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LITERATURE REVIEW: POLYPHARMACOTHERAPY AND ITS NEUROLOGICAL EFFECTS IN THE ELDERLY IN POLAND AND EUROPE

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ABSTRACT

In recent years both in Poland and Europe there have been observed progressive demographic changes and aging of the population. Polypharmacy can be defined as the simultaneous and regular use of at least five different drugs and is particularly often used in elderly patients due to the multimorbidity. According to some sources, elderly people take between two and nine different medications daily, of which even about 60% are inappropriate. The aim of this paper is to summarize information on polypharmacy in seniors in order to plan it as best as possible and at the same time to avoid potential adverse effects, with particular emphasis on the nervous system.

One of the most significant for polypharmacy is the age structure of the society. Poland is one of the European countries where the fastest growth of this ratio is observed. Huge problem seems to be the system of educating doctors, which is not adjusted to the changing demographics of the society. Furthermore, one of the factors contributing to polypharmacy is the excessive consumption of dietary supplements by Poles, especially geriatric patients - almost half of Poles consume them regularly.

Polypharmacy can be defined as the simultaneous use of at least five different drugs. It is particularly often used in elderly patients due to the multimorbidity and lack of healthcare access. The advantage of polypharmacotherapy is faster achievement of target values, which may improve the patient-doctor relationship, while the disadvantage is the increased risk of side effects. Polypharmacy is a significant problem in the European elderly, to avoid its negative effects, drugs with high bioavailability, short half-lives and a broad therapeutic spectrum are the best choice.

KEYWORDS

Polypharmacotherapy, Geriatrics, Neurology

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In the recent years both in Poland and Europe there have been observed progressive demographic changes and ageing of the population. According to forecasts these tendencies are to intensify in the upcoming years. In 2011 the elderly accounted for about 11% of the population, but taking into account the current pace of demographic changes, it is suggested that in 2050 even one in five people in the world will be at least 60 years old.[1] This process is primarily influenced by the medical progress, which allows not only to prevent diseases, but also to treat patients more and more effectively. Polypharmacy can be defined as the simultaneous and regular use of at least five different drugs and is particularly often used in elderly patients due to the multimorbidity. Other reasons for polypharmacy include patient management by several different doctors, treatment in long-term care facilities and failure to update medical records.[2] Other definitions of polypharmacy include for example taking drugs without proper indications, using them inappropriately or visiting many different pharmacies.[3] However, these are terms used primarily in English-language literature. The concept of polypharmacy should be distinguished from polytherapy and polypharmacy. Combining different drugs in such a way that it increases their therapeutic effect (but not the risk of side effects) is polytherapy. It is based on synergism which allows for the patient's effective therapy. On the other hand, polypharmacy is the administration of several drugs to the patient which not only significantly increases the risk of side effects, but also does not enhance its therapeutic effect.[4] This not only leads to unfavorable side effects but also increases the cost of patient care. A study conducted in 2007 found the use of polypharmacy in 39.4% of patients over the age of sixty-five[5], and more recent studies suggest its prevalence by up to 50%.[1] According to some sources, elderly people take between two and nine different medications daily, of which even 11.5-62.5% are inappropriate. For this reason, special attention should be paid to planning pharmacotherapy in seniors.[6]

There are many reasons for polypharmacy in Poland. One of the most significant is the age structure of the society. In the period 2001-2018, the percentage of people over 65 increased from 12.4 to 17.1%. According to statistics, in thirty years, there would be only two people of working age per one post-working age person.[7] Poland, next to Slovakia and Ireland, is one of the European countries where the fastest growth of this ratio is observed.[8]

The elderly in Poland have the worst health condition in the European Union. As many as 58% of people 65+ suffer from chronic diseases. For comparison, in Slovakia this percentage is 22% in the same age group, and the lowest is in the Netherlands - around 20%. The occurrence of only one medical condition usually requires the use of several tablets. On the other hand, the multitude of ailments means that an elderly patient has to be under the care of various specialists from whom he receives new prescriptions. Doctors often do not have access to a patient's complete medical record and are therefore unable to account for potential interactions between prescribed and taken medications. [9,10]

Seniors requiring professional health care face another problem, which is the low number of doctors and nurses in European countries. In Poland, there are only 2.4 doctors per 1,000 inhabitants, while the average for the European Union is 3.8. Geriatric patients deprived of access to health services themselves reach for generally available dietary supplements, which may cause interactions dangerous to health and life with drugs taken due to chronic diseases.[11]

