient's condition and goals of care. This includes a careful consideration of the medications that should be discontinued or substituted [31] (table 1).

It is particularly important to reconsider medication appropriateness late in life. A model for appropriate prescribing for patients late in life has been proposed [32] (table 2). The process considers the patients’ remaining life expectancy and the goals of care in reviewing the need for existing medications and in making new prescribing decisions. For example, if a patient's life expectancy is short and the goals of care are palliative, then prescribing a prophylactic medication requiring several years to realize a benefit may not be considered appropriate. This is increasingly being recognized as an important consideration when managing individuals with advanced dementia [33]. Additionally, therapeutic medications (e.g., antibiotics for pneumonia) may not increase comfort or quality of life when palliative care is the objective [34].

INAPPROPRIATE MEDICATIONS — Various criteria have been developed by expert panels in Canada [35] and in the United States [36-41] to assess the quality of prescribing practices and medication use in older adult individuals. The most widely used criteria for inappropriate medications are the Beers criteria. (See 'Beers criteria' below.)

In another approach, a Drug Burden Index has been modelled incorporating drugs with anticholinergic or sedative effects, total number of medications, and daily dosing [42,43]. An increased drug burden for anticholinergic and sedative medications was associated with impaired performance on mobility and cognitive testing in high-functioning community-based older adults. Zolpidem, in particular, was implicated in 21 percent of emergency department visits for adverse drug events (ADEs) related to psychiatric medication among adults 65 years and older [44].

Total number of medications was not associated with impaired performance when sedatives and anticholinergics were excluded [42,43]. A high Drug Burden Index has been correlated with increased risk for functional decline in community dwellers [43] and with increased risk of falls in residents in long-term care facilities [45].

Anticholinergic activity — Anticholinergic medications are associated with multiple adverse effects to which older individuals are particularly susceptible. Nonetheless, an analysis of United States medication expenditures between 2005 and 2009 found that 23.3 percent of community-dwelling persons >65 years with dementia were prescribed medications with clinically significant anticholinergic activity (AA) [46].

Adverse effects associated with anticholinergic use in older adults include memory impairment, confusion, hallucinations, dry mouth, blurred vision, constipation, nausea, urinary retention, impaired sweating, and tachycardia. A case-control study found an association between anticholinergic use and risk of community-acquired pneumonia [47]. Anticholinergics can precipitate an acute glaucoma episode in patients with narrow angle glaucoma and acute urinary retention in patients with benign prostatic hypertrophy. Specific studies of the relationship between dementia and anticholinergic use include the following:

- In a population study of 6912 men and women 65 years and older, those taking anticholinergic drugs were at increased risk for cognitive decline and dementia and risk decreased with medication discontinuation [48].

- In a population of 3434 men and women age 65 and older in one health care setting, who had no baseline dementia and who were followed for 10 years, the risk of dementia and Alzheimer's disease...
increased in a dose-response relationship with use of anticholinergic drug classes (primarily first-generation antihistamines, tricyclic antidepressants, and bladder antimuscarinics) [49].

- In another population of 13,004 individuals aged 65 and older, use of anticholinergic medications was also shown to be associated with greater decline in cognition as measured by the Mini-Mental State Examination [50]. In addition, anticholinergic medication use was associated with increased mortality over a two-year period after adjustment for multiple factors, including comorbid health conditions.

Multiple scales, including the Drug Burden Index [42], have been developed to identify the anticholinergic burden of medications. For nine scales evaluated in one study, a higher score was associated with increased risk for hospitalization and length of stay, falls, and medical utilization [51]. A listing of medication classes that contain significant AA is shown in a table (table 3).

A study measured the in vitro AA of 107 medications commonly used in older adults [52]. At usual doses, AA was most significantly elevated for amitriptyline, atropine, clozapine, dicyclomine, doxepin, L-hyoscyamine, thioridazine, and tolterodine. AA also was increased for chlorpromazine, diphenhydramine, nortriptyline, olanzapine, oxybutynin, and paroxetine. It should be noted, however, that higher doses of an agent with relatively low or moderate AA can produce significant AA effects. Additionally, the cumulative effects of more than one agent with low AA can produce significant AA effects.

Alternative drugs with lower AA are available in many classes represented by these drugs. However, adverse drug reactions (ADRs) other than AA should also be taken into account in weighing the clinical benefits of possible substitutions (eg, dyskinesias and sedation with haloperidol and perphenazine).

Beers criteria — The Beers criteria, initially developed by an expert consensus panel in 1991 to target nursing home residents, are the most widely cited criteria used to assess inappropriate drug prescribing [36]. The panel produced a list of medications considered inappropriate for older patients, either because of ineffectiveness or high risk for adverse events.

The original Beers criteria have been revised in 1997, 2003, 2012, and most recently in 2015 [37,38,53,54]. The 2015 revised Beers criteria are available through the American Geriatrics Society website. The criteria include over 50 medications designated in one of three categories: those that should always be avoided (eg, barbiturates, chlorpropamide); those that are potentially inappropriate in older adults with particular health conditions or syndromes; and those that should be used with caution. New additions since 2012 are a table of non-antiinfective drug interactions and a table of non-antiinfective medications to avoid or adjust for decreased renal function [54]. Some notable changes in the 2015 listings are removal of loratadine from the list of medications with strong anticholinergic properties; a more liberal renal threshold (now creatinine clearance <30 rather than <60 mL/min) for withholding nitrofurantoin; avoidance of long-term proton pump inhibitors because of risk of Clostridium difficile infections and bone loss; and stricter guidelines to avoid antipsychotics for behavioral problems unless other options have failed and the older adult is threatening harm to self or others.

Several studies, using older versions of the Beers criteria, have identified that use of drugs identified as "inappropriate" was widespread in the United States, Canada, and Europe [55-57]. In a sample of community-dwelling older adults in the United States, 43 percent used at least one medication that would be deemed potentially inappropriate by the updated Beers criteria, with nonsteroidal antiinflammatory drugs (NSAIDs) being the most common [58]. Another study, using Medicare data and the 2012 Beers criteria, found that the point prevalence in each calendar month of potentially inappropriate medications used in
adults ≥65 years was 34.2 percent in 2012 [59].

Some of the inappropriate drug therapies identified on the Beers list are available as over-the-counter products [60]. This reinforces the need to always consider over-the-counter drug therapies when reviewing a patient's medications and to educate individuals on potential problems that can arise from the use of over-the-counter preparations.

The Beer's criteria are increasingly being used to monitor quality of care for older adults. The validity of these consensus-derived criteria in predicting adverse outcomes therefore is becoming increasingly more important. Studies of earlier versions of the Beers criteria found that while the criteria did predict adverse outcomes, some medications that were not on the earlier criteria correlated more closely with adverse outcomes:

- Data from the 1996 Medical Expenditure Panel survey showed that risks of hospitalization and death were greater for nursing home patients who had been prescribed medications defined as potentially inappropriate by the 2003 combined Beers criteria [61].

- A systematic review of 18 retrospective cohort studies found that for patients >65 years old in the community setting, inappropriate medication use (defined by Beers criteria 1991, 1997, and 2003) was associated with increased hospitalization rates but not mortality; for patients in the nursing home setting, the relationship between inappropriate medications and hospitalization rates was inconclusive [62].

