Polypharmacy in elderly people: epidemiology, consequences and prevention strategies

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Abstract. Aging is a status often associated with multiple comorbidities which require pharmacologic intervention and complex medication regimens. Aging population results to the increase of chronic diseases and subsequent comorbidities that require concomitant multiple medications. It is reported that about 80% of elderly have at least one chronic condition, and about half of them have at least two (such as heart disease, hypertension, diabetes mellitus, arthritis, and cancer). According to the literature the worldwide polypharmacy prevalence has a wide range (between 5 to 78%) due to different definitions on the number of medications taken (ranging between 2 and 9) and the different samples studied. In most studies polypharmacy was more common between women and in more elderly people. Many multicenter studies have been performed to define the term of polypharmacy and its prevalence in the elderly population. Polypharmacy is of growing concern for the older adults, because it can be very dangerous for this population due to altered absorption, distribution, metabolism and excretion of the drugs within their body reflecting unexpected pharmacokinetics and pharmacodynamics of various medications. This fact can lead to adverse drug reactions (ADR), drug interactions, noncompliance and reduced adherence, reduced functional status, geriatric syndromes, high risk of hospitalization and possible death. Over the last decade, there are several evaluation tools which can help the General Practitioner prevent the polypharmacy in the elderly. As prescribing for this group of individuals is a very challenging procedure, the General Practitioner should balance between under-treatment, over-treatment and risks and benefits. This review concluded that we need more cross-sectional clinical studies on practical preventive interventions to be applied not only on the population which is already exposed to polypharmacy, but also to the general population.

Keywords: polypharmacy; elderly; medication; diabetes mellitus

Introduction
As population grows older, people aged more than 65 years predominate. It is estimated that by 2030, there will increase to 72 million. Aging population results to the increase of chronic diseases and subsequent comorbidities that require concomitant multiple medications. It is reported that about 80% of elderly have at least one chronic condition, and about half of them have at least two (such as heart disease, hypertension, diabetes mellitus (DM), arthritis, and cancer) [1]. Besides, it is estimated that almost 39% of the elderly take ≥ 5 medications and about 72% of this population take at least one nonprescription medication (OTC) [2, 3]. The problem of polypharmacy in the elderly population is proved of high scientific interest, which is witnessed from the numerous studies that have been performed in various settings (ambulatory care, hospital setting, nursing home setting) [3].

There are many definitions for the term polypharmacy. Most commonly polypharmacy is defined as the concurrent use of two to nine medications to treat multiple comorbidities, such as chronic heart failure and DM. Polypharmacy is also defined by medication count as Excessive when the patient uses 10 or more medications. This form is the most commonly found as the population is aging. Another form of polypharmacy is that of the unnecessary use of at least one drug without indication or effectiveness or even when it is a therapeutic duplication [4].

The terminology polypharmacy has been used in many papers and reports in different notions each time, describing multiple, excessive, unnecessary of non-indicated medication...
intake. It’s worth underlining that each type of polypharmacy is associated to different consequences for the patient and the healthcare services and requires different treatment [3, 5].

Epidemiology

**Excessive polypharmacy — prevalence**

According to the literature the worldwide polypharmacy prevalence has a wide range (between 5 to 78 %) due to different definitions on the number of medications taken (ranging between 2 and 9) and the different samples studied. In most studies polypharmacy was more common between women and in more elderly people. Studies from USA on ambulatory elderly populations found that 57 % of women aged > 65 years took at least five medications, and 12 % took at least 10 medications [6], whereas findings from a respective European study reported similar prevalence rates, as 51 % of the elderly took at least six prescription and nonprescription medications daily [3, 7].

On the other hand, studies on hospitalized elderly people in Italy measured the prevalence of polypharmacy in 52 % with a mean number of 4.9 medications upon admission, which increased to 67 % and 6.0 respectively upon discharge [3, 8]. Besides, can significantly differ from the previously mentioned when older people are included (> 75 years old). Large national studies reported the prevalence of polypharmacy and mean number of medications upon admission to 58 % and 7.5 medications respectively in Austrian hospitals and 50 % and > 7 medications respectively in hospitals of USA [9]. On the contrary, another large national study of 13,507 nursing home residents found a polypharmacy and reported the highest number of medications which was at least nine [10]. Actually, the prevalence of polypharmacy was typically higher in the nursing home settings [11].

