

# Pharmaceutical therapy management of osteoporosis

Ph.D. Thesis

**Edit Veszelyné Kotán**

Semmelweis University  
PhD School of Pharmaceutical Sciences



Supervisors: Dr. Zoltán Vincze D.Sc., Professor  
Dr. Ágnes Mészáros Ph.D., Associate Professor

Opponents:  
Dr. Márta Péntek Ph.D., Professor  
Dr. Tamás Tábi Ph.D., Associate Professor

Head of the Final Examination Committee:  
Dr. Éva Szökő D.Sc., Professor

Members of the Final Examination Committee:  
Dr. Judit Lám Ph.D., Associate Professor  
Dr. Gábor Miklós Halmos Ph.D., Professor

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## **PH.D. THESIS**

### **SUPERVISORS**

**PROF. DR. ZOLTÁN VINCZE D.SC. AND DR. ÁGNES MÉSZÁROS**  
SEMMELWEIS UNIVERSITY, PHD SCHOOL OF PHARMACEUTICAL SCIENCES,  
UNIVERSITY PHARMACY DEPARTMENT OF PHARMACY ADMINISTRATION

**EDIT VESZELYNÉ KOTÁN**

### **PHARMACEUTICAL THERAPY MANAGEMENT OF OSTEOPOROSIS**

The pharmaceutical therapy management of osteoporotic patients is a complex task, which is a challenge for pharmacists working in public and also in hospital pharmacies. Pharmacists' participation in the primary prevention of this initially asymptomatic disease, and also fracture prevention of diagnosed osteoporosis patients is highly important.

The aim of this work – which was carried out from three different angles – was to increase the adherence of osteoporotic patients. First, the connection of adherence, quality of life and patients' preferences were analysed. Although a significant relationship could not be established between these factors, the following trends were observed: in the patients' group where osteoporosis was considered important, there were fewer patients with low adherence, and where osteoporosis was considered less important, the quality of life of the patients was lower than that of the other patients' groups. Identifiable risk groups were defined, which can facilitate the pharmaceutical management of these patients.

As a result of the prescription data analysis of the bisphosphonate drugs in Hungary, it can be stated that lowering the reimbursement of bisphosphonates in the year 2007, significantly lowered the expenditures of the National Health Insurance Fund, and also lowered the number of years bisphosphonates were provided. The changes of reimbursement resulted in the spread of intravenous bisphosphonate medications in osteoporosis therapies, which have been found to bring about higher adherence.

In the third part of my work, data on the Hungarian bisphosphonate-related osteonecrosis of the jaw (BRONJ) population are provided for the very first time, based on the analysis of the database of the National Healthcare Services Center. The results reveal that men, oncology patients, and patients administering intravenous bisphosphonates have a higher proportion of BRONJ while women, osteoporotic patients, and patients using oral bisphosphonates have a higher number of cases because of the higher number of patients in these subgroups. Using the results of this study, pharmacists can consider actual Hungarian data in the management of bisphosphonate therapies.

## **DOKTORI ÉRTEKEZÉS**

GYÓGYSZERTUDOMÁNYOK DOKTORI ISKOLA  
SEMMELWEIS EGYETEM EGYETEMI GYÓGYSZERTÁR  
GYÓGYSZERÜGYI SZERVEZÉSI INTÉZET

TÉMAVEZETŐK: PROF. DR. VINCZE ZOLTÁN D.SC. ÉS DR. MÉSZÁROS ÁGNES

VESZELYNÉ KOTÁN EDIT

### **AZ OSTEOPOROSIS GYÓGYSZERÉSZI GONDOZÁSA**

Az osteoporosisos betegek gyógyszerészi gondozása komplex feladat, mely a közforgalmú és az intézeti gyógyszertárakban dolgozó gyógyszerészek számára is kihívás. A sokáig tünetmentes megbetegedés primaer prevenciójában, valamint a diagnosztizált betegek törésprevenciójában történő gyógyszerészi szerepvállalás is kiemelkedő jelentőségű.

