

Medication in the elderly - considerations and therapy prescription guidelines

Davorka Vrdoljak^{1*}, Josip Anđelo Borovac²

¹Department of Family Medicine, University of Split School of Medicine, Split, Croatia, ²University of Split School of Medicine, Split, Croatia

*Corresponding author:
davorka.vrdoljak@mefst.hr
Tel.: + 385 21557 823
Fax.: + 385 21 568 696

Received: 25 October 2015
Accepted: 30 November 2015

Key words: Elderly ■ Rational prescription
■ General practitioner ■ Family medicine.

Introduction

Treatment of elderly patients exhibits special characteristics and is often a sensitive process within the scope of a general practitioner's work. Elderly patients present with more comorbidities, they often suffer from multiple disease conditions (multimorbidity), they commonly use more than a few

The aim of this study was to integrate and present pertinent findings from the literature dealing with the treatment of the elderly within a primary care setting. Medical care for the elderly is an integral part of a general practitioner's (GPs) everyday work and is challenging for many reasons. Older people often experience multiple chronic diseases concurrently (comorbidity, multimorbidity) and they often have deteriorated organ function and decreased physiological reserves due to the natural aging process. The choice of appropriate medication for each particular disease is a complex process and can cause "therapeutic confusion", especially among younger GPs in the field. Elderly people are prone to develop adverse side-effects to usual dosages of medications and the side-effects are even 7 times more frequent in elderly than in younger patients. Moreover, in therapy for elder patients, a responsible clinician always needs to think about potential drug to drug interactions and possible compromised pharmacokinetic dynamics in the aging body. Professional geriatric societies in many countries (USA, Germany, UK) have developed lists of potentially inappropriate medications for the elderly, and they update them systematically. Lists such as The Beers Criteria list and STOPP/START criteria should always be consulted when administering therapy to elderly patients. In this paper we emphasized the importance of medication lists as an important practical support in a GP's everyday work. Implementation of such therapeutic aids reduces the possibility of medical error and minimizes the chance of an inappropriate prescription for this vulnerable population stratum. **Conclusion.** When prescribing drugs for the elderly, GPs should take into account the specificities of the elderly, their biological and chronological framework and should always apply the principles of rational, conservative and evidence-based pharmacotherapy.

medications (polypharmacy) and they have physiologically deteriorated organ function due to the natural process of aging. Quite often, it is a real challenge to administer proper therapy in elderly patients where there is significant potential for developing side-effects due to chronic use of drugs that can elicit strong systemic interactions.

Moreover, elderly patients are more prone to develop side-effects due to therapy, in comparison to younger adults. For example, use of antipsychotic medications among the elderly can induce severe anticholinergic reactions, Parkinsonian events, tardive dyskinesia, orthostatic hypertension, cardiac conduction disturbances, reduced bone mineral density, sedation and cognitive dysfunction (1). Likewise, elderly patients over the age of 70 are 3.5 times more likely than younger individuals to be admitted to hospital due to adverse drug reactions associated with psychotropic medications (2).

The aim of this article was to review recent literature on prescribing for the elderly.

Characteristics of elderly patients

According to the population census of 2001, 15.6% of the Croatian population was 65 years of age or older, and this population grew to 17.7% in the most recent census from 2011 (3). This trend places Croatia among the countries with a "very old population", according to criteria of the United Nations (UN) and the World Health Organization (WHO). The average life expectancy in Croatia is 71.1 years for men and 78.1 for women. Projections of the WHO are that in 2050 more than 25%, (even > 30%) of the population in Croatia will be aged 65 and over, with all the social, health and economic consequences of this process for the family and society as a whole (4). The elderly often suffer from chronic diseases and have multiple diseases at the same time (multimorbidity, comorbidity), which then often lead to polymedication, and sometimes polypharmacy (5). Polymedication is defined by some authorities as the use of more than four drugs simultaneously and is common in the treatment of elderly patients (6). There is a "thin line" that divides polymedication and polypharmacy while the latter involves inappropriate and purposeless

