University of Szeged
Faculty of Pharmacy
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Summary of Ph.D. Thesis

GERIATRIC FALLS AND RISK FACTORS

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Geriatric falls and risk factors

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1. INTRODUCTION

Falls are prevalent among elderly people, leading to hospital trauma admissions and early death. Nursing home residents are especially endangered, about 30-50% of people living in long-term care institutions fall each year, which is twice the rate of falls among community-dwelling older adults. Even though comorbidities in older people often require taking numerous prescription drugs, taking 4 or more chronic medications (defined as polypharmacy) was found to be an independent risk factor for falls. Polypharmacy (PP) also increases the prevalence of drug-related problems, such as drug–drug interactions, adverse drug reactions (ADRs) and prescription errors. To reduce the risk of falls and to minimize the prevalence of ADRs, potentially inappropriate medication (PIM) lists have been implemented, among which the 'Beers criteria' is the most widely used list. The most recently updated (2015) criteria identify not only the potentially inappropriate drugs, but also offer recommendation on alternative medications or therapies. Following the Beers criteria, numerous countries have created their specific national PIM list. Using these medication lists is a substantial strategy to reduce the risk of adverse events and falls in older adults. Guidelines and policies on fall prevention need to be adverted on populations under the greatest risk, such as nursing home residents.

Osteoporosis is a metabolic bone disease, characterised by decreased bone mass, quality and strength, and increased susceptibility to fracture, even to minimal trauma (such as falls). Therefore osteoporotic patients with brittle bones are under high risk of developing low-energy fractures - as a consequence of falls. Osteoporotic fractures, especially hip fractures, are responsible for high hospital admission- and mortality rates worldwide, significantly affect quality of life, and put huge financial burden on the society. From the 10 million residents of Hungary, it is estimated that in the population over 50 years of age 94,949 males and 452,158 females suffered from osteoporosis in 2010. Similar prevalence rates were found in the European Union, while the rate was higher in the U.S.A. Undoubtedly, postmenopausal women are under the greatest risk of osteoporotic bone fractures; however, outcomes are even much worse among male patients. In the case of hip fracture, the mortality rate is almost double in males than in females: 26.8-32.5% versus 17.0-21.9% within one year. The treatment and rehabilitation costs of fractures are estimated to be more than double than the expenses of pharmacological prevention and treatment would take. Moreover, 50% of osteoporotic fractures would be preventable with screening the population at risk and with appropriate pharmacological treatment.

Besides osteoporosis, many studies have proven that low vitamin D level increases the risk of bone fractures. Adequate vitamin D level is essential to prevent bone loss and structural damage of the bone matrix, which also prevents fractures. Though there are insufficient data to confirm a causal relationship between vitamin D deficiency and the immune, cardiovascular, and metabolic systems, many epidemiological studies proved that low levels of vitamin D are important risk factors in several diseases, such as diabetes, cardiovascular diseases, hypertension, cancer, autoimmune diseases. Low vitamin D levels are also associated with decreased muscle strength and coordination, which can lead to falls.

2. AIMS

Our objective was to identify the main risk factors of geriatric falls on different population levels.

a) A gender- and age-specific analysis was performed regarding the utilisation of anti-osteoporotic drugs on national level in Hungary, covering a 5-year period (between 2007 and 2011). Further goals were to analyse the differences of treatment characteristics and hip-fracture trends between males and females.

b) Secondly, our aim was to evaluate the medication use of nursing home residents by using the Hungarian PIM list - created and developed by our research group-, as well as to investigate the possible predictors of geriatric falls annualised over a 5-year-long period (between 2011 and 2015), under the frame of a cohort study.

c) Finally, in a pilot study, we compared vitamin D levels of elderly, hospitalised hip fractured patients with hospitalised non-fractured patients. Additionally, the prevalence of falls was detected and the differences between the groups were analysed.

3. MATERIALS AND METHODS

3.1. Gender- and age-specific utilisation study of anti-osteoporotic drugs

Data source

The source of our crude data was the Hungarian National Health Insurance Fund (NHIF), which is the sole, mandatory, national health insurance fund, covering 100% of the Hungarian population. All prescription claims are recorded by the providers; the NHIF database contains data on age, gender, residence, date of claim, medication, and diagnosis by ICD codes (International Classification of Diseases, 2010). Microsoft Access and Microsoft Excel programs were used for data management and analysis. For our study the NHIF provided anonymous, aggregated crude data; therefore this study did not require ethical approval.

Database screening for anti-osteoporotic medications

The following details on medication use were available in the crude data: calendar year (2007–2011), gender, age group (in 5-year-long clusters), ATC code (Anatomical Therapeutic Chemical Classification), active pharmaceutical ingredient, product name, strength, ICD code (first 3 digits), number of packaging units, number of patients, and total number of DDDs (Defined Daily Dose). The primary screening method was based on the ATC codes (2013 version) of drugs. The DDD is the average maintenance daily dose of the medication used for its main therapeutic indication in adults. The medication use was expressed as the number of DDDs per 1000 inhabitants per day, which technical unit enables to compare the drug use of populations of different sizes. For each year, the gender and age-standardised data on population size were gained from the Hungarian Central Statistical Office. The secondary screening method was based on the indications of drugs, coded by ICD (included ICDs: E55-58, M80, M81).

