

## ORIGINAL ARTICLE

# Alzheimer's disease: cost cuts call for novel drugs development and national strategy

## Alzheimerova nemoc: význam nových léků a národní strategie pro snížení nákladů na léčbu

Petra Marešová • Blanka Klímová • Kamil Kuča

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### Souhrn

Duševní zdraví ovlivňuje kvalitu života velkého počtu osob a jejich rodinných příslušníků. V současné době činí celosvětově náklady na péči o lidi trpící demencemi více než 1 % hrubého domácího produktu (HDP). V budoucnu se předpokládá nárůst těchto výdajů zejména s ohledem na fakt, že populace vyspělých zemích stárnou a je prokázáno, že demence úzce souvisí se zvyšujícím se věkem. Je zřejmé, že vlády budou nuceny vyčlenit příslušné finanční, materiální a lidské zdroje na léčbu a péči o tyto pacienty. Cílem příspěvku je specifikovat současný stav v oblasti léčby a péče o pacienty trpící Alzheimerovou chorobou a analyzovat přímé a nepřímé náklady související s touto problematikou. Kromě toho je pozornost věnována problematice přístupu vlád a existence strategických plánů v oblasti Alzheimerovy choroby, které by řešily všechny související aspekty včetně investic do výzkumu vývoje léků. V současné době neexistuje léčba, která by uspokojivým způsobem zlepšovala stav těchto pacientů, a to zejména v časně fázi, stejně jako v České republice neexistuje žádný dobře fungující národní strategický plán.

**Klíčová slova:** Alzheimerova choroba • náklady • léčba • strategický plán

### Summary

Mental health affects the quality of life for a large number of individuals and family members. Currently, globally costs for people with dementia amount to more than 1% of gross domestic product (GDP). In the future, the growth of expenditure is expected with regard to the fact that the population of developed countries is aging and the dementia is closely associated with increasing age. It is evident that governments have to allocate adequate financial, material and human resources to address a health problem on this scale. The purpose of this article is to explore the current state of treatment and care of patients suffering from Alzheimer's disease (AD), analyze direct and indirect health care costs resulting from this disease. In addition, the authors of this article draw attention to the implementation of a strategic plan which would handle all the aspects of AD, including the research of drugs development since nowadays there are not still many drugs which would improve AD patients' state, particularly in the early phases, as well as there does not exist any well-functioning national strategic plan in the Czech Republic which would bring a radical improvement in reducing the effects of AD.

**Key words:** Alzheimer's disease • costs • treatment • strategic plan

### Introduction

The aging population is the most characteristic feature of the demographic trend in the developed countries. This demographic trend seems to continue in future years<sup>1)</sup>. By 2050 the demographic weight of Europe in the world will have diminished by more than two thirds. As for the population of the 27 member EU, today, at 492.3 million, it represents 7.4% of the world population (6,624 millions). Whilst the demographic importance of Europe may seem to be decreasing ineluctably, bearing in mind its low birth rate, one of the biggest challenges facing the

Ing. Mgr. Petra Marešová, Ph.D. (✉) • B. Klímová  
University of Hradec Králové  
Faculty of Informatics and Management, Department of Economics  
Rokitanskeho 62, 500 03 Hradec Králové, Czech Republic  
e-mail: petra.maresova@uhk.cz

K. Kuča  
University of Hradec Králové, Center for Basic and Applied Research  
University Hospital Hradec Králové, Biomedical Research Center,  
Hradec Králové

Union today is not this decline in numbers but the aging of its population<sup>2</sup>). According to Eurostat's latest set of population, projections were made till 2080. EU-28's population is expected to increase to 520 million by 2080. As a result of the population movement between age groups, the EU-28's old-age dependency ratio is projected to almost double from 27.5 % in 2013 to 51.0 % by 2080. The total age dependency ratio is projected to rise from 51.1 % in 2013 to 77.9 % by 2080<sup>3</sup>). Figure 1 illustrates the development of population at the age of 80 and above at all continents by 2100.

According to these data, the average economic burden on a patient increases with increasing age and the cost of treatment rises with medical progress. There is a synergy effect of ageing population and increasing costs of treatment, which might together cause an increased share of treatment costs around the year 2050<sup>4</sup>). The most frequently mentioned diseases in old age include dementia.

