

Reducing the Risk of Adverse Drug Events in Older Adults

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Adverse drug events occur in 15 percent or more of older patients presenting to offices, hospitals, and extended care facilities. These events are potentially preventable up to 50 percent of the time. Common serious manifestations include falls, orthostatic hypotension, heart failure, and delirium. The most common causes of death are gastrointestinal or intracranial bleeding and renal failure. Antithrombotic and antidiabetic medications, diuretics, and non-steroidal anti-inflammatory drugs cause most of the preventable hospital admissions due to adverse drug events. Strategies to reduce the risk of adverse drug events include discontinuing medications, prescribing new medications sparingly, reducing the number of prescribers, and frequently reconciling medications. The Beers, STOPP (screening tool of older persons' potentially inappropriate prescriptions), and START (screening tool to alert doctors to right treatment) criteria can help identify medications causing adverse drug events. Not all potentially inappropriate medications can be avoided. Clinicians should involve patients in shared decision making and individualize prescribing decisions based on medical, functional, and social conditions; quality of life; and prognosis. (*Am Fam Physician*. 2013;87(5):331-336. Copyright © 2013 American Academy of Family Physicians.)



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► Patient information:

A handout on adverse drug events in older adults, written by the authors of this article, is available at <http://www.aafp.org/afp/2013/0301/p331-s1.html>. Access to the handout is free and unrestricted.

The effects of medications in older adults are not often studied adequately, even though more than one-half of all prescription medications are dispensed to persons older than 60 years.¹ More than 90 percent of noninstitutionalized older adults in the United States take at least one prescription medication,² and those who are seen in the office take six to eight medications on average.³⁻⁵

One in six hospital admissions of older adults is because of an adverse drug event,⁶ a proportion that is four times that of younger persons. For persons older than 75 years, hospital admissions because of an adverse drug event increase even further to one in three.^{7,8} While in the hospital, one in six older patients experiences an adverse drug event.⁹ In the office and community settings, one in five older adults is taking potentially inappropriate medications.^{3,5,10}

There are five categories of adverse drug events: adverse drug reaction, medication error, therapeutic failure, adverse drug withdrawal event, and overdose.¹¹ Adverse drug reactions are the most common, accounting for three-fourths of hospitalizations from adverse drug events; the remainder are caused by nonadherence,

or omission or cessation of treatment.⁷ The World Health Organization further identifies adverse drug events as unintended and undesired effects of a medication at the normal dose; therapeutic failures, overdoses, and medication abuse are excluded.^{6,12}

Reducing the risk of adverse drug events in older adults requires close monitoring of functional status, early identification of symptoms, and recognition of the impact a medication can have on multiple organ systems. Because of the many variables that must be considered in caring for older adults, clinical judgment is paramount.

Pharmacokinetics

Physiologic changes in older adults increase the risk of harm from medications metabolized by the liver and kidneys. Hepatic blood flow decreases by nearly one-half (40 percent) in older adults,¹³ and some degree of chronic kidney disease is present in one-half of older adults.¹⁴ Furthermore, median renal blood flow decreases by one-half by the time patients reach 80 years of age, although the individual rate of decline varies and one-third of older adults maintain normal renal function.¹⁵ Heart failure, which affects more than 40 percent

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
The use of antipsychotics, antidepressants, benzodiazepines, and sedative/hypnotics in older adults should be limited to reduce the risk of falls.	C	31
The number of medications in older adults should be limited, because each new medication adds more than one adverse drug event each year and taking six or more medications increases this risk fourfold.	C	3, 4, 30
Ideally, the primary care physician should prescribe all medications, because each additional prescriber increases the risk of adverse drug events in older adults by 30 percent.	C	33
Patients with several chronic health conditions should be asked often about adverse drug events, because the odds of an event double for four or five conditions and triple for six or more.	C	33

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort.xml>.

of persons older than 80 years, can further reduce function of the aging kidneys and liver.¹⁶