Age- and gender-specific incidence of hip fractures was studied in 2007 and 2011 in Hungary. Our crude data came from the "Tables of basic data on Hungarian health care". Hip fractures were identified according to ICD codes (S72.0, S72.1, and S72.2).

3.2. Medication use and fall prevalence among nursing home residents

Patients and setting

A retrospective analysis was performed regarding the medication use and fall prevalence in nursing home residents, all recruited from the same institution, between August 2011 and August 2015 in Szeged, Hungary. Every patient who was the resident of the investigated nursing home for at least 12 months was included in the study. Patient data were recorded and analysed for the first 12 months of residency, starting from the date of admission. Relevant medication lists and demographic information were collected from the patient medical documentation of the facility. Detailed data on falls were available from hospital discharge documents since, after noticed falls, all residents were admitted to hospital for further investigation. Due to the local policy, deceased patients were excluded from this study, because we had no data access on those patients' medical information. The present study was approved by the Regional Human Biomedical Research Ethics Committee of the University of Szeged.

Data analysis and statistical methods

Microsoft Excel, IBM SPSS Statistics (version 23) and R (3.2.2) programs were used for data management and analysis. A Chi-squared test was applied to compare the categorical variables, Student's t-test was performed to compare the continuous variables between the investigated groups, and Fisher's test in case of polypharmacy.

We examined the prevalence and PPV (positive predictive value) with 95% confidence intervals (CI 95%), to estimate the possible impact of each medication (active substance) on risk of falls. PPV is the proportion of patients taking a particular drug and who had fall(s). The predictive values of a clinical test depend critically on the prevalence of the condition (falls) in the patients being tested within a particular environment. Number needed to harm (NNH) was calculated for those active agents which had high PPV, and where the lower CI 95% value exceeded the annual fall prevalence rate. The NNH index expresses how many patients need to be exposed to a certain risk-factor (drug) to cause harmful effect (fall) in one patient over a specific time period (1 year). NNH values calculated in our study cannot be extended for the entire population of elderly people; they are valid only for those nursing home residents involved in this analysis. Binary logistic regression analysis was carried out to determine the association of falls with other variables found significant in univariate analysis. Logistic regression was characterised by the accuracy of test. To identify the potentially inappropriate medications, four commonly used PIM lists have been adopted to the Hungarian drug market and to our data on medication use, the updated Beers criteria (2015), the French LaRoche list (2007), the German Priscus list (2010) and the Austrian Mann list (2012).

3.3. Vitamin D levels of elderly hospitalised patients

A prospective pilot study was done to compare vitamin D levels of hospitalised hip fractured patients (from the Traumatology Department) with hospitalised non-fractured patients (from the Department of Internal Medicine and Geriatrics) in Szeged, Hungary. The recruitment period was from 2011 June to 2011 September. Control group was matched according to age and gender. Microsoft Excel and R (3.2.2) programs were used for data management and analysis. Student's t-test was performed to compare the continuous variables between groups.

Table 1 Laboratory references of 25(OH)D_3 vitamin (based on national guidelines, this rate may vary in different countries)

Laboratory references of 25(OH)D_3 vitamin	
above 30 ng/ml (above 75 nmol/L)	**Sufficiency** (adequately supplied)
< 30 ng/ml (< 75 nmol/L)	**Insufficiency** (deficient)
< 20 ng/ ml (< 50 nmol/L)	**Deficiency** (seriously deficient)

An international consent uses 25(OH)D_3 (cholecalciferol) as a reference to assess the general level of vitamin D in the body (Table 1). Cholecalciferol levels were measured with ELISA kit and were expressed in ng/ml. All hip fractures derived from falls; therefore fall prevalence rate was considered 100% in the fractured group. Subjects were asked about previous falls during a personal interview. The study was approved by the Regional Human Biomedical Research Ethics Committee of the University of Szeged.

4. RESULTS

4.1. Gender- and age-specific utilisation study of anti-osteoporotic drugs

Gender- and population-based results

Medication use by females was substantially higher in the case of every medication than by males (Figure 1). During the examined 5-year period, the utilisation of vitamin D and analogues showed constant increase from 7.91 DDD/TID to 13.73 DDD/TID. A similar tendency was revealed in female and male patients. However, there was an approximately ten-fold difference between genders, male patients were remarkably undertreated. The utilisation of calcium compounds increased from 1.43 DDD/TID in 2007 to 4.49 DDD/TID in 2011, which is a more than three-fold growth. This tendency mainly arose from the treatment of female patients; males were significantly undertreated (F:M ratio was 10.8 in 2011).

