

Polypharmacy, Adverse Drug Reactions, and Geriatric Syndromes

Bhavik M. Shah, PharmD, BCPS*, Emily R. Hajjar, PharmD, BCPS, BCACP, CGP

KEYWORDS

- Polypharmacy
- Elderly
- Geriatric syndromes
- Adverse drug reactions

The older population, composed of adults aged 65 years or older, is the fastest growing segment of the United States population. The Administration of Aging of the United States Department of Health and Human Services reported that there were approximately 40 million older adults in 2009, an increase of 12.5% from 1999. The Administration projects the greatest increases to the older population to occur over the next two decades as the first baby boomers reach the age of 65 in 2011. By 2030, there will be approximately 72 million older adults.¹ Chronic diseases are prevalent among the older population; about 80% of older adults have at least one chronic condition, and about half have at least two.² These chronic conditions, which include heart disease, hypertension, diabetes, arthritis, and cancer, often require multiple medications for optimal management.

Although the use of multiple medications is widely referred to as polypharmacy, no consensus exists on what number should define the term. In the literature, polypharmacy has been arbitrarily defined as taking at least two to nine medications concurrently.³⁻⁷ This definition is controversial because polypharmacy may be appropriate to treat a patient with multiple comorbid conditions. This appropriateness is especially true for disease states such as chronic heart failure and diabetes, which require multiple drug therapies as directed by disease state guidelines. For example, a patient with Class IV New York Heart Association heart failure may be prescribed a loop diuretic, an aldosterone inhibiting diuretic, a β -blocker, an angiotensin-converting enzyme inhibitor, digoxin to treat the heart failure, and other medications for any other comorbid condition. Excessive polypharmacy is another type of polypharmacy that is defined by medication count and generally uses cut points of 10 or more

B. Shah has no relationships to disclose.

E. Hajjar is a consultant for Prime Therapeutics.

Jefferson School of Pharmacy, Thomas Jefferson University, 130 South 9th Street, Suite 1540, Philadelphia, PA 19107, USA

* Corresponding author.

E-mail address: bhavik.shah@jefferson.edu

Clin Geriatr Med 28 (2012) 173–186

doi:10.1016/j.cger.2012.01.002

0749-0690/12/\$ – see front matter © 2012 Elsevier Inc. All rights reserved.

geriatric.theclinics.com

medications. This definition is becoming increasingly studied as the population continues to age and use more medications.

Alternately, polypharmacy has also been defined as taking at least one medication that is not clinically indicated. This indication-based definition is argued to be more practical and appropriate because it is independent of the multiple medications necessary to treat the multiple comorbidities elderly patients are likely to have.⁷ This definition necessitates a medication review and takes medication appropriateness into account. Those that lack an indication or effectiveness or are determined to be a therapeutic duplication are considered as polypharmacy or unnecessary medications. An example would be a patient started on a proton pump inhibitor while an inpatient for stress ulcer prophylaxis. If the medication is continued on an outpatient basis, this medication would be considered unnecessary because there is no longer an indication for the medication.

EPIDEMIOLOGY

Prevalence of Polypharmacy Defined by Medication Count

Overall medication use has increased recently. According to IMS Health data, the number of prescriptions filled in 2010 was about 4 billion.⁸ Although making up about 13% of the US population, older adults filled one-third of all prescriptions and 40% of nonprescription medications.⁹ The average older adult filled 31 prescriptions per year in 2009, twice as many as all other age groups combined.¹⁰ Similar disproportionate use has been reported in Canada and the United Kingdom.^{11,12}

The prevalence of polypharmacy reported in the literature, ranging from 5% to 78%, varies because of the different definitions used and samples studied.⁷ Furthermore, the reported average number of prescriptions taken daily by ambulatory elderly patients ranges between two and nine medications.¹³ Polypharmacy is more common in women, and its prevalence increases with advancing age.⁷ A large national survey of prescription and nonprescription medication use in ambulatory adults found that 57% of women aged 65 years or older took at least five medications, and 12% took at least 10 medications.¹⁴ A European study of ambulatory older adults reported a similar prevalence rate; 51% of elderly patients took at least six prescription and nonprescription medications per day.¹⁵

Nobili and colleagues¹⁶ reported the rate of polypharmacy among hospitalized Italian elderly patients of 52% with a mean number of 4.9 medications (N = 1332, mean age 79.4 years) upon admission; the rate of polypharmacy increased to 67% upon discharge with a mean number of 6.0 medications.¹⁶ Schuler and colleagues¹⁷ reported a polypharmacy rate of 58% upon admission in Austrian hospitals, with a mean number of 7.5 medications (N = 543, median age 82 years). In the United States, about half of elderly patients admitted to hospitals take seven or more medications.¹⁸

