Polypharmacy in the Elderly

How to Reduce Adverse Drug Events

Managing medications in the elderly can be complicated by the physiologic effects of aging and the prevalence of comorbidities. Consistent use of tools such as the Beers criteria and the STOPP/START criteria, as well as medication reconciliation, can reduce polypharmacy and its adverse drug effects, improving health outcomes in this population.

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LEARNING OBJECTIVES

- Identify patients who are at the greatest risk for the effects of polypharmacy.
- Recognize which medications are most likely to cause adverse drug events (ADEs) in the elderly population.
- Understand the effects of aging on the pharmacokinetics and pharmacodynamics of medications.
- Learn strategies to reduce the risk for polypharmacy and ADEs, including use of the Beers Criteria and the STOPP/START Criteria.

Older adults (those 65 and older) often have a number of comorbidities requiring pharmacologic intervention, making medication management a complicated but essential part of caring for the elderly. A recent analysis of trends in prescription drug use by community-dwelling adults found that 39% of older adults used five or more prescribed medications.[1] Furthermore, about 72% of older adults also take a nonprescription medication (OTC or supplement); while OTC medication use has declined in this population in recent years, dietary supplement use has increased.[2]

These patients are also more susceptible to adverse drug events (ADEs)—including adverse drug reactions (ADRs)—resulting from the physiologic changes of aging. By one estimate, ADRs are about seven times more common in those older than 70 than in younger persons.[3] One out of every 30 urgent hospital admissions in patients ages 65 and older is related to an ADR.[4]

Providers must therefore be cognizant of drug indications, dosing, and drug interactions when prescribing medications to elderly patients. Fortunately, tools and methods to avoid polypharmacy and the adverse effects of commonly prescribed medications—such as anticholinergics and psychotropic drugs—are available.

POLYPHARMACY AND PRESCRIPTION CASCADING

While there is no specific number of medications required to define *polypharmacy*, the term is generally used when a nonhospitalized individual is taking five or more medications.[5] The more medications a patient is taking, the more at risk he or she will be for ADRs, drug interactions, and prescription cascading.

Prescription cascading begins when an ADR is thought to be a new symptom and a new drug is prescribed to control it. Ultimately, a cascade of prescriptions occurs to control avoidable ADRs, resulting in polypharmacy. As many as 57% of women older than 65 in the United States are currently prescribed five or more medications, with 12% prescribed nine or more drugs.[6] Not only do these medications cause independent ADRs, but there is also increased risk for drug interactions—and potentially, additional avoidable ADRs.

The elderly population is at greater risk for ADEs because these patients are more likely to have multiple comorbidities and chronic diseases, requiring multiple therapies.[7] Polypharmacy is also more dangerous in the elderly because the physiologic changes that occur during natural aging can affect both the pharmacokinetics and pharmacodynamics of medications. The absorption, distribution, metabolism, and excretion of drugs within the human body changes as a person ages, while certain drug classes can alter the way the body functions. For example, muscle mass naturally declines and the proportion of body fat to muscle increases; this change affects the distribution of drugs such as benzodiazepines or lithium.[7] If the medication dosage is not corrected, the toxicity of the drug will be increased.[7]

Medication excretion is largely controlled by the kidneys. Renal perfusion and function decline with age, leading to a decrease in glomerular filtration rate—which requires closer monitoring of medication selection and dosing. The risk is heightened when the elderly patient becomes acutely ill. An acute decrease in kidney function results in decreased excretion of medications, leading to an increase in ADRs.[7]

Ultimately, the safety of many medications in the elderly patient is unknown.[8] But there is a growing body of knowledge on the adverse effects of some classes of medication in this population.

