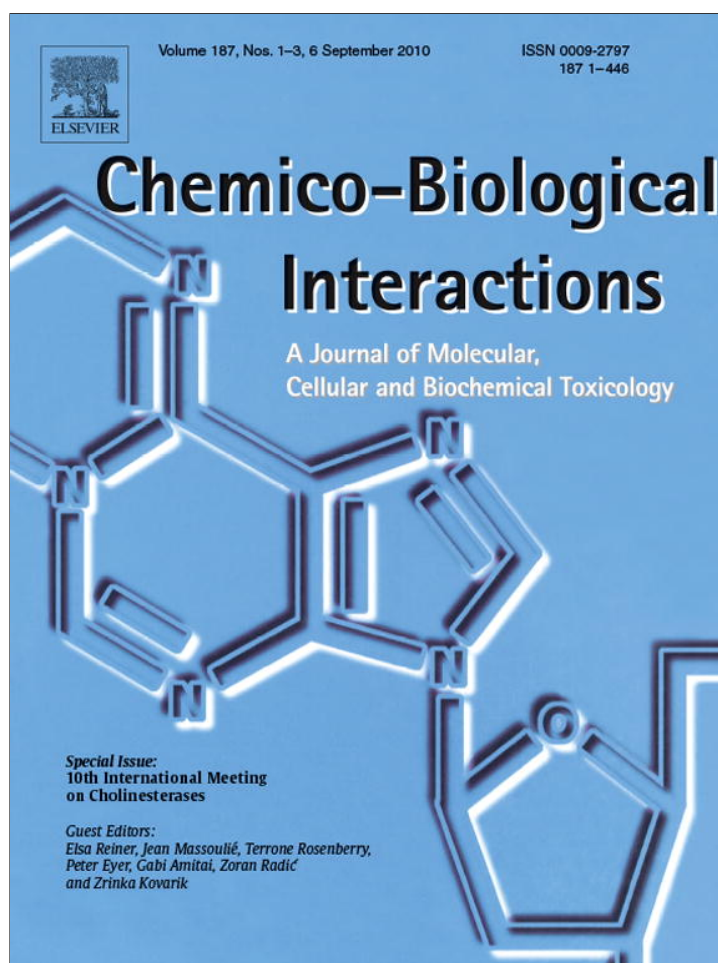


Provided for non-commercial research and education use.
Not for reproduction, distribution or commercial use.



This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

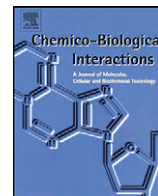
In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/copyright>



Contents lists available at ScienceDirect

Chemico-Biological Interactions

journal homepage: www.elsevier.com/locate/chembioint

Current treatment options for people with Alzheimer's disease in Croatia

Ninoslav Mimica^{a,b,*}, Paola Presečki^c^a Psychiatric Hospital Vrapče, Bolnička cesta 32, HR-10090 Zagreb, Croatia^b School of Medicine, University of Zagreb, Šalata 3b, HR-10000 Zagreb, Croatia^c Psychiatric Hospital Sveti Ivan, Jankomir 11, HR-10090 Zagreb, Croatia

ARTICLE INFO

Article history:

Available online 20 March 2010

Keywords:

Alzheimer's disease
Antidementia drugs
Cholinesterase inhibitors
Croatia
Dementia

ABSTRACT

About 16% of the population in Croatia is older than 65 years. Croatia has no register of persons with dementia (PWD), but based on a calculation that 10% of persons over 65 years are affected by dementia, the approximate number of PWD would be 80,000, the majority being patients with Alzheimer's disease (AD). Psychogeriatric departments exist in hospitals, but there are almost no nursing homes and an insufficient number of daily care centres for PWD. Antidementia drugs registered in Croatia are donepezil, rivastigmine and memantine. Clinical studies of new antidementia drugs have been conducted in Croatia since 1989. At present, studies of several antidementia drugs are underway at different testing stages.

© 2010 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

In 2001, Croatia had 4,437,460 inhabitants and 15.7% were older than 65 years [1,2]. The same source of information registered 1455 persons between 95 and 108 years of age. In the database of the Croatian Institute for Health Insurance, 806,070 persons older than 65 years were registered in December 2006 [3]. The newest estimate for the Croatian population, from July 2009, is 4,489,409 [4]. Life expectancy at birth is estimated to be 79 years for the female population and 72 years for the male population [4].

Demographic trends observed over the past 5–6 decades show depopulation, and the overall population getting older [5]. An extrapolation of these data to the year 2050 predicts 26.2% of people older than 65 years [6]. The above data place Croatia among the oldest populations among European countries [7].

Croatia has no register of persons with dementia (PWD). If 10% of people above 65 years of age are affected by dementia [3], the number of PWD would be about 80,000, the majority being patients with Alzheimer's disease (AD) [8]. It is assessed that up to 15,000 PWD live in Zagreb [8], the capital of Croatia.