Munkám célja az osteoporosisos betegek gyógyszeres adherenciájának növelésére irányult, melyet három irányból közelíttem meg. Első lépésben kutattam a betegek adherenciájának, preferenciáinak és életminőségének összefüggését. Bár szignifikáns összefüggéseket éppen ezek között a változók között nem tudtam kimutatni, a következő trendeket figyeltem meg: abban a betegcsoportban, melyben a betegek fontosnak tartották a csontritkulást, az alacsony adherenciájú betegek kevesebben voltak, valamint ahol az osteoporosis közepesen fontos volt, ott a betegek életminősége nem érte el a többi csoportokét. Kutatásom eredményeként meghatároztam azokat a rizikócsoportokat, melyeknek kiszűrése az osteoporosis gyógyszerészi terápia-menedzsmentjét megkönnyítheti.

A biszfoszfonátok vényforgalmát feldolgozó adatelemzés eredményeként az osteoporosisos betegekre vonatkozóan megállapítható, hogy a 2007. évi támogatás csökkenés valóban csökkentette a gyógyszerkassza kiadásait és az ellátott terápiás évek számát is. A támogatásváltozások azonban teret adtak az adherencia szempontjából eredményesebbnek talált intravénás készítményeknek is.

Munkám harmadik részében elsőként szolgáltatok egzakt adatokat a magyar lakosság biszfoszfonát által okozott állcsont-osteonecrosis (BRONJ) általi érintettségéről a Nemzeti Egészségbiztosítási Alapkezelő adatbázisának vizsgálata alapján. Az adatok elemzése szerint a férfi betegek, az onkológiai betegek, valamint az intravénás biszfoszfonát alkalmazók produkálják nagyobb arányban a BRONJ-t, de a nők, az osteoporosisos betegek és a per os készítményeket használó betegek lényegesen nagyobb száma miatt ezekben a csoportokban jelentkezik nagyobb esetszám. Az eredmények felhasználásával a gyógyszeres terápia segítése konkrét hazai adatokra épülhet.

## **INTRODUCTION**

Osteoporosis (OP) is a generalized, progressive disease of the bones, where a decrease in the bone mass and bone quality is present. Bones become increasingly fragile as their porosity increases, and the risk of fractures becomes higher. The clinical relevance of this disease lies in the appearance of low trauma fractures.

Because of its high prevalence, OP is a high priority healthcare problem. A fragility fracture occurs approximately every three seconds, which means that there are 200 million osteoporotic people all over the world. The proportion of osteoporotic patients is growing mostly in aging populations. OP related healthcare expenditures are expected to increase all over the world, especially in China, Asia, the Middle-East and Latin-America. Half of the fragility fractures occur in the USA and Europe.

There are approximately 900 thousand osteoporotic people in Hungary, the male and female ratio is 2:1 in the population over 50 years. The most important consequence of osteoporosis is hip fracture: the mortality rate is 12 to 20% in one year, and only 20% of the patients can recover. After a hip fracture in the 60 to 90-year-old population, 9% of the patients die within a month, 30% die within a year in Hungary.

The goal of antiporotic therapy is the reduction of fracture risk. From the drug agents used in the treatment of OP, I analysed the bisphosphonate drug group in detail. Bisphosphonates are used in the treatment of osteoporosis and also in decreasing the progression of malignant diseases affecting the bone. There is a difference in the used drug agents between the two therapeutic indications, but there are agents which are used in both indications. In those agents which are used in both therapeutic fields, there is a difference between the fields in the dosage and the frequency of administration of the agents.

As a rule, it can be stated that after a fragility fracture, less than 20% of the patients get adequate antiporotic therapy, and half of the patients give up the therapy in its first year. This happens despite the fact that Hungarian data analyses prove the risk decreasing effect of the proper adherence status.

## **AIMS**

The first aim of my work was to find methods which can be used in the pharmaceutical therapy management of osteoporotic patients in order to increase their adherence. First, a questionnaire study was carried out to analyze the connection of the patients' preferences with quality of life and adherence. As there were problems with the use of bisphosphonates

through this study, I prepared a prescription data analysis of the Hungarian bisphosphonate population. As the Hungarian reimbursement system consists of one financier, this analysis contains the data of the whole Hungarian population. This work led me to investigate the bisphosphonate-related osteonecrosis of the jaw (BRONJ), which is a characteristic side effect of the bisphosphonate drug group.

