

Geriatric Polypharmacy: Unraveling the Mystery

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ABSTRACT

PURPOSE: To increase the awareness of prescribing pitfalls commonly facing primary care clinicians who provide care for older individuals.

EPIDEMIOLOGY: Medicare beneficiaries (14% of the US population) constitute 43% of total drug expenditures. Forty percent take ≥ 5 prescription medications daily and those in long-term care facilities may take more than 9 or 10 per day.

REVIEW SUMMARY: Geriatric polypharmacy—the use of excessive and frequently inappropriate medications—is of prime importance to physicians because the clinical consequences of polypharmacy are numerous and serious. This article reviews the problem and highlights the unique pharmacokinetic and pharmacodynamic effects seen in older patients. Etiologies and consequences of polypharmacy are explored along with currently available interventions and future recommendations to reduce this problem.

TYPE OF AVAILABLE EVIDENCE: Systematic reviews/meta-analyses, randomized-controlled trials, cohort studies, unstructured reviews, textbooks.

GRADE OF AVAILABLE EVIDENCE: Fair. Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; its generalizability to routine practice; or the indirect nature of the evidence on health outcomes.

CONCLUSION: It is imperative for clinicians to determine what medications their older patients are taking and how, and to work with older patients, caregivers, and pharmacists to develop the optimal therapeutic regimen. Future goals should be directed at including a larger number of older adults in clinical trials, improved tracking of adverse events and redundant medications for each patient, and development of tools to improve patient compliance. (*Adv Stud Med.* 2006;6(4):182-188)

“As older patients move through time, often from physician to physician, they are at increasing risk of accumulating layer upon layer of drug therapy, as a reef accumulates layer upon layer of coral.”

Jerry Avorn, MD; 2004¹

Individuals aged 65 and older in the United States use a disproportionate number of prescription and over-the-counter medications. Medicare beneficiaries account for only 14% of the US population yet they constitute 43% of total drug

expenditures.² Only 58% of older patients inform their primary care providers of the various over-the-counter medications that they are taking—often because they do not perceive these to be medications if they are available without a prescription.³

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Off-Label Product Discussion: The author of this article does not include discussion of off-label/unapproved use of products.

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Polypharmacy commonly is defined as the concomitant ingestion of 4 or more medications, especially in the ambulatory setting. But in institutionalized settings this can mean 9 or more medications. Alternately, polypharmacy may simply describe the “prescription, administration, or use of more medications than are clinically indicated in a given patient.”^{4,5} It is important to note that the number of medications itself does not constitute polypharmacy; rather, using medications that are not indicated or duplicative therapy with unclear need do require additional evaluation.

The clinical consequences of polypharmacy are numerous and can be quite serious, including excessive costs to individuals living on fixed incomes, nonadherence, adverse drug reactions (ADRs), drug-drug interactions, medication errors, and an increased risk of hospitalization as a result of ADRs and/or medication errors.⁵ Adverse effects of medications increase as medication use increases, but older individuals also undergo many physiologic changes that affect the pharmacokinetic (ie, absorption, distribution, metabolism, and elimination) and pharmacodynamic parameters of the medications they take.⁶ For instance, older adults have lower serum albumin, higher alpha₁-acid glycoprotein concentrations, and lower protein affinity. These result in an increase in the free fraction of highly protein-bound medications (eg, phenytoin, warfarin, and thyroid hormone). Therefore, report of a therapeutic level of phenytoin may be misleading in an individual with a low albumin level; the high free phenytoin concentration would place the patient at risk for side effects such as ataxia and falls.

Geriatric polypharmacy has shown a trend towards steady increase during the last 20 years. In 1992 seniors used 648 million prescription medications. By 2000 the number had grown to 1 billion annually. Projections for the average number of prescriptions written on behalf of older Americans is expected to reach 1.6 billion by 2010, an increase of 35% from 2000.⁷

A major contributor to these growing numbers is the fact that more medications developed by pharmaceutical companies target the chronic illnesses that are prevalent in our aging population. However, evidence-based guidelines and clinical trials may not include individuals older than age 85. Therefore, clinicians are challenged with the daunting task of evaluating the relative risks versus the benefits of prescribing a particular medication for an older patient.