Other factors influence pharmacokinetics in older adults. Aging decreases first-pass clearance in the liver, and a number of commonly prescribed medications (e.g., warfarin [Coumadin], benzodiazepines, opiates) require much lower doses in older adults. Distribution of drugs to body compartments is changed by the decrease in the ratio of lean body weight to body fat. Levels of serum proteins, which bind many drugs, decrease in older adults because of malnutrition and dietary changes that are common for both intentional (e.g., lifestyle changes) and unintentional reasons (e.g., dentures, altered appetites, changes in food preparers, comorbidities, dietary restrictions). Drug metabolism can be affected by substance abuse, including alcohol; up to 10 percent of older adults are heavy or problem drinkers.¹⁷

Sources of Adverse Drug Events

Overall, 30 percent of adverse drug events in the outpatient setting are potentially preventable¹⁸ (Table 1^{10,19-25}), and some studies have shown that more than one-half of hospital admissions for adverse drug events are preventable.⁷ A systematic review of nine international studies attributed most preventable medication-related admissions to antithrombotic medications, diuretics, and nonsteroidal anti-inflammatory drugs.²⁴ In another study, two-thirds of all medication-related admissions to the hospital involved antithrombotic and antidiabetic medications, almost always by unintentional overdose.²⁶ In a prospective study of 1,225 hospital admissions related to adverse drug events, 20 of 28 deaths were due to gastrointestinal or intracranial bleeding and five were due to renal failure.²⁷

Alternative medications can cause adverse drug events as well. The U.S. public spent \$14.8 billion on nonvitamin, nonmineral, and natural products in 2007, which is equivalent to one-third of the total out-of-pocket spending on prescription medications.²⁸ The rate of use

of over-the-counter medications is threefold higher in older adults compared with younger adults, and the use of herbal preparations is twofold higher.²⁹

A Systematic Approach

A systematic approach for detecting adverse drug events should be used at all visits, including comprehensive visits and any visits in which new symptoms are present. Additional time should be allocated for this purpose during visits with older adults. Table 2 lists recommendations for assessing older patients for adverse drug events.^{3,4,25,30} Common serious manifestations of adverse drug events, which should prompt an immediate review of the medication list, are falls and orthostatic hypotension (24 percent), heart failure (17 percent), and delirium (15 percent).⁷ Because older adults with orthostatic hypotension are up to eight times more likely to experience an adverse drug event,⁴ blood pressure and heart rate should be measured in the supine and standing positions in older patients, particularly those who fall or have cardiovascular symptoms. The use of antipsychotics, antidepressants, benzodiazepines, and sedative/hypnotics in older adults should be limited to reduce the risk of falls.³¹

When prescribing medications in older adults, the old maxim “start low and go slow” still applies (Table 3).^{2,5,18,23,30} Identifying the quality-of-life outcomes most valued by the patient should take precedence over the routine implementation of practice guidelines that recommend medications for generic clinical scenarios. Carefully considering the patient’s priorities before taking any action is often the critical first step in reducing the risk of adverse drug events. Likewise, clinicians should avoid the tendency to treat every symptom with a medication, particularly because the symptom in question may be the adverse effect of another medication. In some cases, the best strategy is to avoid prescribing new medications altogether, because each new medication adds more than one additional adverse drug event per

