

Rational Drug Use in the Elderly

Gulistan Bahat^{1*}, Fatih Tufan¹, Sibel Akin¹, Asli Tufan¹, Nilgun Erten² and Mehmet Akif Karan³

¹Fellow, Department of Internal Medicine, Division of Geriatrics, Istanbul Medical School, Istanbul University, Capa, 34390, Istanbul, Turkey

²Professor, Department of Internal Medicine, Istanbul Medical School, Istanbul University, Capa, 34390, Istanbul, Turkey

³Professor, Department of Internal Medicine, Division of Geriatrics, Istanbul Medical School, Istanbul University, Capa, 34390, Istanbul, Turkey

Abstract

Polypharmacy is a commonly addressed problem in the elderly. It is the use of a minimum of four medicines simultaneously. However, the elderly population suffers not only from the overuse of the medicines but also from the underuse. Furthermore, not uncommonly, use of a minimum of four medicines designated as polypharmacy, may be rational in many clinical circumstances in the elderly. In this article, we review the principles of rational drug use in the elderly. The main aim of the geriatric management increasing the quality of life should also be the purpose of the drug therapy. The physiological changes that occur by aging should be taken into account. The patient or caregiver should be informed on the drug list, instruction on use, possible side effects and indication of the current regimen. The drugs taken by the patient should be checked against the recommended regimen. The regimen should be reviewed for indication, appropriateness and possible switch to a safer or cheaper agent, minimum effective dosage, timing, effectiveness, side effects and toxicity, and potential drug-drug interaction one by one. This checking should be performed in a periodical manner and also in any acute deterioration. The potentially useful drugs should not be underused. This approach may decrease both the overuse and underuse of medicines resulting in the rational drug use of the vulnerable elderly.

Keywords: Drug; Elderly; Overuse; Polypharmacy; Underuse; Quality of life

Rational Drug Use in the Elderly

Inappropriate drug use in the elderly is a very prevalent problem. The regimen given to an individual may be designated as “inappropriate” in a number of different circumstances. A drug may be inappropriate if it has unacceptable side effect profile, requires close monitoring that could not be assured, has a significant but underestimated interaction with the concurrent medications, has a better (i.e. cheaper, with less side effect profile, less frequent dosing) alternative, has no current indication. However lack of use of a drug with proven benefit also ends with the inappropriate drug regimen. In this article we review the principles of rational drug use in the elderly.

Polypharmacy is usually defined as the use of a minimum of 4-5 drugs [1-3]. Prevalence differs among countries increasing with advanced age, and is almost 35-40% in the elderly above 75 years of age [4,5]. Its prevalence also differs between community-dwelling elderly and the nursing home residents. Among community-dwelling elderly, the prevalences of 41%, 43.4%, 35.8%, 46.8%, have been reported from Iceland, USA, Australia and Italy, respectively [6-9]. A prevalence of 49.7% was reported by a very recent study reported from nursing homes of 8 different European countries as a report of Shelter study [10] Furthermore, in USA, approximately 40% of nursing home residents were reported to use even ≥ 9 medicines concurrently [11].

The etiology of polypharmacy is generally multiple. Many chronic diseases increase in prevalence by aging necessitating multiple drug use. Additionally, aged people usually administer to multiple doctors which usually do not inquire the drugs given by the other. Use of multiple drugs typically results sometimes even with the same ingredients or belonging to the same class. Perpetuation of unnecessary medications is another hazard of multiple prescribers together making the number of prescribing physician an independent risk factor for drug adverse effects [12]. Furthermore, generally symptoms of the elderly are commented to be due to a disease process or aging itself. Therefore, prescription of a new drug to compensate an unconsidered effect of the current regimen is not unusual in the elderly. This is the condition what so called “prescription cascade” [1]. Advanced age and living in nursing home are already documented risk factors for polypharmacy [1,13]. Some patient and/or caregiver related factors may also be the

causative of polypharmacy. Such factors include cognition problems, visual disturbances and other functional impairments, and lack of education. Additional physician related factors for polypharmacy are incomplete knowledge on the drug effects and interactions [14].