PREVALENCE AND ETIOLOGY OF POLYPHARMACY

Polypharmacy is not a new concept or a new problem. However, the definition and application have varied across studies. A US survey conducted between 1998 and 2000 of a random sample of 2590 commu-

nity-dwelling adults aged 18 or older demonstrated the highest prevalence of medication use was among women aged ≥ 65 years; of this group 12% took at least 10 medications and 23% took at least 5 prescription drugs.⁴ Additional estimates of polypharmacy in community-dwelling individuals older than age 65 show that approximately 23% of women and 19% of men take at least 5 prescribed medications per day.⁸ Residents of nursing homes take on average 7 to 8 medications per month with approximately one third of residents taking 9 or more medications.⁹ In particular, risk factors for polypharmacy have been found to be: female sex, advanced age, rural residence, lower level of education, and the availability of prescription coverage.⁵

Older individuals have more chronic conditions and often see multiple healthcare providers, which can complicate the medication regimen. Further, there is the challenging task of examining the benefits and risks of the various available pharmacologic and nonpharmacologic treatments.

Tinetti et al note that evidence-based guidelines for the treatment of a variety of serious health conditions undoubtedly have improved and standardized patient care, resulting in benefits such as the prevention of serious disease-specific outcomes and a reduction in hospitalizations and mortality for many chronic conditions, such as diabetes, hypertension, and heart disease. In their analysis, the authors argue that it is less clear what the outcomes are for older patients, who frequently are treated for multiple health conditions simultaneously, because this population has been excluded from many evidence-generating randomized-controlled trials.¹⁰⁻¹² In a study by Alter of 81 584 patients in various age strata, all of whom had been hospitalized with acute coronary syndromes, the authors argue that “baseline mortality is so much higher for elderly patients that neither sharp reductions in the relative efficacy of therapies nor increases in the rates of serious complications are likely to negate the benefits of therapy,” and that it is acceptable to focus more on overall trial results rather than the results for any given age-specific subgroup.¹³

Whereas the results of this study may be reassuring, the researchers raise concerns about “the generalizability of the results to the types of patients who have been excluded from trials” because the effects of their multiple health conditions remains unknown for many medications.¹⁰⁻¹² In addition, other authors point out that in randomized clinical trials, adverse events frequently are not evaluated to the same degree as are the beneficial effects of any given medication. Ioannidis et al conducted a survey of safety reporting in 192 randomized drug trials (n=130,074), and found that the severity of clinical adverse effects and toxicity was only “adequately defined” in 39% and 29% of reports,

respectively.¹⁴ Finally, Tinetti et al emphasize that clinical trials and evidence-based guidelines often look at the short-term, disease-specific benefits of individual medications, or at some specific combinations of medications, for specific patients who are similar to the carefully selected trial participants and who take their medications as prescribed.¹⁰

In the real world, this leaves many questions unanswered in terms of the risks versus the benefits for a chronically ill, older patient. Even if older individuals do comply with their multidrug regimens, what are the effects of multiple medications with various drug interactions/adverse effects in the context of multiple coexisting conditions—especially over the long term? Are there significant benefits to be gained by adding an 11th drug for an 80-year-old patient already taking 10 separate medications? When attempting to apply evidence-based treatment guidelines for a specific medical condition in this population, it is imperative to take into account the patient's preferences and quality of life.^{10,15,16}

THE PRESCRIBING CASCADE

In a culture in which patients expect to have “a pill for every ill” there is almost an expectation on the part of patient and provider alike that each clinician visit will result in at least 1 prescription. The expectations of patients are complicated by direct-to-consumer marketing as well as the media attention given to medications. Whereas ready access to such information may help raise awareness of disease states and available treatments, it also may lead to inappropriate prescribing and requests from patients, caregivers, and family members.

The “prescribing cascade” refers to the practice of treating a side effect of a medication with another medication.¹⁷ For example, a patient may complain of stomach upset that is caused by over-the-counter ibuprofen, however, instead of ascertaining this from the history and discontinuing the culprit drug, the clinician may place the patient on a proton pump inhibitor to treat the stomach upset. Another common area for a prescribing cascade is treatment of hypertension. Patients may be prescribed increasingly potent doses of antihypertensive medication or additional medications when their blood pressure is elevated. However, the elevated blood pressure may be the result of poor compliance with the medical regimen—because the drugs are too costly or because of unpleasant side effects—or it may be that another medication prescribed by a separate clinician has increased the patient's blood pressure.

Further, consumers under tight financial constraints often shop around to multiple pharmacies to have their various prescriptions filled. Such patients may be unaware of the multiple brand and generic names for the same drug (eg, digoxin and lanoxin).

This is a potentially dangerous scenario, because the patient may wind up filling/taking duplicate prescriptions/medications.