A large national study of 13,507 nursing home residents showed a polypharmacy rate of 40%. Polypharmacy was defined as at least nine medications, a higher threshold compared with other studies in ambulatory or hospitalized settings.¹⁹ Data on the prevalence rate in assisted living facilities is more limited. However, one study of 2014 residents, the majority of whom were 85 years or older, in 193 assisted living facilities reported a mean of 5.8 medications.²⁰

Prevalence of Polypharmacy Defined as Unnecessary Drug Use

Medication use that is not clinically warranted is another definition of polypharmacy.⁷ Lipton and colleagues²¹ found that 60% of 236 ambulatory elderly patients aged 65 years or older were taking medications that lacked an indication or were suboptimal. In a study of 196 elderly veteran patients, Steinman and colleagues²² evaluated

unnecessary medications by using the Medication Appropriateness Index (MAI), defined as medications with no indication, lack of effectiveness, or therapeutic duplication. They reported that 57% of patients were taking at least one unnecessary medication. Using the MAI criteria for unnecessary medication, Schmadler and colleagues²³ found that a mean number of 0.65 unnecessary medications were taken in a study of 834 frail elderly veterans. Additionally, a study of 384 hospitalized frail elderly veterans found that 44% of patients were discharged with at least one unnecessary medication, as defined by the MAI.²⁴ A majority of these patients (75%) had at least one unnecessary medication prior to hospital admission. The most common reason was a lack of indication (33%). Hanlon and colleagues²⁵ reported similar findings; lack of indication was the most common reason for unnecessary medications in a study of 397 hospitalized elderly veterans. Common unnecessary medications include gastrointestinal, central nervous system, and therapeutic nutrient/mineral agents.²⁴

Most Common Medications

Kaufman and colleagues¹⁴ reported in 2002 that the most common prescription medications among ambulatory older patients were conjugated estrogens, levothyroxine, hydrochlorothiazide, atorvastatin, and lisinopril. A study of ambulatory Medicare patients revealed that the most common drug classes prescribed in a 1-year period were cardiovascular agents, antibiotics, diuretics, analgesics, antihyperlipidemics, and gastrointestinal agents.²⁶ This result is to be expected because the drugs reflect the common conditions that occur in community-dwelling elders. The most common nonprescription medications consumed by older adults were analgesics (aspirin, acetaminophen, and ibuprofen), cough and cold medications (diphenhydramine and pseudoephedrine), vitamins and minerals (multivitamins, vitamins E and C, calcium), and herbal products (ginseng, Ginkgo biloba extract).¹⁴ Other nonprescription medications commonly used by elderly patients include antacids and laxatives.²⁷ A survey of institutionalized older adults found that the most common medications were gastrointestinal agents, central nervous system agents (antidepressants, antipsychotics, antimanics), and analgesics (opioids and nonopioids).¹⁹

CONSEQUENCES OF POLYPHARMACY

There are many consequences of polypharmacy. Aside from increased direct drug costs, patients are at higher risk for adverse drug reactions, drug interactions, nonadherence, diminished functional status, and various geriatric syndromes.

Adverse Drug Reactions

The number of adverse drug reactions (ADRs) for all age groups has increased over recent years, with an estimated 4.3 million ADR-related health care visits in 2005.²⁸ Age 65 years or older and polypharmacy were significant risk factors for ADR-related visits. ADRs occur in up to 35% of outpatients and 44% of hospitalized elderly patients and account for approximately 10% of emergency room visits.^{29,30} Polypharmacy increases the risk of ADRs from 13% (two medications) to 58% (five drugs).³¹ Seven or more medications further increases the risk of ADRs to 82%.³¹ The most common drug classes associated with ADRs were cardiovascular drugs, diuretics, anticoagulants, nonsteroidal antiinflammatory drugs, antibiotics, and hypoglycemics.^{26,30} These medications are prescribed for common conditions, and providers should be aware of the risks for each medication class.

Drug Interactions

The elderly are at high risk for drug interactions due to polypharmacy, comorbidities, and decreased nutritional status, which may affect the pharmacokinetic and pharmacodynamic properties of medications.³² Potential drug-drug interactions are common. In a prospective, randomized controlled longitudinal multicenter European study of 1601 community-dwelling elderly adults, 46% of patients had a potential drug-drug interaction.³³ This result is consistent with other studies that report the prevalence of potential drug-drug interactions between 35% and 60% in elderly patients.²⁹ The risk of drug-drug interactions increases with the number of drugs and can approach 100% with eight or more medications.³⁴ In elderly patients, drug-drug interactions are a common reason for preventable adverse drug reactions and hospitalizations related to drug toxicity.^{26,35}

The prevalence of drug-disease interactions is reported to be 15% to 40% in frail elderly patients.^{36,37} The investigators noted the most common interactions were aspirin and peptic ulcer disease, calcium channel blockers and heart failure, and β -blockers and diabetes. The risk of drug-disease interactions has been shown to increase as the number of drugs as well as the number of comorbidities increase.³⁷ Risk of drug-disease interactions are of concern because few patients suffer from just one chronic condition.

