REVIEW

CONTROVERSIAL ISSUES RELATED TO DRUG TREATMENT IN OLDER ADULTS

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Abstract

Drug therapy in older adults continues to pose problems and cause controversy with its different aspects. Polypharmacy and inappropriate medication, appears to be the major problem worldwide in terms of both geriatric health and healthcare. Also increases the risk of geriatric syndrome and affects the morbidity/mortality rates negatively. A definition for inappropriate medication is "any drug in which the risks outweigh the benefits or where these do not align with goals of care", since it encompasses both ineffective or unnecessary treatment and those treatments with high risk. A range of assessment tools have been developed to identify and measure inappropriate prescribing. The most commonly recommended criteria for the use of drugs in older adults are the Beers criteria by American Geriatrics Society. The "Screening Tool of Older People Prescriptions (STOPP)" and the "Screening Tool to Alert doctors to Right Treatment (START)" are other frequently recommended screening approaches. It seems suitable also to establish consideration of deprescribing within the continuum of treatment recommendations in clinical guidelines. Deprescribing is defined as "the planned, supervised process of medication discontinuation, addressing unnecessary polypharmacy which continues to be a problem among older adults". Evidence-based deprescribing guidelines could be a useful component in the effort to address the global problem of polypharmacy. However, it is important to keep in mind that it is essential to consider the ethical and legal dimensions in all these approaches. Another issue is the herbal products and since the general knowledge about food/beverage-drug interactions are found to be poor, there seems a need to enhance the community awareness of these interactions especially for older adults.

Keywords: Geriatrics; Drug Therapy; Inappropriate Prescribing; Polypharmacy; Deprescriptions.

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INTRODUCTION

Geriatric syndromes are difficult to understand due to the complexity of the multiple factors and the synergistic effects of the various risks. These situations are called syndromes to emphasize that the combined manifestations are related to a large number of factors (1). One of these is polypharmacy, which appears to be a major problem worldwide in terms of both geriatric health and healthcare. Also increases the risk of geriatric syndrome and negatively affects the morbidity/mortality rates.

Concomitant medications were found to be related to a 13% increased risk of a serious adverse event (2). And inadequate or incomplete information about the drug treatment increases the risks of drug interactions and side effects. Adverse drug reactions associated with inappropriate use of drugs lead to many problems and it is stated that, polypharmacy appears as one of the significant reasons for hospitalization (3).

POLYPHARMACY

Although it has been emphasized that polypharmacy must be addressed carefully, the desired awareness cannot be achieved in daily clinical practice. A review of the literature shows that there are still many question marks about polypharmacy. One of the top issues dealt with recently seems to be the relationship between polypharmacy and functional capacity. It is a fact that both of these are associated with mortality and morbidity, and this increases the importance of the issue.

Unfortunately polypharmacy is common in older adults with the highest number of drugs taken by those residing in nursing homes. Nearly 50% of older adults take one or more medications that are not medically necessary. It has clearly been established that there is a strong relationship between polypharmacy and negative clinical consequences. As clearly stated by Maher et al, although there is considerable data on those living in nursing homes, the factors affecting the relationship between polypharmacy and functional capacity in the elderly living in communities have not been fully identified yet (4). Literature shows that, polypharmacy in older persons also complicates therapy, increases cost, and is a challenge for healthcare agencies.

The incidence of drug interactions and adverse reactions increases exponentially with the increase in polypharmacy. In a study evaluating 1430 older persons in different geographical regions of Turkey showed that, polypharmacy was correlated with various factors including age, sex, marital status, number of children, status of retirement, and presence of chronic medical conditions but not educational status (5). Being one of the leading causes of hospitalization, polypharmacy seems to be associated with some important parameters in terms of elderly heath, such as frailty, increased incidence of falls, prolonged hospital stay, increased rate of recurrent hospitalizations, and greater economic burden (6-10).

A recent study included 675 people aged over 65 years from 8 centers in various geographical regions of Turkey. The polypharmacy status was categorized as non-polypharmacy (0–4 drugs) and polypharmacy (≥5 drugs). The subjects' physical function was assessed based on their "physical activity levels, Holden ambulation scores, gait speeds, and hand grip strengths". Their nutritional status based on the "Mini Nutritional Assessment"; and their psychological status based on the "Center for Epidemiologic Studies Depression Scale ". The Charlson Comorbidity Index was used for the evaluation of comorbid conditions. The presence of polypharmacy in this population was found to be 30%. A statistically significant difference was found between the groups on the level of physical activity, Holden ambulation score, and nutrition status. There was a statistically significant difference between the groups also on hand grip strength, Mini Nutritional Assessment score and Charlson score. On the light of this study, the authors concluded that, polyphar-

macy was found to have a significant association with physical function, nutrition, and depression in the elderly aged 65 and over. The relationships between these clinical conditions, each of which is defined as a geriatric syndrome, should be considered in our clinical practice with particular attention on reducing the rates of morbidity and mortality (11).

