

Minimizing Adverse Drug Events in Older Patients

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Adverse drug events are common in older patients, particularly in those taking at least five medications, but such events are predictable and often preventable. A rational approach to prescribing in older adults integrates physiologic changes of aging with knowledge of pharmacology. Focusing on specific outcomes, such as the prompt recognition of adverse drug events, allows the family physician to approach prescribing cautiously and confidently. Physicians need to find ways to streamline the medical regimen, such as periodically reviewing all medications in relation to the Beers criteria and avoiding new prescriptions to counteract adverse drug reactions. The incorporation of computerized alerts and a multidisciplinary approach can reduce adverse drug events. (*Am Fam Physician* 2007;76:1837-44. Copyright © 2007 American Academy of Family Physicians.)

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► See related editorial on page 1768.

Older adults experience a disproportionate share of unwanted and unexpected adverse effects from medication. Falls, hip fractures, delirium, and urticaria lead the list of preventable adverse drug events.¹ About one in three older persons taking at least five medications will experience an adverse drug event each year, and about two thirds of these patients will require medical attention.² Approximately 95 percent of these reactions are predictable, and about 28 percent are preventable.³

Although adverse drug reactions tend to be unexpected in younger persons, many reactions in older adults are exaggerations of expected physiologic effects of the drugs. A number of unique and important pharmacokinetic changes in older adults, which have been covered in detail elsewhere, have been postulated as the reasons for such observations.⁴

However, age is not the only risk factor for an adverse drug reaction in older patients.⁵

Preventable adverse drug events in older adults are often the result of misuse, overuse, or underuse of medications.⁶ This review summarizes interventions for reducing inappropriate prescribing to older adults

in the community and in skilled nursing facilities and the evidence, where available, to support these interventions.

Avoiding Misuse of Medications

The fact that drugs affect older adults differently has been apparent for some time, and work in geriatrics has moved from theoretical considerations to specific recommendations. In 1991, an expert consensus panel developed the Beers criteria, a list of drugs that should generally be avoided in adults residing in skilled nursing facilities.⁷ This list was updated in 1997 to address a wider population of older adults. The panel also identified “high-severity” medications on the list, based on the risk of adverse event occurrence combined with the clinical significance of the outcome.⁸ An expert panel convened in 2002 to incorporate additional data and new medications.⁹

These criteria label certain medications as “potentially inappropriate,” either for older persons in general or for older persons with specific medical conditions. The list relies heavily on expert opinion because so little research evidence on older persons is available. There is conflicting research on the ability of these criteria to predict adverse drug events, improve quality of life, or decrease costs.¹⁰⁻¹² Despite the lack of outcomes data

Between 14 and 24 percent of older adults are receiving potentially inappropriate medications.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
Identify potentially inappropriate medications using the Beers criteria and the CMS guidelines.	C	7, 16
Perform a review of medications with every new patient, every six to 12 months thereafter, and with any medication change.	C	20
Closely monitor patients taking psychotropic medications and those taking more than four medications because they are at greater risk of falls.	B	23
Use the Hamdy questions to decide which drugs to discontinue during a medication review.	C	24
Explore nonpharmacologic treatments and consider whether drugs with proven benefit are still indicated.	C	24, 27
Estimate renal function using formulas such as the Cockcroft-Gault or MDRD study equations and adjust medication dosages accordingly.	C	29
Consider switching to combination medications or once-daily dosing to improve adherence, being careful to balance improved convenience with increased cost.	C	41
Combine cognitive aids and patient education to improve adherence.	C	38

CMS = Centers for Medicare and Medicaid Services; MDRD = Modification of Diet in Renal Disease.

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, see page 1760 or <http://www.aafp.org/afpsort.xml>.

and the development of a more nuanced list by Zhan and colleagues,¹³ the Beers criteria have been widely adopted. The list is the most commonly used research tool for studying inappropriate prescribing practices. These criteria, when applied to older adults, show that between 14 and 24 percent of patients receive potentially inappropriate medications.¹⁴

Medications with a potential for higher severity adverse drug events are listed in *Table 1*.⁹ For patients who have not yet started these medications, all of these drugs are easily avoidable, because safer and equally effective alternatives are available. Discontinuation is not always required in patients receiving long-term treatment with one of these drugs. However, the lowest effective dose should be used rather than waiting until an adverse drug event occurs, and discontinuation should be strongly considered.