**Non clinically indicated polypharmacy (inappropriate) — prevalence**

Polypharmacy is also defined as the use of at least one non-clinically warranted medication. According to the literature the incidence of unnecessary medications due to lack of indication is 57–60 %, for lack of effectiveness is ~ 33 % and for therapeutic duplication is found to be 16 % [2]. One study which included hospitalized frail elderly veterans found that 44 % of them were discharged with at least one unnecessary medication due to lack of indication, whereas the most of them had at least one unnecessary medication prior admission. The most commonly unnecessarily prescribed medications in the previous subgroup of elderly patients are gastrointestinal, central nervous system, and therapeutic nutrient/mineral agents [11, 12]. Besides, large studies in community-dwelling elderly patients found that > 90 % and 50 % took > 1 or 2–4 over the counter medications and most individuals in this age population takes vitamin or mineral (47–59 %) or herbal (11–14 %) supplements [6].

Epidemiology of kind of medications

Large retrospective studies report that the most common medications prescribed for the elderly are estrogens, levethyroxine, hydrochlorothiazide, atorvastatin, and lisinopril. Another study (Medicare) concluded that the most usual medications in the older population were cardiovascular agents, antibiotics, diuretics, angiolesics, antihyperlipidemics, and gastrointestinal agents [13]. On the other hand, the commonest non-prescribed medications consumed by elderly individuals living in community were analgesics (aspirin, acetyaminophen, and ibuprofen), cough and cold medications (diphenhydramine and pseudoephedrine), antacids, laxatives, vitamins and minerals (multivitamins, vitamins E and C, calcium), and herbal products (ginseng, Ginkgo biloba extract). Besides, in institutionalized individuals the commonest medications were gastrointestinal agents, central nervous system agents (antidepressants, antipsychotics, antianemics), and analgesics (opioids and nonopioids) [2, 10].

**Risk factors for the elderly population**

The risk factors associated with the polypharmacy in the elderly population can be divided to those related to the individual and those related to the General Practitioner. Other studies have classified the risk factors for polypharmacy into 3 groups: The first is demographic factors such as increased age, white race and education status. The second reflects the Health status including risk factors like poor health, depression, hypertension, anemia, asthma, angina, diverticulosis, osteoarthritis, gout, DM and the use of > 9 medications. The third and last risk factor group associated with the polypharmacy is related to the access to the health care system (number of consultations, supplemental insurance and multiple providers [2, 14].

**Multimorbidty** is one of the most common problems in the elderly population which makes them vulnerable in polypharmacy and subsequent prescription problems. Under this framework the physician should choose among guidelines for different diseases and select the best medication protocol for each specific individual keeping in mind possible contraindications and interactions between different drug groups. It is notable that the available guidelines usually refer to a single disease and disregard possible co-morbidities within the same patient. Very often the patients consult various specialists due to comorbidity, which might lead to drug duplication and maybe prescription of a formulation containing the same active substance that the patient is already taking [14, 15].

**Decline of liver and renal function** can alter the pharmacokinetics and pharmacodynamics of the medications taken. Liver metabolism can change due to reduced liver enzyme function, reduced hepatic blood flow and hepatic mass so the drugs metabolized in the liver (warfarin, theophylline, phenytoin) show an altered metabolism and excretion. As the renal clearance lowers and so does the renal glomerular filtration rate and muscle mass, they both result to decreased distribution and excretion of the drugs, leading to various adverse drug reactions. Therefore, the prescription of renally-excreted drugs (e.g. digoxin, lithium and gentamicin) demands caution and dose adjustment [16].

**Self-medication** and the availability of various over-the-counter drugs are potential causes of polypharmacy [14, 15].