The incidence of drug interactions and adverse reactions increases exponentially with increases in the number of medications consumed. A study was conducted to investigate drug consumption, in particular nonsteroidal anti-inflammatory drugs, and to assess the relationship between drug consumption and cognitive function and disability in a group of older people residing in a nursing home. Two hundred residents (108 women, 92 men, mean age 77.2 +/- 8.7 years) of a nursing home were evaluated. Mini-Mental State Examination and Functional Independence Measure were used to assess the cognitive and functional status. The majority (94.4% of men and 80.4% of women) were prescribed at least one drug, with a mean of 3.59 prescriptions prescribed to women 2.39 to men. The mean number of self-prescribed drugs used by the elderly was higher than found in previous studies. The drugs self prescribed most commonly were nonsteroidal anti-inflammatory drugs, with a rate of 72.5%. Authors found a significant positive correlation between nonprescribed drug use and the scores of Mini-Mental State Examination and Functional Independence Measure. The high drug consumption was correlated with poor cognitive and functional status in elderly residents of this nursing home (12).

Also a wide multicentric study, aiming to evaluate the prevalence of chronic illnesses and the characteristics of drug use in a population of nursing home residents aged 60 and older in 23 cities in Turkey, self-reported adverse drug reactions and their relationship to number of medications used were evaluated. One thousand nine hundred forty-four subjects (1,196 male, 748 female) were enrolled in the study. The mean age ± standard deviation was 74.3 ± 7.7 for men and 77.1 ± 8.7 for women. Hypertension was the most prevalent chronic disease seen in the study population (30.7%), followed by osteoarthritis, heart failure, diabetes mellitus, and coronary artery disease. Age and number of medications were not correlated. The usage of analgesic and nonsteroidal antiinflammatory drugs was more common in women than men. There was a correlation between polypharmacy and adverse reactions. Subjects using nonprescribed drugs reported more adverse reactions. The most common adverse reactions reported by the subjects were gastrointestinal side effects, followed by dizziness, sleep disorders, itching, diarrhea or constipation, dry mouth, and swelling of the legs (13).

Not only the polypharmacy but safety of drug use, which is defined by the maximum efficacy, safety of drug and its convenience for the patient and cost-benefit relation, is significant for all age groups as well. However, this is much more so for geriatrics. Therefore, the physicians and the other health professionals working in this chain should pay great attention for safe use of drugs in the older group. It was clearly stated that, studies were needed to find the most effective way to reduce polypharmacy, especially in the frail elder population, and to quantify the real advantages of simplifying their drug regimens in terms of improved quality of life (14).

INAPPROPRIATE MEDICATION USE

Potentially inappropriate prescribing polypharmacy has been identified as one of the most common risk factors for deterioration of physical and instrumental daily life activities in older people (15). A definition for inappropriate medication is "any drug in which the risks outweigh the benefits or where these do not align with goals of care", since it encompasses both ineffective or unnecessary treatment and those treatments which are high risk. According to Reeve et al, the term "inappropriate" is imperfect due to its own variations in definition and the exclusion of "dose reduction and substitution" and "ta-

pering" from the definition may be questioned by some, although the justifications for these decisions are provided (16).

Factors that set the stage for the use of multidrugs in the elderly are various. The patients are increasingly receiving a large number of prescriptions from different physicians, there is a fact that physicians tend to prescribe a large number of drugs, the patients expectations of a large number of medication, the use of drugs for symptoms rather than diagnosis in the elderly. Also there is the tendency of physicians to cut off the old drug and start a new one, automatic rewriting of drugs used as a patient's or physician's choice, sale of a large number of over-the-counter drugs, as well as elderly patients tending to take medication from family members or friends. In addition, having been hospitalized in the last six months, being a woman, being depressed, low level of education are risks for multiple and inappropriate drug use in the older age group (17).

In the last years research on prescribing quality in older adults is rapidly expanding and a range of assessment tools have been developed to identify and measure inappropriate prescribing (18). It is stated that, there is no gold standard on how to ensure high quality of prescribing for older adults. Regarding the daily practice the question remains if the interventions also result in improved clinical outcomes. Inspite of increasing awareness, such tools can never replace good clinical judgement (19).