prescribing of a number of drugs, that are not clinically indicated, to the same patient (7). These definitions have not yet been internationally standardized and the actual differentiation point that would define polypharmacy or polymedication is still an open question. With the increase in the number of prescribed medications, the risk of side effects and interactions dramatically increases. A study by Steinman et al. found that use of one or more inappropriate medications was documented in 65% of patients while 37% patients were taking medication in violation of the Beers drugs-to-avoid criteria, while as many as 57% patients took medications that were ineffective, not indicated or duplicative. In summary, inappropriate medication and overuse were common in elder people taking five or more medications, and this was present in more than 40% of patients (8). Likewise, the number of drug-related problems increased linearly with the increasing number of drugs used by patients in the study by Viktil et al. (9).

Altered and diminished physiological functions among elderly

When prescribing medications to the elderly, a responsible clinician needs to bear in mind that the pharmacodynamic (what the drug does to body physiologically) and pharmacokinetic (absorption, distribution, metabolism, excretion – what the body does to a drug) profiles are different among the elderly, in comparison to younger patients. This mostly occurs due to the natural aging process and it can be significantly altered in cases of various comorbidities and pathologies that increase with age. Absorption and distribution are reduced due to the reduction of total body water (10-15%) and serum albumins, as the major "carriers" of many drugs, decrease in the elderly by about 1/3 of the total concentration. The degradation and biotransformation of drugs in the liver

is also slower among the elderly because of the significant changes in liver physiology and functionality that are associated with aging. It has been proven that liver volume and blood flow decline with age in humans, and the clearance of drugs is diminished, particularly of those drugs that are oxidized by the microsomal cytochrome P450-dependent mono-oxygenase system (10). Moreover, the aging liver undergoes various histological changes, such as the increase of amounts of lipofuscin and shifts in the expression of various proteins that are synthesized by the liver (11). In addition to reduced hepatic clearance associated with age, kidney function also decreases due to a gradual reduction in the glomerular filtration rate (GFR) and the decrease in functional renal reserves (12). Many additional factors, such as the long-term attachment to bed, dehydration, congestive heart failure, and muscle atrophy, can significantly alter the pharmacokinetics with increasing age (13). Furthermore, the concurrent usage of multiple medications for different chronic conditions can precipitate significant drug interactions and may lead to drastic changes in the pharmacokinetic properties of medication administered (14). Non-compliance to drug therapy may be due to visual impairment, weakened motor skills and cognitive problems in the elderly, especially if a patient is taking anxiolytics or anticholinergics (15). Moreover, taking drugs without the assistance and/or control of family members may result in overdose and potentially lethal poisoning (16). Buying drugs over the counter (OTC drugs) as an addition to prescription drugs is also a source of potential danger due to adverse interactions (17). Some of the classic interactions are, for example: *Hypericum perforatum* with digitalis glycosides; Ginkgo biloba with acetylsalicylic acid (ASA); multivitamin preparations that contain vitamin K and coumarin anticoagulants or St. John's wort and concomitant use of antidepressants

(18). From the most commonly used drugs among the elderly, the most common side-effects are well known in five classes of drugs: diuretics, digitalis glycosides, anti-depressants, analgesics and anti-hypertensive agents. The decisive role and full responsibility in prescribing for the elderly (which is not an easy task by any means) should be inherent to the family doctor's (GP) function. The GP alone has complete insight into all recommendations on medication for his elderly patient, which are given by different clinical specialists. The aim of this review is to examine the principles of rational and meaningful prescription, point out the specificities and offer some practical guidelines in medication prescription for the elderly in a GP's daily care.

Selection criteria

We reviewed the medical database Medline/PubMed and Google Scholar, using the 4 MESH keywords: elderly, prescription, general practice and family medicine. In respect to PubMed, the search yielded a total of 1597 articles and this was filtered down to 181 articles when those published within the last 5 years were selected. When searching Google Scholar, we chose those articles that had a high citation index and a substantial impact in the field of general/family medicine and that were ranked by their significance and total citations. By combining these two criteria, we not only aimed to select those articles that were recent and contemporary, but also to include those that had pertinent impact and relevancy in the field of clinical family medicine and the general practitioner's arena, regardless of publication date.