**Low literacy and poor cognitive status** are common in the elderly contributing to miscommunication and misunderstanding the physicians orders especially when the last prescribe complex regimens. The level of education itself plays an important role in polypharmacy. Thus, patients of higher level of
education were more knowledgeable about their medications and health status and were even self-monitored by accepting healthcare interventions, whereas the less educated elderly were more susceptible to polypharmacy. The problem is aggravated especially in patients who visit several physicians at several sites, which don’t have access to their previous or current medication list and this results to duplication or unnecessary medication. Another issue is that older people very often confuse their pills, due to similarity in shape or color or even repeat their prearranged dose due to dementia [14, 15, 17].

Physician might also contribute to inappropriate or unnecessary polypharmacy, by surrendering to the patients’ demand for a prescription in the end of the visit. The prescription cascade is continued by the repeat prescriptions signed by the doctor without proper review of the patients’ history and poor knowledge of the side-effects of the long-term intake of each drug and the respective drug interactions. Lack of time during the consultation to the General Practitioner can also lead to incorrect or prolonged medication intake and consequent adverse drug reactions.

Consequences

The most common consequences of polypharmacy, apart from the tremendous increase of drug cost, are adverse drug reactions (ADR), drug interactions, noncompliance and reduced adherence, reduced functional status, geriatric syndromes, high risk of hospitalization and possibly death [18].

1. Adverse drug events (ADEs). The ADEs can result from medication intake errors, overdose, allergic reactions and ADRs and are divided in predictable or related to normal pharmacokinetics (bleeding on warfarin) and unpredictable or unexpected (anaphylaxis, Stevens-Johnson syndrome). The most common drug side effects are sedation, nephrotoxicity, hepatotoxicity, cardiotoxicity, confusion, dizziness, hypotension and hypoglycemia. The all age ADRs has increased globally and are the principal cause of 10 % of the emergency room visits, and although they can affect both outpatients (35 %) and hospitalized (44 %) elderly people. Others estimate that ADRs due to polypharmacy are seven times more common in people > 70 years old than in young individuals [18, 19]. Recent statistics accuse them for the 4.3 million healthcare visits reported in 2005, while the most suspicious drug groups are anticholinergic and psychotropic drugs (antipsychotics and benzodiazepines), cardiovascular drugs, diuretics, anticoagulants, nonsteroidal anti-inflammatory drugs, antibiotics, and hypoglycemic [20]. The incidence of ADRs is linearly correlated with polypharmacy and especially the number of medications taken. So, the risk of ADRs is reported to be about 13 % for 2 medications, 58 % for intake of 5 drugs and is estimated to be more than 82 % if > 7 drugs are taken [21, 22]. The problem of ADRs is that very often are misreported as new symptoms and further medications are prescribed, exaggerating the incidence of polypharmacy and the prescription cascading.

2. Drug interactions. They are divided in two categories, the drug-drug interactions and the drug-disease interactions. The first are very common in the elderly due to polypharmacy, comorbidities, decrease nutritional status, dehydration and diminished liver and renal function. The prevalence of drug-drug interactions is estimated 35 %–60 % in the elderly with a direct association to the number of medications [23]. Besides, the prevalence of drug-disease interactions in the elderly is reported to be 15–40 %. The most common interactions of this kind are between aspirin and digestive ulcer disease, Ca2+ channel blockers and heart failure and β-blockers and diabetes [24]. As drug-drug interactions are a frequent cause of preventable ADEs and medication-related hospitalizations, the healthcare providers should keep this in mind when they prescribe new medications [3].

3. Adherence — Noncompliance. The range of noncompliance prevalence in the elderly is 43 %–95 % and is usually associated with complex medication regimens, polypharmacy, mental status of the patient, visual or hearing impairment and advanced age. It is thought as a principal cause of disease progression, treatment failure, hospitalization, even life-threatening adverse drug events [25] and eventually increase the need of further medication. It is estimated that 11–30 % of the drug-related hospital admissions of the elderly result from noncompliance [26].

4. Reduced functional ability. Several prospective studies have correlated the excessive medication intake (> 5 drugs) with the functional decline of the elderly patients. Diminished functional status included both the physical functioning and a decreased ability to carry out instrumental activities of daily living (IADLs). Therefore, physicians should keep in mind of the association between polypharmacy and functional decline when prescribing multiple medications in the elderly [3, 27].

