

EPIDEMIOLOGICAL CHARACTERISTICS OF DEMENTIA TREATMENT IN CROATIA

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SUMMARY

Background: In spite of the increase in the number of patients with dementia in countries with older population, basic epidemiologic data are still scarce. The objective of this paper is to investigate pharmacoepidemiological characteristics of treatment of dementia in Croatia, and to present them in the context of certain epidemiological characteristics that illustrate the growing pressure this disease exerts on the healthcare system.

Subjects and methods: Data on medication utilization were taken from Croatian Health Insurance Fund (HZZO) and Agency for Medicinal Products and Medical Devices of Croatia (HALMED). Data on the number of hospital stays were supplied by Croatian Institute of Public Health (HZJZ). Internal data on the number of outpatient examinations from the Clinical hospital "Sveti Duh" were used as well.

Results: In the observed period (2012–2014), 4568 patients were treated with anti-dementia medications, of which 1275 (32%) with donepezil, and 2753 (68%) with memantine. According to HALMED, the utilization of those medications is constantly increasing, and has increased manifold from 2005 to 2014. The estimate of the proportion of treated patients with dementia aged 60 years and over is around 9.2%. The number of dementia-related hospital stays is also increasing, and has increased by 9.6% in the last 5-year period, compared to the preceding 5-year period. The number of outpatient examinations in Clinical Hospital "Sveti Duh" grew from 351 in 2007 to 1151 in 2015 (January 1st - October 26th).

Conclusion: The strain this condition exerts on the healthcare system is increasing yearly. In spite of the large increase in the medication utilization over the previous years, the proportion of treated patients is still small, and further increase in their use is to be expected. It is necessary to monitor this in the years ahead.

Key words: dementia – epidemiology - medication therapy – pharmacoepidemiology - Croatia

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INTRODUCTION

Dementia is a syndrome – most commonly chronic or progressive – characterized by a decrease in cognitive functions, which is more pronounced than it would be expected with aging effects. It affects memory, thinking, orientation, comprehension, calculation, learning abilities, language, and judgement (World Health Organization 2015). The current trend of rapid growth of population older than 60 years of age leads to increased prevalence of chronic conditions such as dementia (World Health Organization 2012). The most prominent causes of dementia in Europe are Alzheimer's disease and vascular diseases (Lobo et al. 2000, Fratiglioni et al. 2000). Risk factors for developing dementia include age (the risk increases with age), a case of dementia in the family, and Down syndrome (Alzheimer's Australia 2007). According to some research, diabetes (Ahtiluoto et al. 2000) and arterial hypertension (Nagai et al. 2010) are also considered risk factors for developing dementia. Oxidative stress has been proposed as a contributing factor in dementia, although no clear benefit was observed in use of antioxidant medications (Padurariu et

al. 2013). Dementia is a condition which represents a significant strain and challenge for the individual, and consequently for the society, which is presented in the results of Global Burden of Disease research conducted by WHO (World Health Organization 2004). In this paper, a Disability-adjusted life year scale (DALY - potential number of healthy years lost due to ill health or disability) is used to measure the severity of the disease, and dementia is ranked among the conditions with high DALY values. Increase in prevalence, economic strain for the individual and the country, as well as society's prejudice towards people suffering from dementia are important public health problems.

According to the World Alzheimer Report 2015, the most recent review paper related to the prevalence and incidence of dementia, 46.8 million people worldwide suffer from dementia (Alzheimer's Disease International 2015). The survey was conducted in WHO / GBD regions of the world. Croatia is located in the region of Central Europe. This prevalence assessing study of dementia used meta-analytic methods. According to that paper, the prevalence of dementia in people older than 60 years in Central Europe is 4.65, in Western Europe