RECOMMENDED CRITERIA

The most commonly recommended criteria for the use of drugs in the elderly are the Beers criteria by American Geriatrics Society. Beers is a list of drugs that have a high risk of side/undesirable effects in elderly people. It is a fairly extensive list. However, it is necessary to take into account some of its features and these are; Beers criteria do not take into account the patient's medical diagnosis, psychosocial status, daily life activities, availability of the drug, whether it has Food and Drug Administration Federal agency (FDA) or European Medicines Agency (EMEA) approval (20). The American Geriatrics Society Beers Criteria is defined as an explicit list of potentially inappropriate medications that are typically best avoided by older adults in most circumstances or under specific situations, such as in certain diseases or conditions. Considering some of the negative aspects that have already been identified, American Geriatrics Society has been updating the criteria since 2011 and carries out these updates on a 3-year cycle. In the light of the evidence published since 2015, the last update was made by a group of experts from different disciplines. New criteria were determined by updating for 2019 for clinicians, educators, researchers, and regulators that are widely used by health care managers (21).

The "Screening Tool of Older People Prescriptions (STOPP)" and the "Screening Tool to Alert doctors to Right Treatment (START)" are other frequently recommended screening approaches; STOPP consists of 65 rules related to potentially inappropriate prescribing. START, on the other hand, directs physicians to the right treatment (22, 23). Especially in multimorbid elderly, minimizing inappropriate prescribing is necessary. Prescriber education in terms of geriatric pharmacotherapy, close consultation between clinical pharmacists and clinicians, considering screening tool for older people's prescriptions/ screening tool to alert to right treatment (STOPP/START) criteria and electronic prescribing would be of benefit (24).

In a multicenter study, prospective data were collected from 900 consecutive older patients admitted to six university teaching hospitals (150 patients per centre) in Geneva (Switzerland), Madrid (Spain), Oostende (Belgium), Perugia (Italy), Prague (Czech Republic) and Cork (Ireland). STOPP and Beers' criteria were applied to detect potentially inappropriate medicines. START criteria were applied to detect potentially inappropriate prescribing

omissions. And the results of this study showed that potentially inappropriate drug prescribing and the omission of beneficial drugs are highly prevalent in acutely ill hospitalized older people in six European centres (25).

RATIONALE MEDICATION MANAGEMENT

For rationale medication management through a case-based format, there are some questions to be asked: Does each drug used match a known medical problem? (Is there inadequacy/overlap?), What are the categories of drugs and their mechanisms of action?, What is the patient's creatinine clearance level?, Are the doses for each drug appropriate for the patient's kidney, liver functions and age?, Are there any problems in terms of potential drug-drug, drug-disease interactions and drug complications?, What are the patient's current complaints (onset, duration)?, Can a drug be responsible for these complaints?, Are there any new drugs added or removed?, Is there a relationship between the complaints and the start date of the drug?, Can the medication regimen be simplified? (17, 26, 27).

It is clearly stated that, drug treatment is essential in both treatment and prevention of diseases among older adults and unfortunately this is of concern (28). Reasons are: 1-Most evidence regarding medication efficacy and safety is derived from small samples of younger and healthier populations (29). 2-Older people are extra vulnerable to adverse effects of drug use due to age- and disease related changes, multimorbidity, and complex drug regimens. There are initiatives to develop deprescribing guidelines (30).

The guidelines that came to the fore in clinical practice were often based on expert opinions and did not provide flexibility for the personal characteristics of patients. The principles on which the guidelines are based, are developed in such a way that best evidence, clinical experience and patient preferences can be used together to support optimal treatment decisions. It seems suitable time to establish consideration of deprescribing within the continuum of treatment recommendations in clinical guidelines as the rule rather than the exception. According to Moriartya et al, this aim is an important opportunity to improve patient care that those who wish to enhance evidence-based clinical practice should endeavour to support. It should be taken into account that, reducing use of medications which may no longer be of benefit or may be causing harm is logical (31).

DEPRESCRIBING

It seems important to determine which definitions have been made and to create a definition that can combine them. A systematic literature review aiming this purpose was performed on the basis of MEDLINE, Embase, CINAHL, Informit, Scopus and Google Scholar. The findings of this study indicate that there is no complete consensus on the definition of deprescribing, and the authors proposed a definition as; "Deprescribing is the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes". They also added that this proposed definition has not yet been confirmed or validated and has not been accepted internationally (16).

