CHAPTER 12

POLYPHARMACY AND RATIONAL DRUG USE IN THE ELDERLY

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INTRODUCTION

Incorrect and unnecessary drug use is an important public health problem in our country as well as all over the world. This problem is more pronounced especially in the elderly. Since chronic diseases are more common in the elderly than in the young, they apply to health services more than the young. The fact that the elderly have many comorbidities and therefore apply to many clinics brings along the problem of prescribing a large number of drugs to the elderly. There are many other reasons for the use of multiple drugs in the elderly. There are several disadvantages of using a large number of drugs, as well as not using the necessary drug or using it incorrectly. In this section, why polypharmacy and inappropriate drug use are so common and important in the elderly, how to combat this problem, and what should be considered in order to ensure rational drug use will be discussed.

Polypharmacy and inappropriate drug use

The word polypharmacy consists of the Greek words 'polus' (many) and 'pharmakeia' (use of medicine) and means 'multiple drug use'. There is no commonly accepted definition of polypharmacy. Although definitions according to the number of drugs used in the literature are frequently encountered, there is no consensus on the number of drugs defining polypharmacy. It is often defined as the simultaneous use of four or five drugs or more(1). On the other hand, some authors define polypharmacy as the use of more drugs than clinical indications or the use of at least one unnecessary drug (2). Although polypharmacy generally refers to prescription drugs, over-the-counter drugs and herbal supplements should also be considered (3).

Polypharmacy is one of the most common geriatric syndromes in the elderly(4). Inappropriate drug use is as important as polypharmacy in the elderly. Not giving the drug with the necessary indication to the patient, not discontinuing the drug

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that has no indication or whose indication has expired, prescribing drugs without paying attention to drug side effects, overlooking drug-drug and or drug-disease interactions, treatment duplication, having a more suitable alternative for the patient (side effects, in terms of ease of use, cost, etc.) can all be evaluated under the heading of inappropriate drug use(5). The fact that a patient is using a large number of drugs does not mean that he or she is using inappropriate drugs. Since the patient has many comorbidities, it may be necessary to use a large number of drugs. All drugs he uses may also be necessary and appropriate. However, it should always be considered that the use of too many drugs both increases the risk of drug side effects and increases the potential for inappropriate drug use(6).

WHY İS POLYPHARMACY AND INAPPROPRİATE DRUG USE IMPORTANT?

Polypharmacy and inappropriate drug use is very common problem in the elderly.

Although the incidence of polypharmacy varies according to the population studied and the accepted definition of polypharmacy, it is seen that the frequency of polypharmacy increases with age in almost every study.

In the United States, there are studies reporting that 35-40% of individuals between the ages of 75-85 use at least 5 drugs in a day, while 70% of the elderly living in nursing homes use more than 9 drugs in a day (7,8). Gallagher et al., evaluated the studies conducted in different European countries; reported that in emergency geriatric medicine units, 39% of patients aged 65 and overused 1-5 drugs in a day, 44% used 6-10 drugs in a day, and 14% used more than 10 drugs in a day (9). In a study conducted in the United States, it was observed that 43% of the elderly living in the community used at least one drug that could potentially be considered inappropriate, and nonsteroidal anti-inflammatory drugs were the leading drugs used inappropriately (10).

Polypharmacy and inappropriate drug use reach the highest rates in nursing homes and hospitals in the world and in our country. In an evaluation that included eight European countries, the rate of polypharmacy in nursing homes was found to be around 50%(11). In a study by Hajjar et al., it was reported that 44% of frail elderly hospitalized and discharged patients were given at least one unnecessary drug(12). In the study of Bahat et al., in our country, the average number of drugs used in patients staying in nursing homes and not bedridden was found to be 7.1 (13). In the study of Cankurtaran et al., it was determined that geriatric individuals who applied to the outpatient clinic used an average of 3.79 drugs

before their application to the outpatient clinic, and an average of 6.13 drugs were recommended to the patient at the outpatient clinic(14).

It is directly related to increased morbidity, mortality, and cost.

Polypharmacy and inappropriate drug use cause an increase in drug side effects. It reduces adherence to treatment. It can make worse the current condition of the patient by causing drug-drug or drug-disease interaction. It leads to an increase in hospitalizations. The rates of hospitalization due to drug side effects are four times higher in the elderly than in the young. 20-25% of hospitalizations of the elderly are due to serious drug side effects(15).

