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HOW DO WE TREAT PEOPLE WITH DEMENTIA IN CROATIA

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SUMMARY

The current clinical view on pharmacological treatment and the Croatian reality regarding approved antidementia drugs is presented. Dementia is a syndrome of high incidence and Alzheimer's disease is the most common cause of dementia. New data show that dementia prevalence will nearly double every 20 years, and we believe that current estimated number of persons with dementia (PWD) for Croatia is more than 80,000. The standard treatment with antidementia drugs is unavailable in Croatia, for the majority of PWD, because antidementia drugs are not on the reimbursement list, although Croatian algorithm for psychopharmacological treatment and Alzheimer Disease Societies Croatia recommend early and adequate treatment. Alzheimer's dementia is becoming a world's health priority in 21st century, so we strongly believe that antidementia drugs should be reimbursed in Croatia.

Key words: *Alzheimer's disease - dementia – Croatia - antidementia drugs - cholinesterase inhibitors – memantine*

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Epidemiology of Alzheimer's disease

Alois Alzheimer (1864-1915) was a German psychiatrist and neuropathologist who described the first case of "presenile dementia" in a 51-year-old patient Auguste D in 1906, at the 37th Conference of South-West German Psychiatrists in Tübingen, Germany (Grand & Feldman 2007). In 1910 Emil Kraepelin first used the name Alzheimer's disease (AD) for this condition in his Textbook of Psychiatry (Kraepelin 1910), and that's how we got one of the world's most known eponym. Today, dementia is a syndrome of high incidence. In Europe, there are more new cases of dementia per year than stroke, diabetes or breast cancer (Wilkinson et al. 2005). Alzheimer's disease remains the most common cause of dementia, responsible for 60–70% of all cases in Europe, until part of vascular dementia is 15-20% and of other dementias 10-25% (e.g. Lewy body disease, Parkinson's disease) (Fratiglioni et al. 2000). We believe that the same proportion of dementias is present in Croatia (Silobrčić Radić & Hrabak Žerjavić 2008). Dementia prevalence is growing now days in older people, particularly prevalence of Alzheimer's dementia, because risk factors for vascular dementia can be more satisfactory reduced with preventive programs (Szoeke et al. 2009). Recent epidemiological evidence suggested a 2001 prevalence of 24.3 million cases of dementia worldwide. There are 4.6 million new cases of dementia reported every year – that is one new case every 7 seconds (Ferri et al. 2005). According to the most recent count of population, from year 2001, Croatia has 4,437,460 inhabitants, among them 15.7% of people were older than 65 years (www.dzs.hr/). The newest estimation for Croatian population, from July 2009, is 4,489,409 (www.cia.gov/). Due to the fact that almost everybody in Croatia has health insurance, we can also relay on the database of Croatian Institute for Health Insurance which stated that on 4th of December 2006 in Croatia there were 806,070 people older than 65 years (Pecotić & Perkov 2007). Regarding oldest old, in year 2001 in Croatia there were 1,455 people between 95 and 108 years of age, among them 282 were living in Zagreb (Tomek Roksandić et al. 2009). Demographic trends in Croatia, which were observed in last 5-6 decades, are showing depopulation while whole population is getting older and older (Wertheimer-Baletić 2007). There is an approximation that in year 2050 Croatia will have 26.2% people older than 65 years (United Nations 2000). Everything mentioned above places Croatia among European countries with oldest population (Folnegović-Šmalc 2007).

The World Health Organization asked respondents from 109 countries across the world, including Croatia, to name the five most commonly encountered neurological diseases encountered in specialist care. Dementia was frequently reported in developed countries. For example, 50% of respondents in the Americas counted dementia as one of the 'top five' neurological conditions encountered by specialists (World Health Organization 2004). Dementia is a huge problem in Europe (Dementia in Europe 2006) according to calculations based on EURODEM prevalence data which are pointing that in 25 countries of European Union there are more than 5.8 million persons with dementia (PWD) (Hofman et al. 1991). Even more impressive are data coming from the newest 2009 World Alzheimer's Report from Alzheimer's Disease International (ADI), a London-based, non-profit, international federation of 71 national Alzheimer organizations, released on September 21, 2009, which states that 35 million people worldwide will suffer from dementia in 2010, 65 million in 2030 and more than 115 million in year 2050 (www.alz.co.uk/adi/).