Polypharmacy is rather important because it may be very hazardous to the elderly people. The elderly is very prone to adverse effects of the drugs. The number of used drugs and the history of adverse drug events are the two most predictive data on the emergence of adverse drug event [1]. Adverse drug effects can affect 35% of community dwelling elderly receiving polypharmacy of which 95% are predictable [15]. Such adverse reactions were reported to cause 10.7% of hospitalizations in the elderly [16]. Polypharmacy also increases the risk of nonspecific syndromes including weight loss, falls, and decline in functional and cognitive status [17-21]. A meta-analysis found a fourfold increase in the rate of hospitalization related to adverse drug events in older adults compared with younger adults (16.6% vs 4.1%) [22]. The polypharmacy and inappropriate medicine use increases the likelihood of nursing home placement, impaired mobility, morbidity, hospitalizations, and death [23,24].

However, polypharmacy is not always inappropriate because prescribing 4 or more drugs may be necessary occasionally [25]. Therefore, the major concern should not be the total number of drugs but the appropriateness of the regimen to the goals of care. So, rather than focusing on the total number of drugs, focusing on the goals of care is the principle of prescription management in the elderly. The goals of care should be determined as extension of longevity, reduction in symptoms, and minimization of pill burden, medication side effects,

***Corresponding author:** Gulistan Bahat, Istanbul University, Istanbul Medical School, Department of Internal Medicine, Capa, 34390, Istanbul, Turkey, Tel: +90 212 414 20 00-33204; Fax: +90 212 532 42 08; E-mail: gbahatozturk@yahoo.com

Received January 05, 2012; Accepted February 08, 2012; Published February 10, 2012

Citation: Bahat G, Tufan F, Akin S, Tufan A, Erten N et al. (2012) Rational Drug Use in the Elderly. J Gerontol Geriat Res 1:104. doi:10.4172/2167-7182.1000104

Copyright: © 2012 Bahat G, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

and costs [26]. The main aim of the geriatric management -increasing the quality of life, should also be the purpose of the drug therapy. Nevertheless, the higher number of drugs is a known and independent risk factor for the inappropriate medication use and development of adverse drug effects [27,28]. Adverse drug effects are reported to affect as much as 35% of community dwelling elderly [15]. Such adverse effects cause almost 25% of hospital admissions more than 10% of hospitalizations in the elderly [16,29]. As it is expected, hospitalization need for an adverse drug effect is more in the elderly [22]. Strikingly, the preventability of an adverse drug effect resulting in hospitalization need is also more in the elderly than in the younger counterparts [22]. So, one can prevent adverse drug effect needing hospitalization more easily in the old patients than in the young. There are well defined drugs to be avoided or used in great caution in the elderly (Table 1) [1,27]. Anticholinergic and sedative drugs are the two of major concerns [30,31]. They easily impair the physical and cognitive performance [32]. Their adverse effects include memory impairment, confusion, hallucinations, dry mouth, blurred vision, constipation, nausea, urinary retention, impaired sweating, and tachycardia each may be devastating to the elderly [1]. Additionally, digoxin, hypoglycemics and warfarin are the other 3 drugs to be used with great caution in the elderly. Strikingly, they are found to be responsible from 1/3 of emergency visits of the elderly [33]. In this context, the most commonly cited criteria of drugs to be avoided in the elderly-Beers criteria [34-37] was noted as shortcoming [33]. The new tool of Screening Tool of Older Person's Prescriptions (STOPP) [38] is put forward as a better tool [39-41]. Very recently, "The Good Palliative-Geriatric Practice algorithm" for drug discontinuation has been shown to be effective in reducing polypharmacy and improving mortality and morbidity in both community dwelling elders and nursing home inpatients [42,43]. In long term facilities, preventable adverse drug events are mostly related to antipsychotic and warfarin use.