## **METHODS**

### **1. PATIENTS' PREFERENCES AND ADHERENCE STUDY**

This study was carried out in the rheumatology wards of four Hungarian hospitals. Two hundred sets of questionnaires had been distributed to patients with diagnosed OP. The exclusion criterion was the presence of any kind of malignant disease. The analysis of 191 sets of questionnaires was carried out. The patients' socioeconomic status was mapped, and they filled in standard questionnaires of quality of life (EQ5D with Visual Analogue Scale) and medication adherence (©MMAS8) as well. Subsequently, they were asked about their possibly present chronic comorbidities parallel to OP. They had to rank order their chronic morbidities including OP, according to how important they felt them in their lives. From the results of the ranking, groups of OP importances were created. These groups were compared according to the factors influencing adherence in osteoporosis. Three groups of OP importance were created: the group of High OP importance consisted of those patients who ranked their OP on the first place. Low OP importance patients were defined as the patients who ranked their OP on any other places. In the No OP importance group, there were the patients who did not rank their OP at all. Correlations were analysed between these groups. Paired difference tests were carried out in the case of each factors. The statistical analyses were conducted by SPSS version 22.

### **2. PRESCRIPTION DATA ANALYSIS OF BISPHOSPHONATES**

In this study, the prescription data of the Hungarian bisphosphonate (BP) population was analysed. In Hungary, the National Health Insurance Fund (NHIF) is the only organization to reimburse health care-related expenditures including medicines and health care institutions. The NHSC handles the databases of the NHIF, which contain the data of the whole Hungarian population. Using this database there are data with nationwide relevance: the patients' population was the population of Hungary. The study time period was the nine years between 1 January 2006 and 31 January 2014. First, the bisphosphonate prescriptions were filtered from the database according to the Anatomic, Therapeutic and Chemical (ATC) codes of

bisphosphonates: M05BA – Bisphosphonates and M05BB – Bisphosphonate combinations. The second step was to isolate the prescribed medicines used in oncological indications from those used in rheumatology indications. The determination of the therapeutic field was carried out according to the drug compound, the dose and the packaging of the medication, and the reimbursement category of the prescription as follows:

- Drug agent: Alendronate, risedronate and combinations are used in rheumatologic indication, pamidronate and clodronate are used in oncology. Ibandronate and zoledronic acid are used in both therapeutic fields.
- Dose and packaging: Dosing of these drugs is different in the malignant and non-malignant indications. This results in medications with the same drug agent, different strength, doses and different packaging and trade names in the different therapeutic fields.
- The reimbursement category of the prescribed medicine: In osteoporosis bisphosphonates are reimbursed in a different, lower category than in malignant diseases.

### **3. STUDY OF THE BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAW IN HUNGARY**

BRONJ is a very rare but serious side effect of bisphosphonates. This disease is present when there is a denuded bone surface in the maxillofacial region of the patient, which exists after eight weeks from the diagnosis, the patient has a bisphosphonate treatment in the anamnesis, but there is no irradiation to the head and neck area. This side effect has no independent code either in the ICD, or in the ICPM systems, which is why it is difficult to define which patients are affected.

This study is also a data analysis of the NHIF. To obtain enough data for the analysis of this rare side effect, the Hungarian population was analysed. The data used in this study stem from 1 January 2010 to 31 December 2014. The BP prescription data were collected from the NHIF database to define the Hungarian bisphosphonate population. As there is a so called 'Reimbursement Identification Code' for each Hungarian person, and the reimbursement of the prescribed medicines is only allocated when this code is recorded from the prescription to the database, the medication can be connected to the person. From this connection, the person's anamnesis can be analysed from the system. Since the mentioned code is classified as personal data, these codes had been encoded before the analysis and the personal data had been anonymized.

Irradiation to the head and neck region was considered an exclusion criterion to differentiate the BRONJ from osteoradionecrosis. The ICPM codes (International Classification of

Procedures in Medicine and Related Health Problems) of the irradiations were defined from the in- and outpatient care ICPM database of Hungary. NHIF refers to the ICPM codes as a basis of reimbursement of the medical procedures. BP type medicines included in this study under ATC (Anatomical Therapeutic Chemical Classification System) codes were as follows: M05BA – *Bisphosphonates* and M05BB – *Bisphosphonate combinations*. BRONJ patients were selected from the NHIF inpatient care database. In this study, the *BP patients* selected according to both ICD (International Classification of Diseases) and ICPM codes were defined as *BRONJ patients*. The parameters in the *BRONJ patients*' group were analyzed until the first ICD or ICPM code in connection with BRONJ appeared. The *No BRONJ* group consisted of patients chosen from the database based on the ATC code of the prescribed medicine and based on the fact that they had not developed BRONJ during the study time period. In this group, these parameters were taken into consideration for the whole time period of the study.