The prevalence rates should be interpreted cautiously, because they may be overestimated due to how interactions and their clinical importance are defined.³² Additionally, many of the studies evaluated potential interactions, which may not be clinically relevant.³⁰ Nevertheless, the elderly are at risk for drug interactions. These interactions are significant because they may decrease the efficacy or increase the risk of toxicity of a drug. As a result, the prescriber may change the dose or add more medications, further increasing the risk for other interactions and side effects.

Nonadherence

Complex medication regimens related to polypharmacy can lead to nonadherence in the elderly.¹³ Studies in community-dwelling elderly adults have reported medication adherence rates between 43% and 95%.³⁸ The variability can be attributed to different definitions for adherence, population characteristics, and how adherence was measured. The number of medications has been shown to be a stronger predictor of nonadherence than advancing age, with higher rates of nonadherence as the number of medications increases.^{39,40} Nonadherence can lead to serious sequelae including disease progression, treatment failure, hospitalization, and adverse drug events.⁴⁰

Diminished Activities of Daily Living and Instrumental Activities of Daily Living

Polypharmacy has also been associated with functional decline in older patients. In a prospective study of over 600 community-dwelling elderly, increased prescription medication use was associated with decreased physical functioning and decreased ability to carry out instrumental activities of daily living (IADLs) after controlling for age, education, health, number of conditions, and baseline functional status.⁴¹ Another cross-sectional study based on the Women's Health and Aging Study found that the use of five or more medications resulted in diminished ability to perform IADLs, especially being able to shop for personal items (including medications).⁴² Yet another study of approximately 300 patients reported that excessive polypharmacy (using >10 drugs) was associated with a decline in the ability to perform IADLs. Only 30% of patients with no polypharmacy were found to have difficulty performing

IADLs, whereas 74% of those with excessive polypharmacy were found to have difficulty with IADLs.⁴³ Higher medication use has also been positively associated with functional decline in patients who have suffered a fall in the previous year.⁴⁴ Although medication may be used to preserve some functional capacity, providers should be aware of the association between polypharmacy and functional decline.

Increased Health Service Utilization and Resources

The use of multiple medications leads to increased costs for both the patient and the health system as a whole. Whereas the proper use of medications may lead to decreased hospital and emergency room admissions, the use of inappropriate medications may not only increase patients' drug costs but cause them to use more health care services. A retrospective population study in Ireland concluded that approximately 9% of the total drug-related expenditures were on potentially inappropriate medications.⁴⁵ Consequences of polypharmacy can also lead to an increase in health resources as well. A retrospective cohort study of elderly Japanese patients reported that patients with polypharmacy were at risk of having a potentially inappropriate medication, which then increased the risk for hospitalization and outpatient visits and resulted in a 33% increase in medical costs.⁴⁶

Increased Risk of Geriatric Syndromes

Cognitive impairments

Cognitive impairment, which includes delirium and dementia, occurs commonly in the elderly. In a review of 42 cohorts of medical inpatients composed of mostly older adults, the rate of delirium ranged from 11% to 42%.⁴⁷ Whereas the cause of delirium is multifactorial, drugs are a common risk factor and may be the precipitating cause in 12% to 39% of cases.⁴⁸ Inouye and Charpentier⁴⁹ reported that the number of medications (four or more) added the day before a delirium episode was a risk factor for delirium. Another study of 156 hospitalized older adults found that the number of medications was an independent risk factor for delirium.⁵⁰ The most common drugs associated with delirium are opioids, benzodiazepines, and anticholinergics. Similarly, drug classes that can exacerbate dementia are benzodiazepines, anticonvulsants, and anticholinergic drugs such as tricyclic antidepressants.⁵¹

Cognitive impairment measured by the Mini-Mental State Examination (MMSE) has also been found to be negatively associated with polypharmacy. A cohort study of 294 Finnish elders reported that those with polypharmacy were found to have a decrease of 1.36 points in their MMSE scores. Twenty-two percent of patients with no polypharmacy were found to have impaired cognition as opposed to 33% and 54% with polypharmacy and excessive polypharmacy, respectively.⁴³

Falls

Falls are an especially concerning problem in the elderly, causing increased morbidity and mortality. Unfortunately, many medications are known to increase the risk of falls. A cross-sectional study in older outpatients found that the number of prescribed medications was significantly associated with the risk of falls.⁵² Another study evaluating risk factors for those who have not fallen compared with those who have fallen once and those who have experienced multiple falls found that the number of medications was associated with an increased risk of falls.⁵³ In the Longitudinal Aging Study Amsterdam, it was found that use of four or more medications was associated with increased risk of falling as well as increased risk of recurrent falls.⁵⁴ Other studies have shown there is an increased risk of falls from polypharmacy for both hospital and nursing home populations.⁵⁵