The use of potentially inappropriate medications is more common among skilled nursing facility residents.¹⁵ As a result, the Centers for Medicare and Medicaid Services (CMS) has

developed regulations on the use of medicines in skilled nursing facilities that care for patients supported by Medicare funds.¹⁶ These regulations draw heavily from the list of potentially inappropriate drugs.

Skilled nursing facilities are required to have mechanisms by which physicians are notified when their prescribing is in conflict with these regulations. A pharmacist who conducts a monthly review of patients' medications usually performs this notification. For some of the regulations, the skilled nursing facility is cited if their physicians' orders are not in compliance.

In addition to monitoring for use of the drugs listed in *Table 1*,⁹ the CMS guidelines also address dosage guidelines and criteria for the initiation or continuation of psychotropic medications. Increasing evidence associates the use of atypical antipsychotics for dementia in skilled nursing facilities with a higher risk of cerebrovascular accidents and mortality.¹⁷ *Table 2* lists the indications for using antipsychotic medications in skilled nursing facility residents, as well as common situations in which they should not be used.¹⁶

More than 40 percent of ambulatory adults older than 65 years use at least five medications per week.

Table 1. Drug Therapy with High Potential for Severe Adverse Outcomes in Older Patients (Beers Criteria)

Medication or class	Concern
Amiodarone (Cordarone)	Increases risk of QT interval prolongation and torsade de pointes
Amitriptyline (Elavil)*	Strong anticholinergic and sedating properties; safer antidepressants exist
Amphetamines and anorexics	Potentially increase risk of hypertension, angina, and myocardial infarction; cause dependence
Anticholinergics and antihistamines (i.e., chlorpheniramine [Chlor-Trimeton], diphenhydramine [Benadryl], hydroxyzine [Vistaril], cyproheptadine [Periactin],* promethazine [Phenergan], tripeleennamine [Vaginex],* and dexchlorpheniramine [Polaramine]*)	Nonanticholinergic antihistamines are preferred for allergic reactions
Barbiturates (except phenobarbital)	Higher incidence of adverse effects than other sedatives and hypnotics; addictive
Benzodiazepines, long-acting (chlordiazepoxide [Librium], diazepam [Valium], flurazepam [Dalmane])	Prolonged sedation, increased risk of falls, and fractures
Benzodiazepines, short-acting (lorazepam [Ativan], > 3 mg; oxazepam [Serax],* > 60 mg; alprazolam [Xanax], > 2 mg; temazepam [Restoril], > 15 mg; triazolam [Halcion], > 0.25 mg)	Smaller doses are safer
Chlorpropamide (Diabinese)	Prolonged half-life in older patients, which can cause prolonged hypoglycemia
Desiccated thyroid (Armour)	May have cardiac adverse effects
Digoxin in dosages > 0.125 mg per day	Increased serum levels in older patients because of decreased renal excretion
Disopyramide (Norpace)	Strongly anticholinergic, decreases cardiac output and can cause heart failure
Doxepin	Strongly anticholinergic and sedating; safer antidepressants exist
Fluoxetine (Prozac)	Longer half-life increases CNS stimulation, sleep disturbances, and agitation; safer antidepressants exist
GI antispasmodics (dicyclomine [Bentyl], hyoscyamine [Levsin], clidinium†)	Highly anticholinergic at effective doses in older patients
Guanadrel (Hylorel)†	May produce orthostatic hypotension
Guanethidine (Ismelin)†	May produce orthostatic hypotension
Indomethacin (Indocin)	Produces more CNS adverse effects than other NSAIDs
Ketorolac*	Produces GI adverse effects
Laxatives (bisacodyl [Correctol], cascara sagrada [Nature's Remedy]†, castor oil [Purge])	Stimulant laxatives may worsen bowel function
Meperidine (Demerol)	Not an effective oral analgesic; metabolite can accumulate and cause seizures
Meprobamate (Miltown)	Highly addictive and sedating
Mesoridazine (Serentil)*	May cause CNS and extrapyramidal symptoms
Methyldopa (Aldomet)*	Can cause bradycardia and worsen depression
Methyltestosterone (Android)	May worsen prostatic hypertrophy and cardiac problems
Muscle relaxants (methocarbamol [Robaxin], carisoprodol [Soma], chlorzoxazone [Relax DS], metaxalone [Skelaxin], cyclobenzaprine [Amrix], oxybutynin [Ditropan])	Effectiveness is questionable; can cause anticholinergic adverse effects, weakness, and sedation
Nifedipine (Procardia)	May cause hypotension and constipation
Nitrofurantoin (Macrobid)	May worsen renal impairment
NSAIDs, long half-life (naproxen [Naprosyn], oxaprozin [Daypro], piroxicam [Feldene])	Long-term use increases risk of GI bleeds, hypertension, heart failure, and renal failure
Orphenadrine (Norflex)	Strongly anticholinergic and sedating
Pentazocine (Talwin)	Causes more CNS adverse effects than other narcotics, including confusion and hallucinations
Thioridazine (Mellaril)*	May cause CNS and extrapyramidal symptoms
Trimethobenzamide (Tigan)	Less effective than other antiemetics; causes extrapyramidal adverse effects