6.8, and in Eastern Europe 5.7 percent. In North America, which includes only the USA, prevalence is 5.73 percent (Alzheimer's Disease International 2015). Estimated number of people suffering from dementia older than 60 years in Croatia obtained by the use of these data is 47958 people. It is assumed that the growth of prevalence is going to continue in the future, especially in countries with low and medium-high income, finally leading to 74.7 million people affected by dementia in 2030 worldwide. There are significant gender differences in dementia prevalence. In Western Europe, East Asia, South Asia, Caribbean and Latin America predicted prevalence in women is between 14% and 32% higher than in men. One of the reasons for higher prevalence in women is greater life expectancy among women and as it is known, age is one of the most important risk factors for dementia. Not only that women are at higher risk for developing dementia, but the symptoms of the condition are more severe among women (Alzheimer's Disease International 2015). The quality of the research conducted so far related to dementia is lacking in quality; diagnostic procedures performed are insufficiently comprehensive and the study design is often misused (Alzheimer's Disease International 2015). It is believed that further research, repeated at set intervals, with the support of government institutions is necessary (Alzheimer's Disease International 2015, Alzheimer's Disease International 2009). According to available data, a systematic study of the prevalence and incidence of dementia in Croatia has not been conducted yet.

Dementia is often accompanied by various psychiatric symptoms, which are often treated pharmacologically, although it would be advisable to use nonpharmacological interventions as first line of treatment (Sadowsky & Galvin 2012). The approach to pharmacologic treatment of those symptoms may include the following: in treating symptoms in the depression spectrum, it is advised to base theselection of a particular antidepressant on previous treatment response, tolerance and the advantage of potential side effects, for example, whether sedation or activation are more beneficial. Psychotic symptoms should be treated by lower initial doses of antipsychotics, and patients should be regularly assessed for adverse effects. Typical antipsychotic agents should be administered if there is no response to atypical antipsychotic agents. Benzodiazepines are also often used, and advantage should be given to agents such as lorazepam and oxazepam (Cummings et al. 2002, Sadowsky & Galvin 2012). If benzodiazepines are used, the patients are at risk for cognitive worsening, sedation, delirium, and are at an increased risk for falls (Folnegovic-Smalc et al. 2002). Before resorting to pharmacotherapy of psychiatric symptoms, it is necessary to ensure the symptoms are not due to other medications or illnesses (Meeks et al. 2008).

The aim of this study was to investigate the basic demographic characteristics of the population treated for dementia from 2012 to 2014, to evaluate the charac-

teristics of pharmacological treatment of dementia in Croatia, and to assess the proportion of patients with dementia treated pharmacologically. Furthermore, this paper presents epidemiological data related to the number of hospitalizations and medical visits due to dementia, which help to place the extent of the problem of dementia in society in a broader context.

SUBJECTS AND METHODS

Design of the study was approved by local ethical committee. Data on the utilization of medication for treatment of dementia analysed in this study were obtained with the permission of the Croatian Institute for Health Insurance (HZZO) and the Croatian Agency for Medicinal Products and Medical Devices (HALMED).

Data provided by HZZO apply for three years: 2012, 2013 and 2014. Each and every patient treated with medication observed in this research is filed under his/her unique identification number; no other personal information is included. Each identification number is associated with the data on the patient's age, sex, year in which he/she was treated, and whether the medication was received via prescription or in hospital health care / specialist-consultative health care. The paper also provides the data on the amount of medication that is prescribed during the year, either as the number of boxes or individual tablets of the medication, and the total cost of treatment with particular medication in a given year. Defined daily doses (DDD) for each medication are presented, too.

Medications in the HZZO database are memantine (on the supplementary list of HZZO since 2012) and donepezil (on the supplementary list since 2013). Rivastigmine was added to the HZZO supplementary list in 2015 and is not included in this database.

Data provided by HALMED agency contain information about the outpatient utilization of each medication for dementia treatment, regardless of whether and when the medication has been included on the supplementary list of HZZO. Consumption is expressed as the number of defined daily doses per 1000 people in the general population daily – DDD/1000/day. Data refer to the period from 2005 to 2014.

The data obtained from the Croatian Institute for Public Health (HZJZ) were collected using a patient-statistical forms (PSF; in Croatian BSO – bolesnički statistički obrazac) from 2005 to 2014, and include an analysis of patients treated for diagnoses associated with dementia (F00-F03, G30; ICD-10).

Data on the number of outpatients examined for diagnosis of dementia (ICD-10 F00-F03) from the Clinical Hospital "Sveti Duh" were collected via Patients Reception System (SPP 2.0), i.e. hospital information system documenting processing and treatment of patients.

All data were processed in Microsoft Excel. Methods of descriptive statistics were used as well.