Another problem is the system of educating doctors in Poland, which is not adjusted to the changing demographics of the society. Medical universities do not have enough time in geriatrics. Young adepts of medicine do not have a chance to acquire the required geriatric knowledge and, even more so, to consolidate it in practice, which means that they make mistakes consisting in prescribing too many drugs for a given patient in a situation where it is unnecessary and may result in the deterioration of the patient's health.[12][13][14]

Furthermore, one of the factors contributing to polypharmacy is the excessive consumption of dietary supplements by Poles, especially geriatric patients. almost half (48 percent) of Poles consume them regularly, only 27 percent. can define them correctly. Lack of knowledge about the regulations governing the sale of supplements and the possible effects of their use is one of the main problems of this market identified in the report of the Polish Economic Institute. Dietary supplements market in Poland was worth PLN 4.4 billion in 2017, and this value is growing dynamically, what is more, the use of many of them is doubtfully safe, which results from low control over this part of the market.[15][16][17]

Appropriate polypharmacy can have many benefits for the patient. There are disease entities in which the advantage of using polypharmacy over monotherapy has been proven. The most common example is high blood pressure (hypertension). This is since almost 90% of people struggling with this disease need two or more of medications for high blood pressure to keep the target values within the normal range. The ASCOT trial (Angio-Scandinavian Cardiac Outcomes Trial) revealed that combinations of drugs with different mechanisms of action are five times more effective than doubling the dose of the basic drug.[18]

Older patients often don't adhere to medical advice, so physicians are more likely to prescribe the combination drugs. They have many advantages, including reduced number of medicines, so the convenience of a medication regimen, decrease doses of individual preparations and faster achievement of target values. All these factors affect to the improvement of the physician-patient partnership (adherence). Significant improvement in following a list of recommendation from the doctor (compliance) and in the persistence of therapy has been observed in the case of combination preparations. Polypharmacy maximizes the effectiveness of the management of hypertension, because it reduce the clinical inertia. Patients feel more comfortable when they don't have to take several medications at the same time.[19]

Worth noting is the fact that most people living with HIV use at least three drugs. For this reason, HIV treatment regimen have been developed that are based on one tablet taken by the patient once a day. One example is prescription medicine Atripla - each tablet contains 600 mg of efavirenz, 200 mg of emtricitabine and 245 mg of tenofovir disoproxil. Studies have shown that patients using Atripla need for a change of treatment regimen less often compared to those using the two- or three-tablet regimen.[20]

Drug combinations in pain treatment is also very popular. The use of analgesics with different mechanisms of action is beneficial due to the synergistic effect (effect stronger than the sum of its components) or additive effect (sum of the individual effects).[21]

Neuropathic pain can be effectively treated with a combination medication. The use of lower doses of drugs reduces the number of side effects, so that patients don't abandon the prescribed therapy. Combination of gabapentin with tricyclic antidepressants has been documented to produce good results and improve

treatment quality. Combination of pregabalin and SNRIs is experienced by some doctors to result in good pain relief and fewer side effects than monotherapy. [22]

Polypharmacy also has its advantages in alleviating the side effects of neuroleptics. If akathisia occurs after taking classic medications, the simplest solution is to replace the neuroleptic with a drug that will be better tolerated by the patient. It seems that a good effect can be achieved by using β -blockers and additional potentiation with mirtazapine, an antidepressant.[23]

Apart from undoubtedly many positive therapeutic effects, polypharmacy may also carry many risks and side effects. The most common negative effect of using many medications in older people is a decrease in their functional capacity, which may result in frequent falls.[24] However, in the case of polypharmacy, the most serious consequence is an increased risk of death, which is a consequence of incorrect therapy and not the underlying disease.[25] Moreover, as the number of medications used increases, the likelihood of side effects increases. Taking 2 drugs at the same time already causes the risk of drug interactions, and with more than 7, their occurrence is certain.[18]

A common phenomenon is the so-called spiral of diseases and therapies. It consists in the fact that multimorbidities among older people require consultations with numerous specialists, which directly increases the number of drugs used. There is an accumulation of pharmaceuticals that contribute to damage to subsequent organs, which means that new substances are prescribed again.