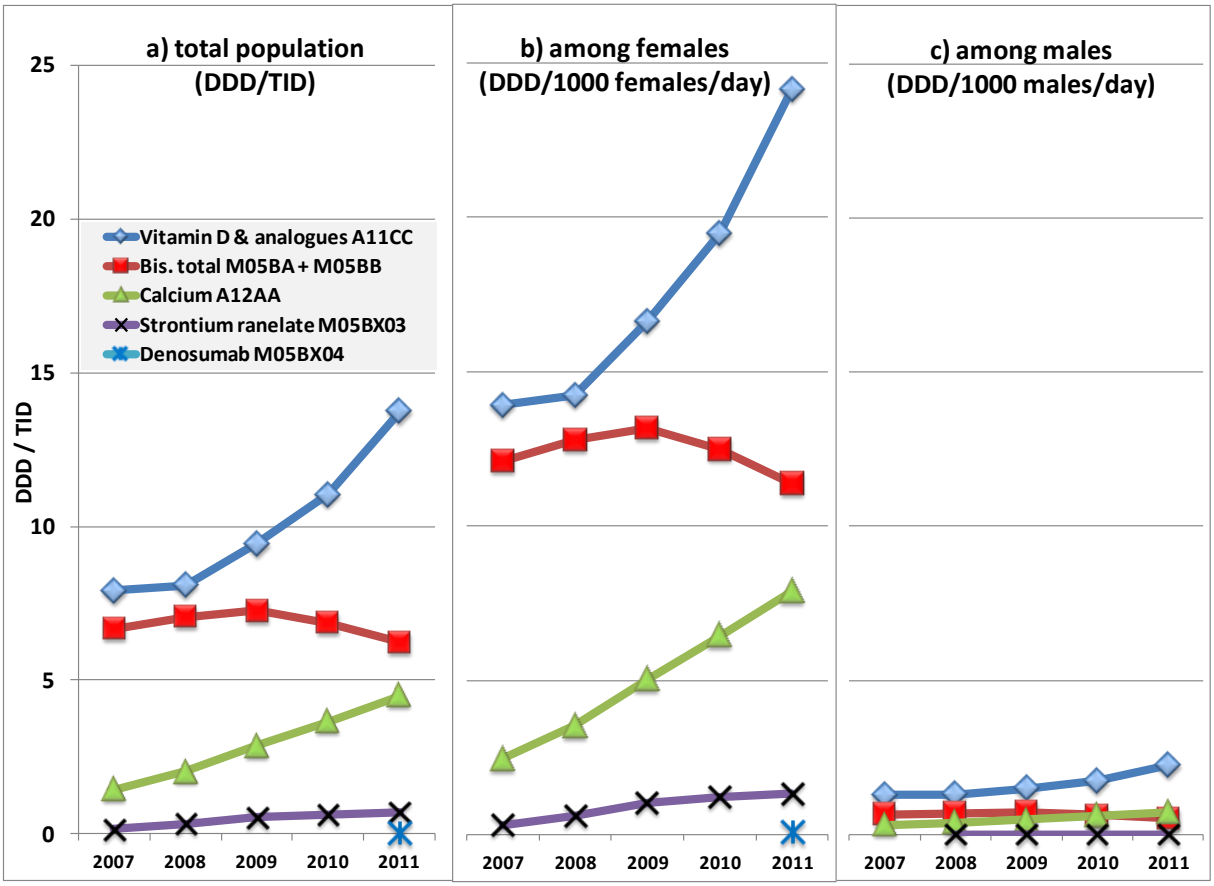

Figure 1 Utilisation of anti-osteoporotic medications in Hungary 2007-2011

The total bisphosphonate use was 6.66 DDD/TID in 2007, it slowly increased in 2008 and 2009, but for 2011 it dropped to 6.22 DDD/TID. Male patients were treated approximately 20 times less than women (F:M ratio was 22.2 in 2011). Strontium ranelate is mainly prescribed for women after the bisphosphonate therapy failed or could not be tolerated. The trade showed a constant increase since 2007. Denosumab, a monoclonal antibody, was introduced to the Hungarian market in 2011 and took 0.04 DDD/TID.