THE CONSEQUENCES OF POLYPHARMACY

The consequences of polypharmacy, as mentioned above, include increased financial burden as well as nonadherence, ADRs, and drug-drug interactions—all of which further result in increased risk for hospitalization.¹⁸⁻²⁰

NONADHERENCE

The problem of nonadherence to pharmacotherapy has been well documented. A *Medline* search of the English-language literature from 1962 to 1997 to identify articles that reported on predictors of medication compliance in the elderly revealed that the frequency of nonadherence among older patients (with adherence defined as taking at least 80% of the medication) ranged from 26% to 59%,²¹ but there were conflicting reasons for this. Polypharmacy was reported by some authors to be associated with nonadherence, along with other factors. Researchers also reported “clear associations” between medication adherence and race, drug and dosage form, number of medications, cost of medications, insurance coverage, and physician-patient communication. However, the findings were inconsistent with regard to the effects of patients' age, sex, socioeconomic status, living arrangements, comorbidities, number of physician visits, and knowledge, attitudes, and beliefs about health.¹⁹

Barat et al²² conducted a study of a randomly selected cross-section of the older population (n=348) in Denmark. Information on all drugs was collected from the subjects during a home visit, at which time drug storage also was examined. Information was obtained from the subjects' general practitioners, as well. Measures of adherence were based on scores of agreement between the physicians' lists and the subjects' actual drug consumption. The authors found disagreement on general drug information in 22% of the study population, on doses in 71%, and concerning regimens prescribed by the physician in 66%. Twenty-four percent of subjects stated that they did not always follow prescription regimens. Most of the deviations from prescriptions were toward lower doses and less frequent drug intake. Sixty percent of the participants knew the purpose of the medication, and 21% knew the consequences of omission of the drugs. Fewer than 6% of the subjects understood the toxic risks, side effects, or potential drug interactions of a drug they were taking. The participants' knowledge of the drugs was positively associated with adherence. A positive association also was seen between nonadherence and increased frequency of drug intake ($P=.01$), the use of

3 or more drugs (odds ratio [OR] 2.5; 95% confidence interval [CI], 1.5–4.1), prescriptions from more than 1 doctor (OR 2.5; 95% CI, 1.3–4.8), and probability of dementia (OR 9.0; 95% CI, 1.1–72.5). Furthermore, older persons living alone were more prone to medication errors (OR 2.0; 95% CI, 1.1–3.5). In specifically addressing the issue of polypharmacy, the authors noted, “We found that the number of prescribed drugs is a very powerful predictor of nonadherence... Based on our findings we suggest that physicians carefully evaluate each drug prescribed in order to reduce the number of drugs and the number of drug-intakes per day.”²²

Similar data have been collected in the United States. Coons et al interviewed 1028 individuals from a randomly selected sample of community-dwelling adults aged 55 years and older in the southeastern United States. Among the 785 subjects in the analysis who were taking prescribed medications, 21% reported having been noncompliant with their regimens during the month preceding the study interview. In this study, noncompliance was significantly associated with a greater number of prescribed medications ($P < .01$), among other issues.²³

Likewise, Botelho et al found that, of the 59 elderly participants in their investigation, 54.7% were noncompliant with their medication regimens. In this sample, nonadherence with a drug regimen was associated with the inability to read medication labels ($P < .01$), but not with impaired visual acuity, number of prescribed medications, type of medication container lid, depression, cognitive impairment, perceived health status, or cost of the medication(s). Frequency of drug administration also affected patient adherence. Mean adherence of patients to prescriptions for drugs to be taken once or twice daily was 72%, whereas drugs to be taken 3 or 4 times daily had a mean adherence rate of 54% ($P < .01$).²⁴

Another small study by Kruse et al concurred that frequent dosing schedules negatively impact adherence in older patients.²⁵ Conn et al found that the complexity of a medication regimen was extremely important to older populations; the authors noted that this issue may have a “larger impact on aspects of medication management” that go beyond just adherence.²⁶