Discussion

When prescribing for the elderly, it is recommended to respect the paradigm of conservative prescribing, and these basic principles

are presented by Schiff and associates in his principles of conservative pharmacotherapy (19). In this light, we will use Schiff's principles as the foundation to further elaborate useful practical guidelines, with additional relevant sources from the literature. Before prescribing, a responsible clinician should:

Consider non-pharmacological treatment alternatives for the disease/condition

Many diseases are caused by unhealthy and sedentary lifestyles that are intrinsically marked by low levels of physical activity (20). Instead of "over-medicalization", counseling on healthy eating, emphasizing the importance of physical activity and smoking cessation recommendations should be propagated by GP's to the highest possible extent. A recent study showed that physicians discuss the risks of smoking with their patients, however, practical cessation support is often inadequate (21). In some cases, instead of the conservative approach, surgery should be advised in instances where a pharmacological approach could impose a significant burden on the patient (22). Likewise, a GP needs to be aware that important life changes and decisions in the life of the elderly patient may be achieved if the patient is in a stable psychological state, without the depressive symptomatology that is often encountered among elderly (23). In that regard, psychotherapy can have beneficial effects on elderly patients and may reduce the unnecessary burden of psychotropic drugs. An IMPACT study conducted in the primary care setting showed that psychotherapy, alongside pharmacotherapy, managed to achieve lower levels of depression, better physical functioning and an enhanced quality of life among depressed older adults (24). Similarly, application of local heat and cold pads can reduce pain and help to achieve analgesia, without excessive utilization of non-steroidal anti-inflammatory (NSAID) drugs for arthritic conditions (25). A TONE study showed

that reduced sodium intake and weight loss, achieved through physical exercise, constitute an effective and safe non-pharmacologic therapy for hypertension in older persons (26). This can significantly reduce the anti-hypertensive medication burden. These are only some of the examples that show how non-pharmacologic interventions can yield substantial benefits among the elderly, and should not be underestimated.

Consider the potential causes of the disease, do not only cure the symptoms

Dyslipidemia among the elderly can be a symptom of unrecognized and therefore, untreated hypothyroidism, osteoporosis can be the underlying cause of arthralgia, while erectile dysfunction can be a physical manifestation of underlying psychological or psychiatric entities, such as performance anxiety, stress or mental disorders. Therefore, we should always search for the principal, underlying cause of the basic disease, and we should not only cure symptoms (27).

Use a preventive approach and not only treat an already developed and advanced disease

Preventive activities are an integral part of the daily work of family doctors. Combating unhealthy lifestyles, such as smoking, inadequate diet, and obesity, with all their possible consequences, and prevention of risky behavior in the "long run" are much more effective. The treatment is much more expensive and less effective (28).

Use the function of time as a diagnostic tool in your clinical judgment

In the prodromal or early febrile phase of some infectious diseases, it is not always simple to evaluate whether the symptoms and signs are caused by viruses or bacteria. In some cases it is appropriate to use the function of time as an aid in diagnosing the

etiology of a disease. This has some practical implications - for example, we might delay the institution of antimicrobial drug therapy by using the technique of “*watchful waiting*”, also known as “*watch and wait*” or WAW, where applicable. This approach could be utilized in situations where there is a high degree of certainty present that the disease could self-resolve, or in situations in which the risks of therapeutic modality might outweigh the potential benefits. Such situations are often encountered by GPs in patients that present with acute otitis media with effusion, inguinal hernia, pneumonia, rhino sinusitis or benign prostatic hyperplasia (BPH) (29-31).

Use a relatively small number of drugs, know them well and use them appropriately

A responsible general practitioner should have a solid knowledge of the most common and important groups of drugs that he/she is prescribing, including indications and contraindications for their use, the most common side-effects and pharmacological interactions. This approach increases the quality of prescriptions and reduces the error. In a recent study, in which polypharmacy was defined as the use of six to nine drugs at the same time in one patient there was a significant association between polypharmacy status and mortality (32). STOPP/START criteria, that measure potential inappropriate prescribing, have a significant correlation with medication-related hospital admissions in older patients (33). A similar study showed that polypharmacy correlates with an increased risk of hip fracture in the elderly (34). Therefore, it is clear that in some instances “*more*” is not always synonymous with “*better*”.