A recent article states that, deprescribing is planned, supervised process of medication discontinuation, addressing unnecessary polypharmacy which continues to be a problem among older adults (32). Tools have also been proposed to support the decision-making around deprescribing (33). Adopting a common deprescribing language in terms of terminology and definitions could be used consistently with healthcare professionals, families and patients. Improving collaboration within and across disciplines would be of value in the enhancement of deprescribing (34). Implementing evidence-based deprescribing guidelines can also increase physicians' self-efficacy in developing

deprescribing plans for certain drug classes (35).

Evidence-Based Deprescribing Guideline Symposium was held in 2018, with an interactive discussion activity alloweing the 107 participants to share experiences and ideas concerning the barriers and facilitators that arise when moving deprescribing guidelines into frontline practice. According to Conklin et al, the results of that symposium indicated that participants were committed to deprescribing and were moving forward with efforts to bring about change. Participants recognized that the implementation of deprescribing is best conceived of as a comprehensive systems change, and that patients and the public need to be involved in deprescribing processes and activities (34). Although deprescribing is the term used to describe the process of withdrawal of an inappropriate medication supervised by a clinician, it seems useful to share the 10 factors proposed by the symposium participants (34).

1- Educating patients and caregivers, including them in the process,
2- Training health care providers to increase awareness and skills in deprescribing,
3- Supporting and promoting advocacy movements led by health care providers,
4- Improving collaboration and communication within and across practice disciplines,
5- Inspiring initiatives to promote deprescribing at different levels,
6- Since deprescribing is a viable and appealing corporate practice, improving financial or business-related incentives are important,
7- Supporting initiatives to expand the evidence base for deprescribing,
8- Creating a culture of deprescribing within the related organizations,
9- Implementing a patient-centred approach to health care provision,
10- Focusing on the current momentum to expand the existing description.

MEDICATION ADHERENCE

One of the major challenges in healthcare services worldwide is ensuring patients to fully comply with their treatments. Medication adherence for patients with chronic diseases is complex, involving motivators which would fluctuate the impact on individuals at different points along the disease progression. It is perceived as a balance between the willingness and preference to take medications with the alternative being toleration of symptoms. Most methods used for increasing medical adherence require combinations of behavioral interventions and reinforcements in addition to increasing the convenience of care, providing educational information about the patient's condition and the treatment, and other forms of supervision or attention (36).

In order to ensure optimal outcome Betancourt et al recommend regular monitoring of clinical/laboratory parameters, educating the patient and caregiver and involving them in deciding treatment goals/plan (37). Patients are mainly concerned about potency and risk of therapy, and have also a desire to participate in the treatment decision process. There has been an advancing interest in assessing patients' preferences for healthcare treatments. This approach is defined as "preference-sensitive" (38).

Since seniors are suffering from several non-fatal and chronic diseases, their treatment can be easily adapted to the preference sensitive therapeutic approach. Insights into the preferences of patients would be useful to optimize policy and clinical decision making through healthcare decision making that better reflects patients' preferences. However, it should be taken account that, there may be a gap between satisfaction of the patient and the deemed appropriate prescription at this point, and disagreement between preferences of patients and physicians becomes more important (39).

Currently, clinicians are encouraged to practice evidence-based medicine, as well as patient-centered medicine. Deprescribing could also be im-

proved by implementing a patient-centered approach to healthcare provision. This approach includes the identification of patient goals/values as well as treating the individual as a whole person instead of a sum of disease states (34, 40).

Thompson and Reeve state that, there is a need in deprescribing research to shift focus to developing ways to address known barriers and harness knowledge of facilitators. That is, translating existing knowledge into strategies and tools that can impact clinical practice and lead to practical and sustained deprescribing efforts (32).

Improving collaboration and communication within and across professional and practice disciplines would enhance deprescribing. Creating a culture of collaboration where trusting relationships can be cultivated should cover not only the family physicians, specialists, pharmacists, nurses, occupational therapists, personal support workers, but family members on the care team as well. It is stated that, professional roles and responsibilities must be clear, and techniques such as huddle conversations may help to identify candidates for deprescribing (34).

HERBAL PRODUCTS

Another issue is herbal medicine and a study was conducted to evaluate the prevalence and documentation of the use of herbal remedies by individuals aged ≥ 65 years and to evaluate possible adverse reactions and herb drug interactions. Data were collected from 1418 participants (age range 65-95 years) via interview-based questionnaires. The prevalence of herbal use among older adults was 30%. As much as 64%used m ore than one prescription medication, and polypharmacy was reported by 47.5 % of participants. Some participants used herbal products that are known to interfere with conventional drugs which are used to treat chronic diseases, such as cardiac glycosides, diuretics, anticoagulants, antidiabetics, anticonvulsants, and monoamine oxidase inhibitors. According to the authors, to ensure good patient care, healthcare professionals should be aware of possible health complications associated with the concomitant use of herbs and medications (41).