Table 1. Medications to Avoid When Possible in Older Adults

<i>Medication</i>	<i>Comment</i>	<i>References</i>
Antipsychotic use for longer than one month	Most common potentially inappropriate type of medication used in nursing homes	19
Nonsteroidal anti-inflammatory drug use for longer than three months	One of the three most common potentially inappropriate medications used in nursing homes 3 percent of older adults are using this medication for this duration at the time of hospital admission	19, 20
Proton pump inhibitor use at maximum therapeutic dosage for longer than eight weeks	One of the three most common potentially inappropriate medications used in nursing homes Most common potentially inappropriate medication being used at the time of hospital admission (21 percent of hospitalized older adults)	19, 20
Aspirin in patients with no history of coronary, cerebral, or peripheral vascular symptoms or arterial occlusive events	11 percent of older adults are taking aspirin under these circumstances at the time of hospital admission	20
Benzodiazepines in patients who have had at least one fall in the past three months	9 percent of older adults are using this potentially inappropriate medication under this circumstance at the time of hospital admission	20
Duplicate drug class prescriptions	9 percent of older adults are using two medications from the same drug class at the time of hospital admission	20
Long-acting benzodiazepine or benzodiazepine with long-acting metabolites use for longer than one month	8 percent of older adults are using this medication for this duration at the time of hospital admission	20
Loop diuretic as first-line monotherapy for hypertension	4 percent of older adults are using this medication for this reason at the time of hospital admission	20
Proton pump inhibitors, long-acting benzodiazepines, nonsteroidal anti-inflammatory drugs, nonselective beta blockers, and tricyclic antidepressants	These five categories of medications caused nearly 80 percent of the inappropriate prescribing detected by the STOPP criteria in the outpatient setting	10
Haloperidol	Although long-term use of antipsychotics should be avoided, haloperidol doubled the risk of death when newly prescribed for older adults in nursing homes (hazard ratio = 2.07 compared with risperidone [Risperdal]) Quetiapine (Seroquel) should be considered (hazard ratio = 0.81)	21
Megestrol (Megace) and sliding-scale insulin	Added to the 2012 Beers criteria	22
Selective serotonin reuptake inhibitors	Increased fall risk (odds ratio = 1.72) even more than tricyclic antidepressants (odds ratio = 1.51)	23
Sulfonylureas	Glyburide added to the 2012 Beers criteria	22

NOTE: Medications are listed in order of highest to lowest prevalence of potentially inappropriate use in older adults. Medications prescribed for common indications that are not avoidable (e.g., antithrombotic and antidiabetic medications) should be carefully reviewed for indications, compliance, and monitoring.^{24,25}

STOPP = screening tool of older persons' potentially inappropriate prescriptions.

Information from references 10, and 19 through 25.

year.³⁰ Taking six or more medications increases this risk fourfold.³

In addition to close medical follow-up (e.g., scheduling the next appointment in two to four weeks) when prescribing new medications, the physician should encourage self-monitoring by informing the patient of the time frame in which any potential adverse drug events may occur. Empiric medication trials, such as those of dementia medications, should include a target date when effectiveness and potential adverse reactions

will be reviewed. Stopping medications can significantly decrease fall risk.³² Because multiple prescribers increase the number of adverse drug events (each additional prescriber increases the risk of adverse drug events by 30 percent),³³ consultants should be asked to make recommendations to the primary care physician, rather than prescribe directly.

What an older patient actually takes on a daily basis may be different from what has been prescribed or what the patient says he or she is taking. Because the

Adverse Drug Events

medication list is the “problem list” in many cases, medication reconciliation should occur at every visit, including vitamins and over-the-counter and herbal medications. This is sometimes referred to as the “brown bag check” in the office setting and the “cupboard check” at a home visit. If discrepancies emerge, pharmacies should be contacted to verify medications and the frequency with which they have been filled, because one-third of medication-related hospital admissions are due to patient adherence problems.²⁴ Other third parties, including emergency medical personnel, family members, visiting home nurses, and extended care facility personnel, may be queried if possible. Patients with several chronic health conditions require further investigation, because the odds of an adverse drug event double for four or five conditions and triple for six or more.³³

Clinical Tools

BEERS CRITERIA

The Beers criteria are the most commonly used criteria to assist clinicians in preventing adverse drug events in older adults.^{22,34} Since their inception more than two decades ago, the Beers criteria have been revised three times, most recently in 2012 by an expert panel sponsored by the American Geriatrics Society. They are comprised of two comprehensive lists of medications to be avoided in older adults, one list independent of diagnosis and the other considering the diagnosis. A third list contains medications to be used with caution.²² New additions to the list of medications to be avoided in older adults include megestrol (Megace), glyburide, and sliding-scale insulin.²² Acetylcholinesterase inhibitors should be avoided in patients with syncope because of the risk of bradycardia.²² Similarly, glitazones should be avoided in patients with heart failure, and selective serotonin reuptake inhibitors should be avoided in patients with falls and fractures.^{22,23} The Beers criteria are accessible on the American Geriatrics Society website at <http://www.americangeriatrics.org>. They also can be printed as a pocket card and downloaded as a smartphone app.