The statistical analyses were done with SPSS software. In the case of discrete variables, chi-squared tests were carried out, and continuous variables were analyzed with Student's t-tests.

## **RESULTS**

### **1. PATIENTS' PREFERENCES AND ADHERENCE STUDY**

The medium age of the study population (n=191) was  $66.9 \pm 9.4$  years, having a minimum of 42 years, and a maximum of 88 years. 174 female (91.1%) and 17 male (8.9%) patients filled in the set of questionnaires. The duration since the diagnosis was set ranged from 0 years (less than or equal to 1 year) to 25 years with a mean of  $8.5 \pm 6.4$  years. 181 patients (94.8%) took medicine for their disease according to the algorithm of the pharmacologic treatment of osteoporosis. 44.0% of the patients had had one or more fractures related to their osteoporosis before they filled in the questionnaire. Among these patients, there were 13 (15.5%) with multiplied fractures on the same location, and 18 patients (21.4%) with multiplied fractures on different locations. T-score results were available for 95.8% of the patients. 151 (79.0%) patients had equal or lower T-scores than -2.5, which is defined as the diagnostic requirement for OP.

Patients were asked about their chronic co-morbidities. No other chronic diseases were reported by 15.7% of the patients. 161 patients (84.3%) had the following number of chronic co-morbidities: 37.2% had one other chronic disease, 29.3% had two, 11.0% had three and

6.8% had four or more chronic diseases parallel to OP. 23.0% of the patients ranked OP to the first place. There were 64 patients who did not rank OP at all (33.5%).

The aim of this study was to find the connection between patients' preferences and the adherence and quality of life. Although a significant connection could not be proved, it can be stated that the mean quality of life was the lowest in the group of Low OP importance, and the proportion of nonadherent patients was the highest in this group. Significant differences were found between the groups of OP importances in age, T-score, working status, type of medication, medication taking, presence of fragility fracture, frequency of pain, co-morbidities and the number of co-morbidities. The risk groups with a need of focused therapy management were defined on the basis of these results, which are as follows:

- patients with asymptomatic OP or few symptoms of OP,
- patients with no fragility fractures,
- patients with no or more than two chronic diseases existing parallel to OP,
- patients with a femoral T-score  $>-3$ ,
- patients who do not remember the name of the antiporotic medicine,
- patients under the age of 70, and
- active workers.

## **2. PRESCRIPTION DATA ANALYSIS OF BISPHOSPHONATES**

The „covered therapeutic years” in rheumatology and oncology indications were compared in the data analysis of the bisphosphonates. The yearly amounts of DOT (Days of Therapy) of the given bisphosphonate drug agent was divided by the yearly mean DOT value of the agent in the therapeutic indication, which equals the number of 'covered therapeutic years' in the given therapeutic indication.

If we assumed that patients were 100 per cent persistent, and all the prescribed medications were used, this number would be equal to the patients' number in the given year.

According to the results, the number of therapeutic years of osteoporosis is significantly higher than that of oncology indications of bisphosphonates. Minor changes in rheumatology indication were perceived, because of the decrease of reimbursement from 90% to 70% in 2007, which resulted in a rapid decrease in the covered therapeutic years. The calcium and Vitamin-D combinations of alendronate and risedronate slightly increased the covered therapeutic years, but not significantly. The therapeutic use of zoledronic acid and parenteral ibandronate increased the number of patients, and the level of the covered therapeutic years reached the level of that before 2007. The changes of the administered bisphosphonate drug

agents can be observed in the study period: the parenteral medications cover an increasingly higher proportion of therapeutic years from those of alendronate and risedronate.

### **3. STUDY OF THE BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAW IN HUNGARY**

Using the method developed for this study, the Hungarian BP population in the study time period amounted to 236,207 patients. As a result of the two screening criteria, the BRONJ patients' number came to 340 (0.1%). Our results show significantly more BRONJ cases in male than in female BP patients,  $p < 0.001$ .

There was a significant difference between the *BRONJ* and the *No BRONJ* groups from the point of view of age,  $p < 0.001$ . In the BRONJ group, the proportion of female patients (F/M: 72.4%/27.7%) was significantly lower than in the whole study population (F/M: 86.5%/13.5%),  $p < 0.001$ . The male patients developed BRONJ with 2.5 higher odds than female patients. The proportion of BP oncology patients was higher in male than in female patients (F/M: 3.2%/25.2%). The rate of necroses in the group of oncology indicated BPs was 7.3 times higher than that of rheumatology indication in males, and 10.9 times higher in the female patients' group. In the patients using intravenous BPs, the proportion of BRONJ patients was 0.3%, significantly higher than in the whole study population ( $p < 0.001$ ).