Physiological changes are important factor to be considered in prescription management of the elderly. Although the absorption is generally unchanged for most of the drugs [44], metabolism, distribution and excretion may change significantly. First-pass metabolism is the intestinal and hepatic degradation or alteration of a drug or substance taken by mouth, after its absorption. It removes some of the active substance from the blood before it enters the general circulation. There is a reduction in first-pass metabolism with advancing age. This is probably due to a reduction in liver mass, and for high clearance drugs, the consequential reduction in blood flow [45]. The bioavailability of drugs undergoing extensive first-pass metabolism can significantly be increased [45]. By contrast, the first-pass activation of several pro-drugs, such as the ACE inhibitors enalapril and perindopril, might be

slowed or reduced [46]. As percentage of body fat increases and body water and fat free mass decrease by aging, an increased or decreased volume of distribution may result according to the physical properties of a given drug. Water soluble drugs (ie gentamicin, digoxin, lithium, theophylline) tend to have smaller volumes of distribution resulting in higher serum levels. Therefore digoxin, lithium intoxication and gentamicin and theophylline side effects are encountered much more in the elderly. Lipid soluble drugs (i.e. benzodiazepines, morphine, lidocaine, amiodarone) tend to have larger volumes of distribution resulting in increased half life [45]. Contrarily, fentanyl transdermal patch may be ineffective in the elderly with reduced body fat due to decreased lipid reservoir of the drug [47]. Pharmacodynamics of some drugs may also be changed by aging. Typical examples are increased sensitivity to opioids, benzodiazepine, anticholinergics and neuroleptics [45,48-52]. Increased sensitivity to the effect of warfarin is important and may result in toxicity when given in the doses that is usual for the youngs. However, not only increased sensitivity but also decreased sensitivity to a drug effect may be the consequence of aging. Examples for such drugs include decreased effect of beta receptor blockers, and verapamil on cardiac conduction function [45]. Such points should be considered during prescription.

Table 2 outlines the principles of rational drug use in the elderly. Community pharmacists may be incorporated for the management of the proper drug use of community dwelling elderly. Where health systems permit, nurses and clinic-based pharmacists should share medication management responsibilities as articulated in the patient-centered medical home model of care.

Elderly frequently use over-the-counter drugs, herbs, vitamins and dietary supplements which they frequently underreport [4,53]. However, such received and referred non-drug supplements may interact with the current regimen. The commonly used herbals and dietary supplements include glucosamine, ginseng, ginkgo biloba extract, St. John's wort, echinacea and valerian root extract. Therefore the patient should also be asked for use of nondrug referred supplements and the list of the regimen should be given to the patient or caregiver including these non-drug referred supplements. Not only the brand but also generic name of the drugs should be written. The patient side should be informed on the frequency, dosing, indication of use and possible side effects. They should also be informed on when to seek medical evaluation and against the possible errors of sound-alike names, look-alike pills and combination drugs. Each visit should be regarded as the opportunity to check the list. Frequently, the regimen intended to be given by the doctors are not the regimen taken by the patients [54,55]. The drug list should be checked against the drug bottles and boxes. This type of checking also gives the opportunity to check the

Drug	Potential harm	Comment
Insulin and sulfonylureas	Hypoglycemia	May often be appropriate; however, aggressive glycemic control may often yield greater harms than benefits in older adults
Warfarin	Gastrointestinal, intracranial bleeding	Although a high-risk drug, benefits of warfarin therapy often outweigh harms; maintenance of prothrombin time international normalized ratio in therapeutic range tightly linked to risk/benefit ratio
Digoxin	Impairment of cognition, heart block	May have a third-line role in management of systolic heart failure; suboptimal choice for rate control in atrial fibrillation
Benzodiazepines	Falls	Associated with as much as a 60 percent increase in fall risk
Diphenhydramine, other first-generation antihistamines	Impaired cognition, urinary retention in men	Poor choice as sleep aid due to anticholinergic effects, next-day sedation, impact on performance including driving; close medication reconciliation important because patients may also obtain over-the-counter drugs
Antipsychotics	Death, pneumonia	Elevated risk of death when used to treat behavioral complications of dementia, although in selected cases, benefits may exceed risks if consistent with patient goals of care

Table 1: Selected high-risk drugs [1,27].