- A study that used electronic data to survey ADEs associated with emergency department visits for patients ≥65 years of age found that drugs meeting Beers criteria for always potentially inappropriate accounted for 3.6 percent (95% CI 2.8-4.5 percent) of the estimated 178,000 visits [63]. Three medications not on the Beers list at the time of the study (warfarin, digoxin, and insulin) accounted for 33.3 percent (95% CI 27.8-38.7 percent) of the visits, and medications in the general class of anticoagulants or antiplatelet agents, antidiabetic agents, and narrow therapeutic index agents accounted for nearly half of all visits, though were prescribed in only 9.4 percent of patients seen.

- Similar methodology was used by the same group to evaluate ADEs resulting in emergency hospitalizations among older Americans [64]. Four types of medication (warfarin, insulin, oral antiplatelet agents, and oral hypoglycemics) accounted for 67.0 percent of the ADEs, while 6.6 percent of the hospitalizations were attributed to Beers-criteria potentially inappropriate medications.

Other criteria sets — The Screening Tool of Older Person's Prescriptions (STOPP) criteria, another tool for identifying inappropriate prescribing, were introduced in 2008 [65-67]. The 2003 Beers criteria have been compared with the Screening Tool of Older Person's Prescriptions (STOPP); STOPP and Beers criteria overlapped in several areas, but earlier versions of the Beers criteria used in this comparison contained some drugs no longer in common use, and STOPP includes consideration of drug-drug interactions and duplication of drugs within a class. In two studies, STOPP identified a significantly higher proportion of older people requiring hospitalization as a result of a medication-related adverse event than did the 2003 Beers criteria [65,67]. In a cluster randomized trial in Ireland, presenting attending physicians with potentially inappropriate medications based on the STOPP/START (Screening Tool to Alert doctors to the Right Treatment) criteria reduced the number of adverse drug events and medication costs during the index hospitalization, but did not reduce length of stay [68].

The FORTA (Fit FOR The Aged) list identifies medications rated in four categories (clear benefit; proven but
limited efficacy or some safety concerns; questionable efficacy or safety profile, consider alternative; clearly avoid and find alternative) with ratings based on the individual patient's indication for the medication [69]. The tool, developed in Germany, has undergone consensus validation with a panel of geriatricians [70], but studies of its impact on clinical outcomes are ongoing.

**Health care financing administration** — The Centers for Medicare and Medicaid Services drug utilization review criteria target eight prescription drug classes (digoxin, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, H2 receptor antagonists, NSAIDs, benzodiazepines, antipsychotics, and antidepressants) and focus on four types of prescribing problems (inappropriate dose, inappropriate duration of therapy, duplication of therapies, and potential for drug-drug interactions). In one study, 19 percent of 2508 community-dwelling older adults were using one or more medications inappropriately; NSAIDs and benzodiazepines were the drug classes with the most potential problems [40].

**Assessing Care of Vulnerable Elders project** — Another expert panel has identified quality indicators for appropriate medication use as part of the Assessing Care of Vulnerable Elders (ACOVE) project [71,72]. These indicators begin with practical suggestions on how to improve prescribing practices:

- Document the indication for a new drug therapy
- Educate patients on the benefits and risks associated with the use of a new therapy
- Maintain a current medication list
- Document response to therapy
- Periodically review the ongoing need for a drug therapy

In addition, these indicators specify drug therapies that either should not be prescribed for older adults or that warrant careful monitoring after they have been initiated (table 4).

**UNDERUTILIZATION OF APPROPRIATE MEDICATION** — Much attention has been paid to over-prescribing for older adults; under-prescribing appropriate medications is also of concern. Prescribing strategies that seek to simply limit the overall number of drugs prescribed to older adults in the name of improving quality of care may be seriously misdirected.

Clinicians may be better at avoiding over-prescribing of inappropriate drug therapies than at prescribing indicated drug therapies. As an example, one study of older adults (n = 372) in two managed care organizations found that 50 percent had not been prescribed some recommended therapy, while only 3 percent were prescribed medications classified as inappropriate [73]. However, under- and overutilization of medications were equally prevalent in another study [74]. In a US Department of Veterans Affairs (VA) outpatient population, mean age 75 years (n = 196), inappropriate medications were documented for 65 percent and medication underuse for 64 percent; simultaneous under and overutilization occurred in 42 percent of patients.

START (Screening Tool to Alert doctors to the Right Treatment) is a set of 22 validated criteria, developed by a consensus process involving experts in geriatric pharmacootherapy, aimed to identify potential prescribing omissions in older hospitalized patients [75]. One or more potential prescribing omissions was identified in nearly 60 percent of patients in one study.

However, it should also be recognized that determination of "under-prescribing" is based on guidelines that address individual disease entities, while most geriatric patients have multiple conditions [21]. As an example, a patient with a myocardial infarction, history of diabetes, and elevated lipids would require a beta-blocker,
angiotensin-converting enzyme (ACE) inhibitor, aspirin, statin, and a hypoglycemic medication. Accordingly, many older adults need to take six or more essential medications. In this context, clinicians may make informed decisions to “under-prescribe” to foster compliance with essential medications, limit drug interactions, and prioritize health benefits for active treatment of serious conditions over preventive therapies or conditions that have less impact on quality of life.

Factors leading to unintended underutilization include clinicians not recognizing medication benefit in the older population, affordability, and dose availability.

**Medication effectiveness** — Studies of drug effectiveness specifically often exclude the geriatric population due to concerns with comorbidities and side effects, causing difficulty in interpretation of study results. Therefore, the benefit of treatment for older adults, especially for preventive purposes, may not be established or may not be recognized by prescribing clinicians. As an example, in a study of statin use for secondary prevention in patients over age 66, the likelihood of being prescribed statin therapy declined 6.4 percent for every year of age; overall, only 19 percent of patients in this high-risk population had been prescribed a statin [76].

**Affordability** — A prescription may be written but not filled, or filled and not taken regularly, due to financial considerations. This may be a particular problem in countries where there is no universal insurance coverage for drug therapy for older adults.

Enhanced drug coverage for older adults can be a powerful incentive to improve the use of beneficial therapies. A comparison of two groups of Medicare patients, as an example, found that statin use was 4.1 percent in patients without drug coverage and 27 percent in those with drug benefits [77]. Significant utilization differences between insured and uninsured patients were seen even for the use of inexpensive medications such as beta-blockers and nitrates.

Cost-related medical noncompliance affected almost 30 percent of disabled Medicare enrollees in 2004, and noncompliance rates were significantly higher for patients with multiple comorbidities [78].

Additional information on the affordability of medications can be found elsewhere in UpToDate. (See "Patient education: Reducing the costs of medicines (Beyond the Basics)".)

**Dose availability** — Older individuals often require lower than usual doses of medications, especially at initiation. If medications are not readily available in prescribed doses, the need to split tablets may make it more difficult for patients to take beneficial drug therapy [79].

**ADVERSE DRUG EVENTS** — A number of factors in older individuals contribute to their increased risk for developing a drug-related problem. These include frailty, coexisting medical problems, memory issues, and use of multiple prescribed and non-prescribed medications [80].