Table 1
Drug regimen review to reduce polypharmacy

| Author and Year | Setting | N | Intervention | Results |
|------------------------------------|---|---|---|--|
| Muir et al, 2004 ⁶³ | General medicine inpatient service in Veterans Affairs medical center | 836 | Medication grid provided to admitting residents that included all medications and administration times over 1 week. | Number of medications reduced in intervention group (−0.92) compared with control (+1.65), as well as the mean number of doses (−2.47 vs +3.83, respectively). ($P < .001$ for both). |
| Zarowitz et al, 2005 ⁶⁴ | Outpatient, managed care | 6693 (first intervention) 6039 (second intervention) | Clinical pharmacists reviewed drug regimens, educated physicians and patients on polypharmacy, and worked with physicians to reduce polypharmacy. | The rate of polypharmacy reduced by 67.5% after first intervention, from 29.01 to 9.43 events/1000 patients. After the second intervention, the polypharmacy rate was reduced by 39%, from 27.99 to 17.07 events/1000 patients. |
| Schamder et al, 2004 ²³ | Inpatient and outpatient frail elderly veterans | 834 | Inpatient and outpatient geriatric evaluation and management consisting of geriatrician, nurse, social worker, and pharmacist. | Geriatric evaluation and management reduced the number of unnecessary and inappropriate drugs in inpatients ($P < .05$), but not in outpatients. |
| Hanlon et al, 1996 ⁶⁵ | Outpatient veterans | 208 | Clinical pharmacist reviewed regimens and communicated recommendations in writing and verbally to primary physician. | Using the Medication Appropriateness Index, inappropriate prescribing significantly decreased in the intervention group compared with the control at 3 months (decrease of 24% versus 6%, respectively, $P = .0006$). This benefit was sustained at 12 months (decrease 28% vs 5%, $P = .002$). This result included lower rates of unnecessary medications in the intervention group based on descriptive data. |

| | | | | |
|----------------------------------|---|---|---|---|
| Galt, 1998 ⁶⁶ | Outpatient veterans | 336 | Pharmacist pharmacotherapy consult. | Reduced average number of prescriptions per patient (2.4). |
| Fillit et al, 1999 ⁶⁷ | Outpatient Medicare beneficiaries | 5737 surveyed, 2615 (46%) responded, 1087 went to physician | Elderly Medicare beneficiaries at risk for polypharmacy were sent letters by managed care organization encouraging them to meet with their primary physicians for medication review. Physicians provided with guidelines on polypharmacy. | Of the 1087 patients who scheduled a medication review, 20% reported having a medication discontinued. |
| Fick et al, 2004 ⁶⁸ | Medicare and Choice southeastern managed care organization primary care physicians and patients | 355 physicians | Physicians were mailed a listing of patients who were taking potentially inappropriate medications, as defined by the Beer's criteria, as well as alternative recommendations provided by multiple independent pharmacists and geriatricians. | 12.5% of potentially inappropriate medications were discontinued. The most common discontinued medications were antihistamines, analgesics, and muscle relaxants. |

Use of certain medications is also of concern when considering risk factors for falls in older adults. Psychotropic and cardiovascular medications are of particular concern because of their association with increased risk of falls.^{56,57} In a study of over 300 community-dwelling male veterans, the use of a psychotropic medication was associated with an increased risk of falls (odds ratio [OR] 1.54; 95% confidence interval [CI] 1.07–2.22). The use of two or more psychotropic medications further increased the risk of falls in this population (OR 2.37; 95% CI 1.14–4.94).⁵⁸ A population-based cohort study of over 2000 Swedish patients evaluated the prevalence of polypharmacy before and after reported hip fracture. Interestingly, the use of five or more medications was seen in 48% percent of the population before they fractured a hip compared with 88% after the hip fracture. The proportion of patients taking 10 or more medication as well as those taking three or more psychotropic medication also increased after hip fracture.⁵⁹ This trend of increasing polypharmacy after a traumatic event such as a hip fracture is of concern because the use of multiple medications puts the patient at risk for the original event. The risk of further events is likely to increase, and providers should be aware of this trend and the risk that each type of medication carries with regard to falls.