5. Geriatric syndromes:

A. Cognitive impairment. There is direct association of polypharmacy and cognitive impairment in the elderly people. Polypharmacy and excessive polypharmacy were reported in 33 % and 54 % of patients with dementia, whereas the increased intake of specific drug groups can also cause (e.g., opioids, benzodiazepines, anticholinergics) or even exacerbate delirium in the elderly (e.g., benzodiazepines, anticonvulsants, tricyclic antidepressants). In a prospective cohort study, 22 % of elderly patients taking ≤ 5 medications were diagnosed with impaired cognition versus 33 % of patients taking 6–9 medications and 54 % in patients taking ≥ 10 medications [28]. Polypharmacy itself has been accused for the 12–39 % of the delirium case in the elderly population [27, 29].

B. Falls. The risk of falls, but also the risk of recurrent falls, in the elderly is found to be directly associated to the number of drugs taken even from the number of 4–5 medications. This finding was proved both for community living and hospital or nursing home populations [30] and is usually associated with intake of antihypertensives, diuretics, laxatives, anti-cholinergics, hypnotics and benzodiazepines. According to a large cohort study, it is remarkable that the prevalence of polypharmacy in elderly people before the incidence of falling (48 %) and the subsequent hip fracture showed further increase after the fall (88 %). After this accident, not only increased the incidence of polypharmacy, but also the total number of drugs per person and the number of psychotropic medications to more than three [27]. It is important that certain drugs, such as benzodiazepines, that affect the central nervous system should be prescribed with caution, even in the minimum dose to minimize the risk of falls and other related adverse reactions.
C. Urinary incontinence is a common problem in the elderly, which can be exacerbated by polypharmacy [31].

D. Nutrition: Polypharmacy also influences the elderly individual’s nutritional status. Prospective studies found correlation between increased number of medications and decreased intake of soluble and nonsoluble fiber, fat-soluble vitamins, B vitamins, and minerals and an increased intake of cholesterol, glucose, and sodium. The prevalence of malnutrition (50%) was positive associated to the polypharmacy, in contrast to those how didn’t show consume few medications (10%) [32].

6. Increased costs. The polypharmacy leads to a 30% increase of medical costs for both the patient and the health system, resulting from increased intake of inappropriate medications, outpatient visits and hospitalizations. On the contrary, reasonable use of medications may decrease hospital and emergency room admissions and consequent medical costs [33].

Prevention

There are several methods predicting and preventing ADEs and unnecessary polypharmacy: these include Electronic medical records, the Beers Criteria and the STOPP/START Criteria.

1. Electronic medical records can help prevent prescription errors and subsequent ADEs [16]. It is important that the General Practitioner (GP) knows the common drug interactions and be aware of the altered pharmacokinetics and metabolism of drugs due to ageing. Also, he should keep in mind the medications which are inducers or inhibitors of the Cytochrome P450 enzymes and adjust the dose of certain drugs or even withdraw them from the therapeutic regimen of the elderly individual. The electronic medical records help the General Practitioner perform a clinical medication review, assessment of compliance and review of side effects during the limited time of the consultation.

2. Appointments for Drug Regimen Review. Several randomized controlled studies support that reviewing drug regimens can reduce polypharmacy. These studies have been subjected both in inpatient and ambulatory settings, with the participation of physicians, pharmacists, and/or managed care organizations. Reviewing the medication regimen in an allocated appointment with a named GP for medication review can prevent repeat prescriptions, help identify possible drug reactions, prolonged unindicated medications, helps the awareness of GP on the history of hospital discharge summaries and changes in regular medications, saves costs of drug wastage and support face-face relationship between patient and GP enhancing the medication compliance. Reviewing the literature, three studies with the upper concept were conducted in ambulatory care setting whereas two other studies focused in long term care settings. Four of them resulted in a statistically significant improvement in the Medication Appropriateness Index, whereas only one showed a reduction of ineffective medications use and only one showed statistically significant reduction in serious ADEs [3]. Ideally, we should minimize the number of prescribed medications in simple dosing regimens under the right indication, stop others which lack of the expected response and regularly check for patient’s adherence. It’s worth mentioning that GP should patiently check all the active substances in generic drugs taken but also ask about the over-the-counter (OTC) medications which the patients forget to report to the health professionals during the consultation. Finally, the GP might suggest nonpharmacologic therapy, instead of medication, such as diet modification or exercise, or when the medication seems to be clinically necessary, he can alter the dose, perhaps starting from lower doses, taking into account the patients pharmacokinetic, pharmacodynamic, and adverse-event profile and renal and hepatic function in order to prevent toxicity or drug-disease or drug-drug interactions [34–36].