COMMONLY PRESCRIBED MEDICATIONS—AND RISKS

ADEs result from medication errors, ADRs, allergic reactions, and overdoses. The incidence of ADEs—specifically ADRs and medication errors—is elevated in elderly patients who are prescribed certain classes of medications or multiple drugs simultaneously.[8] Anticholinergic drugs and psychotropic drugs (specifically antipsychotics and benzodiazepines) are among the medications most commonly prescribed to elderly patients—and among the most likely to contribute to ADEs.[9] Diabetes is a chronic condition whose treatment may also put elderly patients at risk for ADEs.[10]

Anticholinergic medications

Anticholinergic drugs—commonly prescribed for Parkinson disease, depression, urinary incontinence, pulmonary disorders, intestinal motility, and muscle spasms—competitively inhibit the binding of acetylcholine to muscarinic acetylcholine receptors.[9] Because this mechanism tends to be nonselective, the adverse effects may be widespread. Central adverse effects

TABLE 1

Pharmacology of Commonly Prescribed Antipsychotics

Second-generation antipsychotics	MOA	Absorption	Half-life (h)
Asenapine[22]	Postsynaptic blockade of brain dopamine D_2 receptors, with an increased affinity for serotonin 5-HT_{2A} receptors	Rapid: 0.5-1.5 h	24
Lurasidone[23]	See above	1-3 h	18
Olanzapine[24]	See above	6 h (po) 15-45 min (IM)	21-54
Quetiapine[25]	Antagonism of dopamine D_1, D_2, histamine H_1, adrenergic α_{1b} and α_2 receptors, and serotonin 5-HT_{1A} and 5-HT_{2A} receptors	6 h	7

Abbreviations: IM, intramuscular; MOA, mechanism of action; po, by mouth.

include cognitive impairment, confusion, and delirium; peripheral adverse effects include constipation, urinary retention, dry mouth, blurred vision, peristaltic reduction, and tachycardia.[9]

Anticholinergic drugs are commonly prescribed to elderly patients for cardiovascular (CV) and neurologic disorders. (Medications for the former include ß-blockers, calcium channel blockers, diuretics, and ACE inhibitors; for the latter, amitriptyline, quetiapine, nortriptyline, prochlorperazine, haloperidol, and paroxetine.) An assessment of anticholinergic activity classified most neurologic medications as high activity and most CV medications as low—however, the latter are usually given in conjunction with other anticholinergic medications, increasing their ability to cause ADRs.[11]

In many cases, patients are prescribed anticholinergic medications to control symptoms of a disease, not to cure it—which means patients may be taking these medications for years. This cumulative exposure is called the *anticholinergic burden*. Many studies show that the anticholinergic burden is a predictor of cognitive and physical decline; a 2016 study of adults older than 65 who were exposed to 5 mg/d of oxybutynin for more than three years had a 23% increased risk for dementia, compared to low-risk or no exposure groups.[9]

In a retrospective, population-level study conducted in New Zealand, researchers assessed the anticholinergic effects of delirium, urinary retention, and constipation in 2,248 patients (65 and older) who were admitted to the hospital with at least one prescribed medication. Anticholinergic burden was found to be a significant independent predictor; patients taking five anticholinergic medications were more than three times as likely to develop an anticholinergic effect than those taking just one such medication (adjusted odds ratio, 3.21).[11]

Psychotropic drugs

Another often-prescribed medication group is psychotropic drugs, specifically antipsychotics and benzodiazepines, for agitation and behavioral disturbances in dementia. A year-long study of 851 patients in two long-term care nursing homes in Boston found that risk for ADRs—specifically, falls—was increased in those who had a change (initiation or dose increase) in psychotropic medication (ie, benzodiazepine, antipsychotic, or antidepressant).[12]

Second-generation antipsychotics, which are more commonly prescribed than first-generation agents, work on a postsynaptic blockade of brain dopamine D_2 receptors and have an increased affinity for serotonin 5-HT_{2A} receptors (see Table 1 for pharmacology of these medications).[13,14] Adverse

effects of these drugs include hypotension, sedation, and anticholinergic effects. Second-generation antipsychotics also carry a "black box warning" for increased risk for death in elderly patients with dementia-related psychosis.[15]

Benzodiazepines bind to receptors in the gamma-aminobutyric acid receptor complex, which enhances the binding of this inhibitory neurotransmitter (see Table 2, page 42, for pharmacology). Of this class of drugs, lorazepam has the highest potency, whereas midazolam and diazepam have lower potencies. Use of benzodiazepines increases risk for delirium and respiratory depression.[16]