1. Give a list all of the drugs -including prescribed drugs, over-the-counter drugs, herbs, vitamins and nutritional supplements, to the patient or caregiver
 - The drug name (both generic and brand), dosage, frequency, route and indication should always be integrated.
 - The patient or the caregiver should be informed based on this detailed list
2. Check the drugs taken by the patient with the list given by the physician
3. Review the current drug therapy for indication, appropriateness and possible switch to a safer or cheaper agent, minimum effective dosage, timing, effectiveness, side effects and toxicity, and potential drug-drug interaction. Consider non-pharmacological approaches. Match each drug with its indicative disease. Ask for effectiveness and side-effects of each single drug. Compare the benefits and risks of the drugs individually. This checking should be performed in a periodical manner (at least once a year) and also whenever a decline in function or an onset or worsening of geriatric syndromes occur
4. Inform the patient or caregiver for common side effects and when to seek medical advice related to use of drugs
5. Try to simplify the medication dosing schedule
 - Try to minimize dosing frequency
 - Prescribe longer-acting medications- if suitable
 - Dose different drugs at the same time- if suitable
 - Try to use medications that can treat two or three conditions simultaneously- if suitable
6. Address the adherence
7. Consider the new or worsening symptoms as possible side effects of the current medications
9. Monitor for effective level and toxicity of high risk drugs.
10. Do not underuse the potentially useful drugs
11. Determine the goals of care for each individual patient and determine the prioritizations
 - Involve the patient and/or caregiver to the treatment plan, integrate the patient values
12. Integrate quality of life as an essential part of managing an elderly
13. Try to withdraw medications by gradually tapering off to minimize withdrawal reactions and to allow symptom monitoring, unless dangerous signs or symptoms indicate a need for abrupt medication withdrawal

Table 2: Principles of Rational Drug Use in the Elderly.

effectivity of the individual drugs. On the other hand, the more risky drugs may be additionally inquired for the specific adverse effects as hypoglycemia related symptoms for hypoglycemics, anticholinergic symptoms for anticholinergics and bleeding symptoms for warfarin. If the time limitation is a concern as usually does in many daily practices, focusing on the highest risk and highest benefit drugs is recommended [27]. The regimen should be reviewed for indication, appropriateness and possible switch to a safer or cheaper agent, minimum effective dosage, timing, effectiveness, side effects and toxicity, monitoring standards and potential drug-drug interaction one by one. This checking should be performed in a periodical manner and also in any acute deterioration. Because, the acute deterioration may be the result of adverse drug reaction or it may change the goals of care for the individual patient [27]. As an example, a fall may be the result of an antiparkinson drug resulting in orthostatic hypotension and also if the patient would be bedridden due to a fall, goals of care change and it may end up with attenuation of antiparkinson medicine due to limited mobility. Another point is, whenever possible, clinicians should minimize dosing frequency by prescribing longer-acting medications and dosing different drugs at the same time. Pill burden can be reduced by using medications that can treat two or three conditions simultaneously. This is a useful approach to minimize the number of drugs [27].

The elderly population suffers not only from the overuse of the medicines but also from the underuse. According to some studies, underuse may even be more prevalent [56]. In the context of rational drug use, the potentially useful drugs should not be underused. Clinicians may underuse the useful drug if he does not consider its benefit in the old, if the patient can not afford the medication, also if the appropriate dosing for the old is unavailable. START (screening tool to alert doctors to the right treatment) is a tool designed specifically