The patients treated with more types of intravenous BPs were at a significantly higher risk of BRONJ in this population ( $n=15$ ; 0.5%) than patients in the total intravenous BP population,  $p=0.042$ . Relatively more BRONJ patients treated with more types of BP drugs were found in the intravenous BP patients' group (OR: 0.6), but in the oral BP patients' group, the odds of patients who took one type of BP was higher than that of patients who were administered more BP drug types (OR: 1.9).

Concerning the drug types, the proportion of *BRONJ* patients was significantly higher in the clodronate, oral ibandronate, pamidronate and zoledronic acid groups than in the study population. In the alendronate and risedronate groups, the proportion of *BRONJ* patients was significantly lower than in the total population.

In the BP patients' group treated with glucocorticoids (*steroid BP* group;  $n=44,784$ ), the proportion of *BRONJ* (80 patients, 0.2%) was significantly higher than in the steroid non-taker BP group ( $n=191,423$ , BRONJ: 260 patients, 0.1%) ( $p=0.013$ ), where the OR equalled 1.3. There was a 12.5 OR between the oncology and rheumatology indication of BPs treated with steroid co-medication to develop BRONJ.

## CONCLUSIONS

### RESULTS OF THE ANALYSES OF HYPOTHESES

I wished to prove the following hypotheses in my work:

*1.a) Adherence of osteoporotic patients depends on how important they consider their disease. The patients' preferences can be influenced by many factors, such as the presence of comorbidities, socioeconomic factors, the characteristics of the disease and the therapy.*

In this work, a significant relationship between medication adherence and the importance of osteoporosis could not be proven. There were differences between the groups of OP importances in the following factors: age of the patients, working status, presence of the symptoms of osteoporosis, presence of fragility fracture and chronic comorbidity, value of the femoral T-score and drug type.

*1.b) Adherence of osteoporotic patients has a positive correlation to the quality of life.*

In this work, a significant relationship between medication adherence and the quality of life of osteoporotic patients could not be proven. However, an observation could be made: the patients of the Low OP importance group had the lowest mean value of the EQ5D-3L quality of life among the other OP importance groups, and the proportion of the low adherence patients was the highest in this group.

*2.a) The number of patients treated with bisphosphonates in rheumatology indication is significantly higher than that of the oncology indication.*

The covered therapeutic years of rheumatology indicated bisphosphonates was 15 times higher than that of the oncology indicated BPs on average.

*2.b) The changes in the administration of bisphosphonate medications follow the changes in the reimbursement of these medicines. The decrease in the reimbursement has a negative effect on the number of patients treated, and the appearance of new drug agents, administration modes or combinations of drugs changes the prescription and the therapeutic use of these medications.*

It can be seen from the changes of the covered therapeutic years of the rheumatology indicated BPs that the decrease in the reimbursement lowered the number of patients in 2007. This caused also the fall in the whole amount of reimbursement. The mean therapeutic value of the medications decreased because of the therapeutic use of the generic medicines.

3. *International trends are valid also in the Hungarian BP population from the viewpoint of the risk of BRONJ: oncology patients have a significantly higher risk to develop this side effect than rheumatology patients.*

The number of female BRONJ patients in the Hungarian BP population was higher than that of male patients, but the proportion of women was lower than that of men. Duality was typical in gender, main indication and also in the mode of administration of BPs: male, oncology and intravenous BP patients were at a higher risk of developing BRONJ, but the significantly higher number of the opposite population of these groups resulted in a higher BRONJ number of female patients, osteoporosis indicated and oral BPs. On the basis of the results, therapy switch did not have a risk increasing effect in oral therapies, but it increased the risk in intravenous BPs. Corticosteroid co-medication and BPs with malignant indication were the main risk factors of BRONJ in the Hungarian BP population.

## **NEW SCIENTIFIC RESULTS**

### **NEW RESULTS OF THE ANALYSIS OF THE RELATIONSHIP BETWEEN THE PATIENTS' PREFERENCES AND THE MEDICATION ADHERENCE AND QUALITY OF LIFE IN OSTEOPOROSIS**

The questionnaire analysis of the medication adherence and the quality of life, made it possible for the first time to identify those risk groups of osteoporotic patients who need a focused therapy management because of their low adherence and quality of life.