Diabetes treatment

People with diabetes have an increased risk for ADEs; this risk is elevated in older adults due to comorbidities such as peripheral neuropathy, retinopathy, coronary artery disease, and peripheral vascular disease.[10] Hypoglycemic agents, such as insulin and insulin secretagogues, confer a higher risk for falls due to their hypoglycemic effect.[10] Furthermore, metformin is known to increase risk for cognitive impairment in patients with diabetes.[10]

PREVENTING ADEs AND UNNECESSARY POLYPHARMACY

Predicting and preventing ADEs should be a health care provider's priority when treating an elderly patient taking multiple medications—but it is often overlooked. Electronic medical records (EMRs) are helpful in preventing ADEs, specifically prescription errors, by flagging the patient's chart when potentially problematic medications are ordered; however, this captures only a portion of ADEs occurring in this population.[7]

Other options to evaluate a patient for polypharmacy and possible ADRs include the Beers Criteria and the STOPP/START Criteria.[17,18] Additionally, performing thorough and frequent medication reviews helps ensure that patients are prescribed essential medications to treat their comorbidities with the most opportunistic risk-benefit ratio. Patients' medication lists across settings (eg, hospital, primary care, urgent care) can be accessed more easily, efficiently, and accurately with the integration of EMRs.

Beers Criteria

First published by Dr. Mark Beers in 1991 and endorsed by the American Geriatrics Society, the Beers Criteria identifies possible harmful effects of certain commonly prescribed medications to help guide and modify pharmacologic treatments, particularly in adults older than 65. The Beers Criteria classifies medications into three categories:

1. Drugs that should be avoided or dose-adjusted
2. Drugs that are potentially inappropriate in patients with certain conditions or syndromes
3. Drugs that should be prescribed with caution in older adults.[17]

In the most recent update (2015), possible adverse effects of medications based on a patient's hepatic or renal function, the effectiveness of the medication, and possible drug interactions were added. For example, nitrofurantoin and antiarrhythmics (eg, amiodarone and digoxin) should be avoided at a lower threshold of hepatic and renal impairment than previously recommended. The criteria suggest avoiding use of zolpidem, a nonbenzodiazepine receptor agonist, because of its elevated risk for adverse effects and minimal effectiveness in treating insomnia. More information about the 2015 criteria is available from the American Geriatrics Society (**http://onlinelibrary.wiley.com/doi/10.1111/jgs.13702/full**).[19]

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TABLE 2
Pharmacology of Commonly Prescribed Benzodiazepines

Benzodiazepines	MOA	Absorption	Half-life (h)
Midazolam[26]	Binds to receptors in the GABA receptor complex, which enhances the binding of this inhibitory neurotransmitter	15-20 min (IM, po) 3-5 min (IV)	2-6
Diazepam[27]	See above	Variable; dose dependent (po); 15-60 min (IV)	20-70
Lorazepam[28]	See above	2 h	14

Abbreviations: GABA, gamma-aminobutyric acid; IM, intramuscular; MOA, mechanism of action; po, by mouth.

The latest update also takes into account recently published evidence of increased ADEs resulting from drugs such as antipsychotics and proton pump inhibitors (PPIs).[20] Antipsychotics are associated with an increased risk for morbidity and mortality, and PPIs are now recommended only for treatment duration of up to two months because of the possible increased risk for *Clostridium difficile* infection, as well as falls and fractures in patients older than 65.[20] (PPIs indirectly reduce calcium absorption, which may lead to an increased fracture risk, particularly in postmenopausal women.[20])

As with any guideline, the Beers Criteria was designed to supplement, not replace, clinical expertise and judgment. The risks and benefits of a medication should be weighed for the individual patient.

STOPP/START Criteria

Less widely used is the STOPP/START Criteria, an evidence-based set of guidelines consisting of 65 STOPP (Screening Tool of Older Person's potentially inappropriate Prescriptions) and 22 START (Screening Tool to Alert doctors to the Right Treatment) criteria. Although they may be used individually, STOPP and START are best used together to determine the most appropriate medications for an elderly patient.