CNS = central nervous system; GI = gastrointestinal; NSAIDs = nonsteroidal anti-inflammatory drugs.

*—Brand not available in the United States.

†—Discontinued in the United States.

Adapted with permission from Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts [Published correction appears in Arch Intern Med 2004;164:298]. Arch Intern Med 2003;163:2719-20.

Avoiding Overuse of Medications: Polypharmacy and Overdosing

POLYPHARMACY

The term *polymedicine* has been used to describe the increasing number of medications related to a similarly increasing number of medical problems. *Polypharmacy*, on the other hand, denotes an inappropriate use of multiple medications.¹⁸ No commonly accepted definition exists for the threshold at which a patient's polymedicine list becomes polypharmacy. More than 40 percent of ambulatory adults older than 65 years use at least five medications per week, and 12 percent use at least 10 medications per week.¹⁹ Increasing the number of medications also increases the risk of drug-drug interactions and adverse drug events, the most common of which are listed in *Table 3*.⁴

Reviews of a patient's medications should be done at his or her initial assessment (whether in the inpatient or outpatient setting), every six to 12 months thereafter, and with any medication change.²⁰ An easy way to encourage medication review is the "brown-bag" method, in which patients are asked to bring all of their medications to each visit

so the physician can see exactly what they are taking.²¹ To make this more efficient in a busy outpatient setting, a nurse can assist the physician in updating the patient's medication list. This type of intervention can lead to discontinuation of at least one medicine in 20 percent of patients and a change in medication in 29 percent of patients.²² Particular attention to patients taking psychotropic medications or more than four drugs can help prevent falls in older patients.²³ The questions listed in *Table 4* may be useful when deciding which drugs to discontinue during a medication review.²⁴

Two recent systematic reviews have identified proven methods a physician can use to reduce inappropriate prescribing.^{25,26} These include using the Beers criteria, asking pharmacists for their input on reducing inappropriate prescribing, educating patients about the risks of polypharmacy and benefits of medication compliance, and using computerized alerts.²⁵ Two of the approaches deserve brief mention. First, a team approach that provides education to the health care professional and patient, where feasible, is effective in decreasing the number of medications taken by older patients and reducing the occurrence of adverse drug events. Assessment teams involving pharmacists and nurses can evaluate drug regimens and suggest changes. Occasionally, pharmacists will conduct stand-alone medication brown-bag reviews and suggest changes. Serious consideration of these changes may help preempt adverse drug events. Also, use of recent advances in technology, including personal digital assistants and computerized alerts associated with an electronic health record, can reduce adverse events.