to address this issue [57]. It gives the list of evidence based useful but possibly omitted drugs in the elderly [57]. A suggested way to overcome underutilization of potentially useful drugs is to document the patient's conditions and then matching the each medication with the current condition. Furthermore, the risk for an adverse effect should not immediately end up with prescription omission and benefit-risk ratio should be judged. Some drugs may have potential of serious adverse effects but could be prescribed with a powerful clinical indication. A typical examination is use of opioid analgesics for control of severe pain. Although opioids have many undesirable adverse effect potential, they may be the only drugs controlling severe pain. Here, again, goals of care direct the physician to the right prescription model. Use of opioids to control pain would be more appropriate for quality of life while being extremely cautious for possible adverse effects. In this case, ways to overcome adverse effects should be considered and integrated as a standard care. Affordability related underuse is important if the patient does not benefit from health insurance and is reported as much as 30% [58]. As a general geriatric prescription principle, the medications should be started at low dose and increased gradually as needed. Lack of appropriate dosing for its use in the old simply makes medication use more difficult and can decrease the adherence thereby increasing the underuse.

We conclude that both overuse and underuse of drugs are common problem in the elderly. Rational drug use should address the both issues. Determination of goals of care while placing the quality of life in the center may solve the problem in majority of the cases.

References

1. Rochon PA, Schmader KE, Sokol HN (2012) Drug prescribing for older adults.
2. Ferner RE, Aronson JK (2006) Communicating information about drug safety. *BMJ* 333: 143-145.