Polypharmacy and inappropriate drug use are closely associated with many geriatric syndromes. Weight loss and malnutrition are the heads of these syndromes. Many of the drugs have side effects on the gastrointestinal tract. Drugs can cause deterioration of the sense of taste, complaints such as dry mouth, difficulty in swallowing, loss of appetite, nausea, dyspepsia, and absorption problems. The increased risk of malnutrition also increases the risk of sarcopenia and fragility. Side effects of drugs such as sedation, orthostatic hypotension, and dizziness may cause the elderly to limit their physical activities, which further increases the risk of sarcopenia and fragility.

Polypharmacy and inappropriate drug use may lead to worsening of cognitive functions in the elderly(16). In the elderly, there is a decrease in the cholinergic system due to aging-related changes, existing diseases, and drugs used. For this reason, with the addition of an anticholinergic drug to the treatment, even at a low dose, situations such as confusion, disorientation, and memory loss can easily occur. Polypharmacy and inappropriate drug use are both predisposing and precipitating risk factors for delirium. It increases the risk of falls and fractures. In a study conducted by Kucukdaglı et al., it was found that polypharmacy and inappropriate drug use increased the risk of falling 2.6 times(17). In this study, it was shown that the use of four or more drugs and the use of drugs such as sedating agents (such as serotonin reuptake inhibitors, tricyclic antidepressants, neuroleptics, benzodiazepines), anticonvulsants, digoxin, and diuretics are associated with an increased risk of falling. In addition, polypharmacy and inappropriate drug use may cause sleep disturbance, depression, and physical dysfunction in the elderly. It poses a risk for immobility, incontinence, and pressure ulcer development secondarily. It increases the likelihood of being placed in a nursing home. It reduces the quality of life.

What are the effects of aging related changes on drug metabolism?

Depending on aging, various changes occur in the pharmacokinetic processes (such as absorption, distribution, elimination) and pharmacodynamic properties (such as the number of receptors in the organ cells on which the drug acts, signaling ability and signal function, changes in homeostatic control mechanisms) (18). These changes associated with aging are summarized in Table 1. Changes associated with aging also lead to changes in drug efficacy, side-effect profile, drug-drug interactions, and the therapeutic range of the drug. Older people have lower drug tolerance and higher sensitivity to drug side effects than young people. When evaluating serum drug levels in elderly patients, it should be remembered that therapeutic ranges used in clinical practice may not be appropriate for geriatric patients. Because; therapeutic serum ranges are often defined for non-geriatric individuals.

Table 1: Effect of aging-related changes on drug metabolism

Aging-related changes	The effects of the change
Decreased renal clearance	Decreased elimination of renally excreted drugs
Decreased serum albumin level	Increase in free drug concentration
Increase in body fat mass	Increased distribution of fat-soluble drugs (such as diazepam)
Decreased total body water	Decreased distribution of water-soluble drugs (such as lithium, theophylline, digoxin, aminoglycoside antibiotics)
Decreased hepatic metabolic capacity	Accumulation of drugs metabolized in the liver
Decreased cardiac reserves	Tendency to heart failure
Decreased baroreceptor sensitivity	Tendency to orthostatic hypotension
Chronic diseases	Changes in body metabolism
Multiple drug use	Increased drug interaction rates
Individual drug metabolism differences	Variable dose ranges

What are the risk factors for polypharmacy and inappropriate drug use?

It has been determined that many risk factors often coexist in individuals with polypharmacy and inappropriate drug use. These risk factors are summarized in Table 2. Chronological increase in age is one of these risk factors. Drug use rates may also vary with gender. There are studies showing that the frequency of polypharmacy is higher in female individuals (19). With the increase in age, the fre-

quency of chronic diseases and the possibility of co-occurrence of these diseases increase, which causes the use of multiple drugs. As the number of drugs used increases, the risk of side effects due to drugs increases in parallel and exponentially. It becomes inevitable to experience at least one side effect in an elderly person who uses eight or more drugs(20).