Several limitations of the Beers criteria are that some relevant medications are missing and others could be taken off the list; they include some therapeutic duplications; and they do not address common drug-drug interactions. A systematic review found an association between use of medications listed in the Beers criteria and hospitalization in

community-dwelling older adults³⁵; however, data are limited to suggest that using the Beers criteria to manage medications in patients decreases mortality, improves quality of life, or reduces the use of resources.⁸

STOPP AND START CRITERIA

Potentially inappropriate medications, defined by the validated STOPP (screening tool of older persons' potentially inappropriate prescriptions) criteria, are significantly associated with avoidable adverse drug events that cause or contribute to urgent hospitalization in older persons.²⁰ The STOPP criteria are comprised of 65 clinically significant criteria for potentially inappropriate prescribing in older persons. Each criterion is accompanied by a brief explanation about why the prescribing practice is potentially inappropriate. The STOPP criteria represent the more common avoidable instances of inappropriate prescribing in older persons in day-to-day clinical practice. Although the STOPP and Beers criteria overlap (*eTable A*), each set detects potentially inappropriate medications that the other does not. More importantly, the STOPP and Beers criteria are not comprehensive, and a number of older adults are admitted to hospitals with adverse drug events from medications that are not identified by either.²⁵

The STOPP criteria are designed to be used in tandem with the START (screening tool to alert doctors to right treatment) criteria. Both are available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2810806/>.¹⁰

Table 2. Practical Recommendations for Assessing Older Patients for Adverse Drug Events

Diagnosing and managing an adverse drug event in an older patient requires:

- An understanding of the physiology of aging
- An awareness of the most common causes of adverse drug events
- A high index of suspicion in all patients (especially those with a history of adverse drug events and/or nonadherence; with cognitive impairment, psychiatric disease, or substance abuse; and those who live alone)
- Time to examine the older adult, review medications with the patient/caregiver, provide education about altering drug therapy, and review printed medication information

Suspicion for an adverse drug event should be heightened in patients:

- With a change in function (activities of daily living, instrumental activities of daily living), including change in mental status, falls, or hospital admission
- With new symptoms after starting a new medication or changing the dosage of a current medication
- Taking more than four medications

Information from references 3, 4, 25, and 30.

Table 3. Practical Considerations to Reduce the Risk of Adverse Drug Events in Older Adults

Be watchful for medications started at a younger age that have never been adjusted for patient aging or changes in renal and hepatic function.

Medications required in the short-term setting (e.g., hospital) are often not needed in the long-term setting, or they can be used at a much lower dose. The dose for a loop diuretic, for instance, may need to be increased fourfold or more in the hospital setting, yet the baseline dose is often sufficient once the acute crisis has passed.

Avoid adding medications to treat an adverse effect of another medication. The preferred options are to decrease the dose, discontinue the medication, or, if necessary, change to a different medication.

Ask about self-medication with over-the-counter and herbal medications, which can interact with prescribed medications.

Do not automatically increase the dose of a medication because of a subtherapeutic level or suboptimal response without first verifying adherence to therapy.

Identifying an adverse drug event in older adults may be difficult because of atypical presentations or because the symptoms are being attributed to the disease; for example, altered mental status may be attributed to dementia, delirium, or forgetfulness when prescribed medications are the true cause.

When prescribing medications, use those with a wide therapeutic window.

Review medication lists regularly and reconcile them to the patient's problem list to discontinue duplicate therapies, adjust doses and dosing frequency, and discontinue unnecessary medications (i.e., issue is no longer a problem).

Set an end date and use objective criteria to determine the success or failure of an empiric trial and act accordingly. Do not continue these medications, particularly those used for pain, behavior, and cognition, indefinitely.

"Start low and go slow" in dosing new medications.

Set up regular visits (e.g., every two to four weeks), including appropriate laboratory testing, to monitor medication use in patients with multiple comorbidities.

Avoid starting two new medications in the same patient at the same time.

Regularly use a standardized method to review patient medications (e.g., the Beers, STOPP, and START criteria), including when the patient has a change in function (sentinel event) or problems with his or her medication.