Another noticeable and disturbing phenomenon is the intensification of treatment in order to achieve maximum reorganization of pathological changes, known as overtreatment.[25] It involves excessive use of drugs that eliminate given symptoms, recommending excessive doses or several drugs with a similar mechanism of action. This procedure may have a long-term impact on the deterioration of the patient's overall health. It has been shown that the progression of polypharmacy carries the risk of side effects regardless of the type of drugs used, including those obtained without a prescription. For this reason, it is extremely important to conduct a detailed interview with the patient regarding the medications and supplements he takes. When using polypharmacy prescribed by doctors of many specialties, it may occur that the prescription of drugs that the patient absolutely should take due to his/her health condition may be omitted. This condition is referred to in the literature as under-prescribing and largely results from the previously discussed spiral of diseases and therapies.

Each analysis of changes in the patient's clinical picture should be an integral part of conducting a medical interview, because the lack of it may result in the phenomenon of under-dosing. This involves the patient taking too low a dose of the drug, not adapted to the patient's health condition, and therefore the desired therapeutic effect will not be achieved.[18]

In neurology, a common and dangerous effect of polypharmacotherapy is anticholinergic syndrome, which is a life-threatening condition. This problem particularly affects the elderly suffering from diseases that are characterized by significant comorbidities. The Medical Research Council Cognitive Function and Ageing Study found that 50% of the elderly population uses at least one drug with anticholinergic effects.[26] The cumulative effect of taking substances in this group is referred to as anticholinergic drug burden and represents a high risk of physical and cognitive adverse effects.[27]

It is worth noting that cholinolytic drugs are used not only in neurological disorders, but also in cardiovascular, coagulation, gastrointestinal or urinary diseases.[28] We can include first-generation antihistamines, tricyclic antidepressants and some antipsychotics.[29] Their use is common among seniors because of the large number of indications in which they can be used. The metabolism of these pharmaceuticals decreases with age, so there is a greater risk of side effects in the elderly.[30]

It is estimated that mild cognitive impairment (MCI) accounts for 22% among the population of people aged 71.[31] This group is particularly at risk for depression, worse general condition and taking more medications. Green et al. analyzed data in which nearly a third of MCI patients had high scores on the Anticholinergic Cognitive Burden (ACB) scale - 0 is no cholinergic effect and 3 is strong cholinergic effect. Moreover, participants with MCI took an average of 6.8 medications. Much of the anticholinergic burden was due to the cumulative effect of multiple pharmaceuticals; among the most commonly used were metoprolol, furosemide, warfarin, antidepressants, or antihistamines.[32] In addition, these drugs have been shown to have adverse effects on cognitive function, delirium and physical performance. A study by Marie L Ancelin et al. found that mild cognitive impairment occurs in 80% of elderly people using chronic cholinolytics and in 35% of subjects who do not use these drugs.[33]

One group of patients who have a high risk of anticholinergic burden are elderly patients taking darifenacin, fezoterodine, propiverine, solifenacin, tolterodine and oxybutynin in particular for overactive

bladder (OAB).[34] All drugs used in OAB are metabolized by hepatic cytochrome P450 enzymes, so fluoxetine or macrolide antibiotics, which are inhibitors of isoenzymes, can lead to elevated serum levels of these drugs.[35] Bradykinin receptor agonists, 5-phosphodiesterase inhibitors and α -adrenergic receptor agonists, which increase the permeability of the blood-brain barrier, leading to increased concentrations of these substances in the CNS, may also interact with preparations used in OAB.[36]

A group particularly at risk of interactions and other adverse drug reactions resulting from polypharmacotherapy are patients under palliative care. In a randomized, controlled trial, Agar et al. showed that the prescription and use of several cholinolytics increases as death approaches.[37]

Another complication that can occur in a patient undergoing palliative treatment is Neuroleptic Malignant Syndrome (NMS). It appears during therapy with preparations that show antagonistic effects to the dopamine D2 receptor. NMS can occur not only with higher doses of D2 receptor antagonists, but also during polytherapy. The clinical situation in which there is an increased risk of combining and drug interactions is nausea and vomiting, which are commonly seen (40-70%) in oncology patients. The combination of metoclopramide, which inhibits central and peripheral D2 receptors, and haloperidol, which blocks D2 receptors in the area postrema of brainstem, can exacerbate inhibition of the dopaminergic system, which increases the risk of NMS.[38]