Drug-related hospitalizations account for 2.4 to 6.5 percent of all medical admissions in the general population; the proportion is much higher for older patients [81-83]. In the United States, it is estimated that annually from 2007 to 2009 there were 99,628 emergency hospitalizations for adverse drug events (ADEs) in individuals 65 years and older, with two-thirds due to unintentional overdoses [64]. A meta-analysis found a fourfold increase in the rate of hospitalization related to ADEs in older adults compared with younger adults (16.6 versus 4.1 percent); it was estimated that 88 percent of the ADE hospitalizations among older adults were preventable, compared with 24 percent among young persons [84].
Adverse drug reactions (ADRs) are noxious responses to drugs used in usual doses for treatment or prevention of disease. ADEs are any injury that occurs from a drug, including noxious responses, drug administration errors, and any other circumstances that lead to an injury.

**Prescribing cascades** — Prescribing cascades occur when a new drug is prescribed to treat symptoms arising from an unrecognized ADE related to an existing therapy [29]. The patient is then at risk for developing additional ADEs related to the new and potentially unnecessary treatment (table 5). Older adults with chronic disease and multiple drug therapies are at particular risk for prescribing cascades.

Drug-induced symptoms in an older person can be easily misinterpreted as indicating a new disease or attributed to the aging process itself rather than the drug therapy. This misinterpretation is particularly likely when the drug-induced symptoms are indistinguishable from illnesses that are common in older persons. Selected examples of prescribing cascades are described below.

- One of the best recognized examples of a prescribing cascade relates to the initiation of anti-Parkinson therapy for symptoms arising from use of drugs such as antipsychotics [85-87] or **metoclopramide** [88]. The anti-Parkinson drugs can then lead to new symptoms, including orthostatic hypotension and delirium.

  In a case-control study of 3512 Medicaid patients (age 65 to 99 years), patients who had received an antipsychotic medication in the preceding 90 days were 5.4 times more likely to be prescribed anti-Parkinson therapy than patients who had not received an antipsychotic (95% CI 4.8-6.1) [85].

- Some prescribing cascades may be less obvious, especially for drugs whose adverse events are not as commonly recognized. As an example, cholinesterase inhibitors (eg, **donepezil**, **rivastigmine**, and **galantamine**) are commonly used for the management of dementia symptoms in older adults. The adverse events associated with these drugs can be viewed as the reverse of those that might be expected with anticholinergic therapies. Accordingly, while anticholinergic therapies may cause constipation and urinary retention, cholinesterase inhibitors may cause diarrhea and urinary incontinence. A prescribing cascade occurs when the prescription of a cholinesterase inhibitor is followed by a prescription for an anticholinergic therapy (eg, **oxybutynin**) to treat incontinence.

A retrospective cohort study in older adults in Canada (n = 44,884) found that the risk of treatment with an anticholinergic medication for urinary incontinence was greater for patients who had received a cholinesterase inhibitor (adjusted hazard ratio 1.53; 95% CI 1.39-1.72) [89]. This study suggests that clinicians should consider the possible contributing role of cholinesterase inhibitors in new-onset or worsening urinary incontinence.

**Drug-drug interactions** — Older adults are particularly vulnerable to drug-drug interactions because they often have multiple chronic medical conditions requiring multiple drug therapies. The risk of an adverse event due to drug-drug interactions is substantially increased when multiple drugs are taken [90-94]. As an example, the risk of bleeding with **warfarin** therapy is increased with coadministration of selective and nonselective nonsteroidal antiinflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors, **omeprazole**, lipid-lowering agents, **amiodarone**, and **fluorouracil** [90].

A case control study from Canada evaluated hospitalizations for drug-related toxicity in a population of older patients who had received one of three drug therapies: **glyburide**, **digoxin**, or angiotensin-converting enzyme (ACE) inhibitor [94]. Hospitalization for hypoglycemia was six times more likely in patients who had received...
co-trimoxazole. Digoxin toxicity was 12 times more likely for patients who had been started on clarithromycin. Hyperkalemia was 20 times more likely for patients who were treated with a potassium-sparing diuretic.

Care must be taken when prescribing any medication, especially for the older individual, to review existing medications and consider potential drug interactions.

Dose-related adverse drug events — ADEs are often dose-related. Examples include:

- A case-control study from the 1980s related risk of hip fracture in a Medicaid population with use and dose of psychotropic drugs [95]. A dose-related effect was seen for use of long half-life hypnotic-anxiolytics, tricyclic antidepressants, or neuroleptic therapy, and hospitalization for hip fracture.

- A study of people 65 years and older in Quebec (n >250,000) found that more than a quarter (27.6 percent) were dispensed at least one prescription for a benzodiazepine [96]. The risk of injury was dose-related for some benzodiazepines (oxazepam, flurazepam, and chlordiazepoxide), though not for alprazolam.

- Dose of benzodiazepine, but not elimination half-life, was related to risk for hip fracture in a case-control study of adults aged 55 years and older from the Netherlands [6].

Renal impairment — A common cause of dose-related adverse events in older adults is failure to properly adjust doses for renal insufficiency. Renal impairment becomes more common with advancing age. For patients with stable renal function, creatinine clearance can be estimated according to published formulas which factor age into the calculation (calculator 1). Because of decreased muscle mass in older adults, however, serum creatinine levels may not adequately reflect renal function; many older patients with a normal creatinine nonetheless have modestly impaired renal function. In one study, 40 percent of almost 10,000 older adults living in long-term care were found to have renal insufficiency [97]. In a community population over age 65 in France, the prevalence of renal insufficiency (estimated glomerular filtration rate [GFR] <60 mL/min/1.73 m²) was 13.7 percent using the MDRD equation and 36.9 percent using the Cockcroft-Gault formula [98]. (See "Assessment of kidney function").

Dosing guidelines for decreased creatinine clearance are available to calculate dose adjustments for medications that are cleared through the kidney [99]. The list of medications is long and includes many antibiotics. In a community population, 52 percent of adults over age 65 with mild renal insufficiency were taking medications that required dose adjustment for low GFR; antihypertensives, fibrates, sedative/hypnotic, and anxiolytic medications accounted for most of these drugs [98]. The drug database (Lexi-Comp) available through UpToDate includes appropriate dose adjustments for renal function and for older adults, and can be accessed by searching on any individual drug. As a general rule, the initial dose for starting medications in older adults should be significantly reduced, and titrated up as tolerated by monitoring side effects or drug levels.

Decision aids have been moderately effective in decreasing the percentage of in-hospital prescriptions written with inappropriate adjustments for renal status (46 to 33 percent) [100].

Adverse drug events in long-term care setting — Long-term care residents are at a particularly high risk for developing adverse events [101]. The average United States nursing home resident uses seven to eight different medications each month, and about one-third of residents have monthly drug regimens of nine or more medications [102].
A study of ADEs in two large academic long-term care facilities in the United States and Canada found 815 ADEs occurring during 8336 resident months [101]. The overall rate of ADEs was 9.8 per 100 resident-months; 42 percent of the ADEs were deemed preventable. Of the more serious adverse events, 61 percent were deemed preventable. The more serious the adverse event, the more likely it was to be considered potentially preventable. These rates were approximately four-times higher than had been previously reported [103] but may reflect the better documentation of ADEs at these institutions.

Preventable ADEs were most frequently associated with atypical antipsychotics and warfarin therapy (table 6). Neuropsychiatric events (confusion, oversedation, delirium), hemorrhagic events, and gastrointestinal events were the most frequent types of ADEs in the long-term care facilities studied (table 7). In a 12-month observational study of 490 long-term care residents taking warfarin in 25 nursing homes, there were 720 ADEs (625 minor, 82 serious, and 13 life-threatening); 57 percent of the serious events were considered preventable [104].