3. Medicines and older people: implementing medicines-related aspects of the NSF for older people.
4. Qato DM, Alexander GC, Conti RM, Johnson M, Schumm P, et al. (2008) Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. *JAMA* 300: 2867-2878.
5. Patterns of Medication Use in the United States (2006) A Report from the Slone Survey web report.
6. Sigurdardottir AK, Arnadottir SA, Gunnarsdottir ED (2011) Medication use among community-dwelling older Icelanders. Population-based study in urban and rural areas. *Laeknabladid* 97: 675-680.
7. Heuberger RA, Caudell K (2011) Polypharmacy and nutritional status in older adults: a cross-sectional study. *Drugs Aging* 28: 315-323.
8. Beer C, Hyde Z, Almeida OP, Norman P, Hankey GJ, et al. (2011) Quality use of medicines and health outcomes among a cohort of community dwelling older men: an observational study. *Br J Clin Pharmacol* 71: 592-599.
9. Nobili A, Franchi C, Pasina L, Tettamanti M, Baviera M, et al. (2011) Drug utilization and polypharmacy in an Italian elderly population: the EPIFARM-elderly project. *Pharmacoepidemiol Drug Saf* 20: 488-496.
10. Onder G, Liperoti R, Fialova D, Topinkova E, Tosato M, et al. (2012) Polypharmacy in Nursing Home in Europe: Results From the SHELTER Study. *J Gerontol A Biol Sci Med Sci*.
11. Dwyer LL, Han B, Woodwell DA, Rechtsteiner EA (2010) Polypharmacy in nursing home residents in the United States: results of the 2004 National Nursing Home Survey. *Am J Geriatr Pharmacother* 8: 63-72.
12. Green JL, Hawley JN, Rask KJ (2007) Is the number of prescribing physicians an independent risk factor for adverse drug events in an elderly outpatient population? *Am J Geriatr Pharmacother* 5: 31-39.
13. Doshi JA, Shaffer T, Briesacher BA (2005) National estimates of medication use in nursing homes: findings from the 1997 medicare current beneficiary survey and the 1996 medical expenditure survey. *J Am Geriatr Soc* 53: 438-443.
14. Lindley CM, Tully MP, Paramsothy V, Tallis RC (1992) Inappropriate medication use in nursing homes: a major cause of adverse drug reactions in elderly patients. *Age Ageing* 21: 294-300.
15. Hanlon JT, Schmader KE, Koronkowski MJ, Weinberger M, Landsman PB, et al. (1997) Adverse drug events in high risk older outpatients. *J Am Geriatr Soc* 45: 945-948.
16. Kongkaew C, Noyce PR, Ashcroft DM (2008) Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. *Ann Pharmacother* 42: 1017-1025.
17. Chrischilles E, Rubenstein L, Van Gilder R, Voelker M, Wright K, et al. (2007) Risk factors for adverse drug events in older adults with mobility limitations in the community setting. *J Am Geriatr Soc* 55: 29-34.
18. Field TS, Gurwitz JH, Harrold LR, Rothschild J, DeBellis KR, et al. (2004) Risk factors for adverse drug events among older adults in the ambulatory setting. *J Am Geriatr Soc* 52: 1349-1354.
19. Agostini JV, Han L, Tinetti ME (2004) The relationship between number of medications and weight loss or impaired balance in older adults. *J Am Geriatr Soc* 52: 1719-1723.
20. Magaziner J, Cadigan D, Fedder D, J Richard Hebel (1989) Medication use and functional decline among community dwelling older women. *J Aging Health* 1: 470-484.
21. Larson EB, Kukull WA, Buchner D, Reifler BV (1987) Adverse drug reactions associated with global cognitive impairment in elderly persons. *Ann Intern Med* 107: 169-173.
22. Beijer HJ, de Blaey CJ (2002) Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. *Pharm World Sci* 24: 46-54.
23. Beers MH, Ouslander JG, Fingold SF, Morgenstern H, Reuben DB, et al. (1992) Inappropriate medication prescribing in skilled-nursing facilities. *Ann Intern Med* 117: 684-689.
24. Trygstad TK, Christensen D, Garmise J, Sullivan R, Wegner S (2005) Pharmacist response to alerts generated from Medicaid pharmacy claims in a long-term care setting: results from the North Carolina polypharmacy initiative. *J Manag Care Pharm* 11: 575-583.
25. Wyles H, Rehman HU (2005) Inappropriate polypharmacy in the elderly. *Eur J Intern Med* 16: 311-313.
26. Holmes HM, Hayley DC, Alexander GC, Sachs GA (2006) Reconsidering medication appropriateness for patients late in life. *Arch Intern Med* 166: 605-609.
27. Steinman MA, Hanlon JT (2010) Managing medications in clinically complex elders: "There's got to be a happy medium". *JAMA* 304: 1592-1601.
28. Field TS, Gurwitz JH, Avorn J, McCormick D, Jain S, et al. (2001) Risk factors for adverse drug events among nursing home residents. *Arch Intern Med* 161: 1629-1634.
29. Mannesse CK, Derkx FH, de Ridder MA, Man in 't Veld AJ, van der Cammen TJ (2000) Contribution of adverse drug reactions to hospital admission of older patients. *Age Ageing* 29: 35-39.
30. Hilmer SN, Mager DE, Simonsick EM, Cao Y, Ling SM, et al. (2007) A drug burden index to define the functional burden of medications in older people. *Arch Intern Med* 167: 781-787.
31. Hilmer SN, Mager DE, Simonsick EM, Ling SM, Windham BG, et al. (2009) Drug burden index score and functional decline in older people. *Am J Med* 122: 1142-1149.
32. Wilson NM, Hilmer SN, March LM, Cameron ID, Lord SR, et al. (2011) Associations Between Drug Burden Index and Falls in Older People in Residential Aged Care. *J Am Geriatr Soc* 59: 875-880.
33. Budnitz DS, Shehab N, Kegler SR, Richards CL (2007) Medication use leading to emergency department visits for adverse drug events in older adults. *Ann Intern Med* 147: 755-765.
34. Beers MH, Ouslander JG, Rollinger I, Reuben DB, Brooks J, et al. (1991) Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. *Arch Intern Med* 151: 1825-1832.
35. Beers MH (1997) Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Arch Intern Med* 157: 1531-1536.
36. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, et al. (2003) Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. *Arch Intern Med* 163: 2716-2724.
37. Zhan C, Sangl J, Bierman AS, Miller MR, Friedman B, et al. (2001) Potentially inappropriate medication use in the community-dwelling elderly: findings from the 1996 Medical Expenditure Panel Survey. *JAMA* 286: 2823-2829.
38. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D (2008) STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int J Clin Pharmacol Ther* 46: 72-83.
39. Gallagher P, O'Mahony D (2008) STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. *Age Ageing* 37: 673-679.
40. Hamilton H, Gallagher P, Ryan C, Byrne S, O'Mahony D (2011) Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. *Arch Intern Med* 171: 1013-1019.
41. Ryan C, O'Mahony D, Kennedy J, Weedle P, Byrne S (2009) Potentially inappropriate prescribing in an Irish elderly population in primary care. *Br J Clin Pharmacol* 68: 936-947.
42. Garfinkel D, Zur-Gil S, Ben-Israel J (2007) The war against polypharmacy: a new cost-effective geriatric-palliative approach for improving drug therapy in disabled elderly people. *Isr Med Assoc J* 9: 430-434.
43. Garfinkel D, Mangin D (2010) Feasibility study of a systematic approach for discontinuation of multiple medications in older adults: addressing polypharmacy. *Arch Intern Med* 170: 1648-1654.
44. Gainsborough N, Maskrey VL, Nelson ML, Keating J, Sherwood RA, et al. (1993) The association of age with gastric emptying. *Age Ageing* 22: 37-40.
45. Mangoni A, Jansen P, Jackson S (2009) *Clinical Pharmacology of Ageing. Prescribing for elderly patients* (Jackson S, Jansen P, Mangoni A, editors) Chichester: Wiley-Blackwell 1-10.
46. Wilkinson GR (1997) The effects of diet, aging and disease-states on presystemic elimination and oral drug bioavailability in humans. *Adv Drug Deliv Rev* 27: 129-159.