RESULTS

In the assessed period, a total of 4568 patients received dementia treatment medications according to HZZO. Of these, there were 2813 women (62%) and 1755 men (32%). Average age was 75.34±8.27 years, and the range was 22 to 99 years. The age distribution is shown in Table 1.

Table 1. Age distribution of patients treated for dementia

Age group (years)	Total number	Percentage (%)
-24	2	0.04
25-29	2	0.04
30-34	1	0.02
35-39	3	0.06
40-44	10	0.22
45-49	9	0.20
50-54	44	0.96
55-59	123	2.69
60-64	264	5.78
65-69	381	6.71
70-74	787	17.23
75-79	1249	27.34
80-84	1099	24.06
85-89	493	10.79
90-94	93	2.03
95+	7	0.15

Of the total number of patients treated, 1275 people (32%) were treated with donepezil and 2753 (68%) with memantine.

The total number of DDD in each year per medication was obtained by multiplying the total number of pills prescribed along with the amount of

medication in each pill, divided by the defined daily dose (DDD; for memantine 20 mg, 7.5 mg for donepezil). Table 2 shows the difference in utilization of these medications via prescription or via hospital consumption.

Utilization of medications expressed in the number of DDD / 1000 / day for 2014 is 0.25 DDD / 1000 / day for memantine and 0.12 DDD/1000/day for donepezil.

HALMED data for 2014 amounted to 0.23 DDD / 1000 / day of memantine, and 0.10 DDD / 1000 / day for donepezil. The medication utilization according to HALMED records is shown in Table 3.

If the total number of DDD in a year is divided by the number of people treated with the medication, the average number of DDD per person in that year is obtained. In 2014 it amounted to 141.6 DDD for memantine and 143.9 DDD for donepezil, which approximates the number of days an average patient uses the particular medication in a year.

The expenses for dementia treatment medication in HZZO (without participation of patients) increased from 54547 kn in 2012 over 940465 kn in 2013, reaching the high 1488507 kn in 2014. The increase in non-pharmacological costs that this syndrome causes in Croatia is illustrated by the data on hospitalizations for diagnoses associated with dementia yearly on the national level (F01-F03, G30; ICD-10): number of hospitalizations has increased from an average of 1,138 per year for the period 2005–2009 to an average of 1,247 per year in the period 2010–2014 (growth of 9.6%). In 2014, 1447 people were hospitalized due to dementia diagnoses.

Data on the number of ambulatory patients examined for diagnosis of dementia (ICD-10 F00-F03) from the Clinical Hospital “Sveti Duh” also indicate an increasing trend (Figure 1).

Table 2. Amount of each medication per year prescribed either via a prescription or treated during the patient's hospital stay, expressed in the number of defined daily doses (DDD)

DDD	Memantine – treated in a hospital	Memantine - prescriptions	Donepezil – treated in a hospital	Donepezil - prescriptions
2012	44.5	13104	-	-
2013	2360.5	232582	453	40809
2014	5241.5	384468	1789	181682

Table 3. Utilization of each medication in the span of the last ten years according to data from HALMED, expressed as a number of defined daily doses on 1000 people in the general population in a day (DDD/1000/day)

DDD/1000/day	Memantin	Donepezil	Rivastigmin
2005	0.00	0.00	-
2006	0.00	0.00	-
2007	0.01	0.01	-
2008	0.01	0.04	-
2009	0.02	0.01	0.00
2010	0.03	0.02	0.00
2011	0.03	0.03	0.00
2012	0.04	0.02	0.00
2013	0.14	0.04	0.00
2014	0.23	0.10	0.00