Atypical antipsychotics — Atypical antipsychotic medications, used for the management of the behavioral and psychological symptoms of dementia, are among the drugs most frequently associated with adverse events in long-term care facilities [101]. In particular, psychotropic medications are associated with an increased risk for falls. In one meta-analysis of patients age 60 or older, the odds ratio for any psychotropic use among patients who had one or more falls was 1.73 (95% CI 1.52-1.97) [105].

There is limited evidence to support the efficacy of these agents for management of behavioral and psychological symptoms in older adults. (See "Management of neuropsychiatric symptoms of dementia", section on 'Antipsychotic drugs' and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

Nonetheless, use of antipsychotic medications in long-term care facilities is widespread. A study of 19,780 older adults with no history of major psychosis prior to long-term care admission found that antipsychotic therapy was prescribed for 17 percent within 100 days of their long-term care admission and for 24 percent within one year [106]. A study of 485 nursing homes in Canada found that there was about a threefold variation in antipsychotic prescribing, not related to clinical factors, between high- and low-prescribing facilities [107].

A public health advisory warning issued from the US Food and Drug Administration (FDA) warns of fatal adverse events in demented patients treated with atypical antipsychotic therapy [108-110]. Data from 17 trials of older adult patients with dementia have shown that those treated with atypical antipsychotic therapy were 1.6 to 1.7 times more likely to die than those given placebo therapy. Similar concerns have been raised for haloperidol and other conventional antipsychotics [111,112]. A retrospective comparison of patients with dementia who were newly treated with atypical antipsychotics, compared with no antipsychotics, found an increased risk of death at 30 and 180 days for the treated group (at 30 days, adjusted hazard ratio [HR] 1.55, 95% CI 1.15-2.07) [113]. Mortality was further increased, again by a factor of 1.55, for patients receiving conventional antipsychotics compared with atypical antipsychotics. These data point to the need to rethink the role of these therapies in clinical practice. (See "Management of neuropsychiatric symptoms of dementia", section on 'Severe or refractory symptoms'.)

Predicting adverse drug reactions

A tool has been developed to identify older adult patients at increased risk for an adverse drug reaction (ADR) in hospital [114]. The tool, based on logistic regression analysis from a group of Italian patients mean
age 78, and validated in a separate European cohort, found that the number of drugs prescribed and prior history of an ADR were the strongest predictors for a subsequent ADR. Compared with those receiving five or fewer medications, the risk of ADR was approximately doubled (odds ratio [OR] 1.9, 95% CI 1.35-2.68) for those prescribed five to seven medications, and was fourfold (OR 4.07, CI 2.93-5.65) for those receiving eight or more medications. Other variables incorporated in this tool are the presence of four or more comorbid conditions, heart failure, liver disease, or renal failure.

**Preventing adverse drug events** — The occurrence of preventable ADEs is a significant concern. Inappropriate ordering and inadequate monitoring are the most common errors in preventable adverse drug events. Errors in transcription, dispensing, and administration are less commonly identified [101]. Medications that are commonly implicated in preventable ADEs are not generally those identified by widely utilized "bad drug" lists. "Good drugs" prescribed in an inappropriate manner may be far more problematic. When drugs do cause problems, it is often because they are prescribed, dosed, or monitored inappropriately. Prevention of ADEs in the hospital setting is discussed separately. (See "Prevention of adverse drug events in hospitals".)

**Long-term care** — Enhanced surveillance and reporting systems for ADEs occurring in the nursing home setting are needed. Computerized order entry in the hospital setting has been shown to reduce serious medication errors [115]. A computer-based decision aid reduced in-hospital inappropriate dosing of psychotropic medications for geriatric inpatients [116]. However, a randomized trial of computerized order entry with clinical decision support in 29 resident care units at two long-term care facilities in Canada did not affect the rate of ADEs [117].

**Community care** — Patient errors in medication adherence are a significant contributor to ADEs for older patients living in the community, accounting for 21 percent of preventable ADEs in a large ambulatory Medicare population [118]. Patient errors occurred more frequently in patients who were regularly taking three or more medications, compared with those taking two or fewer [119].

Practical recommendations to reduce medical errors in the community have been proposed [120-125]:

- Maintain an accurate list of all medications that a patient is currently using. This list should include the drug name (generic and brand), dose, frequency, route, and indication.

- Advise periodic "brown-bag check-ups." Instruct patients to bring all pill bottles to each medical visit; bottles should be checked against the medication list.

- Patients should be made aware of potential drug confusions: sound-alike names, look-alike pills, and combination medications.

- Patients should be informed of both generic and brand names, including spelling, as well as the reasons for taking their medications. This may prevent unnecessary confusion when drugs are inconsistently labeled. As an example, a patient may be unaware that digoxin (generic) and Lanoxin (brand) are the same therapy.

- Medication organizers that are filled by the patient, family member, or caregiver can facilitate compliance with drug regimens. Blister packs for individual drugs, prepared by the pharmacist, can also be helpful in ensuring that patients take their medications correctly [124].
● Community pharmacists are an important resource and can play a key role in working with older adults to reduce medication errors.

**Transitions in care settings** — Transitions in care, between hospital and nursing home or institutional setting and home, are a common source of medication errors and confusions:

● One Canadian multisite study found that 23 percent of 328 older adults experienced an ADE after discharge home from the hospital; half of these ADEs were considered preventable [120].

● Changes in medication (different dose, discontinued therapies, additional therapies) were identified in 45 of 50 patients discharged from a geriatric ward in the United Kingdom within 6 to 14 days of discharge [121]. Of particular concern is discharge of older patients with new prescriptions for benzodiazepines that were initiated in the hospital, leading to unplanned chronic benzodiazepine use [126].

● Attending clinicians from an academic medical center reported that they believed 89 percent of their discharged patients (n = 99) understood potential side effects of their medications; 58 percent of those discharged patients reported that they understood this information [127].

● ADEs attributed to medication changes occurred in 20 percent of patients on transfer from hospital to a nursing home, occurring most commonly for patients being readmitted to the nursing home (12 of 14 events) [128].

● Frail older people are often found to be on unnecessary drug regimens at the time of hospital discharge. Among 384 older veterans, 44 percent were found to have at least one unnecessary drug therapy at the time of discharge [129]. Factors contributing to this include multiple prescribers, "routine" medications for hospitalization such as antacids or stool softeners, and being on nine or more drug therapies.

Effort must be made to improve communication in "hand-offs" of patient care during transitions in care setting. This is particularly true when the physician responsible for the patient in the hospital is not the same as the physician providing the patient's longitudinal care. Accurate medication lists, direct communications between providers, and a thorough review of all medications at the time of care transition for appropriateness and intended duration of treatment, are steps that should be taken to avoid ADEs. Whenever possible, the number of prescribing physicians for an individual patient should be limited, as the number of prescribing physicians is an independent risk factor for ADEs [130]. Safe and effective hospital discharge principles are discussed separately. (See "Hospital discharge and readmission".)