47. Patel RB (2003) Polypharmacy and the elderly. *J Infus Nurs* 26: 166-169.
48. Reidenberg MM, Levy M, Warner H, Coutinho CB, Schwartz MA, et al. (1978) Relationship between diazepam dose, plasma level, age, and central nervous system depression. *Clin Pharmacol Ther* 23: 371-374.
49. Pomara N, Stanley B, Block R, Guido J, Russ D, et al. (1984) Adverse effects of single therapeutic doses of diazepam on performance in normal geriatric subjects: relationship to plasma concentrations. *Psychopharmacology (Berl)* 84: 342-346.
50. Pomara N, Stanley B, Block R, Berchou RC, Stanley M, et al. (1985) Increased sensitivity of the elderly to the central depressant effects of diazepam. *J Clin Psychiatry* 46: 185-187.
51. Herings RM, Stricker BH, de Boer A, Bakker A, Sturmans F (1995) Benzodiazepines and the risk of falling leading to femur fractures. Dosage more important than elimination half-life. *Arch Intern Med* 155: 1801-1807.
52. Scott JC, Stanski DR (1987) Decreased fentanyl and alfentanil dose requirements with age. A simultaneous pharmacokinetic and pharmacodynamic evaluation. *J Pharmacol Exp Ther* 240: 159-166.
53. Nahin RL, Pecha M, Welmerink DB, Sink K, DeKosky ST, et al. (2009) Concomitant use of prescription drugs and dietary supplements in ambulatory elderly people. *J Am Geriatr Soc* 57: 1197-1205.
54. Kaboli PJ, McClimon BJ, Hoth AB, Barnett MJ (2004) Assessing the accuracy of computerized medication histories. *Am J Manag Care* 10: 872-877.
55. Bedell SE, Jabbour S, Goldberg R, Glaser H, Gobble S, et al. (2000) Discrepancies in the use of medications: their extent and predictors in an outpatient practice. *Arch Intern Med* 160: 2129-2134.
56. Higashi T, Shekelle PG, Solomon DH, Knight EL, Roth C, et al. (2004) The quality of pharmacologic care for vulnerable older patients. *Ann Intern Med* 140: 714-720.
57. Barry PJ, Gallagher P, Ryan C, O'mahony D (2007) START (screening tool to alert doctors to the right treatment)—an evidence-based screening tool to detect prescribing omissions in elderly patients. *Age Ageing* 36: 632-638.
58. Soumerai SB, Pierre-Jacques M, Zhang F, Ross-Degnan D, Adams AS, et al. (2006) Cost-related medication nonadherence among elderly and disabled medicare beneficiaries: a national survey 1 year before the medicare drug benefit. *Arch Intern Med* 166: 1829-1835.