Gender- and age-standardised results

Table 2 Gender- and age-standardised results

		40-44 years	45-49 years	50-54 years	55-59 years	60-64 years	65-69 years	70-74 years	75-79 years	80-84 years	85 and over
Females (DDD/1000females/day)											
Bisphosphonates M05BA + M05BB	**2007**	0.10	1.40	8.18	18.82	30.77	43.36	49.93	48.26	36.18	15.33
	2008	0.05	1.22	8.05	18.72	31.37	44.92	52.58	53.38	39.94	17.02
	2009	0.06	1.07	8.31	18.92	31.36	44.89	53.15	54.92	43.25	19.39
	2010	0.05	0.72	7.17	17.79	28.54	41.14	49.72	53.24	42.93	19.44
	2011	0.04	0.53	5.56	15.78	25.67	36.58	44.79	49.27	41.04	18.62
	% change 2007-2011	**-59.6%**	**-62.0%**	**-32.1%**	**-16.1%**	**-16.6%**	**-15.6%**	**-10.3%**	**2.1%**	**13.4%**	**21.4%**
Strontium ranelate M05BX03	**2007**	—	0.01	0.12	0.40	0.66	1.06	1.42	1.44	1.22	0.45
	2008	—	0.05	0.32	0.81	1.36	2.09	2.53	2.68	2.22	0.98
	2009	—	0.07	0.54	1.39	2.32	3.58	4.20	4.32	3.65	1.76
	2010	—	0.05	0.55	1.55	2.74	4.09	4.92	5.19	4.48	2.04
	2011	—	0.04	0.52	1.64	2.95	4.31	5.33	5.85	5.20	2.72
	% change 2007-2011	—	**523.6%**	**333.1%**	**307.8%**	**346.3%**	**306.8%**	**274.9%**	**306.5%**	**327.1%**	**505.1%**
Denosumab M05BX04	**2011**	—	—	0.08	0.12	0.23	0.24	0.37	0.30	0.12	—
Males (DDD/1000males/day)											
Bisphosphonates M05BA + M05BB	**2007**	0.01	0.09	0.67	1.25	1.96	2.87	3.56	4.20	3.20	1.50
	2008	—	0.12	0.67	1.29	2.03	3.10	3.75	4.51	3.73	1.53
	2009	0.01	0.05	0.56	1.33	2.26	3.27	4.01	4.79	3.61	1.63
	2010	—	0.06	0.36	1.12	1.78	2.95	3.45	3.88	3.58	1.71
	2011	—	0.01	0.16	0.80	1.44	2.30	2.96	3.40	3.43	1.56
	% change 2007-2011	—	**-85.5%**	**-76.7%**	**-35.7%**	**-26.6%**	**-19.7%**	**-16.8%**	**-19.0%**	**7.1%**	**4.2%**
Strontium ranelate M05BX03	**2007**	—	—	—	—	—	—	0.01	—	—	—
	2008	—	—	—	—	—	0.02	0.03	0.01	0.03	—
	2009	—	—	—	—	—	0.02	0.04	0.04	0.02	—
	2010	—	—	—	—	0.01	0.03	0.02	0.05	—	0.04
	2011	—	—	—	—	0.01	0.02	0.03	0.01	0.05	0.03
	% change first trade year - 2011	—	—	—	—	—	**5.5%**	**122.4%**	**-29.1%**	**68.2%**	**-21.6%**
Denosumab M05BX04	**2007-2011**	—	—	—	—	—	—	—	—	—	—

The utilisation of bisphosphonates was the highest in the 75–79-year-old population in both genders, but with very different values: 49.27 DDD/1000females/day and 3.40 DDD/1000males/day in 2011 (Table 2). The highest decrease in bisphosphonate utilisation was detected in the 40-54 age groups in both genders during the study period. The largest differences between genders could be seen in 2011 in all age groups. Strontium ranelate was prescribed to male patients only above the age of 60, but less than 0.05 DDD/1000males/day. In women, a remarkable rise can be seen in all age groups from 2007 to 2011. The trade of denosumab in females peaked in the 70–74-year-old population (0.37 DDD/1000females/day) in 2011. There was no denosumab use among male patients.

4.2. Medication use and fall prevalence among nursing home residents

Demography

A total of 197 nursing home residents were included in the study, 150 (76.2%) women and 47 (23.8%) men (Table 3). Among the 55 fallers, 44 were females and 11 were males, therefore the annual fall prevalence rate was 27.9%. The gender was not found to be a predisposing factor for falls (prevalence in males: 23.4% vs 29.3% in females, p>0.05). Bone fractures occurred in 24 patients (5 males and 19 females, 43.6% of fallers). Regarding age, fallers were older (84.0 years ± 7.0 years) than non-fallers (80.1 years ± 9.3 years, p<0.01).

Table 3 Study population characteristics. *Chi-squared test was applied for categorical variables, Student's t-test for continuous variables, and Fisher's test in case of polypharmacy.