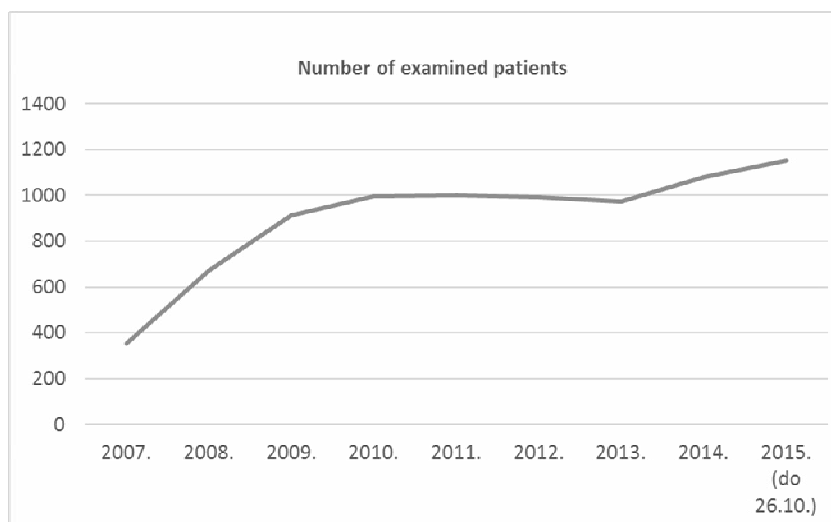


Figure 1. Increase in the number of ambulatory patients examined in Clinical hospital „Sveti Duh“ from 2007 to 2015 diagnosed with dementia associated diagnoses (ICD-10 F00-F03)

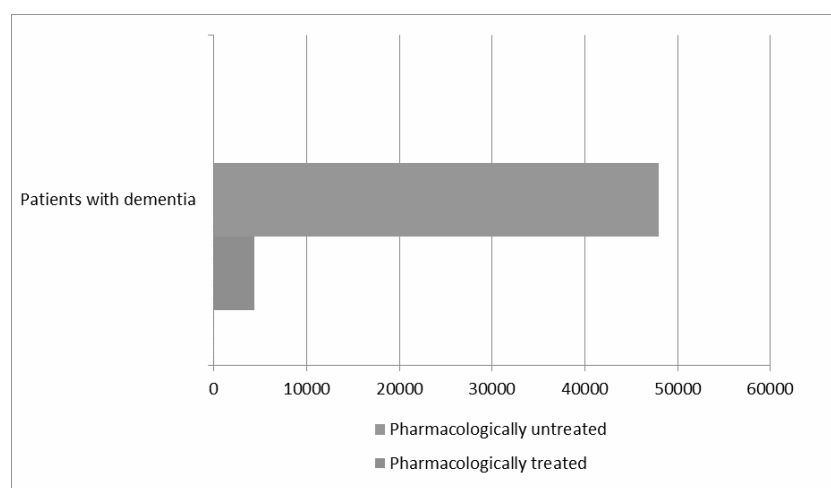


Figure 2. Estimated proportion of pharmacologically treated patients older than 60 years in the total estimated number of patients

According to the analysis that was done in this study, in the Republic of Croatia there is a relatively small number of people treated pharmacologically for dementia. If the total number of pharmacologically treated patients is compared to, based on the data for this part of Europe, the presumed number of people suffering from dementia, it is our estimate that the proportion of treated patients older than 60 years is about 9.2% (Figure 2).

DISCUSSION

Despite the assessment that a relatively small number of people suffering from dementia is pharmacologically treated, at the stage before the pharmacotherapy is introduced, a cost for this disease is high: research shows that the economic strain of dementia is extremely high and displays an increasing trend. The global cost of dementia is estimated at 118 billion US dollars, which is an increase of 35.4% in relation to 2010 (Alzheimer’s Disease International 2015). Accord-

ing to a study conducted in the UK in 2014, the social cost as part of the overall economic cost of dementia was 2.5 times higher than the cost of health care (Alzheimer’s Society 2014).

The results show the effect of the introduction of anti-dementia medications on the supplementary list of HZZO: there was a large increase in the total utilization of anti-dementia medications from the moment of their entry to the list. Given that the entry of these medications on the list does not greatly decrease price for the end user (participation HZZO for both of the medications ranges from 15 - 30%), it is likely that there are other factors affecting the increased consumption. For example, there is a possible greater awareness of both patients and physicians of these medications, psychologically perceived lower prices if it is partially subsidized by HZZO, as well as greater tendency in recommending these medications by specialists. Despite the recent increase in utilization, the number of treated patients remains low, and it is necessary to monitor the dynamics of utilization in the coming years.