**A STEPWISE APPROACH TO PRESCRIBING** — Presented below is one systematic approach to improving prescribing practices when managing older adults. Other systematic approaches have been described incorporating similar elements [131]. Regardless of the sequence of steps, what is essential in prescribing is to continually reappraise the patient's medication regimen in light of his or her current clinical status, goals of care, and the potential risks/benefits of each medication.

A concept of "time to benefit" (TTB) in relation to drug prescribing for older patients with multiple morbidities can be applied to therapeutic decisions [132]. TTB, defined as the time to significant benefit observed in trials of people treated with a drug compared with controls, can be estimated from data from randomized controlled trials. Such information, not routinely available, may in the future help guide decision-making for specific drug prescribing in individual patients.

**Review current drug therapy** — Periodic evaluation of a patient's drug regimen is an essential component
of medical care for an older person. Such a review may indicate the need for changes to prescribed drug therapy. These changes may include discontinuing a therapy prescribed for an indication that no longer exists, substituting a therapy with a potentially safer agent, changing a drug dose, or adding a new medication (table 8). A medication review should consider whether a change in patient status (eg, renal or liver function) might necessitate dosing adjustment, the potential for drug-drug interaction, whether patient symptoms might reflect a drug side effect, or whether the regimen could be simplified [133]. Medication reviews are often not done in a systematic manner. A reasonable approach could be having a patient meet with a pharmacist within a few weeks of starting a new medication.

In addition to routine review of therapy, review of drug therapy is indicated when patients present with an injury or illness that might have been an adverse result of a prescribed medication. As an example, one study reviewed data for a sample of 168,000 Medicare patients seen for medical care with a fracture of a hip, shoulder, or wrist [134]. In the four months prior to presentation, three-quarters of the patients had been taking a nonopioid drug associated with increased fracture risk (eg, sedative, atypical antipsychotic, or antihypertensive). In the four months after the fracture, such drugs were discontinued for 7 percent but were newly prescribed for another 7 percent.

In a survey of Medicare beneficiaries, more than 30 percent of patients reported they had not talked with their doctor about their different medications in the previous 12 months [135]. Ideally, the clinician should ask the patient to bring to the visit all of the bottles of pills that they are using. Patients may not consider over-the-counter products, ointments, vitamins, ophthalmic preparations, or herbal medicines to be drug therapies and need to be specifically told to bring these to the visit.

Unintended medication discrepancies, particularly likely to occur at the time of hospital admissions, are a common source for medication errors. As an example, one study evaluated 151 patients (average age 77 years) admitted to general internal medicine clinical teaching units and found discrepancies in more than half between admission medication orders and the patient's usual drug therapies as identified by a medication history interview [136]. Most discrepancies involved unintentional omission of a maintenance medication and more than a third of these discrepancies had the potential to cause moderate harm.

**Discontinue unnecessary therapy** — Clinicians are often reluctant to stop medications, especially if they did not initiate the treatment and the patient seems to be tolerating the therapy. Sometimes, this exposes the patient to the risks for an adverse event with limited therapeutic benefit. A common example is the use of digoxin in older adults, often prescribed for indications that have not been well-documented. Renal impairment or temporary dehydration may predispose older adults to digoxin toxicity [137]. Although digoxin therapy can be safely discontinued in selected nursing home residents, it is important to recognize that discontinuation in patients with impaired systolic function can have a detrimental effect [138]. (See "Overview of the therapy of heart failure with reduced ejection fraction".)

The decision to discontinue medication is determined in part by the goals of care for that patient and the risks of adverse effects for that patient. Targets for treatment, based on outcomes evidence from studies in younger patients, may not be appropriate for older adults [30]; thus clinical guidelines not targeted to older patients may foster overly aggressive goals for management of hypertension or diabetes in the older adult population.

One approach to assessing whether a drug is truly necessary for a given patient is presented in an algorithm (algorithm 1) [139]. In a feasibility study performed in a cohort of 70 community-dwelling patients seen for
geriatric assessment, implementation of this algorithm led to recommendations to discontinue 58 percent of the medications they had been taking. Eighty-one percent of these medications were discontinued, 2 percent were restarted, and no significant adverse events were attributable to discontinuation over 13-month follow-up.

Some preventive and other therapies may no longer be beneficial to patients with short life expectancies [32]. The appropriateness of these therapies should be reconsidered when other medical conditions develop that impact a patient's long-term prognosis, unless the therapies are thought to increase comfort.

There are limited studies about how best to withdraw medications [31]. It is reasonable to gradually taper off most medications to minimize withdrawal reactions and to allow symptom monitoring, unless dangerous signs or symptoms indicate a need for abrupt medication withdrawal. Certain common drugs require tapering, including beta blockers, opioids, barbiturates, clonidine, gabapentin, and antidepressants.

**Consider adverse drug events for any new symptom** — Before adding a new therapy to the patient's drug regimen, clinicians should carefully consider whether the development of a new medical condition could be the presentation of an atypical ADE to an existing drug therapy. Many prescribing cascade scenarios have been identified (table 5). (See 'Prescribing cascades' above.)

**Consider nonpharmacologic approaches** — Some conditions in older adults may be amenable to lifestyle modification in lieu of pharmacotherapy. The Trial of Nonpharmacologic Interventions in the Elderly (TONE) demonstrated that weight loss and reduced sodium intake could allow discontinuation of antihypertensive medication in about 40 percent of the intervention group [140,141]. (See "Treatment of hypertension in the elderly patient, particularly isolated systolic hypertension", section on 'Lifestyle modifications'.)

**Care in the use of common drugs** — Some commonly prescribed drugs may result in increased toxicity in older adults. As an example, numerous studies have documented adverse events associated with nonsteroidal antiinflammatory drug (NSAID) use, including gastrointestinal bleeding [142], renal impairment [143], and heart failure in this population [144]. NSAIDs should be used cautiously in older adults and generally for a limited duration. (See "Nonselective NSAIDs: Overview of adverse effects".)

**Reduce the dose** — Many ADEs are dose-related. When prescribing drug therapies, it is important to use the minimal dose required to obtain clinical benefit. As an example, one study evaluated the relationship between prescribing of the newer atypical antipsychotic therapies (eg, olanzapine, risperidone, and quetiapine) and the development of parkinsonism in older adults [86]. Relative to those dispensed a low dose, those dispensed a high dose were more than twice as likely to develop parkinsonism (HR 2.07, 95% CI 1.42-3.02). As another example, one case-control study in patients over age 70 who received thyroid supplementation identified a correlation between risk of fracture and dose of levothyroxine, indicating the importance of testing for thyroid levels in this population and adjusting the dose accordingly [145].

**Simplify the dosing schedule** — When multiple medications are required, greater regimen complexity will increase the likelihood of poor compliance or confusion with dosing. Older adults, and particularly those with low health literacy, are not able to efficiently consolidate prescription regimens to optimize a dosing schedule [146]. The Institute of Medicine has proposed a standardized schedule for specifying medication dosing (morning, noon, evening, bedtime), recognizing that 90 percent of prescriptions are taken four or fewer times daily [147].

Simplifying the medication dosing schedule, when possible, is also important in the long-term care setting...
where nursing staff and time requirements for medication administration are substantial. A study illustrated that within a seven-hour shift, on a 20-bed unit, with two scheduled periods of medication administration, the process of administering medications to the residents accounted for a third of the nursing time \[148\]. This makes the nurse less available for other important patient care tasks.