Avoid switching drugs or abrupt withdrawal

Reasons for switching existing medication to new forms should be well-founded. The

rule is that any modification of treatment and / or replacement of one drug with another must be justified and clearly reasoned. For example, institution of a new diuretic or a vasodilatory drug in the treatment plan can induce orthostatic hypotension among elderly patients (35). Likewise, swift removal of beta-blockers from the line of therapy can induce reflexive tachycardia and may decompensate a patient with heart disease (36). In a similar way, sudden withdrawal of an anti-Parkinsonian drug therapy among the elderly may result in neuroleptic malignant syndrome (37).

Start treatment with a single drug, whenever possible

Such prescribing ensures the easy identification of potential side-effects. The less medication we use, the fewer difficulties we have in identifying the causal agent that induced the side-effects. For example, antihypertensive therapy needs to be based on evidence-based medicine (EBM), and administration of a new drug should be clinically justified only in cases in which the therapeutic goals (for example, the desired level of arterial blood pressure) have not been met (38).

Think about the possible side-effects, anticipate them and inform patients about them

Lack of knowledge about side-effects can result in what is known as “*prescription cascade*” - a physician does not properly recognize the side effects of the drug and wrongly misinterprets them as a new entity or a disease (39). Therefore, he/she then prescribes a new drug for the latest condition, which often masks and/or complicates the clinical presentation and so on. It is of cardinal importance for the conscientious general practitioner always to assess any new symptomatology that occurs among patients that

are under therapy, because these undesired symptoms may be the consequence of the patient's drug treatment (40). This cascade can be stopped by de-prescribing. De-prescribing is a process that entails reduction or complete withdrawal of a drug that might cause side-effects and undesired symptoms (41). It has been proven that systematic and careful de-prescribing can improve the quality of life and cognitive function, and can foster better therapy compliance rates among the elderly (42). While the consequences of de-prescribing are fairly rare, the dangers of adverse drug withdrawal events still persist (36). In this respect, it is important to have in mind that discontinuation of certain drugs from the line of therapy requires gradual and titrated withdrawal, and they should not be removed abruptly and in a short period of time, due to the potential risks.

When a new drug appears, do not rush to use it

Information about new drugs should be provided using relevant EBM sources which are impartial and not influenced by the pharmaceutical industry. It takes 5-10 years of use to recognize all the side-effects of a drug. Physicians can often "fall into the trap" of prescribing a new drug because they are pressurised by the pharmaceutical representative, firms, hospital consultants or the patients themselves. The decision to initiate a new drug is often heavily influenced by "who says what" (43). Moreover, an early good experience of using a new drug can strongly influence future use (44). A study by Adair & Holmgren showed that drug samples received from pharmaceutical companies can influence prescribing behaviors among residents (45). It is important to build awareness about such dynamics and avoid them whenever possible.

When prescribing, one should not be exclusively guided by the wishes and desires of the patient

A relevant study found that a physician's behavior in terms of prescribing medication is most strongly associated with the perceived medical need of the patient, which strongly confounded other predictors (46). Patients' requests for medicines are a powerful driver of prescribing decisions. In many cases, physicians prescribe the requested medication although they may be ambivalent about the drug in question (47). This should be avoided in daily practice whenever possible. A responsible GP needs to be observant and open towards the patient's reported needs and preferences, however, the decision about treatment should primarily be based on EBM and good clinical practice.

When the therapeutic effect of the drug fails, consider that non-compliance by the patient could be the reason for the "ineffectiveness", not the drug itself

Low patient compliance can significantly undermine treatment effectiveness as has been proven in multiple studies (48). The health outcomes differ by 26% between groups of patients who had high compliance to therapy vs. those who exhibited poor compliance (49). Every GP should focus his/her efforts on trying to increase compliance to short-term treatments, such as counseling about the importance of compliance, written instructions about taking medicines and reminder packaging, among many others (50).