The treatment of dementia is a significant economic problem. The International Association for Alzheimer's disease (ADI) has computed that on a global level, 13 percent of people older than 60 years needed long-term care, which is 101 million people worldwide<sup>5</sup>). Treatment costs will rise in the future, not only because of the larger number of patients, but also due to the fact that more and more of them will be dependent on institutional care. Now mostly family members, who are doing it for free or with a small contribution, take care of people impaired by Alzheimer's disease. More than two-thirds of persons suffering from Alzheimer's disease stay at home, being taken care after by family and friends. Their illness has a significant impact on their families. As the disease advances, symptoms include confusion, irritability and aggression, mood swings, language breakdown, long-term memory loss, and the general withdrawal as senses decline. Gradually, bodily functions are lost<sup>6</sup>). The disease diminishes patients' independence in Activities of Daily Living (ADL) and quality of life (QoL)<sup>7</sup>.

Unfortunately, nowadays, there are not still many drugs which would improve AD patients' state as well as not a well-functioning national strategic plan which would bring a radical improvement in reducing the effects of AD<sup>8,9</sup>). Therefore, the aim of this article is to explore the current state of treatment and care of patients suffering from Alzheimer's disease (AD), analyze direct and indirect health care costs resulting from this disease and draw national government's attention to the implementation of a strategic plan which would handle all the aspects of AD, including the research of drugs development.

## Methods

For the purpose of this article a method of literature search of available sources describing direct and indirect costs of AD disease and a method of comparison of these costs are used to illustrate a necessity of further research and investment into this disease, particularly during its early stages.

## The costs of Alzheimer's disease

A major problem in the developed countries in future years will be the reimbursement of treating AD. The costs in this case involve the price of all goods and services that are invested to prevent, diagnose, treat and otherwise deal with dementia. Individuals, families and carers are influenced not only economically but also in terms of quality of life. Total costs consist of direct costs (containing hospital resources, medical services, drugs, social services, family payments to formal carers) and indirect costs (for instance, a loss of patient income and losses or restrictions even limitations for family members or carers). Finally, some literature defines intangible costs as those related to pain or deterioration of patient and caregivers' quality of life.<sup>10</sup>

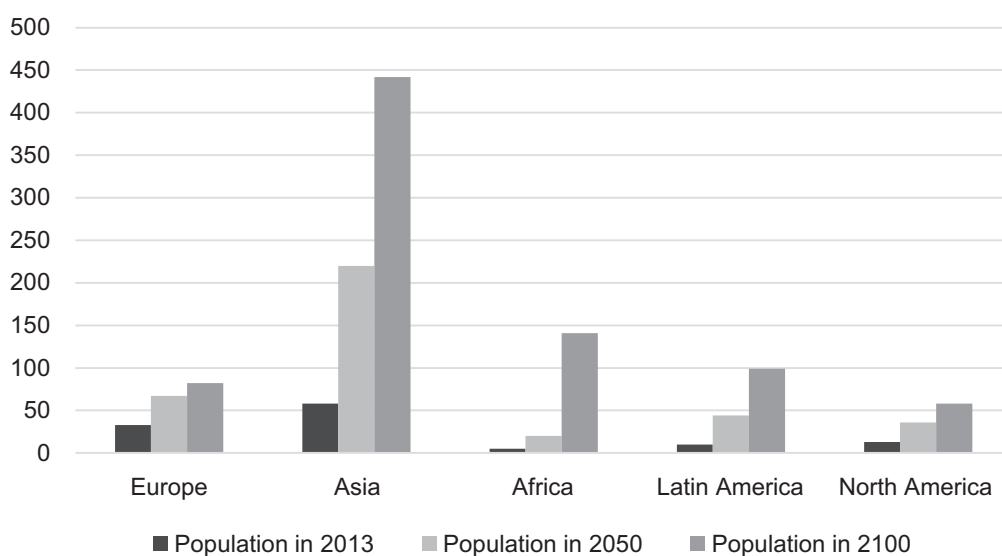


Fig. 1. Population 80+ development in the years of 2013 to 2100

Source: own according to OECD database

**Direct costs**

Research studies specifying costs of AD treatment according to individual phases<sup>11–13</sup>. Table 1 below shows a comparison of treatment costs in three chosen EU countries which are selected on the basis of a similar system of health care financing and at the same time the studies which enable mutual comparison of costs in individual phases of AD. Attention is also paid to the currency of data, whose period is five years at maximum. Thus, the oldest study dates back to 2011. The costs are calculated in the same variable: Total monthly costs- mean (EUR).