**Prescribe beneficial therapy** — The fewer-the-better approach to drug therapy in older adults is often not the best response to optimizing drug regimens. Avoiding medications with known benefits to minimize the number of drugs prescribed is inappropriate. Patients must be informed about the reason to initiate a new medication and what the expected benefits are.

**INFORMATION FOR PATIENTS** — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Taking medicines when you're older (The Basics)" and "Patient education: Side effects from medicines (The Basics)"

**SUMMARY AND RECOMMENDATIONS**

- The possibility of an adverse drug event (ADE) should always be borne in mind when evaluating an older adult; any new symptom should be considered drug-related until proven otherwise. Pharmacokinetic changes lead to increased plasma drug concentrations and pharmacodynamic changes lead to increased drug sensitivity in older adults. (See 'Introduction' above.)

- Clinicians must be alert to the use of herbal and dietary supplements by older patients, who may not volunteer this information and are prone to drug-drug interactions related to these supplements. (See 'Herbal and dietary supplements' above.)

- Various criteria sets exist identifying medications that should not be prescribed, or should be prescribed with caution, in older adults. Compliance with these lists of medications to be avoided is suboptimal. (See 'Inappropriate medications' above.)

- Clinicians also under-prescribe medications, such as statins, that could provide benefit for older adults. Clinicians may be better at avoiding overprescribing of inappropriate drug therapies than at prescribing indicated drug therapies. Patient financial constraints and unavailability of prescribed doses may contribute to medication underutilization. (See 'Underutilization of appropriate medication' above.)

- ADEs result in four times as many hospitalizations in older, compared with younger, adults. Prescribing cascades, drug-drug interactions, and inappropriate drug doses are causes of preventable ADEs. (See 'Adverse drug events' above.)
• ADEs are a particular problem for nursing home residents; atypical antipsychotic medications and warfarin are the most common drugs involved in ADEs in this population. (See 'Adverse drug events in long-term care setting' above.)

• A stepwise approach to prescribing for older adults should include: periodic review of current drug therapy; discontinuing unnecessary medications; considering nonpharmacologic alternative strategies; considering safer alternative medications; using the lowest possible effective dose; including all necessary beneficial medications. (See 'A stepwise approach to prescribing' above.)

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REFERENCES


27. Weng MC, Tsai CF, Sheu KL, et al. The impact of number of drugs prescribed on the risk of potentially inappropriate medication among outpatient older adults with chronic diseases. QJM 2013; 106:1009.


35. McLeod PJ, Huang AR, Tamblyn RM, Gayton DC. Defining inappropriate practices in prescribing for


130. Green JL, Hawley JN, Rask KJ. Is the number of prescribing physicians an independent risk factor for...


## Selected high-risk drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potential harm</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Hypoglycemia</td>
<td>May often be appropriate; however, aggressive glycemic control may often yield greater harms than benefits in older adults.[1-3]</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Hypoglycemia</td>
<td>Older hospitalized patients at significant risk for hypoglycemia; avoid or use with great caution.[4]</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Gastrointestinal, intracranial bleeding</td>
<td>Although a high-risk drug, benefits of warfarin therapy often outweigh harms; maintenance of prothrombin time/international normalized ratio (INR) in therapeutic range tightly linked to risk/benefit ratio.[5]</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Impairment of cognition, heart block</td>
<td>May have a third-line role in management of systolic heart failure; suboptimal choice for rate control in atrial fibrillation.</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Falls</td>
<td>Associated with as much as a 60% increase in fall risk.[6]</td>
</tr>
<tr>
<td>Diphenhydramine, other first-generation antihistamines</td>
<td>Impaired cognition, urinary retention in men</td>
<td>Poor choice as sleep aid due to anticholinergic effects, next-day sedation, impact on performance including driving; close medication reconciliation important because patients may also obtain over-the-counter drugs.</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>Constipation, sedation, confusion, cardiorespiratory depression, seizures</td>
<td>Codeine, meperidine, pentazocine, butorphanol, and nalbuphine are poor choices for analgesia. Fentanyl, morphine, or oxycodone are often appropriate with careful dose adjustment.</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Death, pneumonia</td>
<td>Elevated risk of death when used to treat behavioral complications of dementia, although, in selected cases, benefits may exceed risks if consistent with patient goals of care.[7]</td>
</tr>
<tr>
<td>Chemotherapeutic agents</td>
<td>Myelosuppression (neutropenia, anemia), hepatotoxicity, cardiotoxicity</td>
<td>Comprehensive assessment is required for determining goals of treatment, particularly in light of comorbidities. When indicated, chemotherapy dose and schedule should be carefully individualized for organ function and anticipated toxicities of treatment. In general, greater treatment-related toxicity is accepted when the expected outcome of treatment is cure.</td>
</tr>
<tr>
<td><strong>Selected antimicrobials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Tendon inflammation and rupture, hypoglycemia, cardiac arrhythmias, Clostridium difficile-associated diarrhea, exacerbation of myasthenia gravis</td>
<td>Elevated risk of tendon rupture in combination with glucocorticoids.</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>In chronic use (rarely): Pulmonary fibrosis, neuropathy, hepatotoxicity</td>
<td>Avoid in older adults with creatinine clearance &lt;30 mL/minute; does not reach therapeutic concentrations in urine and increased risk of toxicity.</td>
</tr>
<tr>
<td><strong>Trimethoprim-sulfamethoxazole (co-trimoxazole)</strong></td>
<td><strong>Hyperkalemia, hypoglycemia (with sulfonylurea), severe dermatologic reaction (rare)</strong></td>
<td><strong>Drug interactions include warfarin (↑ INR), agents that increase serum potassium, and sulfonylureas (↑ hypoglycemic effect).</strong></td>
</tr>
</tbody>
</table>

References:


Revisions and additional information included with data from: Steinman MA, Hanlon JT. Managing medications in clinically complex elders: "There's got to be a happy medium." JAMA 2010; 304:1592.
Appropriate prescribing in the elderly

1. Is there an indication for the drug?
2. Is the medication effective for the condition?
3. Is the dosage correct?
4. Are the directions correct?
5. Are the directions practical?
6. Are there clinically significant drug-drug interactions?
7. Are there clinically significant drug-disease/condition interactions?
8. Is there unnecessary duplication with other drugs?
9. Is the duration of therapy acceptable?
10. Is this drug the least expensive alternative compared with others of equal usefulness?