The risks groups with special requirements and a need of focused therapy management are as follows:

- patients with asymptomatic OP or few symptoms of OP,
- patients with no fragility fractures,
- patients with no or more than two chronic diseases existing parallel to OP,
- patients with a femoral T-score >-3,
- patients who do not remember the name of the antiporotic medicine,
- patients under the age of 70, and
- active workers.

Through the dispensing process of an antiporotic medicine, pharmacists can identify patients who fall in one of the risk groups above, as a result of which, their adherence might be unsatisfactory. Having the knowledge about the patient's attitude, pharmacists could present focused information to increase the subjective importance of OP. If healthcare providers can

make the patients consider their disease more important, which results in higher adherence, there is a chance to improve their quality of life.

#### **NEW RESULTS OF THE ANALYSIS OF THE BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAW IN HUNGARY**

In this work, these data are the first to have defined the incidence data of BRONJ in the Hungarian BP population according to the main indications of BPs and the routes of administration. The results show differences between BP drugs in their potential to cause BRONJ independently of their doses. These results draw attention to the need to improve therapy management for Hungarian BP patients. Pharmacists have the opportunity to regularly contact BP patients and on the basis of the present risk factors, they are able to give focused and relevant information on maintaining oral hygiene and taking care of an incomplete set of teeth as well as giving advice on what to do with a problematic dental prosthesis. Through the long-term periodic contact, not only the circumstances of medicine taking have to be discussed, but the pharmacist should also call the patient's attention to the importance of daily oral hygiene and frequent dental check-ups. Mapping the risk factors during counselling requires a long-term strategy having the knowledge of the risk factors and the characteristics of the patients affected. In this way, overloading the patient and nonadherence can be avoided.

The risk of the development of the characteristic side effects can be confirmed by objective national population data in all steps of the patients' care. Knowing the patients' other risk factors clinicians, with the help of these results, might better choose the adequate therapy and can also initiate a therapy switch. With the help of this information, besides the techniques used consistently in order to analyze patients' fears of the side effects of the therapy in pharmaceutical care, pharmacists have a further opportunity to increase therapeutic adherence.

## **PUBLICATIONS**

### **PUBLICATIONS RELATED TO THE DISSERTATION**

Veszelyné Kotán E, Mészáros Á. Therapeutic practice of bisphosphonate use and related pharmaceutical issues I. Acta Pharm Hung 2016;86(1):13-22.

Veszelyné Kotán E, Mészáros Á. Bisphosphonate use and related pharmaceutical issues II. Acta Pharm Hung 2016;86(1):23-34.

Veszelyné Kotán E, Vincze Z, Mészáros Á. How to improve osteoporotic patients' pharmaceutical therapy management Acta Pol Pharm 2019;76(3):569-579 APPDR-00291-2018-02

Veszelyné Kotán E, Bartha-Lieb T, Parisek Zs, Meskóné Bodoky A, Vaszilkó M, Hankó B. Database analysis of the risk factors of bisphosphonate-related osteonecrosis of the jaw in Hungarian patients BMJ Open 2019;9:e025600 DOI: 10.1136/bmjopen-2018-025600

#### Poster presentations

BBBB conference P2H1 - Bisphosphonate related osteonecrosis of the jaw in Hungary - Analysis of the Hungarian National Health Insurance Fund Database Veszelyné Kotán, E., Lieb, T., Parisek, Zs., Meskóné Bodoky, A., Vaszilkó, M., Hankó, B. (2017 Balatonfüred)

2016 Symposion of Hungarian Hospital Pharmacists – Veszelyné K.E., Mészáros Á. P-14: Following the broken adherence: analysis of the factors affecting medication adherence in osteoporosis. (2016 Balatonfüred)

XX. National Congress of Hospital Pharmacists – Veszelyné K.E., Mészáros Á. P-14. Life of bisphosphonates in prescriptions (2015 Visegrád)

### **PUBLICATION NOT RELATED TO THE DISSERTATION**

#### Posters

Congressus Pharmaceuticus Hungaricus XV. – Veszelyné K.E. The way to be solved: – Handling of the clinical studies and clinical study medications in Uzsoki Hospital (2014 Budapest)

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