2. Institutional care for people with dementia

The first Psychogeriatric Department in Croatia was established within the Psychiatric Hospital Vrapče in Zagreb in 1959 [9]. The

hospital is the oldest and largest psychiatric hospital in Croatia; it has been working continuously for 130 years. There are currently several psychiatric hospitals with psychogeriatric departments: another one in Zagreb (Sveti Ivan) and one close to Zagreb (Popovača), one on the Adriatic coast (Lopača near Rijeka), and there are two on the islands of Rab and Ugljan. Croatia, however, has only a few small private nursing homes and several daily care centres for PWD [10].

It is not known when the term "Alzheimer's disease" (AD) was first used for diagnosis in Croatia. However, it is known that the diagnosis of AD was not at all or very rarely used until 1978, and patients with AD were referred to as pre-senile dementia [11]. At the end of 1978, the International Classification of Diseases (ICD-9) [12] became the official classification in Croatia and since then the diagnosis of AD became gradually more often applied.

National associations for Alzheimer's disease have a very important role in AD management of all PWD [13]. The Alzheimer Disease Societies Croatia (ADSC) was founded in Zagreb in 1999 [14], and is functioning on an exclusively voluntary basis [15]. In 2006, ADSC became a member of Alzheimer's Disease International (ADI), and in 2009 of Alzheimer Europe [16].

3. Pharmacological treatment of people with Alzheimer's disease

Five drugs are currently approved by the United States Food and Drug Administration (FDA) for the treatment of PWD. These are tacrine, donepezil, rivastigmine, galantamine and memantine. All but one (memantine) are cholinesterase inhibitors [17,18]. All five drugs are recommended for use in Croatia, but only three are registered in Croatia: donepezil (Aricept; Aricept Evess; Donepezil

* Corresponding author at: Psychiatric Hospital Vrapče, University Department of Psychiatry, Bolnička cesta 32, HR-10090 Zagreb, Croatia. Tel.: +385 1 3780 681; fax: +385 1 3780 683.

E-mail addresses: ninoslav.mimica@bolnica-vrapce.hr, nino.mimica@gmail.com (N. Mimica).

Pliva; Yasnal), rivastigmine (Exelon Patch) and memantine (Ebixa; Memantin Pliva) [19]. However, none of the three is on the reimbursement list of the Croatian Institute for Health Insurance [20]. Due to the high cost of these drugs, the majority of PWD cannot afford to buy these drugs and are taking supportive, adjuvant or alternative medications instead. These are ginkgo biloba, nootropics (piracetam), anti-inflammatories, statins, oestrogens, omega-3 fatty acids, vitamins E and C, nicotinamide adenine dinucleotide (NADH) and trace elements [10].

The Croatian algorithm for psychopharmacological treatment of AD was introduced in 2006. Donepezil constitutes the first-line pharmacotherapy for mild and moderate cognitive deficits. If the response is low, rivastigmine and galantamine are the second-line therapy. If the answer is low again, adding memantine is recommended. In cases of severe dementia, the recommended first-line is memantine augmented by donepezil. If the effect to the combined memantine/donepezil therapy is low, application of rivastigmine or galantamine is recommended [21].

Clinical studies of new antidementia drugs have been conducted in Croatia since 1989, and some PWD participating in these studies benefit directly from them. The trials began with pentoxifylline [22–24] and continued with propentofylline, donepezil, phenserine-tartrate and EVP-6124. Clinical trials will include some novel potential antidementia agents in the near future. Some are based on the cholinergic hypothesis and combine acetylcholinesterase and serotonin reuptake inhibition (BGC20-1259) or acetylcholinesterase and monoamine oxidase inhibition (ladostigil), others belong to the field of passive immunotherapy (bapineuzumab).

4. Conclusions

The predicted world-wide increase in the incidence of dementia, particularly of Alzheimer's disease, is likely to occur also in Croatia, so a better preparedness for the care of PWD is certainly required.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