Graphic 64079 Version 2.0
## Anticholinergic activity of medications

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
<th>Relative anticholinergic potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamines</td>
<td>H&lt;sub&gt;1&lt;/sub&gt; receptor antagonists, first-generation: brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dimenhydrinate, diphenhydramine, doxepin, doxylamine, hydroxyzine, meclizine, triprolidine, others</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>H&lt;sub&gt;1&lt;/sub&gt; receptor antagonists, second-generation: fexofenadine, cetirizine*, loratadine, desloratadine, levocetirizine, others</td>
<td>Low</td>
</tr>
<tr>
<td>Antiparkinson</td>
<td>Benztpine, trihexyphenidyl</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Amantadine, bromocriptine, entacapone</td>
<td>Low</td>
</tr>
<tr>
<td>Analgesic</td>
<td>Opioids: codeine, hydrocodone, fentanyl, meperidine, methadone, morphine, oxycodone, tramadol, others</td>
<td>Low</td>
</tr>
<tr>
<td>Antimuscarinic, overactive bladder</td>
<td>Darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, trospium</td>
<td>High</td>
</tr>
<tr>
<td>Antimuscarinic, spasmyotic</td>
<td>Atropine, belladonna-containing medications, clidinium-chlordiazepoxide, dicyclomine, hyoscyamine, glycopyrrolate, homatropine, methscopolamine, propantheline, scopolamine (hyoscine)</td>
<td>High</td>
</tr>
<tr>
<td>Antimuscarinic, inhaled bronchodilator</td>
<td>Ipratropium, tiotropium</td>
<td>High (local effect)</td>
</tr>
<tr>
<td>Antimuscarinic, ophthalmic drops (mydriatic/cycloplegic)</td>
<td>Atropine, cyclopentolate, homatropine, scopolamine</td>
<td>High (local effect)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Disopyramide</td>
<td>Low</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Antiemetics (eg, hydroxyzine, meclizine, promethazine, scopolamine); also refer to first-generation antihistamines above</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Domperidone, loperamide, prochlorperazine</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>H&lt;sub&gt;2&lt;/sub&gt; receptor antagonists (ranitidine, cimetidine, famotidine&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Low</td>
</tr>
<tr>
<td>Muscle relaxant</td>
<td>Orphenadrine, tizanidine</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Cyclobenzaprin&lt;sup&gt;*&lt;/sup&gt;, baclofen, methocarbamol</td>
<td>Low</td>
</tr>
<tr>
<td>Psychotropic</td>
<td>Antipsychotics, first-generation: chlorpromazine, fluphenazine, loxapine, methotrimeprazine (levomepromazine), thioridazine, trifluoperazine</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics, first-generation: haloperidol, perphenazine&lt;sup&gt;*&lt;/sup&gt;, others</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics, second-generation: clozapine</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics, second-generation: olanzapine*, quetiapine*, ioperidone, risperidone, others</td>
<td>Low</td>
</tr>
</tbody>
</table>
Benzodiazepines: chlordiazepoxide, clonazepam, temazepam, triazolam | Low

Selective serotonin reuptake inhibitor (SSRI) antidepressants: citalopram, fluoxetine, fluvoxamine, paroxetine* | Low

Tricyclic antidepressants: amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, others | High

Other neurologic | Low

Carbamazepine, lithium, nefazodone, oxcarbazepine, phenelzine, trazodone

A large number of medicines are reported to have some anticholinergic activity, and considerable variation exists in potency rankings assigned to specific drugs using available anticholinergic risk scales and in expert lists; this list is not exhaustive. Increasing dose and additive effects from simultaneous use of more than one anticholinergic drug can alter the anticholinergic activity rating provided in this table.

* Classified as moderate or high anticholinergic potency in some references or variable effects reported.
¶ Intravenous famotidine use has been associated with central nervous system effects (eg, delirium and confusion) in hospitalized older adults and patients with renal function impairment; this may be due to a central anticholinergic effect.

Courtesy of Paula A Rochon, MD with additional data from:
### Quality indicators for appropriate medication use in vulnerable elders

<table>
<thead>
<tr>
<th>Indicator title</th>
<th>Description</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication list</td>
<td>An up-to-date medication list that includes over-the-counter medications should be accessible to all healthcare providers in the medical record.</td>
<td>Enables identification of potential drug-related causes of new symptoms, eliminates inappropriate duplications, allows review for drug-drug interactions, and allows streamlining of regimen to improve adherence.</td>
</tr>
<tr>
<td>Annual drug regimen review</td>
<td>All vulnerable older adults should have an annual drug regimen review.</td>
<td>Allows an opportunity for discontinuing unnecessary medications, or addition of necessary drugs that are not currently prescribed.</td>
</tr>
<tr>
<td>Drug indication</td>
<td>All drugs prescribed for vulnerable elders should have a clearly defined indication.</td>
<td>Allows discontinuing medications that may have been prescribed for unclear or transient indications.</td>
</tr>
<tr>
<td>Patient education</td>
<td>All vulnerable older adults (or caregivers) should receive appropriate education about the use of any prescribed drug.</td>
<td>Education may improve adherence and clinical outcomes; also can alert patients or caregivers to potential adverse effects.</td>
</tr>
<tr>
<td>Response to therapy</td>
<td>Response to therapy should be documented for all ongoing medical conditions.</td>
<td>Documenting response will help clarify whether a drug is meeting the therapeutic goal for which it was prescribed and provides a basis for continuation, modification, or discontinuation.</td>
</tr>
<tr>
<td>Education for warfarin therapy</td>
<td>Patients newly prescribed warfarin should receive education about diet, drug interactions, and risk of bleeding, or should be referred to an anticoagulation clinic.</td>
<td>Awareness of drugs and dietary substances that interact with warfarin can decrease the risk of bleeding complications.</td>
</tr>
<tr>
<td>Monitoring warfarin therapy</td>
<td>When warfarin is prescribed, international normalized ratio (INR) should be determined within four days of initiation of therapy and at least every six weeks thereafter.*</td>
<td>Older adults are at high risk for drug toxicity, and close monitoring can help maintain the INR within the therapeutic range.</td>
</tr>
<tr>
<td>Monitoring angiotensin-converting enzyme (ACE) inhibitor therapy</td>
<td>When ACE inhibitor therapy is prescribed, a serum creatinine and potassium should be monitored within two weeks after initiation of therapy and at least yearly thereafter.</td>
<td>Older adults are at increased risk of renal insufficiency and hyperkalemia.</td>
</tr>
<tr>
<td>Monitoring loop diuretic therapy</td>
<td>When loop diuretic therapy is prescribed, electrolytes should be checked within two weeks after initiation and at least annually.</td>
<td>Risk of hypokalemia due to diuretic therapy.</td>
</tr>
<tr>
<td>Avoid propoxyphene</td>
<td>Do not prescribe propoxyphene as an analgesic agent.</td>
<td>Propoxyphene is inferior to, or at best equivalent to, acetaminophen or other analgesics with better safety profiles.</td>
</tr>
<tr>
<td>Avoid chronic or high-dose benzodiazepine use</td>
<td>If a benzodiazepine is taken for more than one month, there should be documentation of discussion of risks and attempt to taper or discontinue.</td>
<td>Benzodiazepines increase the risk of falls, hip fracture, and confusion.</td>
</tr>
<tr>
<td>Avoid drugs with strong anticholinergic properties</td>
<td>Do not prescribe drug therapies with a strong anticholinergic effect if alternative therapies are available.</td>
<td>These therapies are associated with adverse events such as confusion, urinary retention, constipation, visual disturbance, and hypotension.</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Avoid barbiturates</td>
<td>If an older adult does require the therapy for control of seizures, do not use barbiturates.</td>
<td>These therapies are potent central nervous system depressants, have a low therapeutic index, are highly addictive, cause drug interactions, and are associated with an increased risk for falls and hip fracture.</td>
</tr>
<tr>
<td>Avoid meperidine as an opioid analgesic</td>
<td>When analgesia is required, avoid use of meperidine.</td>
<td>This therapy is associated with an increased risk for delirium and may be associated with the development of seizures.</td>
</tr>
<tr>
<td>Avoid chronic use of ketorolac</td>
<td>Ketorolac should not be prescribed for more than five days.</td>
<td>This therapy is associated with a high risk of GI side effects, including bleeding, and other analgesics are safer in older patients.</td>
</tr>
<tr>
<td>Avoid skeletal muscle relaxants</td>
<td>Skeletal muscle relaxants (cyclobenzaprine, methocarbamol, carisoprodol, chlorzoxazone, orphenadrine, tizanidine, metaxalone) should not be prescribed for more than one week.</td>
<td>These medications can cause anticholinergic adverse effects, sedation, confusion, and data of efficacy are limited.</td>
</tr>
<tr>
<td>Avoid ticlopidine</td>
<td>Clopidogrel should be prescribed rather than ticlopidine for patients who require antiplatelet therapy (eg, recent stroke, myocardial infarction, acute coronary syndrome, percutaneous angioplasty).</td>
<td>Ticlopidine may be less effective than clopidogrel and is associated with a higher risk of hematological disorders than clopidogrel.</td>
</tr>
<tr>
<td>Treat iron deficiency anemia with low-dose oral iron therapy</td>
<td>Vulnerable older adults with iron deficiency anemia should take no more than one low-dose oral iron tablet daily.</td>
<td>Low-dose therapy is equally effective with fewer adverse effects than high-dose oral iron therapy.</td>
</tr>
<tr>
<td>Antipsychotic medication response</td>
<td>An assessment of response should be documented within one month for older adults started on an antipsychotic drug.</td>
<td>The use of antipsychotic drugs increases mortality in older adults, and behavioral modification is an effective alternative.</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Older adults prescribed high-dose (≥3 g per day) acetaminophen, or those with liver disease taking acetaminophen chronically, should be advised of the risk of liver toxicity.</td>
<td>The risk of liver toxicity is greater with use of acetaminophen.</td>
</tr>
<tr>
<td>NSAIDs and aspirin</td>
<td>The risk of GI bleeding should be discussed and documented. Individuals at increased risk for GI bleeding (aged &gt;75 years, peptic ulcer disease, history of GI bleeding, warfarin use, chronic glucocorticoid use) should be treated concomitantly with misoprostol or a proton pump inhibitor when treated with a nonselective NSAID.</td>
<td>Risks of GI bleeding are increased in older adults taking NSAIDs or daily aspirin.</td>
</tr>
</tbody>
</table>