We are not sure when the diagnosis of AD was used for the first time in Croatia, because such investigation was not done. But, we know that the oldest

Psychogeriatric department in Croatia was established in 1959 in Psychiatric Hospital Vrapče, Zagreb (Pecotić & Štengl-Martinjak 2006), and that was the place where patient with Alzheimer's dementia were hospitalized. At that time diagnosis of AD was not or very rarely used, and this remains even until 1978. Patients were mainly diagnosed under the term of "Pre-senile dementia" (in Croatian "Presenilna demencija"), code 290.1, due to officinal classification (ICD-8) translated into Serbo-Croatian language in 1968 (Savezni zavod za zdravstvenu zaštitu 1968a, Savezni zavod za zdravstvenu zaštitu 1968b). In the end of 1978 the ICD-9 (Savezni zavod za zdravstvenu zaštitu 1978) became official classification in Croatia, and that was the time when the diagnosis of AD was more often made, although the coding remain the same as in ICD-8. When the ICD-10 classification came out in 1992, the diagnoses of Alzheimer's disease (code G00) and Dementia in Alzheimer's disease (code F00) became for the first time official diagnoses. First Croatian translation of ICD-10 classification was published in 1994 (Hrvatski zavod za javno zdravstvo 1994), which together with 1996 Croatian translation of DSM-IV (Američka psihijatrijska udruga 1996), and 1999 Croatian translation of Chapter F of ICD-10 classification (MKB-10 1999), made that the AD diagnosis became more frequent in Croatian medical documentation and statistics.

As there is no Register of PWD in Croatia, the current number of more than 80,000 PWD is coming from approximation based on calculation that 1.8% of total population or 10% of population over 65 years (Pecotić & Perkov 2007) is affected with dementia. We believe that in the metropolitan area of Zagreb, the capital of Croatia, there are up to 15,000 PWD (Mimica et al. 2006a).

Pharmacotherapy of Alzheimer's disease

The pharmacotherapy of AD includes treatment of cognitive deficits in AD, behavioural disturbances in AD, psychiatric symptoms (depression, anxiety, psychosis with or without hallucinations, manic, obsessive-compulsive disorder, and alcohol dependence) in AD, insomnia in AD and Involuntary Emotional Expression Disorder (IEED) in AD (Mimica 2007). For pharmacological treatment of psychiatric symptoms, insomnia and IEED in AD, practically all drugs needed are available and reimbursed in Croatia, but that is not the case for the treatment of cognitive impairment (Mimica 2007). For the cognitive impairment in AD, till now, five antidementia drugs are approved by the United States Food and Drug Administration (FDA) (Yaari et al. 2008); four cholinesterase inhibitors (ChEIs) - tacrine, donepezil, rivastigmine, galantamin, and one glutamate - or N–methyl-D–aspartat receptor antagonist - memantine (Lieberman & Tasman 2006, Agronin 2008). Novel ChEIs (donepezil, rivastigmine, galantamine) are effective on cognitive functioning, activities of daily living, and behaviour for persons with mild-to-moderately severe AD (Stahl 2005, Birks 2006, Giacobini & Pepeu 2006). Memantine can be used as monotherapy or can be safely combined with a ChEI (Tariot et al. 2004, Jakovljevic et al. 2008, Mimica & Presečki 2009).

Croatian algorithm for psychopharmacological treatment of AD was introduced on 3rd Croatian Congress on Alzheimer's disease, Brijuni, 7-10 September 2006. According to Croatian algorithm donepezil represent the first pharmacotherapy line for mild and moderate cognitive deficits and if the therapy response is low the second line represents rivastigmine or galantamine. If the treatment response to the second line therapy is low for moderate cognitive deficits it is recommended to add memantine. In cases of severe dementia the first line treatment represents memantine and if the response is low it is suggested to add donepezil. If the response is low to the combination of memantin and donepezil in severe cognitive deficits, it is recommended to prescribe rivastigmine or galantamine (Folnegović-Šmalc et al. 2006, Vuksan-Ćusa et al. 2007).

In 2007 the European Federation of Neurological Societies (EFNS) Task Force Working Group provided recommendations for the diagnosis and management of AD and other dementias. The EFNS guidelines are based on the evidence from the original research reports, meta-analyses, and systematic reviews; where there was lack of the evidence, but clear consensus, good practice points were provided. According to the EFNS guidelines ChEIs (donepezil, rivastigmine, galantamine) should be the first-line treatment at the time of AD diagnosis (Waldemar et al. 2007).