The majority of the herbal products used by the seniors are usually suggested by neighbors or elderly relatives and not recommended or prescribed by a physician. Another important issue is, seniors don't know that these products can interact with the prescribed drugs they have to use for their chronic diseases. When they are addmitted to an hospital, they do not need to tell their doctors because they are not aware of the importance of using such supplements, thinking that these products are always harmless. Although physicians should be aware of the widespread and easily accessible information about these products, they also neglect to ask or do not consider this subject as a priority.

It is a fact that, the consumers use internet as a source of information on dietary supplements. Using the 5 most commonly used search engines Morris et al entered the names of the 8 most widely used herbal supplements (ginkgo biloba, St John's wort, echinacea, ginseng, garlic, saw palmetto, kava kava, and valerian root) and they found that, among 443 Web sites, 338 (76%) were retail sites either selling product or directly linked to a vendor. According to the authors, consumers may be misled by vendors' claims that herbal products can treat, prevent, diagnose, or cure specific diseases, despite regulations prohibiting such statements. They stated that, regarding the elderly health, more effective regulations are required to put this class of therapeutics on the same evidence-based footing as other medicinal products (42).

Nutritional supplements are also widely used alone and together with prescription and over-the-counter drugs in older adults. A study investigating the simultaneous use of prescription and decongestant drugs and products in older adults living in the community aged 62 to 85 years consisted

of 2351 participants in 2005-2006 and 2206 participants in 2010-2011. The average age was 70.9 years in 2005-2006 and 71.4 years in 2010-2011. The use of at least one prescription drug increased from 84.1% to 87.7% in 2005-2006, and the simultaneous use of at least 5 prescription drugs increased from 30.6% to 35.8% in 2010-2011.The authors reported that the use of over-the-counter drugs decreased from 44.4% to 37.9%, while the use of dietary supplements increased from 51.8% to 63.7%. They also found clinically significant increases in the use of statins, antiplatelet drugs and omega-3 fish oils. According to the authors; in 2010-2011, about 15.1% of older adults were at risk of a potential major drug-drug interaction compared to a drug. In 2005-2006, this was an estimated 8.4%. Most of these interactive regimens included medications, and dietary supplements were increasingly used in 2010-2011. The results showed that the use of prescription drugs and the simultaneous use of dietary supplements and interactive drugs has increased since 2005, and 15% of older adults are at risk of a potentially large drug-drug interaction (43).

Agbabiaka et al mentioned that, concurrent use of herbal medicinal products and dietary supplements with warfarin, statins, and anti-inflammatory drugs is common among UK older adults. A cross-sectional survey was conducted on a purposive sample of community dwelling older adults using self-administered questionnaires and results showet that, one in three concurrent users is at risk of a potential herb–drug or supplement–drug interaction. According to the authors; a majority of the identified interactions involved potential alterations in the concentration or effect of the prescription drugs, including calcium channel blockers, statins, and aspirin (44). A systematic review about concurrent use of prescription drugs and herbal medicinal products in older adults included twenty-two studies and showet that, prevalence of concurrent use by older adults varied widely between 5.3 and 88.3%. The most commonly used herbal medicinal products are found to be Ginkgo biloba, garlic, ginseng, St John's wort, Echinacea, saw palmetto, evening primrose oil and ginger. The list of prescription medicines identified used in combination with herbal medicinal products was: antihypertensive drugs, β-blockers, diuretics, antihyperlipidemic agents, anticoagulants, analgesics, antihistamines, antidiabetics, antidepressants and statins. As is known, the potential bleeding risks associated with the use of aspirin or warfarin, as well as Ginkgo biloba, garlic, or ginseng, are the most commonly reported herb-drug interactions. The authors added that, they found some data suggesting being female, and having a lower household income and less than a high-school education were associated with concurrent use (45).

A very recent article documented that some populations still have a positive perception towards herbs and their ability to treat diseases. Since the general knowledge about food/beverage-drug interactions was found to be poor, there seems a need to enhance the community awareness of food/beverage/herb-drug interactions (46).

FINAL WORDS

The implementation of evidence-based deprescribing guidelines appeared to increase clinician perceived self-efficacy in both developing and implementing a deprescribing plan for specific drug classes. If this is correct, then evidence-based deprescribing guidelines could be a useful component in the effort to address the global problem of polypharmacy (35).

One can say that, "patient-centered" approach is vital to allow for shared decision-making on pharmacotherapy. Deprescribing longstanding treatment can be interpreted by the patient and family as "giving up hope". Good communication with the patient, family and carer is therefore crucial, but in many cases this is a challenge to realize, especially in patients with dementia (28).