START = screening tool to alert doctors to right treatment; STOPP = screening tool of older persons' potentially inappropriate prescriptions.

Information from references 2, 5, 18, 23, and 30.

The START criteria have been validated in the same fashion as the STOPP criteria and represent the more common instances of inappropriate omission of potentially beneficial medications. The START criteria consist of 22 evidence-based prescribing indicators for commonly encountered diseases in older persons. More research is needed to know whether routine application of the STOPP, START, and Beers criteria leads to meaningful clinical benefits and significant reductions in health care utilization.²⁵

A number of free and low-cost software systems identify potential drug-drug interactions. Improving

the design and content of tools, such as the STOPP, START, and Beers criteria, and incorporating them into electronic prescribing systems can lead to improved sensitivity and greater clinician acceptance while improving specificity of the electronic system with less "alert fatigue" and fewer overrides by clinicians.²⁰

Criteria for potentially inappropriate medications are not meant to replace clinical judgment; rather, they are designed to decrease adverse drug events and improve medical treatment of older patients. Not all potentially inappropriate medications can be avoided, especially when clinicians and patients agree that the benefits of a medication outweigh the risks. Therefore, prescribing decisions should be individualized based on medical, functional, and social conditions; quality of life; and prognosis, and should involve shared decision making.

Data Sources: Scopus and PubMed were searched using the key words elderly, geriatrics, older adult, adverse drug events, and adverse drug reactions. Additional searches were done in the Cochrane database, Agency for Healthcare Research and Quality Clinical Guidelines and Evidence Reports, U.S. Preventive Services Task Force, Bandolier, the Institute for Clinical Systems Improvement, and Essential Evidence Plus. Search date: October 2011 to March 2012.

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eTable A. Using Clinical Tools to Detect Potentially Inappropriate Medications

Case example: An 85-year-old white woman with metabolic syndrome and heart failure comes to the office for a new patient appointment. She also has a history of seizures, anxiety, depression, and alcoholism. She weighs 110 lb (50 kg) and has a serum creatinine level of 1.0 mg per dL (88.4 μ mol per L).

Current medications for case example	Clinical tools		Comments
	Beers criteria ^{A1}	STOPP criteria ^{A2}	
Alprazolam (Xanax), 1 mg orally three times daily	Avoid benzodiazepines (any type) for treatment of insomnia, agitation, and delirium All benzodiazepines increase the risk of falls, fracture, cognitive impairment, delirium, and motor vehicle crashes in older adults	Potentially inappropriate to use long-acting benzodiazepines (e.g., chlordiazepoxide [Librium], flurazepam, clorazepate) and benzodiazepines with long-acting metabolites (e.g., diazepam [Valium]) for longer than one month because of the risk of prolonged sedation, confusion, impaired balance, and falls Also potentially inappropriate to use benzodiazepines in patients who fall, because the sedative may cause reduced sensorium and impair balance	Because of significantly increased risk of falls in older adults, benzodiazepines should be weaned and discontinued
Amlodipine (Norvasc), 10 mg orally daily	Not listed	Potentially inappropriate to use calcium channel blockers in patients with chronic constipation, because they may exacerbate constipation	Decrease dosage or discontinue if the patient's blood pressure is adequately controlled with lisinopril and hydrochlorothiazide
Aspirin, 81 mg orally daily	Avoid aspirin dosage greater than 325 mg daily May exacerbate existing ulcers or cause new or additional ulcers Avoid use in patients with history of peptic ulcer disease unless other alternatives are not effective and patient can take gastroprotective agents (proton pump inhibitor or misoprostol [Cytotec])	Potentially inappropriate to use aspirin in certain circumstances, including in dosages greater than 150 mg daily; in patients with a history of peptic ulcer disease without a histamine H ₂ antagonist or proton pump inhibitor; and in patients without a history of coronary, cerebral, or peripheral vascular symptoms or arterial occlusive event (not indicated) Aspirin can be appropriate in patients with well-controlled hypertension and target organ damage, diabetes mellitus, or atrial fibrillation	Although aspirin meets the Beers and STOPP criteria for use in this patient, data are limited in persons 80 years and older. The potential benefit due to a reduction in myocardial infarction and ischemic stroke should be balanced with the risk of gastrointestinal or intracranial bleeding and falls
Cinnamon bark, two 600-mg capsules orally three times daily with meals	Herbal medications not addressed	Herbal medications not addressed	Consider discontinuing because it decreases serum glucose levels and increases risk of hypoglycemia
Garlic, 400 mg orally three times daily	Herbal medications not addressed	Herbal medications not addressed	Consider discontinuing because it interacts with aspirin and can increase risk of bleeding
Glyburide, 5 mg orally twice daily	Long-duration sulfonylureas should be avoided Glyburide has a higher risk of severe prolonged hypoglycemia in older adults	Not listed	Consider discontinuing because of the high risk of hypoglycemia
Hydrochlorothiazide, 25 mg orally daily	Diuretics not listed	Potentially inappropriate to use thiazide diuretics in patients with a history of gout, because they may exacerbate gout	Lower dose often effective Monitor potassium levels and renal function