The number of patients treated with the individual anti-dementia medication is interesting, taking into account the current guidelines. The medical treatment of dementia usually implies cholinesterase inhibitors donepezil, rivastigmine and galanthamine, and the NMDA antagonist memantine (Qaseem et al. 2008). Donepezil, galantamine and rivastigmine are indicated in the treatment of mild to moderate dementia, and memantine for the treatment of moderate severe to severe dementia (National Institute for Health and Care Excellence (NICE) 2011). The number of patients treated with medical treatment in other countries is small, in the UK respectively; in 2014 it was only 13% of all patients (Health and Social Care Information Center 2014).

There are certain differences in drug utilization in various countries and regions, and in adherence to the current recommendations. There is a lack of nationwide studies on drug utilization, so the following data is to be interpreted with caution. For example, in the United Kingdom the majority of patients are treated with donepezil (National Institute for Health and Care Excellence (NICE) 2011). In India, donepezil is prescribed twice as often as memantine, with memantine mostly being prescribed in combination with donepezil (Patel et al. 2014, Thakkar et al. 2014). In Ontario (Canada), roughly half of home care clients with dementia received anti-dementia medications, most commonly donepezil (Maxwell et al. 2013). In the region of Madrid (Spain), use of anti-dementia medications has increased six fold from 2002 to 2012, and cholinesterase inhibitors account for 76.70% of the total consumption, versus only 23.30% for memantine (de Hoyos-Alonso 2015), whereas in Basque Country rivastigmine was the prevalent, with donepezil only fourth behind memantine and galantamine (Villanueva et al. 2014). In one earlier study performed in Pittsburgh (USA), donepezil was the most prescribed anti-dementia medication, sometimes in combination with memantine, and only a few patients used memantine as a monotherapy (Lopez et al. 2009).

The proportion of patients receiving memantine in Croatia is significantly higher than donepezil, as opposed to the ratio found in most of the aforementioned studies. The discrepancy between the recommendations and the actual situation may point to the fact that patients with dementia in Croatia are not recognized until the later stages of the disease, or that they are not inclined to pharmacological treatment at an earlier stage of the disease, because of financial or other reasons. This is also visible in the number of pharmacologically treated patients with dementia in the total number of patients, which is still lower than the estimated share in other countries (Health and Social Care Information Center 2014). Furthermore, the specialists could be inclined to introducing “stronger” medicine, which is intended for advanced stages of the disease, immediately after the diagnosis. Effort should be made to diagnose more patients in the incipient stages of dementia, in order to start therapy early, when there is

more cognitive function to be preserved. Both psychiatry and neurology specialists should try to recognize early symptoms of dementia in patients, even if this was not a primary reason for the examination of the patient. The patients should then be assessed in terms of cognitive functioning or referred to a facility that conducts such testing. General practitioners could contribute to the cause as well, recognizing the early symptoms in their patients and referring them to a specialist. They should be motivated to perform simple tests of cognitive functioning on patients over a certain age. In the future, certain CSF (cerebrospinal fluid) assays could become available in clinical use as well as an additional method in early recognition of dementia (Strac et al. 2015).

Data on the average number of DDD per patient for a particular medicine may indicate a slight difference between the medications in terms of perseverance of patients in the therapy. This information is not precise because there are a certain percentage of patients who started their therapy during the second half of 2014 and continued with it in 2015, and we do not possess data on the duration of therapy in 2015.

It is important to notice the fact that there are people under 30 years of age being treated for dementia. It is inevitable to question whether this is due to use outside the prescription or for other causes. Limitation of the study is that we obtained data for Clinical hospital “Sveti Duh” that is located in the capital of Croatia and almost all patients are from this area. Further studies that will recollect patient from whole country are needed to demonstrate exact situation regarding pharmacological treatment of dementia in Croatia.

CONCLUSION

We believe it is necessary to stay informed on the use of these medications, as well as of rivastigmine, which has since been included on the supplementary list of HZZO. A low number of patients with dementia are being treated pharmacologically at the moment, so it is necessary to monitor the changes in this number in accordance with the current and future guidelines and knowledge associated with the treatment of dementia.

A greater level of cooperation should exist between psychiatry and neurology specialists, in order to separate symptoms and signs of dementia from other co-existing conditions, both psychiatric and neurological, which are often present in the affected population. An assessment by both specialists could reliably identify proper candidates who could benefit the most by using anti-dementia medications.

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