Many elderly have more than one chronic disease together. Patients apply to doctors in different branches for different diseases, and sometimes a doctor may prescribe medication to the patient without being aware of the other doctor's prescription. The patient may use more than one drug with similar content without being aware of it. Medication-related side effects are sometimes associated with existing disease or the aging process, so the side effects are overlooked. It is also common in clinical practice that new drugs are prescribed to eliminate existing side effects. The initiation of another drug to treat a side effect caused by a given drug and thus prescribing a large number of drugs to the patient in a row is called a "prescription cascade" (21). The fact that physicians do not have enough information about the side effects of the drugs they prescribe and drug-drug, drug-disease interactions is also an important reason for the prescription cascade. Pharmacokinetic and pharmacodynamic changes that occur with aging should be known to all prescribing physicians. In addition, inadequate modification of clinical guidelines for chronic diseases for elderly patients with multiple comorbidities increases the risk of polypharmacy and inappropriate drug use.

It is clearly known that polypharmacy and inappropriate drug use are more common in elderly people in need of care and those staying in nursing homes. At this point, factors belonging to the patient (such as cognition problems, sensory disorders, functional limitations, lack of education) and/or factors belonging to the caregiver (such as lack of interest/knowledge, social and economic limitations) play a part (22). Misuse or incomplete use of given drugs by patients is also a common situation in practice. The reason for this situation may be cognitive impairment, loss of sensation, functional limitation, social-financial impossibilities, as well as being misdirected by a friend and/or social media also. In our country, it is a common situation to use drugs without consulting a doctor.

Table 2: Risk factors for polypharmacy and inappropriate drug use
Chronological age
Number of comorbid diseases
Lack of information (drug-drug interaction, drug-disease interaction, drug side effects)
Prescription cascade

Clinical guidelines are not adequately modified for the elderly with multiple comorbidities
Patient-related factors (sensory loss, disability due to cognitive and/or functional limitations, social and economic limitations)
Institutional care service (such as hospital, nursing home)
Caregiver-related factors (lack of interest/knowledge, social and economic limitations)
Some misdirections by social media

How Can Polypharmacy and Inappropriate Drug Use Be Reduced?

All prescription and nonprescription medications of the patient should be reviewed at each visit. If possible, the patient should explain how he/she uses his/her medication himself/herself. It should be checked whether the indications of the drugs used by the patient continue. It is important to know the aging-related pharmacokinetic and pharmacodynamic changes, drugs side effects, and drug interactions by the clinicians. Also, it is important to follow the side effects of the prescribed drugs, to start the drug at the lowest possible dose, and to gradually increase or stop the drug dose. If non-drug treatment of the current condition is possible, priority should be given to non-pharmacological treatments.

The recommended treatment principles to prevent polypharmacy and inappropriate drug use in the elderly are summarized in Table 3. These principles should be known and applied by all physicians evaluating and prescribing elderly patients. In addition, various internationally accepted criteria sets and guidelines developed to ensure rational drug use in the elderly should be utilized. Commonly used guidelines on drug use in the elderly;

Drug Burden Index (DBI): It is an index that includes drugs with anticholinergic and sedative effects, the total number of these drugs, and their daily doses(23). In a study conducted by Okudur et al. in our country, the prevalence of polypharmacy was found to be 32% in patients aged ≥60 years who applied to the outpatient clinic, and the anticholinergic load scale with the strongest relationship with polypharmacy was found to be DBI (24).

Beers criteria: Developed in 1991 by an expert consensus panel. The criteria is a list of drugs considered inappropriate for use in elderly patients due to the high risk of adverse effects. The drugs are grouped into five categories. These categories are; 1 – potentially unsuitable for the majority of the elderly, 2 – typically avoidance in the elderly with certain conditions, 3 – drugs to be used with caution, 4 – drug-drug interactions, 5 – drug dose adjustment based on kidney function. The criteria were last updated in 2019 (25).

Screening Tool of Older Persons' potentially inappropriate Prescriptions/ Screening Tool to Alert to Right Treatment (STOPP/START): STOPP was prepared by a multidisciplinary team in 2008, taking into account criteria such as drug-drug, drug-disease interaction, causing falls in the elderly, duplication of drugs from the same group. It is widely used to reduce inappropriate drug use. A START study was also conducted for the underuse of potentially beneficial drugs in the elderly. In 2015, the STOPP/START criteria were updated (26).