The Beers Criteria (List) and STOPP/START Criteria – an important foundation for rational pharmacotherapy among the elderly

By respecting all the principles discussed above, excessive prescribing could be con-

verted into a meaningful and rational prescription process. In 1991, Dr. Mark Beers, through a consensus panel of experts using the Delphi method, developed criteria of inappropriate prescribing for the elderly, named after him - The Beers Criteria for Potentially Inappropriate Medication Use in Older Adults, commonly known as the Beers List. This list contains lists of medications that could pose a higher risk than potential benefit for people aged 65 and older (51). It is important to highlight that the Beers List is not a substitute for professional judgment in prescribing decisions for the elderly, but it is intended to serve as guidance material for clinicians. The American Geriatrics Society (AGS) applied these criteria and revised them according to the list of drugs available in the US, with the principal intention of improving prescription for the elderly, reducing the incidence of unwanted side-effects and reducing unnecessary costs of medication (52). According to the AGS Beers' criteria a total of 53 drugs and/or drug groups are stratified in three categories: I. "unsuitable for use in the elderly", II. "unsuitable for use in the elderly in certain diseases and conditions", III. "may be used with caution". A similar process was applied to the list of drugs available on the German market and, thereby the PRISCUS list was created and is nowadays used in Germany as an integral part of geriatric pharmacotherapy (53).

The importance of inappropriate prescribing as a phenomenon has been recognized by Irish researchers, who have created and validated an assessment instrument – the "Screening Tool in Older Persons for Potentially Inappropriate Prescriptions and the Screening Tool to Alert Doctors to the Right Treatment", commonly known as the STOPP/START criteria (54). This study was conducted at University Hospital Cork and it involved the population of elderly patients referred by their family for acute illness conditions. By using the STOPP criteria,

inappropriate medication was detected as follows: 25% of people were receiving one, 7% received two and 2% three inappropriate drugs. The most common errors were application of long-acting benzodiazepines and/or tricyclic antidepressants in patients with clear contraindications, as well as the use of drugs that increase the incidence of falls in patients who are prone to them. In addition, a common error was "duplication" - two prescriptions of NSAIDs, ACE inhibitors, SSRIs or two anti-platelet drugs for the same patient (55). The question is: will regular updating of the list of medicines for the elderly in these countries actually lead to more rational prescribing, fewer prescribing errors, a lower incidence of unwanted side-effects and reducing health care costs in the future? A revised version of the STOPP/START criteria was published in March 2015 and these guidelines are up-to-date with literature reviews and consensus validation by a European panel of experts (56). To sum up, the Beers List and STOPP/START criteria are often used complementarily to guide clinicians in the safe drug prescribing in older adults, and should always be consulted (57).

Final thoughts

GPs play a key role in preventing unnecessary polypharmacy in elderly. Their role is to weigh and assess each treatment recommendation given by clinical specialists. By knowing their elderly patients, their diseases, conditions and family/social situations, GPs are in an ideal position to make an appropriate selection of a drug for an individual patient. In this process, the GP should determine "priority" diseases, always taking into account the possible side-effects and interactions. The Brown Bag Medication Review is a six-month review method that takes into account all medications taken, and it has proved very effective in reducing poly-medication. It implies that the patient, once

in each six-month period, brings all medications taken regularly “in a brown bag” to the office of their GP, including the medication prescribed by the doctor and all others (OTC medicines, herbal remedies etc.). In this way, patients can receive the maximum benefit from their medication and reduce drug wastage (58). Before prescribing a drug to a patient, the GP should always answer several key questions to determine if the treatment regimen is justified (Box 1).

Box 1 The questions that GPs should answer themselves before prescribing any drug to an elderly person within the primary care setting

1. Is the drug really necessary?
2. To which pharmacodynamics group does the drug belong and what is the mechanism of its action?
3. What do I want to achieve with this drug?
4. How do I evaluate the effectiveness of this drug?
5. What dosage shall I give and for how long?
6. Did I choose the simplest therapeutic scheme?
7. Did I assess both the biological and chronological age of the patient before prescribing the drug (because these are not always consistent)?
8. Can the existing disease, other medications, or the age of the patient affect the absorption, metabolism or excretion of a drug?
9. What possible side effects should I expect?
10. Will the patient take the medicine? Could motor weakness, visual, cognitive or other impairments compromise compliance in taking the drug? Is the patient capable of taking medicine alone, or should he/she be helped and/or supervised by others?
11. Do I need to provide further clarification about the mode of taking, actions and side-effects of the drug to the patient or to their family member(s)? Should I write down a scheme of administration (dosage, schedule, depending on meals)?