The STOPP guidelines help determine when the risks of a medication may outweigh the benefits in a given patient. STOPP includes recommendations for the appropriate length of time to use a medication; for example, PPIs should not be used for more than eight weeks (similar to the Beers recommendation) and benzodiazepines and neuroleptics for more than four weeks.[18]

START helps clinicians recognize potential prescribing omissions and to identify when a medication regimen should be implemented based on a patient's history.[18] Examples of START criteria include suggestions of when to initiate calcium and vitamin D supplementation for prevention of osteoporosis and when to begin statins in patients with diabetes, coronary artery disease, and cardiovascular disease.[18]

STOPP/START is organized by physiologic system, which allows for greater usability, and it addresses medications by class rather than specific medications. (The Beers Criteria was criticized for these reasons, as well as its limited transferability outside the United States.) When assessed in systematic reviews, the STOPP/START criteria were found to be fundamentally more sensitive than the Beers Criteria. Overall, it was concluded that the use of the STOPP/START criteria resulted in an absolute risk reduction of 21.2% to 35.7% and greatly improved the appropriateness of prescribing medication to the elderly. Its use also resulted in fewer follow-up appointments with a primary care physician (PCP).[18]

iPhone and Android applications such as iGeriatrics and Medstopper provide clinicians with easy access to Beers Criteria and STOPP/START Criteria, respectively.

Medication reconciliation

Medication reconciliation—in which health care providers review a patient's medication list at hospital admission and discharge, and even at routine office visits—is an increasingly common practice, especially with the implementation of EMRs. The patient's prescribed and OTC medications, as well as dose, route, frequency, and indication, are updated, with the goal of maintaining the most accurate list. Health care providers can utilize both the Beers Criteria and the STOPP/START criteria in their reconciliation process to help reduce polypharmacy in the elderly. It is an essential step in maintaining communication between providers and ultimately decreasing the incidence of ADEs.[17]

IMPROVE … continuity of care

Polypharmacy can decrease patient likelihood to adhere to the regimen, whether due to confusion or intolerance.[8] Patients should be included, along with caregivers and all medical providers, in a holistic assessment of the patient's best interests in terms of long-term care and pharmacologic treatment, since those who have a sense of control in their treatment goals and expectations often achieve a better understanding of their medical status.[10]

However, educating patients about their medications is time-consuming, and time is often at a premium during a typical office visit. A pilot study of 28 male veterans (ages 85 and older)—the Integrated Management and Polypharmacy Review of Vulnerable Elders (IMPROVE) project—devised a model to combat this problem.[21] As an adjunct to a visit with the PCP, a clinical pharmacist trained in patient education and medication management performed face-to-face clinical consults with patients and their caregivers. The results indicated that medical management by *both* the PCP and the pharmacist resulted in better medication management. The pharmacist was able to spend time with the patient and caregiver, resulting in individualized instructions, education, and strategies for safe and effective medication use. The PCP remained involved by cosigning the note with the pharmacist and was available for consultation, if needed.

In IMPROVE, 79% of patients had at least one medication discontinued and 75% had one or more dosing or timing adjustments made. Potentially inappropriate medications were reduced by 14%.[21] When the researchers compared the six-month period before the trial with the six-month period afterward, they found an average pharmacy cost savings of $64 per veteran per month. There was also a decreasing trend in phone calls and visits to the PCP. Cost savings were comparable to or greater than those reported for similar interventions.[21] There has not been sufficient long-term follow-up to assess this method's effects on ADEs, morbidity, and mortality, however.

CONCLUSION

Managing medications in the elderly population is difficult, and polypharmacy is common due to the prevalence of patients with comorbidities. It is important for providers to be aware of possible drug interactions, prescribing cascades, and ADEs. Medications such as anticholinergics and antipsychotics pose an increased risk for ADEs, but the regular implementation of criteria such as Beers or STOPP/START in clinical practice will minimize overprescribing and improve health outcomes. These criteria should be used to supplement the clinical judgment and expertise of providers as a mainstay of patient care in the elderly. **CR**

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