continued

STOPP = screening tool of older persons' potentially inappropriate prescriptions.

eTable A. Using Clinical Tools to Detect Potentially Inappropriate Medications (continued)

Current medications for case example	Clinical tools		Comments
	Beers criteria ^{A1}	STOPP criteria ^{A2}	
Lisinopril (Zestril), 40 mg orally daily	Use in patients with syncope should be avoided to prevent increasing the risk of orthostatic hypotension or bradycardia	Potentially inappropriate to use angiotensin-converting enzyme inhibitors when optimization of monotherapy within a single drug class has not been observed before considering a new class of drug	Consider decreasing dosage because the patient's creatinine clearance is 32 mL per minute per 1.73 m ² (0.53 mL per second per m ²) based on the Cockcroft-Gault equation* Dose range of 2.5 to 10 mg daily often used in older adults
Metformin (Glucophage), 1,000 mg orally twice daily	Not listed	Not listed	Decrease dosage to 500 mg twice daily because of the patient's age and history of heart failure Although the patient's serum creatinine level is less than 1.4 mg per dL (123.76 μmol per L), creatinine clearance is 32 mL per minute per 1.73 m ² , which will increase the risk of acidosis
Phenytoin (Dilantin), 100 mg orally three times daily	Not listed	Not listed	Consider stopping because indication may no longer exist Consider obtaining a free phenytoin level because hypoalbuminemia is common in older adults and phenytoin is highly protein bound
Simvastatin (Zocor), 80 mg daily	Statins not listed	Not listed	Consider decreasing or discontinuing because of uncertain benefit in older adults and association with memory loss ^{A3} The U.S. Food and Drug Administration recommends maximum dosage of 40 mg daily in adults
Tramadol (Ultram), 50 mg orally every six hours as needed	Avoid Lowers seizure threshold	Not listed	Decrease dosage or discontinue because of the effects of age and alcoholism on liver function Tramadol also causes constipation in older adults prone to constipation and small bowel obstructions
Zolpidem (Ambien), 10 mg at bedtime as needed	Avoid long-term use (more than 90 days) because of adverse central nervous system effects Adverse effects include delirium, falls, and fractures Minimal improvement in sleep latency and duration	Not listed	Decrease dosage or discontinue because of increased risk of dependency in older adults

*—For women: $\frac{0.85 \times (140 - \text{age in years}) \times (\text{body weight in kg})}{72 \times \text{serum creatinine in mg per dL}}$ For men: $\frac{(140 - \text{age in years}) \times (\text{body weight in kg})}{72 \times \text{serum creatinine in mg per dL}}$

Information from:

A1. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2012;60(4):616-631.

A2. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (screening tool of older person's prescriptions) and START (screening tool to alert doctors to right treatment). Consensus validation. *Int J Clin Pharmacol Ther.* 2008;46(2):72-83.

A3. Evans MA, Golomb BA. Statin-associated adverse cognitive effects: survey results from 171 patients. *Pharmacotherapy.* 2009;29(7):800-811.