Conclusion

When prescribing drugs for elderly, GPs should always take into account the peculiarities of the elderly and their biological/chronological age. A responsible clinician should always apply the principles of rational pharmacotherapy and conservative prescription, while avoiding the trap of fashionable and harmful prescribing that is not evidence-based.

Authors' contributions: Conception and design: DV; Acquisition, analysis and interpretation of data: DV, JAB; Drafting the article: DV, JAB; Revising it critically for important intellectual content: DV, JAB.

Conflict of interest: The authors declare that they have no conflict of interest.

References

1. Masand PS. Side effects of antipsychotics in the elderly. *J Clin Psychiatry*. 2000;61 (Suppl 8):43-9; discussion 50-1.
2. Brooks JO, Hoblyn JC. Neurocognitive costs and benefits of psychotropic medications in older adults. *J Geriatr Psychiatry Neurol*. 2007;20(4):199-214.
3. Statistics TCBo. Census of Population, Households and Dwellings 2011. Population by Sex and Age. Zagreb: Croatian Bureau of Statistics; 2013.
4. Economic UNDo, Division SAP. World Population Prospects: Sex and age distribution of the world population. New York: UN; 2007.
5. Van den Akker M, Buntinx F, Knottnerus JA. Comorbidity or multimorbidity: what's in a name? A review of literature. *Eur J Gen Pract*. 1996;2(2):65-70.
6. Payne RA, Avery AJ. Polypharmacy: one of the greatest prescribing challenges in general practice. *Br J Gen Pract*. 2011;61(583):83-4.
7. Fulton MM, Allen ER. Polypharmacy in the elderly: A literature review. *J Am Acad Nurse Pract*. 2005;17(4):123-32.
8. Steinman MA, Seth Landefeld C, Rosenthal GE, Berthenthal D, Sen S, Kaboli PJ. Polypharmacy and Prescribing Quality in Older People. *J Am Geriatr Soc*. 2006;54(10):1516-23.
9. Viktil KK, Blix HS, Moger TA, Reikvam A. Polypharmacy as commonly defined is an indicator of limited value in the assessment of drug-related problems. *Br J Clin Pharmacol*. 2007;63(2):187-95.
10. Schmucker D. Liver Function and Phase I Drug Metabolism in the Elderly. *Drugs Aging*. 2001;18(11):837-51.
11. Schmucker DL. Age-related changes in liver structure and function: Implications for disease? *Exp Gerontol*. 2005;40(8-9):650-9.
12. Epstein M. Aging and the kidney. *J Am Soc Nephrol*. 1996;7(8):1106-22.
13. Duraković Z. Medication in the elderly - considerations and therapy prescription guidelines [in Croatian]. *Medix*. 2000;32(1):43-8.