Urinary incontinence

Urinary incontinence is yet another problem that commonly affects older adults, and the use of multiple medications can exacerbate the problem. A retrospective study of 128 patients found that approximately 60% of patients with urinary incontinence were on at least four medications.⁶⁰ A cross-sectional study found that medications that cause polyuria, decreased sensory input, and decreased bladder contractility were associated with the patient's self-reported urinary incontinence.⁶¹

Nutrition

Polypharmacy also puts elders at increased risk of poor nutritional status. A survey conducted in community-dwelling elders aged 65 and older reported that polypharmacy was associated with poorer nutritional status. Higher medication use was associated with a decreased intake of soluble and nonsoluble fiber, fat-soluble vitamins, B vitamins, and minerals and an increased intake of cholesterol, glucose, and sodium.⁶² A prospective cohort study found that nutritional assessment measured by the mini-nutritional assessment–short version was also negatively impacted by polypharmacy. Only 10% of patients with no polypharmacy were found to be either malnourished or at risk of malnourishment as compared with 50% in those with excessive polypharmacy.⁴³

CLINICAL APPROACH TO IMPROVING POLYPHARMACY

Drug Regimen Review

Several studies support reviewing drug regimens to reduce polypharmacy.^{23,63–68} These studies have been conducted in inpatient and ambulatory settings, with regimens reviewed by physicians, pharmacists, and/or managed care organizations. The studies are summarized in **Table 1**.

Principles for Optimizing Drug Use in the Elderly

Extensive medication histories should be obtained at the initial visit and updated with each subsequent encounter. Medication histories should include both prescription and nonprescription medications and any other health-related food or drink the patient is consuming. Patients and/or their caregivers should be encouraged to bring in all prescription and over-the-counter (OTC) products with them to each health care

visit. If the patient cannot bring in the actual products, an updated list of all medications should be kept with the patient to give to all providers so health records can be kept as up-to-date as possible. Both primary care and specialist providers need to have inclusive lists as to not create polypharmacy because of incomplete health care related data. Additional questioning is most likely needed to ascertain all of the OTC products that a patient takes. Items such as vitamins, supplements, and OTC items such as antacids may be inadvertently left off medication lists or not be included with other medications, because patients often perceive these to be without risk or unimportant for the health care provider to know about. Informing patients or caregivers of drug interactions with nonprescription agents may be one way to stress the importance of providing a comprehensive list of medications to all providers.

Once a complete medication list has been obtained, the provider can then determine if a medication is warranted and if the benefits outweigh the risks for that drug. All medications should have an indication, and if they do not, an evaluation is needed to see if the medication is necessary. Discontinuation of unnecessary medications is reasonable for most drugs, but some may need to be tapered off to prevent any adverse drug withdrawal events. It is also important to determine if a new medication is being used to treat the side effects of another medication. Although sometimes a prescribing cascade is necessary (eg, potassium supplementation in a patient receiving a diuretic), many times it adds an unnecessary burden to the patient's already complicated medication regimen. Existing therapies should also be evaluated to determine if they need to be continued or if optimization could occur. As patients age and their health status changes, medications may become ineffective, more harmful, or require dosage changes to prevent ADRs from occurring. Nonpharmacologic therapy, such as diet and exercise, should be considered whenever possible. If a medication is determined to be necessary, health care providers need to consider the medication's pharmacokinetic and pharmacodynamic properties, side effect profile, and current hepatic and renal function for accurate dosing. Medication cost, patient preference, and potential for drug-drug and drug-disease interactions should also be considered in prescribing. Reasonable therapeutic goals and monitoring parameters will help guide therapy to prevent unwanted side effects. It is also wise for health care providers to create their own personal formularies where they become very familiar with prescribing a few drugs. Simplifying medication regimens as well as educating patients regarding medications can improve adherence.⁶⁹ Adherence may also be improved with the use of generic medications whenever possible, pill boxes and other adherence tools, and educating caregivers.

Two techniques, often referred to as SAIL and TIDE, are helpful in remembering ways to reduce polypharmacy.⁹ Summarized in **Table 2**, they refer to the following:

- **Simple:** Keep the regimen as simple as possible. Use medications that can be dosed once or twice a day. Use a medication that can treat multiple indications. When drug therapy has been titrated to ideal doses, try to combine medications into single pills to reduce pill burden.
- **Adverse effects:** Know the potential adverse effects of medications. Choose medications that have broad therapeutic indices when possible. Identify medications that are treating adverse effects of other medications. Discontinue the drug that is causing the adverse effect, if possible.
- **Indication:** Ensure each medication has an indication and a defined, realistic therapeutic goal.