Another way to avoid adverse drug events is to explore nonpharmacologic treatment options. For instance, the use of physical therapy and exercise for musculoskeletal complaints is effective and much less toxic than chronic use of nonsteroidal anti-inflammatory drugs. Referring a patient to a senior community center can help with depression and even allow for the avoidance of antidepressant medications. Relaxation techniques and cognitive behavior therapy are effective in controlling anxiety and can take the place

Table 2. When Antipsychotics Should and Should Not Be Used in Skilled Nursing Facility Residents

Valid indications for use	Invalid indications for use
Acute psychotic episodes	Agitated behaviors that are not dangerous to the resident or others
Atypical psychosis	Anxiety
Brief reactive psychosis	Depression (without psychotic features)
Delusional disorder	Fidgeting
Huntington's disease	Impaired memory
Organic mental syndromes (i.e., delirium, dementia, and amnesic and other cognitive disorders) with associated psychotic and/or agitated behaviors	Indifference to surroundings
Psychotic mood disorder (including mania and depression with psychotic features)	Insomnia
Schizoaffective disorder	Nervousness
Schizophrenia	Poor self-care
Schizophreniform disorder	Restlessness
Tourette's syndrome	Uncooperativeness
	Unsociability
	Wandering

Information from reference 16.

Table 3. Common, Important Drug-Drug Interactions

Primary drug	Interacting drug	Effect
Increased effect		
Azathioprine (Imuran)	Allopurinol (Zyloprim)	Bone marrow suppression
Digoxin	Diuretics, quinidine	Digitalis intoxication
Methotrexate	Aspirin, sulfisoxazole (Gantrisin)	Bone marrow suppression
Phenytoin (Dilantin)	Chloramphenicol (Chloromycetin),* isoniazid (Nydravid), phenylbutazone (Butazolidin)*	Cerebellar ataxia, nystagmus, sedation
Propranolol (Inderal)	Cimetidine (Tagamet)	Bradycardia
Sedative hypnotics	Ethanol	Excessive sedation
Sulfonylureas	Chloramphenicol, phenylbutazone, sulfaphenazole,* warfarin	Hypoglycemia
Warfarin (Coumadin)	Aspirin, metronidazole (Flagyl), phenylbutazone	Hemorrhage
Decreased effect		
Chlorpropamide (Diabinese)	Corticosteroids	Decreased hypoglycemic effects
Lincomycin (Lincocin)	Kaolin-pectin (Kaodene NN)	Decreased bioavailability
Metformin (Glucophage)	Risperidone (Risperdal)	Decreased hypoglycemic effects
Pioglitazone (Actos)	Olanzapine (Zyprexa)	Decreased hypoglycemic effects
Prednisone	Barbiturates	Decreased corticosteroid effect
Quinidine	Barbiturates, rifampin (Rifadin)	Loss of antiarrhythmic effect
Tetracycline	Antacids-iron	Decreased bioavailability
Warfarin	Barbiturates, aminoglutethimide (Cytadren), rifampin	Loss of anticoagulation

*—Brand not available in the United States.

Adapted with permission from Bressler R, Bahl JJ. Principles of drug therapy for the elderly patient. *Mayo Clin Proc* 2003;78:1575.

of anxiolytics.²⁷ Lifestyle modification can help patients lower high blood pressure and elevated cholesterol and obviate the need for antihypertensives and statins. The focus should be on maintaining functional status.

OVERDOSING

Proper dosing of medication is even more important in older patients. Renal function remains one of the most important pharmacokinetic factors to alter the effect of a drug. Serum creatinine level is not a reliable measure in older adults, because it assumes a muscle mass that older patients may not have.²⁸ Although a 24-hour urine assessment is the most accurate measure of a patient's renal function, it is inconvenient. In the absence of 24-hour urine measurements, the Cockcroft-Gault equation and the Modification of Diet in Renal Disease (MDRD) study equation provide an age-adjusted estimate of the glomerular filtration rate (GFR).²⁹ A GFR of less than 50 mL per minute per 1.73 mm² is a predictor for

drug-related problems, even though dosage adjustments for renally excreted drugs often are not recommended until the GFR is less than 30 mL per minute per 1.73 mm². Free online versions of the Cockcroft-Gault (<http://nephron.com/cgi-bin/CGSI.cgi>) and MDRD (http://www.nephron.com/MDRD_GFR.cgi) equations are available.