Evidence-based medicine can be defined as the formal practice of making decisions regarding the best treatment of patients based on the systematic and detailed approach of current best research evidence. This approach is not only about taking account the external evidence to design tailor-made treatment plans; it also encourages a dialogue between patients and clinicians. Thus, patients can share their opinions and express their values and preferences at the decision-making stage. The main benefit of this approach is that clinicians listen to patients' concerns about treatment and take them into account to determine the appropriate treatment plan.

Regarding deprescribing, important ethical implications such as how to deal with autonomy of patients are very important to overcome barriers in implementing deprescribing in practice. According to Reeve et al, cessation of inappropriate medication use has a large financial benefit to the individual and the community. However, the principle of justice also dictates equal rights to treatment regardless of age (47).

Polypharmacy and inappropriate medication use has been discussed in various media for many years. Although there are rules for rationale medication management and recommended criteria, it cannot be said that any definite success has been achieved in these matters.

Deprescribing is relatively a new approach which also needs to be discussed in many dimentions. It is important to keep in mind that it is essential to consider the ethical dimension in these approaches. The concept of "depriscribing", which has been developed for the prevention of polypharmacy, may be reflected in clinical practice after careful analysis of the positive and negative aspects; not only in terms of medical, but also in terms of ethical and legal rights as well. One of the most important concepts that should be considered, especially in people with chronic diseases at an advanced age, is medication adherence. During all these careful evaluation approaches, herbal product use should be constantly taken into account. Educational programs aimed at raising awareness of these issues, both in health professionals and in society, have an indisputable benefit.

It must be remembered that tailor-made treatment plans should be brought to the forefront, since there are no diseases, there are patients, and our tradition from Hippocrates is primarily adhering to the principle of "Primum non nocere".

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REFERENCES

1. Gökçe Kutsal Y. Geriatric Syndromes. International Journal on Ageing in Developing Countries, 2019; 4 (1): 41-56. [Internet] Available from: https://www.inia.org.mt/wp-content/uploads/2019/08/4.1.1-Ageing-in-Turkey-pg-6-17-Final.pdf Accessed: 20.01.2022
2. Bechman K, Clarke BD, Rutherford AI et al. Polypharmacy is associated with treatment response and serious adverse events: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Baillieres Clin Rheumatol 2019; 58(10):1767–1776. (PMID: 30982886)
3. Eyigor S, Gokce Kutsal Y. Polypharmacy in the elderly: To prescribe or not prescribe, that is the question. Turkish Journal of Geriatrics 2012;15(4):445-454. [Internet]. Available from: http://geriatri.dergisi.org/uploads/pdf/pdf_TJG_689.pdf. Accessed: 25.1.2022.
4. Maher RL, Hanlon JT, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf. 2014 Jan;13(1):57-65. (PMID: 24073682)
5. Gokce Kutsal Y, Barak A, Atalay A, et al. Polypharmacy in the elderly: A multicenter study. J Am Med Dir Assoc. 2009;10(7):486-90. (PMID: 19716065)

6. Eyigor, S., Kutsal, Y. G., Duran, E., et al. Frailty prevalence and related factors in the older adult—FrailTURK project. AGE, 2015; 37(3):9791. (PMID: 25948502)

7. Ivanova, I., Wauters, M., Stichele, R. V., et al. Medication use in a cohort of newly admitted nursing home residents (Ageing@NH) in relation to evolving physical and mental health. Archives of Gerontology and Geriatrics, 2018; 75, 202–208. (PMID: 29353187).

8. Morandi, A., Bellelli, G., Vasilevskis, E. E., et al. Predictors of rehospitalization among elderly patients admitted to a rehabilitation hospital: The role of polypharmacy, functional status, and length of stay. Journal of the American Medical Directors Association, 2013; 14(10), 761–767. (PMID: 23664484)

9. Volaklis, K. A., Thorand, B., Peters, A., et al. Physical activity, muscular strength, and polypharmacy among older multimorbid persons: Results from the KORA-Age study. Scandinavian Journal of Medicine and Science in Sports, 2017; 28(2), 604–612. (PMID: 28329413)

10. Wastesson, J. W., Morin, L., Tan, E. C. K., & Johnell, K. An update on the clinical consequences of polypharmacy in older adults: A narrative review. Expert Opinion on Drug Safety, 2018; 17(12), 1185–1196. (PMID: 30540223)