14. Turnheim K. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. *Exp Gerontol*. 2003;38(8):843-53.
15. Peron EP, Gray SL, Hanlon JT. Medication Use and Functional Status Decline in Older Adults: A Narrative Review. *Am J Geriatr Pharmacother*. 2011;9(6):378-91.
16. Qato DM, Alexander G, Conti RM, Johnson M, Schumm P, Lindau S. Use of prescription and over-the-counter medications and dietary supplements among older adults in the united states. *JAMA*. 2008;300(24):2867-78.
17. Hersh EV, Pinto A, Moore PA. Adverse drug interactions involving common prescription and over-the-counter analgesic agents. *Clin Ther*. 2007;29(Suppl):2477-97.
18. Lantz MS, Buchalter E, Giambanco V. St. John's Wort and Antidepressant Drug Interactions in the Elderly. *J Geriatr Psychiatry Neurol*. 1999;12(1):7-10.
19. Schiff GD, Galanter WL, Duhig J, Lodolce AE, Koronkowski MJ, Lambert BL. Principles of conservative prescribing. *Arch Intern Med*. 2011;171(16):1433-40.
20. Thompson PD, Buchner D, Piña IL, Balady GJ, Williams MA, Marcus BH, et al. Exercise and Physical Activity in the Prevention and Treatment of Atherosclerotic Cardiovascular Disease: A Statement From the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). *Circulation*. 2003;107(24):3109-16.
21. Keto J, Jokelainen J, Timonen M, Linden K, Ylisaukko-oja T. Physicians discuss the risks of smoking with their patients, but seldom offer practical cessation support. *Subst Abuse Treat Prev Policy*. 2015;10:43.
22. Sugiyama M, Tokuhara M, Atomi Y. Is percutaneous cholecystostomy the optimal treatment for acute cholecystitis in the very elderly? *World J Surg*. 1998;22(5):459-63.
23. Pinquart M, Duberstein PR, Lyness JM. Effects of psychotherapy and other behavioral interventions on clinically depressed older adults: A meta-analysis. *Aging Ment Health*. 2007;11(6):645-57.
24. Hunkeler EM, Katon W, Tang L, Williams JW, Kroenke K, Lin EHB, et al. Long term outcomes from the IMPACT randomised trial for depressed elderly patients in primary care. *BMJ*. 2006;332(7536):259-63.
25. Oosterveld FGJ, Rasker JJ. Treating arthritis with locally applied heat or cold. *Semin Arthritis Rheum*. 1994;24(2):82-90.
26. Whelton PK, Appel LJ, Espeland MA, Applegate WB, Ettinger WH Jr, Kostis JB, et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: A randomized controlled trial of nonpharmacologic interventions in the elderly (tone). *JAMA*. 1998;279(11):839-46.
27. Black ER, Bordley DR, Tape TG, Panzer RJ, editors. *Diagnostic Strategies for Common Medical Problems*. 2nd ed. Philadelphia, PA: ACP; 1999.
28. Asaria P, Chisholm D, Mathers C, Ezzati M, Beaglehole R. Chronic disease prevention: health effects and financial costs of strategies to reduce salt intake and control tobacco use. *Lancet*. 2007;370(9604):2044-53.
29. Wasson JH, Reda DJ, Bruskewitz RC, Elinson J, Keller AM, Henderson WG. A comparison of transurethral surgery with watchful waiting for moderate symptoms of benign prostatic hyperplasia. *N Engl J Med*. 1995;332(2):75-9.
30. Fitzgibbons RJ, Giobbie-Hurder A, Gibbs JO, Dunlop DD, Reda DJ, McCarthy M, et al. Watchful waiting vs repair of inguinal hernia in minimally symptomatic men: a randomized clinical trial. *JAMA*. 2006;295(3):285-92.
31. Speets A, Hoes A, Van Der Graaf Y, Kalmijn S, Sachs A, Mali WTM. Chest radiography and pneumonia in primary care: diagnostic yield and consequences for patient management. *Eur Respir J*. 2006;28(5):933-8.
32. Jyrkkä J, Enlund H, Korhonen M, Sulkava R, Hartikainen S. Polypharmacy Status as an Indicator of Mortality in an Elderly Population. *Drugs Aging*. 2009;26(12):1039-48.
33. van der Stelt CA, Vermeulen Windsant-van den Tweel AM, Egberts AC, van den Bemt PM, Leendertse AJ, Hermens WA, et al. The Association Between Potentially Inappropriate Prescribing and Medication-Related Hospital Admissions in Older Patients: A Nested Case Control Study. *Drug Saf*. 2015 Nov 9. [Epub ahead of print]
34. Lai S-W, Liao K-F, Liao C-C, Muo C-H, Liu C-S, Sung F-C. Polypharmacy Correlates With Increased Risk for Hip Fracture in the Elderly: A Population-Based Study. *Medicine (Baltimore)*. 2010;89(5):295-9.
35. Poon IO, Braun U. High prevalence of orthostatic hypotension and its correlation with potentially causative medications among elderly veterans. *J Clin Pharm Ther*. 2005;30(2):173-8.
36. Graves T, Hanlon JT, Schmader KE, Landsman PB, Samsa GP, Pieper CF, et al. Adverse events after discontinuing medications in elderly outpatients. *Arch Intern Med*. 1997;157(19):2205-10.