GI: gastrointestinal; NSAIDs: nonsteroidal antiinflammatory drugs. * These monitoring frequencies represent minimal indications; many experts would advise daily monitoring initially and monitoring every four weeks once a stable and at-goal therapeutic INR has been achieved.

Graphic 73834 Version 6.0
Examples of prescribing cascades

<table>
<thead>
<tr>
<th>Initial drug therapy</th>
<th>Adverse drug event</th>
<th>Subsequent drug therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td>Extrapyramidal signs and symptoms</td>
<td>Antiparkinsonian therapy</td>
</tr>
<tr>
<td>Cholinesterase inhibitors</td>
<td>Urinary incontinence</td>
<td>Incontinence treatment</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>Hyperuricemia</td>
<td>Gout treatment</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Increased blood pressure</td>
<td>Antihypertensive therapy</td>
</tr>
</tbody>
</table>

Medication prescribing cascades occur when patients are prescribed medications to treat the adverse side effects of previously prescribed medications. This leads to polypharmacy and further increases the risk for adverse drug events. Periodic review of medication lists, especially in older adults, can minimize this risk.

NSAIDs: nonsteroidal antiinflammatory drugs.


Graphic 74478 Version 4.0
### Frequency of adverse drug events and preventable adverse drug events by drug class

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Total adverse drug events (n = 815) N (percent)</th>
<th>Preventable adverse drug events (n = 338) N (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>121 (15)</td>
<td>42 (12)</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>92 (11)</td>
<td>42 (12)</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>69 (8)</td>
<td>33 (10)</td>
</tr>
<tr>
<td>Opioids</td>
<td>51 (6)</td>
<td>26 (8)</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>46 (6)</td>
<td>23 (7)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>45 (6)</td>
<td>27 (8)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>43 (5)</td>
<td>25 (7)</td>
</tr>
<tr>
<td>Laxatives</td>
<td>43 (5)</td>
<td>16 (5)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>39 (5)</td>
<td>30 (9)</td>
</tr>
<tr>
<td>(intermediate acting)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulins</td>
<td>37 (5)</td>
<td>18 (5)</td>
</tr>
</tbody>
</table>

Only drug classes with the frequency of adverse drug events of 5 percent and more are presented. Some adverse drug events were associated with more than one drug class.

ACE: angiotensin-converting enzyme.


Graphic 71281 Version 2.0
### Frequency of adverse drug events by type

<table>
<thead>
<tr>
<th>Type</th>
<th>Total adverse drug events (n = 815) N (percent)</th>
<th>Preventable adverse drug events (n = 338) N (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropsychiatric</td>
<td>199 (24)</td>
<td>97 (29)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>159 (20)</td>
<td>53 (16)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>140 (17)</td>
<td>55 (16)</td>
</tr>
<tr>
<td>Renal/electrolytes</td>
<td>80 (10)</td>
<td>40 (12)</td>
</tr>
<tr>
<td>Metabolic/endocrine</td>
<td>64 (8)</td>
<td>35 (10)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>36 (4)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>36 (4)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Extrapyramidal symptoms</td>
<td>30 (4)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Fall with injury</td>
<td>21 (3)</td>
<td>17 (5)</td>
</tr>
<tr>
<td>Fall without injury</td>
<td>21 (3)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Infection</td>
<td>19 (2)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Syncope/dizziness</td>
<td>16 (2)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>9 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Ataxia/difficulty with gait</td>
<td>9 (1)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>8 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>6 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Functional decline</td>
<td>3 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

Adverse drug events could manifest as more than one type. Neuropsychiatric events include oversedation, confusion, hallucinations, and delirium. Anticholinergic effects include dry mouth, dry eyes, urinary retention, and constipation.


Graphic 72518 Version 3.0
A step-wise approach to reviewing medications for older adults

<table>
<thead>
<tr>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review current drug therapy</td>
</tr>
<tr>
<td>Discontinue potentially unnecessary therapy</td>
</tr>
<tr>
<td>Consider adverse drug events as a potential cause for any new symptom</td>
</tr>
<tr>
<td>Consider nonpharmacologic approaches</td>
</tr>
<tr>
<td>Substitute with safer alternatives</td>
</tr>
<tr>
<td>Reduce the dose</td>
</tr>
<tr>
<td>Use beneficial therapies when indicated</td>
</tr>
</tbody>
</table>


Graphic 52450 Version 3.0
Medication review

Discuss the following with the patient/guardian

An evidence-based consensus exists for using the drug for the indication given in its current dosing rate in this patient’s age group and disability level, and the benefit outweighs all possible known adverse effects

Yes

No/Not sure

Indication seems valid and relevant in this patient’s age group and disability level

Yes

No

Do the known possible adverse reactions of the drug outweigh possible benefit in old, disabled patients?

Yes

Stop drug

No

Any adverse symptoms or signs that may be related to the drug?

Yes

Shift to another drug

No

Is there another drug that may be superior to the one in question?

Yes

Shift to another drug

No

Can the dosing rate be reduced with no significant risk?

Yes

Reduce dose

No

Continue with the same dosing rate

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Daniel J Sullivan, MD, MPH Nothing to disclose

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