11. Eyigor S, Gökçe Kutsal Y, Toraman F, et al. Polypharmacy, Physical and Nutritional Status, and Depression in the Elderly: Do Polypharmacy Deserve Some Credits in These Problems? Experimental Aging Research, Jan-Feb 2021;47(1):79-91. (PMID: 33183169)

12. Esengen, Ş., Seçkin, Ü., Borman, P., Bodur, H., Gökçe-Kutsal, Y., Yücel, M. Drug consumrtion in a group of elderly residents of a nursing home: relationship to cognitive impairment and disability. J Am Med Dir Assoc 2000;1(5): 197-201. (PMID: 12812619)

13. Arslan Ş, Atalay A, Gökçe-Kutsal Y. Drug use in older people. J Am Geriatr Soc 2002 Jun;50(6):1163-4. (PMID: 12110084)

14. Gokce Kutsal Y. Polypharmacy in elderly. Turkish Journal of Geriatrics 2006; 9 (Special Issue):37-44. [Internet]. Available from: http://geriatri.dergisi.org/uploads/pdf/pdf_TJG_326.pdf Accessed: 25.1.2022.

15. Tommelein E, Mehuys E, Petrovic M, Somers A, Colin P, Boussery K. Potentially inappropriate prescribing in community-dwelling older people across Europe: a systematic literature review. Eur J Clin Pharmacol 2015; 71(12):1415–1427. (PMID: 26407687)

16. Reeve E, Gnjidic 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 Dec; 80(6): 1254–1268. (PMID: 27006985)

17. Gökçe Kutsal Y. Antirheumatic drug use in elderly. Bodur H, Ataman Ş (Eds): Rheumatology e book 2021 (in Turkish). [Internet]. Available from: http://www.trasdromatolojiekitap.org/icindekiler.php?id=49. Accessed: 25.1.2022.

18. Kaufmann CP, Tremp R, Hersberger KE, Lampert ML. Inappropriate prescribing: a systematic overview of published assessment tools. Eur J Clin Pharmacol. 2014; 70:1e11. (PMID: 24019054)

19. Cooper JA, Cadogan CA, Patterson SM, et al. Interventions to improve the appropriate use of polypharmacy in older people: a cochrane systematic review. BMJ Open. 2015;5(12). e009235e2015-009235. (PMID: 26656020)

20. Vishwas HN, Harugeri A, Parthasarathi G, Ramesh M. Potentially inappropriate medication use in Indian elderly: Comparison of Beers' criteria and Screening Tool of Older Persons' potentially inappropriate prescriptions. Geriatr Gerontol Int. 2012;12(3):506- 14. (PMID: 22239067)

21. American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated AGS beers criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2019; 67(4):674–694. (PMID: 30693946)

22. 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. (PMID: 18218287)

23. Ryan C, O'Mahony D, Byrne S. Application of STOPP and START criteria: interrater reliability among pharmacists. Ann Pharmacother. 2009; 43:1239-44. (PMID: 19584381)

24. Lahaye C, Tatar Z, Dubost JJ, Tournadre A, Soubrier M. Management of inflammatory rheumatic conditions in the elderly. Rheumatology 2019; 58(5):748–764. (PMID: 29982766)

25. Gallagher P, Lang PO, Cherubini A, et al. Prevalence of potentially inappropriate prescribing in an acutely ill population of older patients admitted to six European hospitals. Eur J Clin Pharmacol.

2011;67(11):1175-88. (PMID: 21584788)