Table 2
SAIL and TIDE techniques to reduce polypharmacy⁹

| Technique | Description |
|-------------------|---|
| SAIL | |
| Simplify | Simplify drug regimens to reduce pill burden. Use medications that can be dosed once or twice daily. Use medications that can treat multiple conditions. |
| Adverse effects | Be familiar with adverse effects of medications. Choose medications that have broad therapeutic indices when possible. Discontinue a medication that is causing an adverse effect when possible. |
| Indication | Ensure each medication has an indication and a defined, realistic therapeutic goal. |
| List | List the name and dose of each medication in the chart and share it with the patient and/or caregiver. |
| TIDE | |
| Time | Allow sufficient time to address and discuss medication issues during each encounter. |
| Individualize | Apply pharmacokinetic and pharmacodynamic principles to individualize medication regimens. Consider dose adjustments for renal and/or hepatic impairment. Start medications at lower doses than usual and titrate slowly. |
| Drug interactions | Consider potential drug-drug and drug-disease interactions. Avoid potentially dangerous interactions, such as those that can increase the risk for torsades de pointes. |
| Educate | Educate the patient and caregiver regarding pharmacologic and nonpharmacologic treatments. Discuss expected medication effects, potential adverse effects, and monitoring parameters. |

- **List:** Write down the name and dose of each medication in the chart and share it with the patient.
- **Time:** Allow sufficient time to address and discuss medication issues.
- **Individualize:** Apply pharmacokinetic and pharmacodynamic principles to individual patients to select the most appropriate medication and dose. Consider dose adjustments for the patient's renal or hepatic function. Medications should start at lower than usual doses and be titrated slowly, often referred to as "start low, go slow."
- **Drug-drug and drug-disease interactions:** Consider potential drug-drug and drug-disease interactions, and avoid potentially dangerous interactions such as those leading to torsades de pointes.
- **Educate:** Educate the patient and caregiver regarding pharmacologic and nonpharmacologic treatments. Discuss expected medication effects, potential adverse effects, and drug-drug interactions and monitoring parameters.

SUMMARY

The elderly are at risk for polypharmacy, which is associated with significant consequences such as adverse effects, medication nonadherence, drug-drug and drug-disease interactions, and increased risk of geriatric syndromes. Providers should evaluate all existing medications at each patient visit for appropriateness and weigh the risks and benefits of starting new medications to minimize polypharmacy.

REFERENCES

1. Administration on Aging of the United State Department of Health and Human Services. A profile of older Americans: 2010. Available at: http://www.aoa.gov/aoaroot/aging_statistics/Profile/2010/docs/2010profile.pdf. Updated February 25, 2011. Accessed August 10, 2011.
2. Centers for Disease Control and Prevention. Public health and aging: trends in aging — United States and worldwide. *MMWR Morb Mortal Wkly Rep* 2003;52:101–10.
3. Stewart RB, Cooper JW. Polypharmacy in the aged. Practical solutions. *Drugs Aging* 1994;4:449–61.
4. Bikowski R, Ripsin C, Lorraine V. Physician-patient congruence regarding medication regimens. *J Am Geriatr Soc* 2001;49:1353–7.
5. Joorgensen T, Johansson S, Kennerfalk A, et al. Prescription drug use, diagnoses, and healthcare utilization among the elderly. *Ann Pharmacother* 2001;35:1004–9.
6. Linjakumpu T, Hartkainen S, Klaukka T, et al. Use of medications and polypharmacy are increasing among the elderly. *J Clin Epidemiol* 2002;55:809–17.
7. Fulton MM, Allen ER. Polypharmacy in the elderly: a literature review. *J Am Acad Nurse Pract* 2005;17:123–32.
8. Top-line Market Data. IMS Health Web site. Available at: http://www.imshealth.com/deployedfiles/ims/Global/Content/Corporate/Press%20Room/Top-line%20Market%20Data/2010%20Top-line%20Market%20Data/2010_Top_Therapeutic_Classes_by_RX.pdf. Accessed August 18, 2011.
9. Werder SF, Preskorn SH. Managing polypharmacy: walking a fine line between help and harm. *Current Psychiatry Online*. 2003;2. Available at: <http://www.jfponline.com/Pages.asp?AID=601>. Accessed August 20, 2011.
10. United States prescription drugs. Kaiser Family Health Foundation. Available at: <http://www.statehealthfacts.org/profileind.jsp?sub=66&rgn=1&cat=5>. Accessed August 20, 2011.
11. Barat I, Andreasen F, Damsgaard EM. The consumption of drugs by 75-year-old individuals living in their own homes. *Eur J Clin Pharmacol* 2000;56:501–9.
12. Kennerfalk A, Ruigomez A, Wallander MA, et al. Geriatric drug therapy and healthcare utilization in the United Kingdom. *Ann Pharmacother* 2002;36:797–803.
13. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. *Am J Geriatr Pharmacother* 2007;5:345–51.
14. Kaufman D, Kelly J, Rosenberg L, et al. Recent patterns of medication use in the ambulatory adult population of the United States: The Slone survey. *JAMA* 2002;287:337–44.
15. Fialova D, Topinkova E, Gamrassi G, et al. Potentially inappropriate medication use among elderly home care patients in Europe. *JAMA* 2005;293:1348–58.
16. Nobili A, Licata G, Salerno F, et al. Polypharmacy, length of hospital stay, and in-hospital mortality among elderly patients in internal medicine wards. The REPOSI study. *Eur J Clin Pharmacol* 2011;67:507–19.
17. Schuler J, Dückelmann C, Beindl W, et al. Polypharmacy and inappropriate prescribing in elderly internal-medicine patients in Austria. *Wien Klin Wochenschr* 2008;120:733–41.
18. Flaherty JH, Perry HM 3rd, Lynchard GS, et al. Polypharmacy and hospitalization among older home care patients. *J Gerontol A Biol Sci Med Sci* 2000;55:554–9.
19. Dwyer LL, Han B, Woodwell DA, et al. Polypharmacy in nursing home residents in the United States: results of the 2004 National Nursing Home Survey. *Am J Geriatr Pharmacother* 2010;8:63–72.