Table 4. Questions to Ask During a Medication Review (the Hamdy Questions)

- Is the indication for which the medication was originally prescribed still present?
- Are there duplications in drug therapy (i.e., same class)? Are simplifications possible?
- Does the regimen include drugs prescribed for an adverse reaction? If so, can the original drug be withdrawn?
- Is the present dosage likely to be subtherapeutic or toxic because of the patient's age and renal status?
- Are any significant drug-drug or drug-illness interactions present?

Adapted with permission from Hamdy RC, Moore SW, Whalen K, Donnelly JP, Compton R, Testerman F, et al. Reducing polypharmacy in extended care. *South Med J* 1995; 88:534-8.

Avoiding Underuse of Medications: Underprescribing and Nonadherence UNDERPRESCRIBING

Despite concerns about overprescribing, many conditions remain underdiagnosed or undertreated. For example, a recent survey of older adults in assisted living centers found that 60 percent of those with a history of myocardial infarction were not receiving aspirin, and 76 percent were not receiving a beta blocker.³⁰ Another study found that only 55 to 75 percent of patients with diabetes received angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers when they were clinically indicated.³¹ Ascribing all symptoms to degenerative disease or old age will potentially miss treatable conditions.

Rheumatoid arthritis beginning in older adulthood, depression, diastolic heart failure, and ataxia secondary to normal-pressure hydrocephalus are examples of conditions that should be diagnosed and treated in older patients but are often missed. Prevention and treatment of osteoporosis must be improved in older adults, particularly among men and women with a history of minimal trauma fracture.³² Simple interventions, such as a single monthly high dose of vitamin D, have been shown to improve outcomes in this population.³³ Pain can be undertreated or overtreated, especially in the context of neuropathic pain and cancer, because physicians can prescribe dosages that are too high or too low in relation to the amount of pain the patient has.^{34,35}

NONADHERENCE

Nonadherence (also called noncompliance) refers to the discordance between physician recommendations and the patient's subsequent behaviors. Patient nonadherence occurs with 40 to 60 percent of prescriptions³⁶ and is complex in its presentation and origins. Although nonadherence commonly refers to patients failing to take their recommended medications, it can also refer to patients consuming too much of a medication or remaining on a medication despite physician suggestions to stop.

Nonadherence is a complex phenomenon determined by a variety of issues, including physician-patient communication, cognitive decline, and the cost of medication. Interventions aimed at increasing adherence have focused on addressing such factors.³⁷ However, using these interventions often assumes that the problem lies in some deficit of information and that a correction of that deficit will change behaviors. They fail to recognize that some patients actively choose to be nonadherent despite having all the correct information.³⁸ Nonadherence is not simply a knowledge discrepancy, but it can also involve feelings, reactions to the physician, cost, availability, and competing medical belief systems.

The recent implementation of Medicare Part D drug benefits and a complex scheme involving annual dollar limits may magnify issues of cost to some patients.³⁹ Two thirds of older patients do not tell their physicians in advance that they plan to underuse a medication because of its cost, and 35 percent never discuss at subsequent visits that they have underused the medication.⁴⁰ Many will not talk about it if they are not asked. Simply asking whether a patient plans to use his or her prescription may be useful. In many cases, more expensive drugs initiated by another physician have generic substitutes that are equally effective and much less expensive. Examples include using omeprazole (Prilosec) instead of esomeprazole (Nexium), lisinopril (Zestril) instead of an angiotensin receptor blocker, and lovastatin (Mevacor) or simvastatin (Zocor) instead of atorvastatin (Lipitor) or rosuvastatin (Crestor).

Two individual drugs may be less expensive than one combination drug, although adherence may increase if the drug regimen is simplified through the use of combination drugs.⁴¹ Using drugs with once-daily dosing also can simplify the drug regimen, as has been shown with antihypertensive therapy.⁴² In one meta-analysis of adherence studies in older adults, most studies on this topic were noted to have flawed designs.³⁸ Most interventions fell into one of two categories: educational intervention and external cognitive

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aids. Individual interventions showed mixed evidence of benefit. However, studies using combinations of cognitive aids and educational intervention were more promising.

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Adverse Drug Events in Older Patients

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