References

- [1] www.dzs.hr/hrv/censuses/census2001/census.htm.
- [2] S. Tomek Roksandić, E. Žuškin, Z. Duraković, N. Smolej-Narančić, J. Mustajbegović, J. Pucarín-Cvetković, M. Mišigoj Duraković, J. Doko Jelinić, N. Turčić, M. Milošević, Human lifespan: to live and outlive 100 years, *Arh. Hig. Rada Toksikol.* 60 (2009) 375–386 (in Croatian, summary in English).
- [3] Z. Pecotić, D. Perkov, Alzheimer's Dementia, second revised edition, Hrvatska udruga za Alzheimerovu bolest, Zagreb, 2007 (in Croatian).
- [4] www.cia.gov/library/publications/the-world-factbook/geos/hr.html.
- [5] A. Wertheimer-Baletić, Croatian demography, in: Z. Duraković (Ed.), Geriatrics. Medicine of Old Age, C.T.-Poslovne informacije, d.o.o, Zagreb, 2007, pp. 581–588 (in Croatian).
- [6] United Nations, Population Division, World Population Prospects, The 1998 Revision, Vol. II: Sex and Age, United Nations, Population Division, New York, 2000.
- [7] V. Folnegović-Šmalc, Alzheimer's disease, *Medix* 13 (2007) 147–149 (in Croatian).
- [8] N. Mimica, M. Dajčić, V. Ivanković, Z. Pecotić, G. Šimić, A. Vidas, Alzheimer disease societies Croatia, *Lijec. vjesn.* 128 (Suppl. 1) (2006) 170–171 (in Croatian).
- [9] Z. Pecotić, M. Štengl-Martinjak, Psychiatric Hospital Vrapče–Zagreb: Department for Psychogeriatrics, in: N. Mimica, V. Jukić (Eds.), Book of Posters by Professionals of Psychiatric Hospital Vrapče 1978–2006, Psihijatrijska bolnica Vrapče, Zagreb, 2006, pp. 158–159 (in Croatian).
- [10] N. Mimica, Contemporary treatment and care for people with Alzheimer's disease and Croatian reality, *Period. Biol.* 109 (Suppl. 2) (2007) 42–44.
- [11] World Health Organization, International Classification of Diseases, Eighth Revision, vol. 1, Savremena administracija, Beograd, 1968 (in Serbo-Croatian).
- [12] World Health Organization, International Classification of Diseases and Related Health Problems, Ninth Revision, vol. 1, Institut za dokumentaciju zaštite na radu, Niš, 1978 (in Serbo-Croatian).
- [13] www.alzheimer.hr (in Croatian).
- [14] N. Mimica, M. Dajčić, V. Ivanković, Z. Pecotić, G. Šimić, A. Kačanski Vidas, P. Presečki, Alzheimer Disease Societies Croatia, in: 22nd Conference of Alzheimer's Disease International, Abstracts, October 12–14, 2006, Berlin, Germany, 2006, pp. 102–103.
- [15] N. Mimica, G. Šimić, K. Grbić, E. Novy-Radonić, V. Ivanković, M. Dajčić, Z. Pecotić, A. Vidas Kačanski, Raising awareness of Alzheimer's dementia, *Clin. Neuropathol.* 25 (Suppl. 6) (2006) 303–304.
- [16] N. Mimica, G. Šimić, M. Dajčić, M. Mladinov, M. Treščec-Ivičić, E. Novy-Radonić, K. Glamuzina, Alzheimer's disease and stigma fight in Croatia, in: 24th Conference of Alzheimer's Disease International, Programme and Abstracts Handbook, March 25–28, 2009, Singapore, 2009, p. 68.
- [17] E. Giacobini, G. Pepeu (Eds.), The Brain Cholinergic System in Health and Disease, Informa Healthcare, London, 2006.
- [18] N. Mimica, P. Presečki, Side effects of approved antidementives, *Psychiatr. Danub.* 21 (Suppl. 1) (2009) 108–113.
- [19] L. Bencarić, Croatian Drug Registry, 52nd ed., Udruga poslodavaca u zdravstvu, Zagreb, 2009 (in Croatian).
- [20] L. Bencarić, List of Drugs of Croatian Institute for Health Insurance, Udruga poslodavaca u zdravstvu, Zagreb, 2009 (in Croatian).
- [21] V. Folnegović-Šmalc, N. Mimica, G. Makarić, R. Varda, A. Silić, Croatian therapeutic algorithm for treatment of Alzheimer's disease, *Neurol. Croat.* 55 (Suppl. 4) (2006) 38.
- [22] V. Folnegović-Šmalc, N. Mimica, G. Makarić, V. Loos, B. Kittner, N. Mimica, Rating scales and computed tomography in multi-infarct dementia, *Neurol. Croat.* 41 (1992) 183–190.
- [23] V. Folnegović-Šmalc, B. Kittner, G. Makarić, N. Mimica, The use of measurement scales to diagnose and assess the psychic condition of pentoxifylline-treated MID cases, in: 15th Danube Symposium of Psychiatry, Abstracts, October 7–10, 1992, Regensburg, Germany, 1992, p. 130.
- [24] V. Folnegović-Šmalc, B. Kittner, G. Makarić, N. Mimica, M. Rößner, Pentoxifylline treated MID patients; results of a European double-blind placebo-controlled multicentre study, in: 26th Danube Symposium for Neurological Sciences, Abstracts, September 30–October 2, 1993, Innsbruck, Austria, 1993, p. 19.