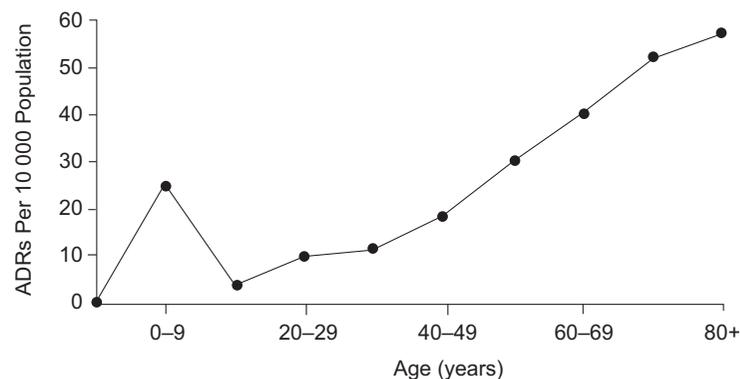
ADVERSE DRUG REACTIONS

In 1998 there was a surprising and disturbing result from a meta-analysis by Lazarou et al of 39 prospective studies examining incidence of ADRs in US hospitals that would have placed fatal ADRs as “between the fourth and the sixth leading cause of death” in the United States if this category were ranked as a disease.²⁷ By definition, an ADR is: “any undesirable or unintended effect at drug dosages typically standard for treatment, but that can occur at any dosage or drug

concentration.”²⁸ The majority of ADRs result from an extension of the desired pharmacologic drug effects because of patient variability and altered pharmacokinetics and pharmacodynamics. This is particularly true for drugs that have narrow toxic-therapeutic ranges, such as the aminoglycoside antibiotics, digoxin, and theophylline. Again, older patients may or may not have been studied in clinical trials for a particular drug they are taking. Therefore, the so-called “standard dose” for an older adult patient may be unknown and may be quite different from that of a younger person. As noted earlier, this may put older adults at higher risk for unintended side effects or ADRs.

All of the existing variables, including kinetic and dynamic changes and comorbidities that require additional medications, no doubt result in clinicians seeing a disproportionate increase in age-related ADRs. In evaluating drug intake among geriatric patients it has been determined that, if an elderly patient takes ≥ 5 prescription medications, he/she has a 35% chance of experiencing an adverse reaction.²⁷ Factoring in prescribing rates to potential drug interactions, as one approaches 9 or 10 medications—as do some patients in long-term care—there is an astonishing 100% chance that some type of drug-drug interaction will occur.^{29,30} Ghose examined ADRs as a function of increasing age (Figure).³¹ For adults, ADRs steadily increased from the second decade of life (approximately 10 adverse events per 10 000 adults) to the 8th decade of life, when ADRs exceeded 60 per 10 000.

Figure. Adverse Drug Reactions as a Function of Increasing Age



Reprinted with permission from Ghose K.³¹
ADR = adverse drug reaction.

Writing in the *Journal of the American Medical Association* in 2003, Gurwitz et al stated that, "Adverse drug events are among the top 5 greatest and most preventable threats to the health of the elderly."³² Indeed, 36% of reported adverse drug events involve an older patient.⁵ Hanlon et al studied 167 high-risk (taking ≥ 5 scheduled medications) ambulatory older veterans and found that 63% had required physician intervention for an ADR, 10% required a visit to the emergency department, and 11% had required hospitalization.²⁹ Overall, 28% of hospitalizations of older adults are owing to ADRs and noncompliance (17% and 11%, respectively).⁶ Finally, approximately 32 000 older patients suffer hip fractures each year from falls possibly due to medication-related side effects.⁵ The consequences of the latter are grave: 14% to 36% of elderly patients who have suffered hip fractures die within a year of surgery³³ and 50% of survivors are less independent after the injury. Additional adverse events commonly experienced by seniors include depression, constipation, immobility, and confusion.³⁴

If older patients are hospitalized for any reason and are taking ≥ 3 medications for chronic conditions, they face a 33% chance of rehospitalization within 6 months⁵; 20% of these readmissions are due to medication-related problems. The transition from the home to the hospital, and then back home, can be rife with confusion regarding medication use. Specifically, the patient may be discharged on a myriad of new drugs that may be duplicates of drugs he/she already has at home or that may cause adverse effects not manageable in the home environment.

However, this problem is confined neither to the hospital setting nor to patients who have been hospitalized. A large cohort study of medication safety among Medicare enrollees (30 397 person-years of observation) conducted over a 12-month period examined the incidence and preventability of adverse drug events in the ambulatory setting. The authors reported 1523 documented adverse drug events; 578 (38%) were categorized as serious, life threatening, or fatal. Nearly half (42.2%) of the 244 more severe events were deemed preventable compared with 177 (18.7%) of the 945 significant adverse drug events. Errors associated with preventable adverse drug events occurred most often at the stages of prescribing (n=246 [58.4%]) and monitoring (n=256 [60.8%]), but errors involving patient adherence (n=89 [21.1%]) also were common. Cardiovascular medications (24.5%), followed by diuretics (22.1%), nonopioid analgesics (15.4%), hypoglycemics (10.9%), and anticoagulants (10.2%) were the most common medication categories associated with preventable adverse drug events. Electrolyte/renal (26.6%), gastrointestinal tract (21.1%), hemorrhagic (15.9%), metabolic/endocrine