Antidementia drugs and Croatian reality

In Croatia we treat PWD mainly inadequately! The reason for this unpleasant statement is in fact that only minority of PWD are receiving standard treatment (ChEI and/or memantine), and vast majority of PWD, although antidementia drugs are prescribed to them, are not taking the antidementia drugs because they can not afford to buy them (Bencarić 2010). Some of the patients undergo clinical trials and are treaded with investigational agents which, if they are lucky, may be adequate treatment for them, but usually with short or limited duration (Mimica & Presečki 2010). So, in Croatia, majority of PWD in reality are treated with supportive/adjuvant (alternative) medication like gingko biloba, nootropics (piracetam), anti-inflammatories, statins, oestrogens, omega-3 fatty acid, vitamin E, vitamin C, NADH, trace elements, mainly because these substances are cheaper than antidementia drugs (Mimica 2007). Even though three antidementia drugs (donepezil, rivastigmine, memantine) are registered in the Republic of Croatia (Mimica 2009), these drugs are unavailable for majority of PWD, because they are not on reimbursement list (Bencarić 2009).

PWD in Croatia and their carers are not satisfied with current situation because all European countries

surrounding Croatia and in the region, have reimbursement policy for antidementia drugs (including Slovenia, Serbia, Albania). According to 2006 data in European Union, only Bulgaria and Malta do not reimburse antidementia drugs (World Health Organization 2004).

Importance of national AD associations in management of AD

National AD associations in management of AD are very important. The Alzheimer Disease Societies Croatia (ADSC) was founded in Zagreb in 1999. ADSC does not have paid staff and the whole work is done by volunteers (www.alzheimer.hr). The aim of ADSC is to help PWD, families and caregivers, to fight stigma, bring education to target and general population (Mimica et al. 2006b). ADSC is helping PWD by: organizing professional meetings on AD, like 3rd and 4th Croatian Congress on Alzheimer's disease with international participation which was held on Brijuni in 2006 and St. Andrew's Island near Rovinj in 2008; organizing public events for raising awareness on AD with motto "Act locally, think globally"; celebrating The World Alzheimer's Day at September 21st; raising awareness about AD through art & culture events (sculpture exhibition, painting exhibition, fashion show) (Mimica et al. 2006c).

In 2006 ADSC became a member of Alzheimer's disease International (ADI) and in 2009 of Alzheimer Europe. The main role of Croatian national Alzheimer's associations is in achieving standard treatment for PWD which is at the moment in Croatia inadequate, and to fight stigma (Mimica et al. 2009). In year 2010, from September 22 – 25, ADSC will organise 5th Croatian Congress on AD with international participation in Zadar, Croatia (www.alzheimer2010.com).

Conclusion

Currently for the treatment of cognitive deficits in PWD, only five drugs (tacrine; donepezil; rivastigmine; galantamine and memantine) are approved by the FDA. Four of them are ChEIs, three of them are approved for the treatment of mild to moderate AD and one of them for treatment of all three stages of AD. Among above mentioned antidementia drugs, in Croatia, till now, only three - donepezil (Aricept; Aricept Evess; Donepezil Pliva; Yasnal), rivastigmine (Exelon Patch) and memantine (Ebixa; Memantin Pliva) are registered, but not on the reimbursement list of the Croatian Institute for Health Insurance. Thus, these drugs have relatively high cost which makes them almost unavailable to patients. Even though Croatian algorithm for psychopharmacological treatment of AD, done by the Croatian Association for Clinical Psychiatry, exists and suggests which antidementia drug should be given in particular stage of AD, these patients are more often prescribed alternative or adjuvant treatment only (i. e. ginkgo biloba; nootropics; statins; nonsteroidal anti-inflammatory drugs; omega-3 fatty acids; vitamins; NADH; trace elements; etc.). Because of mentioned difficulties with prescribing antidementia drugs the majority of PWD are not adequately treated in Croatia.

The national and world clinical Guidelines for treatment of AD should be implemented in Croatia. The ADSC recommendations for management of AD should be accepted, because AD is a world health priority in 21st century.

We strongly believe that antidementia drugs, which are registered in Croatia, will soon be added on reimbursement list and that PWD in Croatia will be adequately treated.

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