		Fallers	**Non-fallers**	**p-value***	**Total**
		(55; 27.9%)	**(142; 72.1%)**		**(197; 100.0%)**
Gender	females (% of all females)	44 (29.3%)	106 (70.7%)	p=0.427	150 (76.2%)
	males (% of all males)	11 (23.4%)	36 (76.6%)		47 (23.8%)
Age (years)	mean ± SD	84.0 ± 7.0	80.1 ± 9.3	**p=0.002**	81.2 ± 8.9
	min-max	61 - 99	52 - 104	-	52 - 104
Age group 80 years or older (% of group)		47 (35.9%)	84 (64.1%)	**p<0.001**	131 (66.5%)
Age group less than 80 years (% of group)		8 (12.1%)	58 (87.9%)		66 (33.5%)
Number of chronic medications	mean ± SD	9.1 ± 3.8	8.0 ± 3.9	p=0.093	8.32 ± 3.88
	min-max	3 - 19	0 - 18	-	0 - 19
	males (mean ± SD)	12.4 ± 4.0	6.9 ± 4.2	**p<0.001**	8.2 ± 4.7
	females (mean ± SD)	8.3 ± 3.3	8.4 ± 3.7	p=0.810	8.4 ± 3.6
Polypharmacy	yes (% of group)	54 (98.2%)	122 (85.9%)	**p=0.010**	176 (89.3%)
	no (% of group)	1 (1.8%)	20 (14.1%)		21 (10.7%)
PIM	yes (% of group)	40 (72.7%)	112 (78.9%)	p=0.357	152 (77.2%)
	no (% of group)	15 (27.3%)	30 (21.1%)		45 (22.8%)
PIM fall risk	yes (% of group)	39 (70.9%)	107 (75.3%)	p=0.523	146 (74.1%)
	no (% of group)	16 (29.1%)	35 (24.6%)		51 (25.9%)

The age above or equal to 80 years was found to be a significant risk factor for falls ($p<0.001$). Among fallers, 47 residents (85.5%) were 80 years old or older, and all the 13 multiple fallers (more than 1 fall per year) were in this group.

Medication patterns

The number of chronic medications taken did not significantly differ between fallers and non-fallers (9.1 ± 3.8 vs. 8.0 ± 3.9, $p>0.05$) (Table 3), but did differ among male fallers and male non-fallers (12.4 ± 4.0 vs. 6.9 ± 4.2, $p<0.001$). Also, polypharmacy (taking 4 or more chronic medications) was a significant risk factor of falls ($p=0.010$). Polypharmacy occurred in 85.9% among non-faller patients, but in 98.2% among fallers. Regarding the prevalence of PIM medication use, 77.2% of the residents took one or more PIM-list positive drug, and there was no significance in prevalence between fallers and non-fallers (72.7% vs. 78.9%, $p>0.05$). Those PIMs carrying risk of falls (PIM fall risk) were taken by 70.9% of fallers and 75.3% of non-fallers ($p>0.05$).

Table 4 Positive predictive values (PPV) of drugs (with 95% CI: confidence intervals). Displayed drugs were taken by minimum 20 individuals (10% of all residents).

Active substance	No. of takers (%)	No. of fallers	PPV (95% CI)
trimetazidine	**23 (11.68%)**	**11**	**0.48 (0.30-0.66)**
isosorbide mononitrate	20 (10.15%)	9	0.45 (0.26-0.65)
vinpocetine	**36 (18.27%)**	**16**	**0.44 (0.31-0.59)**
tiapride	28 (14.21%)	12	0.43 (0.27-0.60)
atorvastatin	29 (14.72%)	12	0.41 (0.27-0.58)
pantoprazole	**52 (26.4%)**	**21**	**0.40 (0.30-0.52)**
allopurinol	21 (10.66%)	8	0.38 (0.21-0.58)
glyceryl trinitrate	36 (18.27%)	13	0.36 (0.24-0.51)
famotidine	33 (16.75%)	11	0.33 (0.21-0.49)
levothyroxine sodium	30 (15.23%)	10	0.33 (0.20-0.50)
acetylsalicylic acid	74 (37.56%)	24	0.32 (0.25-0.41)
alprazolam	63 (31.98%)	20	0.32 (0.23-0.42)
bisoprolol	33 (16.75%)	10	0.30 (0.18-0.46)
amlodipine	42 (21.32%)	12	0.29 (0.18-0.42)
pentoxifylline	29 (14.72%)	8	0.28 (0.15-0.45)
metoprolol	43 (21.83%)	10	0.23 (0.14-0.36)
furosemide	65 (32.99%)	15	0.23 (0.16-0.33)
potassium chloride	68 (34.52%)	15	0.22 (0.15-0.31)
perindopril and amlodipine	28 (14.21%)	6	0.21 (0.10-0.39)
acenocoumarol	20 (10.15%)	4	0.20 (0.08-0.42)
piracetam	40 (20.3%)	7	0.18 (0.09-0.31)
metformin	22 (11.17%)	3	0.14 (0.05-0.34)

Except for 2 non-medicated residents, 195 were taking 227 different drugs, out of which 22 drugs were taken by at least 10% of the patients (minimum 20 individuals). For the most

prevalent drugs, positive predictive values (with 95% confidence intervals) were calculated to estimate the impact of each medication on fall risk (Table 4). Considering the 27.9% annual fall prevalence rate in the nursing home, the lower confidence interval exceeded this margin in case of trimetazidine (PPV (95% CI) 0.48 (0.30-0.66), vinpocetine 0.44 (0.31-0.59) and pantoprazole 0.40 (0.30-0.52). Hence, those drugs seem to be significant risk factors for falls.