(13.8%), and neuropsychiatric (8.6%) events were the most common types of preventable adverse drug events.³²

FINANCIAL BURDEN

The overwhelming cost of multiple medication regimens to seniors on fixed incomes has reached crisis proportions^{35,36} with prescription drug costs growing faster than any other aspect of healthcare-related cost. More recently, a study by the Kaiser Family Foundation noted that 23% of seniors reported spending \$100 or more per month on prescription drugs.²

Certainly this problem is not to be overlooked, yet the issue extends beyond cost to the individual to a broader financial toll on society. In 2000 it was estimated that medication-related problems in the older adult population cost the US economy \$85 billion.³⁷ Bootman et al, Bates et al, and Johnson et al broke down costs for adverse events to approximately \$76.6 billion for ambulatory care, \$20 billion for hospital care, and \$4 billion for nursing home facilities, respectively.³⁸⁻⁴⁰

PREVENTION OF POLYPHARMACY

In Healthy People 2010, an objective for combating polypharmacy is to increase the proportion of primary care providers, pharmacists, and other healthcare professionals who routinely review with their older patients and those patients with chronic illnesses or disabilities all new prescribed and over-the-counter medicines.⁴¹ At least once a year, patients should bring all of their medications—including those prescribed and over the counter, eye drops, and creams—to their healthcare provider(s) for a comprehensive review.

Pharmacists are key healthcare professionals in recognizing individuals struggling with medications and it is imperative that all healthcare professionals work together to tackle this public health concern. An interdisciplinary medication review of older individuals in the community helped to reduce the cost as well as number of medications.⁴²

A process to streamline and simplify medication regimens includes:

1. Determining what medications the patient is taking (which often is not clear to patients who may have been given many medications by multiple providers)
2. Reducing or eliminating any unnecessary or redundant drugs
3. Utilizing medications with the simplest schedule and instructions for use.

Numerous emerging technologies may soon assist in reminding patients to take medications or in administration of drug regimens, yet some more basic principles can be used with success by clinicians, as well (Table).

CONCLUSION

The fundamental principle of managing drug therapy in older patients, “start low and go slow,” underscores the need to accommodate age-related changes in the body. These include changes in receptor sites and normal physiologic and structural changes in the body’s organs, coupled with the onset of chronic diseases, cognitive decline, decreasing sensory acuity and mobility, and psychiatric and social issues that may influence the ability to take medications as directed and also increase the likelihood of adverse reactions. Clinicians must take these factors into account and pay careful attention to the individual needs of patients in order to tailor a medication regimen that “first [does] no harm.” It also is imperative for healthcare professionals to work together to address these issues. A growing number of pharmacists focus on caring for the medication-related needs of older individuals and can be found at: www.seniorcarepharmacist.com or www.ccgp.org.

As we continue to develop new therapeutic agents and the aging population continues to live longer—perhaps with more chronic illnesses—it will be vital to add older patients with comorbidities to clinical trials. It is important that we understand how new pharmaceuticals affect older individuals. In addition, the continued development of computerized tracking tools will assist clinicians and pharmacists alike in the prevention of harmful or fatal adverse effects and drug interactions. Finally, lowered costs, packaging design that keeps older patients in mind (eg, with larger print, easy-to-open vials, etc), and use of memory aids hopefully will further enhance compliance.⁴⁷ However, clinicians also will need to be even more vigilant in monitoring the types and amounts of medicines their older patients consume to help make geriatric polypharmacy a thing of the past.

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Table. Approaches to Polypharmacy^{5,42-47}

- Identify indication for use to avoid unnecessary drug therapy
- Evaluate all medications, prescription and over the counter, to avoid inappropriate prescribing
- Examine all doses, taking in consideration comorbidities and kidney function
- Communicate and educate staff, caregivers, and/or patients to address unmet needs of patients and to assess the need for drug therapy
- Document adverse drug reactions (ADRs) to avoid adverse drug events
- Assess Medication Administration Record, prescription records, or vials to evaluate a patient’s adherence to therapy
- Decrease the number of doses and, possibly, of medications to simplify regimens
- Provide information about alternative or nonpharmacologic options
- Identify and mobilize both internal and external resources (ie, family, visiting nurse, pharmacist, neighbor) to improve and/or oversee the medications
- Take a critical look at medications during times of transitions (ie, home to hospital and back to home) and develop a medication reconciliation system

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