37. Mizuno Y, Takubo H, Mizuta E, Kuno S. Malignant syndrome in Parkinson's disease: concept and review of the literature. *Parkinsonism Relat Disord.* 2003;9 Suppl 1:S3-9.
38. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med.* 2008;358(18):1887-98.
39. Farrell B, Szeto W, Shamji S. Drug-related problems in the frail elderly. *Can Fam Physician.* 2011;57(2):168-9.
40. Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people: the prescribing cascade. *BMJ.* 1997;315(7115):1096-9.
41. Reeve E, Gnjjidic D, Long J, Hilmer S. A systematic review of the emerging definition of 'deprescribing' with network analysis: implications for future research and clinical practice. *Br J Clin Pharmacol.* 2015;80:1254-68.
42. Gnjjidic D, Le Couteur DG, Kouladjian L, Hilmer SN. Deprescribing trials: methods to reduce polypharmacy and the impact on prescribing and clinical outcomes. *Clin Geriatr Med.* 2012;28(2):237-53.
43. Prosser H, Almond S, Walley T. Influences on GPs' decision to prescribe new drugs-the importance of who says what. *Fam Pract.* 2003;20(1):61-8.
44. Jones MI, Greenfield SM, Bradley CP. Prescribing new drugs: qualitative study of influences on consultants and general practitioners. *BMJ.* 2001;323(7309):378.
45. Adair RF, Holmgren LR. Do drug samples influence resident prescribing behavior? A randomized trial. *Am J Med.* 2005;118(8):881-4.
46. Little P, Dorward M, Warner G, Stephens K, Senior J, Moore M. Importance of patient pressure and perceived pressure and perceived medical need for investigations, referral, and prescribing in primary care: nested observational study. *BMJ.* 2004;328(7437):444.
47. Mintzes B, Barer ML, Kravitz RL, Kazanjian A, Bassett K, Lexchin J, et al. Influence of direct to consumer pharmaceutical advertising and patients' requests on prescribing decisions: two site cross sectional survey. *BMJ.* 2002;324(7332):278-9.
48. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther.* 2001;26(5):331-42.
49. Robin DiMatteo M, Giordani PJ, Lepper HS, Croghan TW. Patient Adherence and Medical Treatment Outcomes: A Meta-Analysis. *Med Care.* 2002;40(9):794-811.
50. Haynes R, McDonald HP, Garg AX. Helping patients follow prescribed treatment: Clinical applications. *JAMA.* 2002;288(22):2880-3.
51. Beers MH, Ouslander JG, Rollinger I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining inappropriate medication use in nursing home residents. *Arch Intern Med.* 1991;151(9):1825-32.
52. Campanelli CM. American Geriatrics Society updated beers criteria for potentially inappropriate medication use in older adults: the American Geriatrics Society 2012 Beers Criteria Update Expert Panel. *J Am Geriatr Soc.* 2012;60(4):616.
53. Holt S, Schmiedl S, Thürmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. *Dtsch Arztebl Int.* 2010;107(31-32):543.
54. Gallagher P, O'Mahony D. STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. *Age Ageing.* 2008;37(6):673-9.
55. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. 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.* 2008;46(2):72-83.
56. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing.* 2015;44(2):213-8.
57. Hamilton H, Gallagher P, Ryan C, Byrne S, O'Mahony D. Potentially inappropriate medications defined by stopp criteria and the risk of adverse drug events in older hospitalized patients. *Arch Intern Med.* 2011;171(11):1013-9.
58. Nathan A, Goodyer L, Lovejoy A, Rashid A. 'Brown bag' medication reviews as a means of optimizing patients' use of medication and of identifying potential clinical problems. *Fam Pract.* 1999;16(3):278-82.