20. Sloane PD, Zimmerman S, Brown LC, et al. Inappropriate medication prescribing in residential care/assisted living facilities. *J Am Geriatr Soc* 2002;50:1001–11.
21. Lipton HL, Bero LA, Bird JA, et al. The impact of clinical pharmacists' consultations on physicians' geriatric drug prescribing. A randomized controlled trial. *Med Care* 1992; 30:646–58.
22. Steinman MA, Landerfeld CS, Rosenthal GE, et al. Polypharmacy and prescribing quality in older people. *J Am Geriatr Soc* 2006;54:1516–23.
23. Schmader KE, Hanlon JT, Pieper CF, et al. Effects of geriatric evaluation and management on adverse reactions and suboptimal prescribing in the frail elderly. *Am J Med* 2004;116:394–401.
24. Hajjar ER, Hanlon JT, Sloane RJ, et al. Unnecessary drug use in frail older people at hospital discharge. *J Am Geriatr Soc* 2005;53:1518–23.
25. Hanlon JT, Artz MB, Pieper CF, et al. Inappropriate medication use among frail elderly inpatients. *Ann Pharmacother* 2004;38:9–14.
26. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA* 2003;289:1107–16.
27. Stoehr GP, Ganguli M, Seaberg EC, et al. Over-the-counter medication use in an older rural community: the MoVIES project. *J Am Geriatr Soc* 1997;45:158–65.
28. Bourgeois FT, Shannon MW, Valim C, et al. Adverse drug events in the outpatient setting: an 11-year national analysis. *Pharmacoepidemiol Drug Saf* 2010;19:901–10.
29. Rollason V, Vogt N. Reduction of polypharmacy in the elderly. A systematic review of the role of the pharmacist. *Drugs Aging* 2003;20:817–32.
30. Hohl CM, Dankoff J, Colacone A, et al. Polypharmacy, adverse drug-related events, and potential adverse drug interactions in elderly patients presenting to an emergency department. *Ann Emerg Med* 2001;38:666–71.
31. Prybys K, Melville K, Hanna J, et al. Polypharmacy in the elderly: Clinical challenges in emergency practice: Part 1: Overview, etiology, and drug interactions. *Emerg Med Rep* 2002;23:145–53.
32. Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. *Lancet* 2007;370:185–91.
33. Bjorkman IK, Fastbom J, Schmidt IK, et al. Drug-drug interactions in the elderly. *Ann Pharmacother* 2002;36:1675–81
34. Sloan RW. Drug interactions. *Am Fam Physician* 1983;27:229–38.
35. Juurlink DN, Mamdani M, Kopp A, et al. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *JAMA* 2003;289:1652–8.
36. Lindblad CI, Hanlon JT, Gross CR, et al. Clinically important drug-disease interactions and their prevalence in older adults. *Clin Ther* 2006;28:1133–43.
37. Lindblad CI, Artz MB, Pieper CF, et al. Potential drug-disease interactions in frail, hospitalized elderly veterans. *Ann Pharmacother* 2005;39:412–7.
38. Vik SA, Maxwell CJ, Hogan DB. Measurement, correlates, and health outcomes of medication adherence among seniors. *Ann Pharmacother* 2004;38:303–12.
39. Colley CA, Lucas LM. Polypharmacy: the cure becomes the disease. *J Gen Int Med* 1993;8:278–83.
40. Salazar JA, Poon I, Nair M. Clinical consequences of polypharmacy in the elderly: expect the unexpected, think the unthinkable. *Expert Opin Drug Saf* 2007;6:695–704.
41. Magaziner J, Cadigan DA, Fedder DO, et al. Medication use and functional decline among community-dwelling older women. *J Aging Health* 1989;1:470–84.
42. Crenstil V, Ricks MO, Xue QL, et al. A pharmacoepidemiologic study of community-dwelling, disabled older women: factors associated with medication use. *Am J Geriatr Pharmacother* 2010;8:215–24.