For the same drugs, the number needed to harm (NNH, 95% CI) was calculated (groups were the following: particular drug user or non-user, and the outcome/risk was falls). Accordingly, approximately 4-5 patients are needed to be exposed to trimetazidine and vinpocetine use to sustain a fall, while this number is about 6 in the case of pantoprazole exposure (Table 5). These numbers are clinically remarkable.

Table 5 Number needed to harm (NNH) values (with 95% CI: confidence intervals) of trimetazidine, vinpocetine and pantoprazole (N: number of takers).

Drugs (number of drug users)	NNH	95% CI
trimetazidine (N=23)	4.5	2.3 - 55.1
vinpocetine (N=36)	5.0	2.7 - 32.6
pantoprazole (N=52)	5.9	3.2 - 47.0

The variables of the binary logistic regression model were the following: age group 80 years and above, persons taking pantoprazole, vinpocetine and trimetazidine. Binary logistic regression confirmed the significant impact of the 80+ age group, pantoprazole, and vinpocetine on fall risk, odd ratios were respectively 3.92, 2.59 and 2.32, with 73.6% accuracy detected (Table 6).

Table 6 Results of binary logistic regression analysis (95% CI: confidence interval; OR: odds ratio).

Variables	Coefficients (p value)	OR (95% CI)
age group 80 years old or above	1.3660 (p=0.00175)	3.92 (1.67 - 9.22)
pantoprazole	0.9498 (p=0.01049)	2.59 (1.25 - 5.35)
vinpocetine	0.8411 (p=0.03760)	2.32 (1.05 - 5.12)
trimetazidine	0.7181 (p=0.13296)	2.05 (0.80 - 5.23)

4.3. Vitamin D levels of elderly hospitalised patients

Demography

Twenty-two patients were in the fractured group (mean age 84.1 years, SD ± 6.8) and 33 patients were in the control group (mean age 80.5 years, SD ± 6.6; p>0.05, t-test). The majority of patients were women in both groups (20 fractured and 29 controls). Therefore the investigated groups did not differ significantly in demographic pattern.

Vitamin D level

Serum vitamin D level was normal (sufficient; >30 ng/ml) in 66.7% of the controls, and in 45.4% of fractured patients. Vitamin D insufficiency (20-30 ng/ml) was higher in the fractured group (27.3% vs. 21.2%), as well as the prevalence of deficiency (<20 ng/ml)

(27.3% vs. 12.1%), though we couldn't find any statistical significance between the groups. The mean vitamin D level was 33.8 ng/ml in the fractured group and 39.7 ng/ml in the control group (p=0.230). Distribution of patients was similar in both groups (Figure 2).

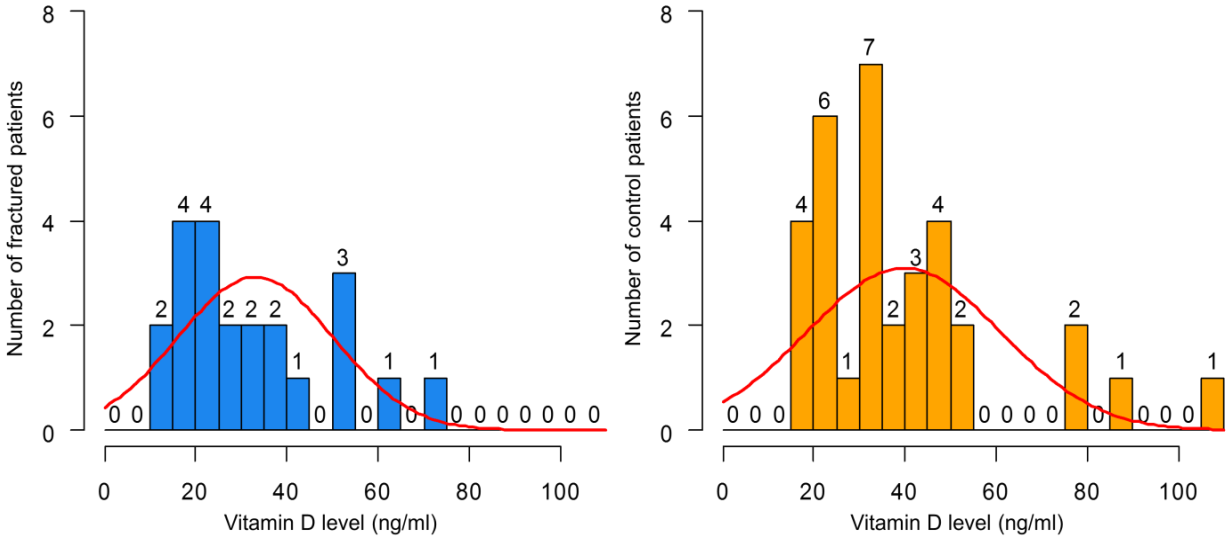

Figure 2 Distribution of fractured (dark) and control patients (bright) by vitamin D levels

Falls reported

Patients in fractured group reported considerably more falls within one year than in the control group. Nearly 55% of fractured patients and roughly one-third of controls reported multiple falls in the previous year. An important finding may be that about 36.4% of fractured patients and 30.3% of control patients reported more than 2 falls in the previous year.