Fit FOR The Aged (FORTA): It is a drug administration tool developed in Germany. It has passed consensus validation with a panel of geriatricians. In this tool, drugs are graded into four categories. These categories are; 1 – drugs with clear benefit 2 – drugs with proven but limited efficacy or some safety concerns 3 – drugs with questionable efficacy or safety profile and alternatives for which to be considered 4 – drugs to be avoided and found alternatives (27). Studies evaluating its effect on clinical outcomes are ongoing.

Turkish Inappropriate Medication Use in the Elderly (TIME) Criteria: It was developed in Turkey, under the leadership of the Academic Geriatrics Society – Rational Medicine Working Group, based on the STOPP/START criteria. It has been prepared with the participation of many faculty members who are experts in their field and experienced in elderly patient care. Drugs are grouped according to organ systems. TIME criteria consist of two parts as TIME-to STOP (112 criteria) and TIME-to START (41 criteria)(28). An international validity study has been published(29). There are studies evaluating the benefits of clinical use in our country as well. Having an application that can be downloaded free of charge to smartphones provides clinicians with ease of use and compliance.

There are other criteria sets regarding drug use in the elderly, such as Improved Prescribing in the Elderly Tool (IPET), Medication Appropriateness Index, Assessing Care of Elders (ACOVE) project, Criteria to Assess Appropriate Medication for Elderly Complex Patients (CRIME). Strict commitment to guidelines may not always be possible or appropriate. Before prescribing, the patient should undergo a comprehensive geriatric assessment. While prescribing, the patient's limitations and living conditions should be considered, and the clinical experience of the physician should not be ignored also.

CONCLUSION

Polypharmacy and inappropriate drug use are very common in the elderly and are directly related to increased morbidity and mortality. Elderly patients have to use a large number of drugs due to polymorbidities, difficulties in elderly patient

management, and lack of knowledge. In addition, due to aging-related changes, elderly people have lower drug tolerance and higher sensitivity to drug side effects than younger people. For all these reasons, polypharmacy and inappropriate drug use should constitute an important part of the comprehensive geriatric assessment. In order to combat polypharmacy and inappropriate drug use, it is necessary to raise awareness of rational drug use in society and to encourage physicians to use scientific evidence-based guidelines and criteria when prescribing drugs.

Table 3: Suggested treatment principles to prevent polypharmacy and inappropriate drug use in the elderly
A healthy patient-physician relationship should be established.
Comprehensive geriatric assessment should be performed.
Help should be sought from the drug use criteria developed for the elderly.
The treatment goal and plan should be created individually for each patient and the treatment should be individualized.
Treatment should be done with the least possible number of drugs, and the treatment program should be simplified.
The treatment should be started at the lowest possible dose, and the dose increase should be done very slowly and carefully.
If possible, more than one drug should not be started at the same time, and the other drug should be added to the treatment after compliance with one drug and the side effects of the drug are evaluated.
All medications used by the patient should be checked by the doctor at each examination and notes should be taken.
The drugs that the patient should use should be given to the patient and/or caregiver in writing, along with drug doses and times.
The characteristics, side effects, and possible interactions of the prescribed drug (such as food-drug, drug-drug, drug-disease) should be known by the prescribing physician.
Patients and caregivers should be informed about possible side effects and what to do in case of side effects.
Difficulty in swallowing, refusal to use medication, tube feeding, functional limitation, living alone should be taken into account, and the most appropriate drug formulation for the patient should be preferred (such as tablet/capsule/ampoule/strip/drop/solution).
Treatment should be reviewed at regular intervals – drugs whose indications expire should be discontinued – treatment benefit-loss ratio should be re-evaluated at each examination.
If the current medical problem has non-drug treatment options, initially the problem should be tried to be solved in this way.
If there is a newly developed symptom/sign in the elderly, it should be questioned whether it is a new or discontinued drug; If a new drug is started, this symptom/sign should be considered as a drug side effect until proven otherwise.

Drugs that have a sedating effect should be used for the shortest time possible and in the lowest dose possible, and patients and/or caregivers should be warned about possible side effects and risks (such as falling, incontinence, deterioration in physical and cognitive functions).

The elderly are very sensitive to drugs with anticholinergic effects. Medicines with anticholinergic effects (such as antispasmolytics, muscle relaxants, urinary anticholinergics, antipsychotics) should be recognized by clinicians.

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