3. Beers Criteria. The Beers Criteria were introduced by Dr Mark Beers in 1991 to describe the possible ADRs from commonly prescribed medications and aim to guide the modification of treatments in the elderly. The Beers Criteria classifies the medications taken by the elderly in 3 categories, those that: 1) should be avoided or dose-adjusted; 2) are potentially inappropriate for patients with syndromes and specific conditions and 3) should be prescribed with caution in the elderly. Beers et al. had found that 21.3% of the elderly were taking at least one inappropriate medication and 2.6% at least one absolutely forbidden drug. The recent update of Beers Criteria describes extra drug interactions, possible ADEs of drugs depending the hepatic and renal status of the patient and the effectiveness of the medication [37, 38]. It’s worth mentioning that in the latest review of Beers Criteria antipsychotics were associated with an increased risk for morbidity and mortality, and PPIs treatment was recommended only for two months due to possible increased risk for Clostridium difficile infection, as well as falls and fractures in patients > 65 years old [39].

4. STOPP/START Criteria. The STOPP/START Criteria is an evidence-based set of guidelines which should ideally be used together to determine the most appropriate medications for an elderly individual. The STOPP (Screening Tool of Older Person’s potentially inappropriate Prescriptions) which consists of 65 criteria helps to determine if the risks of a particular medication may outweigh the benefits in a certain patient. These guidelines include recommendations for the appropriate duration of each medication (e.g., PPIs not > 8 weeks and benzodiazepines and neuroleptics not > 4 weeks). The START (Screening Tool to Alert doctors to the Right Treatment) consists of 22 criteria and is made to help clinicians to recognize any prescribing omissions and to adjust the medication regimen to the individual’s history. It mainly refers to preventive subscription of medications, such as calcium and vitamin D supplements for osteoporosis prevention or statins in individuals with diabetes, coronary artery disease, and cardiovascular disease. Evaluating its effectiveness, the STOPP/START criteria were proved more sensitive than the Beers Criteria, as they were associated with a reduction of the absolute risk from 21.2% to 35.7% and they resulted to less follow-up appointments with the GPs. These criteria have focused in avoiding the duplication of the drugs, using furosemide for peripheral edema without heart failure, using vaso-dilators in cases of persistent postural hypotension, and using tricyclic antidepressant (e.g., amitriptyline) in glaucoma [40].

5. Integrated Management and Polypharmacy Review of Vulnerable Elders (IMPROVE) project was based on a pilot study of 28 male veterans (> 85 years old). This project was scheduled to stress the benefit of educating the patient by spending
enough time on medication consultation during every visit to the physician with the presence of a clinical pharmacist. They proved that the medical management by both the physician and a clinical pharmacist trained in medication management was successful and resulted to stoppage of at least one medication in 79% of the cases and dose or time adjustment drug intake in 75% of them. Furthermore, inappropriate medications were reduced by 14% and so did the consequent medication cost measured during the 6-month follow up [35, 41].