5. DISCUSSION

5.1. Utilisation study of anti-osteoporotic drugs

Men were disproportionately undertreated in all age groups compared to women, and treatment choice was restricted for vitamin D, calcium supplementation and bisphosphonates compared to women. The persistent 10-20-fold difference between males and females does not reflect the estimated 1:5 proportion of males and females affected by osteoporosis in Hungary. In a similar age and gender-standardised Australian study, a much milder 3-4-fold gender difference was found between the use of alendronic- and risedronic acid in 2005-2006. Recently, results of numerous randomised controlled trials have confirmed that anti-osteoporosis drugs are equally effective in males and females. Based on those findings, the recommended treatment options for male patients are calcium and vitamin D supplementation as first line treatment, and in combination with alendronate, risedronate, zoledronate, denosumab and teriparatide. All of these drugs are available in Hungary, however, in practice, besides health professional considerations, drug choice is also determined by the costs and reimbursement criteria.

Bisphosphonate use showed a gradually declining tendency. The peak age of utilisation was 75–79 years in both genders, while in Australia the peak age was 80–89 years in females and 85–94 years in males. This age utilisation profile only partially corresponds to the population with the highest prevalence of osteoporotic fractures, as hip fractures are the highest in the 85+ populations in Hungary. Appropriate and proportional treatment of the 80+ populations would be an important issue in both men and women. Also, pharmacological fracture prevention may be started in earlier ages to reduce late-age incidence of hip fractures in both genders. This intervention may improve mortality rates and decrease fracture-related costs.

5.2. Medication use and fall prevalence among nursing home residents

The age of 80 years or above was found to be statistically significant risk factor of falls, and fallers were 4 years older than non-faller nursing home residents on average. Therefore, attention should be paid to the 80+ population, since they had almost a 4-fold risk of falling (odds ratio 3.92) compared to those who were under the age of 80 years. We found 27.9% annual fall prevalence rate among nursing home residents, which is slightly lower than the literature data. This fact bears evidence of the high-standard nursing care service the investigated nursing home provides. Although many falls remain unreported, patients often fall more than once a year. In a typical nursing home, the annual average number of falls is 2.6 per patient. Although many geriatricians consider polypharmacy to be unavoidable among older patients, PP was a significant risk factor of falls in our study, as it is supported by different surveys and reviews. Higher numbers of chronic medications was a predisposing factor for falls in male patients. This is an important finding, since fatal fall outcome rates are much higher in men (46%) than in women (27%) over the age of 65 years. Some studies found that males suffer from more co-morbid conditions or they may fall from greater heights and, having poorer health status, they are less likely to survive a fall-related injury than women of comparable age. Thus guidelines and policies on fall prevention need to be designed on gender perspective, particularly in vulnerable nursing home populations.

As the most serious non-fatal consequence of falls, bone fractures occurred in 24 patients (43.6% among fallers). Although huge differences can be seen in fracture rates worldwide, our study reports higher percentages than a Sweden study (1-33%) or a US study (10-25%) do, and lower than the one identified in a recent Australian paper (about 48%).

One possible way of reducing fall risk (and consequences) of elderly patients is the frequent and regular medication review, as some of the medications are considered potentially inappropriate for elderly people. Neither trimetazidine nor vinpocetine have been considered as PIM agents in the literature previously. Pantoprazole was included in the 2015 Beers

criteria, but was not included in any PIM lists before. The updated Beers criteria suggests the avoidance of the use of pantoprazole beyond 8 weeks without justification, since long-term proton-pump inhibitor exposure carries high risk of Clostridium difficile infection, bone loss and fractures. Thus, our empirical findings extend the relevancy of pantoprazole being mentioned as a PIM agent with a new aspect: its use showed 2.5-fold risk of falls compared to non-takers, and one in every six patients would be expected to result in a fall (NNH 5.9).

Both vinpocetine and trimetazidine can have side effects that may increase the risk of falls, such as tremors, gait instability and dizziness. However, we could not find any research that would confirm the direct association between falls and the use of these medications. Our results from the binary logistic regression analysis revealed that taking vinpocetine will double the risk of falls (odds ratio 2.32), and the obtained NNH values suggest that every fourth or fifth exposure to trimetazidine or vinpocetine will result in a fall – within the given circumstances. We would like to emphasise that the role of trimetazidine as a risk factor for falls was confirmed only by univariate analysis. Larger patient numbers are necessary to support this finding.

Our methods applied in this study would fit in larger population analysis as well, and it may allow us deeper understanding of the role of each medication (or their combinations) concerning falls, especially as geriatric falls are multifactorial. Wider, comprehensive epidemiological studies would be necessary to confirm the role of particular active agents, and to help professionals prescribe, evaluate and review geriatric medication use by real-life epidemiological data. Our results may contribute to and inspire further research in this field.