The polypharmacy problem in epilepsy is still poorly understood, although patients are likely to experience a high burden of multiple drug groups.[39] Consider the "total drug load" which better correlates with the number of possible side effects in relation to the number of medications prescribed.[40] Ataxia and dizziness are the most common occurrences, and in most cases also cognitive impairment such as somnolence and slowing down.[41] Serum drug levels that are close to the toxic range and polypharmacy also impair cognition, giving the false impression of a decline in intellectual ability. There is a false impression of the severity of epileptic states with improperly selected drugs and when the dose of drugs is too low.[42] The concentration of the medicament in the serum is related to the amount of albumin, the significantly reduced amount of which in the elderly affects the desired therapeutic effect, especially in the case of carbamazepine or valproic acid. In this group of patients, valproic acid, compared to carbamazepine, does not cause induction of liver enzymes.[43]

Several traditional antiepileptic drugs are potent inducers of cytochrome P450, so special attention should be paid to the interaction with contraceptives, immunosuppressants, corticosteroids and anticancer chemotherapeutic drugs.[40] The plasma concentration of lamotrigine is reduced by about 50% when simultaneously using contraceptives, while at the same time decreasing the concentration of levonorgestrel.[44] Drugs enhancing inhibition through GABA receptors may cause sedation, dysphoria, and depression in patients with a psychiatric history.[40]

The diagnosis of psychiatric comorbidities like depression and psychoses is often hindered by the influence of antiepileptic drugs which mask or mimic the symptoms of other disorders[45] An example is the treatment of hypertension with non-dihydropyridine calcium channel antagonists, the concentration of which in plasma may be reduced by up to 5-10 times as a result of simultaneous administration of inducers of the microsomal system such as phenytoin or phenobarbital.[46].

In the elderly, non-psychotropic agents contribute to the exacerbation of mental disorders, for example opioids, which in combination with carbamazepine or valproic acid can cause life-threatening serotonin syndrome. Other agents contributing to exacerbations may include antibiotics, cardiological, gastrointestinal and hormonal drugs. Increased sensitivity to drugs and decreased ability to homeostasis in the elderly affect the development of the mentioned syndrome symptoms despite the use of drugs in therapeutic doses.[47]

Prevention of polypharmacy is not an easy task. It is associated with characteristic needs of geriatric patients, which most often have multiple different diseases treated by medical specialists of different fields. Lack of communication between medical doctors leads to use of multiple medications, which in turn can interact with each other and cause side effects. Keeping detailed medical records is the key to success in preventing the dangers of polypharmacy. It is crucial to keep a list of all medications, supplements, herbs that are being taken by the patient. With the full knowledge of patient's medication intake there is a possibility to deeply analyze interactions that can occur between medications, prioritize certain diseases and discontinue or reduce the dose of the drug, which overload the patient's body and generate unnecessary costs. Both the addition and withdrawal of the drug should be associated with a medical history of the patient, his examination and observation. Medical doctor should be in constant contact with the patient and carry out regular check-ups.

There are complex conditions for which polypharmacy is necessary, but it is not appropriate to prescribe medications only to keep the patient's results within the normal range of guidelines. The patient's well-being

should always be taken into account, as the effectiveness of the treatment largely depends on his motivation. Knowing how to prescribe medications is as important as withdraw them. When issuing a prescription to extend the therapy, one should always analyze whether or it is still necessary.

A problem that can be prevented is the patient's lack of knowledge about the effect, dosage, or side effects of the drug. It is important to interview the senior or his family, in which you should emphasize the basic information on taking a new pharmaceutical, dispel any doubts and answer bothering questions. It is a mistake to ignore the patient's needs, because his active participation in setting treatment priorities is the basis for the effectiveness of therapy. It is the doctor's duty to educate patients that shortening the list of medications will be beneficial for their health.[48]

To avoid polypharmacy and adverse drug interactions, physicians should understand the catabolic pathways of drugs, their effects on cytochrome P450, and protein binding. The human body undergoes changes with age in terms of pharmacodynamics and pharmacokinetics, which significantly increase the risk of side effects of polypharmacy. The balance of benefits and losses resulting from the use of individual drugs should always be considered. When a new substance is implemented, it should be started with the minimum possible dose and then gradually increased it. Drugs with high bioavailability, short half-lives and a broad therapeutic spectrum are the best choice. Those that are rapidly metabolized should be avoided.[49]

An important element of prophylaxis is warning patient's against self-medication and not following the doctor's instructions. Dosage changes or drug discontinuation should always be discussed with a specialist. Unclear messages and rush from the doctor can also cause misunderstandings, which translates into errors in the therapy. In order to avoid situations that are potentially dangerous to the health of the patient, the STOPP / START criteria were created, which inform about potential drug interactions in geriatric patients.[50]

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