6. ARMOR is a Tool to evaluate polypharmacy in the elderly people. It includes Assess (of Beers Criteria, intake of Beta blockers, pain medications, antidepressants, antipsychotics, other psychotropics, vitamins and supplements), Review (of Drug-disease interactions, Drug-drug interactions, Adverse drug reactions), Minimize (the number of medications according to functional status rather than the evidence-based medicine), Optimize dose (for renal/hepatic clearance, PT/PTT, beta-blockers, pacemaker, function, anticoagulants, pain medications, and hypoglycemic, GDR for antidepressants) and Reassess (Functional/cognitive status in 1 week, Clinical status and medication compliance). The tool was initiated by a team of healthcare providers, such as medical director, director of nursing, assistant director of nursing, physical/occupational therapy director, recreational therapist, and social worker. Using this tool has been proved to significantly reduce polypharmacy, cost of care and hospitalization [42].

7. Practical issues. In case of obligated polypharmacy there are few monitored dose systems (MDSs), which include dosette boxes and blister packs. Educating both patients and their families verbally, considering generic options, utilizing compliance aids (e.g., pillboxes, medication calendars), limiting the prescribing of non-indicated drugs and simplifying and periodically assessing the medication regimens can enhance medication adherence [36].

8. General Principles for Optimizing Subscription in the Elderly. Obtain extensive medication history at the first consultation and often update it. Include both prescription and nonprescription medications, even encouraging patients bring with them all the over-the-counter (OTC) products they use (vitamins, supplements, antacids etc.). All medications should have an indication and the unnecessary ones should be discontinued. Before starting a new medication to cure a symptom be aware of the possibility that this symptom isn’t side effect of another. Dose adjustment should be considered in case of a necessary medication, after keeping in mind of the medication’s specific pharmacokinetic and pharmacodynamic properties, side effect profile, and the patient’s current hepatic and renal function. Simplifying medication regimens, starting from lower doses and later titrate slowly, as well as educating patients regarding medications can improve compliance of the elderly population. There are some practical monumental tools (SAIL and TIDE) to help the healthcare practitioners [1]:

— Simple. Regimen as simple as possible, even mono-dose regimens or twice/day.
— Adverse effects. Choose medications with broad therapeutic indications. Stop drugs which cause adverse effects, if possible.
— Indication. Each medication should have an indication and a defined therapeutic goal.

— Time. Time for discussion with the patient during the consultation.
— Individualize. Medication and dose adjustment according to the patient’s specific pharmacokinetic and pharmacodynamics, renal and hepatic function. Lower doses at the beginning and gradually titration.
— Drug-drug and drug-disease interactions.
— Educate. Inform the patient to be aware of possible medication effects, potential adverse effects, and drug-drug interactions and monitoring parameters in order to cooperate effectively with the caregiver.

Conclusions

As global population grows older, the multi-morbidity increases and polypharmacy intensifies. Unfortunately, this worldwide increase in polypharmacy results in higher healthcare costs, ADEs, drug-interactions, medication nonadherence, decreased functional status and geriatric syndromes among the elderly population. As prescribing for this group of individuals is a very challenging procedure, the General Practitioner should balance between under-treatment, overtreatment and risks and benefits. This review concluded that we need more cross-sectional clinical studies on practical preventive interventions to be applied not only on the population which is already exposed to polypharmacy, but also to the general population.

Conflicts of interests. Author declares the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

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Полипрагмазия у людей пожилого возраста: распространенность, последствия и стратегии профилактики

**Резюме.** Полипрагмазия включает в себя прием нескольких препаратов одновременно, что может быть очень опасным для людей пожилого возраста. Старение населения приводит к увеличению частоты хронических заболеваний, требующих одновременного приема многих препаратов. Пожилой возраст и процессы старения часто связаны с багатыми супутними захвораюваньми, что потребуют фармакологического вмешательства, которое может привести к побочным реакциям на лекарственные средства, лекарственные взаимодействия, несоответствию и снижению уровня приема, ухудшению самочувствия, высокому риску госпитализации и другим возможным реакциям. За последние десятилетия разработано несколько рекомендаций, которые помогут семейному врачу предотвратить полипрагмазию у пожилых людей. В результате необходимо больше перекрестных клинических исследований и профилактических вмешательств, которые будут применяться не только к населению, которое уже подверглось полипрагмазии, но и к общей популяции.

**Ключевые слова:** полипрагмазия; пожилой возраст; сахарный диабет; артрит; рак

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