5.3. Vitamin D levels of elderly hospitalised patients

Despite serum cholecalciferol level of old, hospitalised patients was measured during summertime, the insufficiency was markedly presented in both patient groups, and was higher in the fractured group. Prevalence of vitamin D deficiency was more than double in the fractured group. Correspondently, the mean vitamin D level was slightly higher in the control group. Falls were prevalent in both investigated groups: nearly 55% of fractured patients and roughly one-third of controls reported multiple falls in the previous year. However, the statistical significance could not be verified of these findings, some conclusions might be made.

Adequate vitamin D status is elementary part of treating osteoporosis in both women and men. However, numerous studies refer to the extra-skeletal functions of cholecalciferol. Vitamin D administration can improve the grip strength, the maximum voluntary contraction and maximal relaxation rate of quadriceps muscle. Thus, vitamin D supplementation may improve falls, as functional outcomes. In a meta-analysis vitamin D was associated with

statistically significant reduction in the risk of falls (odds ratio 0.86), showing more reduction in deficient patients and when calcium was co-administered. Vitamin D supplementation with calcium reduced the prevalence of hip fractures more effectively in community-dwelling elderly, than without calcium.

Nevertheless, optimal serum concentration levels of vitamin D, with respect to its extra-osseal effects, are still debated. The British National Osteoporosis Society (NOS) suggests that serum 25(OH)D_3 >50 nmol/L is sufficient for almost the whole population. The most recent Bischoff-Ferrari study set out 50-75 nmol/L serum level as on optimal range, since higher serum vitamin D levels (over 111 nmol/L) were associated with more than 5 times higher risk of falls compared to the deficient group. For reaching the desirable 50 nmol/L value, the Institute of Medicine (IOM) recommends 600 IU (international units) daily vitamin D intake between the ages of 19-70, and 800 IU per day over 70 years. The Endocrine Society (ENDO) suggests general vitamin D supplementation of 800 IU over 65 years to prevent falls. The ENDO considers the optimal vitamin D level to be above 75 nmol/L, and it can be reached by giving 1500-2000 IU daily amount, and continue as maintenance therapy. The Hungarian guidelines (issued in 2012) agree with this standpoint. In two studies, high dose vitamin D treatment (500,000 IU once yearly and 60,000 IU monthly) was associated with increased risk of falls. With respect to the origin of vitamin D, the International Osteoporosis Foundation prioritises natural sources (UVB radiation, diet), supplemented by pharmacological vitamin D products if needed.

Based on the above, we can come to the conclusion that in our study, more than 50% of fractured patients and about one-third of controls should receive vitamin D supplementation and it should be between 1500-2000 IU per day until the desirable range is reached. If available, UVB exposure and dietary sources should be also implemented to the supplementation therapy. The current recommendations do not suggest higher doses than 800 IU daily vitamin D over 70 years as maintenance dose –not even to prevent falls.

Key messages and novelties

Gender- and age-specific utilisation study of anti-osteoporotic drugs

- Osteoporosis in no longer the condition of postmenopausal women, significant portion of men is also affected, and survival rate of hip fractures is worse in men.
- Males over 65 years should be also screened for osteoporosis and treated accordingly.
- Pharmacological fracture prevention may be started in earlier ages to reduce late-age incidence of hip fractures in both genders. This intervention may improve mortality rates and decrease fracture-related costs.

Medication use and fall prevalence among nursing home residents

- Geriatric falls are prevalent among individuals living in long-term care institutions, and are the leading causes of injury-related deaths.
- Older age, polypharmacy, and the independent use of 3 active agents (pantoprazole, vinpocetine and trimetazidine) were found to be major risk factors for falls in our study.
- Frequent and regular medication review is one possible way to reduce the risk of falling in elderly patients.

Vitamin D levels of elderly hospitalised patients

- Suboptimal vitamin D levels are prevalent among hospitalised older adults, as well as the prevalence of falls: nearly 55% of fractured patients and roughly one-third of controls reported multiple falls in the previous year.
- Vitamin D insufficiency was higher among hip fractured patients compared to controls; however we cannot prove the statistical significance.
- Based on current guidelines, elderly people under the normal cholecalciferol level (30 ng/ml or 75 nmol/L) should receive vitamin D supplementation.

Publications related to the Ph.D. thesis:

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3. **Bor Andrea,** Matuz Mária, Gyimesi Nóra, Benkő Ria, Soós Gyöngyvér, Csatordai Márta, Doró Péter Nemi különbségek az osteoporosis gyógyszeres terápiájában (Gender differences in osteoporosis therapy) In: Kórházi Gyógyszerészek XX. Kongresszusa. Place and date of conference: Visegrád, Hungary, 24/04/2015-26/04/2015. p. 74.
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