43. Jyrkka J, Enlund H, Lavikainen P, et al. Association of polypharmacy with nutritional status, functional ability and cognitive capacity over a three-year period in an elderly population. *Pharmacoepidemiol Drug Saf* 2010;20:514–22.
44. Stel VS, Smit JH, Plujim SM, et al. Consequences of falling in older men and women and risk factors for health service use and functional decline. *Age Aging* 2004;33:58–65.
45. Cahir C, Fahey T, Teeling M, et al. Potentially inappropriate prescribing and cost outcomes for older people: a national population study. *Br J Clin Pharmacol* 2010;69:543–52.
46. Akazawa M, Imai H, Igarashi A, et al. Potentially inappropriate medication use in elderly Japanese patients. *Am J Geriatr Pharmacother* 2010;8:146–60.
47. Siddiqi N, Horne AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age Ageing* 2006;35:350–64.
48. Alagiakrishnan K, Wiens CA. An approach to drug-induced delirium in the elderly. *Postgrad Med J* 2004;80:388–93.
49. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons: predictive model and interrelationship with baseline vulnerability. *JAMA* 1996;275:852–7.
50. Martin NJ, Stones MJ, Young JE, et al. Development of delirium: a prospective cohort study in a community hospital. *Int Psychogeriatr* 2000;12:117–27.
51. Hayes BD, Klein-Schwartz W, Barrueto F Jr. Polypharmacy and the geriatric patient. *Clin Geriatr Med* 2007;23:371–90.
52. Kojima T, Akishita M, Nakamura T, et al. Association of polypharmacy with fall risk among geriatric outpatients. *Geriatr Gerontol Int* 2011;11:438–44.
53. Fletcher PC, Berg K, Dalby DM, et al. Risk factors for falling among community-based seniors. *J Patient Saf* 2009;5:61–6.
54. Tromp AM, Plujim SM, Smit JH, et al. Fall-risk screening test: a positive study of predictors for falls in community-dwelling elderly. *J Clin Epidemiol* 2001;54:837–44.
55. Boyle N, Naganathan V, Cumming RG. Medication and falls: risk and optimization. *Clin Geriatr Med* 2010;26:583–605.
56. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc* 1999;47:30–9.
57. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. *J Am Geriatr Soc* 1999;47:40–50.
58. Weiner DK, Hanlon JT, Studenski SA. Effects of central nervous system polypharmacy on falls liability in community-dwelling elderly. *Gerontol* 1998;44:217–21.
59. Kragh A, Elmstahl S, Atroshi I. Older adults medication use 6 months before and after hip fracture: A population-based cohort study. *J Am Geriatr Soc* 2011;58:863–8.
60. Gormely EA, Griffiths DJ, McCracken PN, et al. Polypharmacy and its effect of urinary incontinence in a geriatric population. *Br J Urol* 1993;71:265–9.
61. Ruby CM, Hanlon JT, Fillenbaum GG, et al. Medication use and control of urination among community-dwelling older adults. *J Aging Health* 2005;17:661–74.
62. Heuberger RA, Caudell K. Polypharmacy and nutritional status in older adults. *Drugs Aging* 2011;28:315–23.
63. Muir AJ, Sanders LL, Wilkinson WE, et al. Reducing medication regimen complexity. A controlled trial. *J Gen Intern Med* 2004;16:77–82.
64. Zarowitz BJ, Stebelsky LA, Muma BK, et al. Reduction of high-risk polypharmacy drug combinations in patients in a managed care setting. *Pharmacotherapy* 2005;25:1636–45.

65. Hanlon JT, Weinberger M, Samsa GP, et al. A randomized, controlled trial of a clinical pharmacist intervention to improve inappropriate prescribing in elderly outpatients with polypharmacy. *Am J Med* 1996;100:428–37.
66. Galt KA. Cost avoidance, acceptance, and outcomes associated with a pharmacotherapy consult clinic in a Veterans Affairs Medical Center. *Pharmacotherapy* 1998; 18:1103–11.
67. Fillit HM, Futterman R, Orland BI, et al. Polypharmacy management in Medicare managed care: changes in prescribing by primary care physicians resulting from a program promoting medication reviews. *Am J Manag Care* 1999;5:587–94.
68. Fick DM, Maclean JR, Rodriguez NA, et al. A randomized study to decrease the use of potentially inappropriate medications among community-dwelling older adults in a southeastern managed care organization. *Am J Manag Care* 2004;10:761–8.
69. Schrader SL, Dressing B, Blue R, et al. The medication reduction project: combating polypharmacy in South Dakota elders through community-based interventions. *S D J Med* 1996;49:441–8.