26. George CJ, Jacobs LG. Geriatrics Medication Management Rounds: A Novel Approach to Teaching Rational Prescribing with the Use of the Medication Screening Questionnaire-(MSQ). JAGS 2011: 59(1):138-42. (PMID: 21198464)
27. Peron EP, Marcum ZA, Boyce R, Hanlon JT, Handler SM. Year in review: medication mishaps in the elderly. Am J Geriatr Pharmacother 2011;9(1):1-10. (PMID: 21459304)
28. Gerd Granas A, Bakken MS, Ruths S, Taxis K. Deprescribing for frail older people e Learning from the case of Mrs. Hansen. Research in Social and Administrative Pharmacy 2018; 14 (6): 612-616. (PMID: 28733142)
29. Duijnhoven RG, Straus SM, Raine JM, de Boer A, Hoes AW, De Bruin ML. Number of patients studied prior to approval of new medicines: a database analysis. PLoS Med. 2013;10: e1001407. (PMID: 23526887)
30. Lindsay J, Dooley M, Martin J, et al. The development and evaluation of an oncological palliative care deprescribing guideline: the 'OncPal deprescribing guideline'. Support Care Cancer. 2015;23(1):71-78 (PMID: 24975044)
31. Moriartya F, Pottieb K, Doloviche L, McCarthyg L, Rojas-Fernandezi C, Farrell B. Deprescribing recommendations: An essential consideration for clinical guideline developers. Research in Social and Administrative Pharmacy 2019; 15 (6): 806-810. (PMID: 30241877)
32. Thompson W, Reeve E. Deprescribing: Moving beyond barriers and facilitators. Research in Social and Administrative Pharmacy 2021 Apr 15; S1551-7411(21)00127-3 (PMID: 33867278)
33. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. JAMA Intern Med. 2015; 175:827-834. (PMID: 25798731)
34. Conklin J, Farrell B, Suleman S. Implementing deprescribing guidelines into frontline practice: barriers and facilitators. Res Social Adm Pharm 2019;15(6):796–800. (PMID: 30241874)
35. Farrell B, Richardson L, Raman-Wilms L, de Launay D, Alsabbagh MW, Conklin J. Self efficacy for deprescribing: a survey for health care professionals usingevidence-based deprescribing guidelines. Res Social Adm Pharm 2018; 14(1):18–25. (PMID: 28214150)
36. Yıldız V, Özdemir O, Gökçe Kutsal Y. Medication nonadherence in eldery and recommendations to imrove adherence. Turkish Journal of Geriatrics 2017; 20 (4):344-50. [Internet]. Available from: http://geriatri.dergisi.org/uploads/pdf/pdf_TJG_1009.pdf Accessed: 10.1.2022.
37. Betancourt BY, Biehl A, Katz JD, Ananta Subedi A. Pharmacotherapy pearls in rheumatology for the care of older adult patients: focus on oral disease-modifying antirheumatic drugs and the newest small molecule inhibitors. Rheum Dis Clin North Am 2018; 44(3):371–391. (PMID: 30001781)
38. Hiligsmann M, Pinto D, Dennison E, Al-Daghri N, Beaudart C, Branco J, et al. Patients' preferences for osteoarthritis treatment: The value of stated preference studies. Aging Clin Exp Res 2019;31: 1-3. (PMID: 30607878)
39. Gökçe Kutsal Y, Eyigör S, Karahan S. Et al. Incorporating patient preferences into osteoarthritis treatment. Arch Rheumatol 2021;36(4):577-586. doi: 10.46497/ArchRheumatol.2021.8291 [Internet]. Available from: https://archivesofrheumatology.org/abstract/1256 Accessed: 25.1.2022.
40. Coskun Benlidayı I, Gökçe Kutsal Y. Antirheumatic drugs in older adults and polypharmacy issues. Z Gerontol Geriat 2021 Jun [Internet]. Available from: https://link.springer.com/content/pdf/10.1007/s00391-021-01907-6.pdf 25.1.2022. Accessed: 25.1.2022. (PMID: 34114088)
41. Turkmenoglu FP, Gokce Kutsal Y, Barak Dolgun, Diker Y, Baydar T. Evaluation of herbal product use and possible herb-drug interactions in Turkish elderly. Complementary Therapies in Clinical Practice 2016; 23:46-51. (PMID: 27157958)
42. Morris CA, Avorn J. Internet marketing of herbal products. JAMA. 2003 Sep 17;290(11):1505-9. (PMID: 13129992)
43. Qato DM, Wilder J, Schumm LP, Gillet V, Alexander GC. Changes in Prescription and Over-the-Counter Medication and Dietary Supplement Use Among Older Adults in the United States, 2005 vs 2011. JAMA Intern Med. 2016 Apr; 176(4): 473–482.(PMID: 26998708)
44. Agbabiaka TB, Spencer NH, Khanom S, Goodman C. Prevalence of drug–herb and drug–supplement interactions in older adults: a cross-sectional survey. Br J Gen Pract. 2018 Oct; 68(675): e711–e717. (PMID: 30249608)

45. Agbabiaka TB, Wider B, Watson LK, Goodman C. Concurrent Use of Prescription Drugs and Herbal Medicinal Products in Older Adults: A Systematic Review. Drugs Aging. 2017; 34(12): 891–905. (PMID: 29196903)

46. Thiab S, Barakat M, Al-Qudah R, Abutaima R, Jamal R, Riby P. The perception of Jordanian population towards concomitant administration of food, beverages and herbs with drugs and their possible interactions: A cross-sectional study. Int J Clin Pract 2021 Mar; 75(3):e13780. (PMID: 33098614)

47. Reeve E, Denig P, Hilmer SN, Ter Meulen R. The ethics of deprescribing in older adults. J Bioeth Inq. 2016; 13:581-590. (PMID: 27416980)