The British study by Getsios et al. (2012)<sup>11</sup> estimates average assessment costs of 5,176 EUR per one diagnosed patient (2007 annual costs). In comparison with the scenario without the early diagnosis or pharmacologic treatment, the early diagnosis reduces health care costs by 4,545 EUR per patient and societal costs by 9,784 EUR. Savings are also significant with respect to the treatment without the early diagnosis, which makes 1,663EUR in

health care costs, and 7,196 EUR in societal costs. In the probabilistic sensitivity analysis, the early diagnosis leads to savings or is highly cost-effective in the majority of cases. Similarly, in Germany this research was performed by Schwarzkopf et al. (2011)<sup>12</sup>. The generalized linear mixed model confirmed that costs of care rose with progressing dementia. The early diagnosis has significant up-front costs; on the other hand, it can save costs and brings health benefits compared with no treatment or treatment in the absence of the early diagnosis<sup>14</sup>.

At present there are altogether 81 compounds in all phases of AD, ranging from the preclinical phase to phase 4 which includes only four approved drugs<sup>15</sup>. Research studies<sup>16–20</sup> compare costs between these four existing drugs and QALYs. A full table of all key clinical effectiveness estimates, modelled quality-adjusted life years (QALYs), modelled costs and incremental cost-effectiveness ratios (ICERs).

Table 2 below summarises the findings emphasising changes in evidence.

Table 1. Direct costs of Alzheimer disease in chosen European countries according to the dementia stage

	Dementia stage	Total monthly cost-Mean (EUR)	Study (source)
<b>France</b>	Mild (proxy good method)	1,454	Gervès et al. (2014) <sup>9</sup>
	Moderate/severe (proxy good method)	3,373	
	Mild (opportunity cost method)	1,823	
	Moderate/severe (opportunity cost method)	4,288	
<b>Germany</b>	Mild	3,331	Schwarzkopf et al. (2011) <sup>10</sup>
	Moderate	5,233	
<b>United Kingdom</b>	Total direct costs of care (medical and non medical)	1,690	Getsios et al. (2012) <sup>11</sup>

Source: own processing according to<sup>11–13</sup>

Table 2. Summary of cost-effectiveness for drugs for AD relative to BSC

		Findings 2004	Findings 2010
<b>Donepezil versus BSC</b>	Incremental QALYs	0.036	0.035
	Incremental Costs (donepezil – BSC)	€ 3,97	-€ 807,91
	ICER	€ 111,21 per QALY	Donepezil cheaper and more beneficial ('dominates BSC')
<b>Galantamine versus BSC</b>	Incremental QALYs	0.039	0.033
	Incremental Costs (donepezil – BSC)	€ 3,63	-€ 851,88
	ICER	€ 93,48 per QALY	Galantamine cheaper and more beneficial ('dominates BSC')
<b>Rivastigmine versus BSC</b>	Incremental QALYs	0.037	0.029
	Incremental Costs (donepezil – BSC)	€ 2,91	-€ 733,71
	ICER	€ 79,67 per QALY	Rivastigmine cheaper and more beneficial ('dominates BSC')
<b>Memantine versus BSC</b>	Incremental QALYs	Not reported	0.013
	Incremental Costs (donepezil – BSC)	Not reported	€ 556,47
	ICER	€ 50838–72822 per QALY	€ 44,10 per QALY

Source: own processing according to<sup>16</sup>

Table 2 indicates that there was the least additional information concerning the clinical effectiveness of donepezil between 2004 and 2010. The new review confirmed there were statistically significant benefits or trends towards benefit across all the main outcomes. Similarly with rivastigmine there was new evidence<sup>17-19</sup>, and the additional trials contributed across most of the outcomes. Again this led to quantified and much more precise estimates of effect on cognition, function and global impact, leading to much greater confidence about the beneficial effect of rivastigmine. Furthermore, this benefit occurred with the drug in the form of patches as well as tablets. With memantine there was also new evidence, with one new trial randomising 350 patients contributing across most outcomes<sup>20</sup>. An important general observation was that there was no new clinical effectiveness evidence on the impact on rates of, or time to institutionalisation. There were also changes in the evidence on cost effectiveness which were more marked than the changes in evidence on effectiveness. All drugs were more cost-effective compared with BSC than previously thought.

From the studies describing the costs in the individual phases of AD, effectiveness and impacts of the existing drugs, it is clear that investments into drugs development are highly important<sup>21</sup>. In case that drugs prolong the first phase of AD, there are considerable savings of costs, which leads to the reduction of health care system burden but also to the improvement of patients' quality of life.

#### Indirect costs on caregivers

In addition, there are indirect costs on caregivers, particularly family members, whose caregiving burden increases with respect to the worsening of cognitive impairment of AD the patient<sup>22</sup>. Currently, there are about nine million family caregivers who assist their loved ones suffering from AD or a related dementia<sup>23</sup>. The role of these informal caregivers is particularly common in the Czech Republic where family is still the first informal caregiver in the health system. These informal caregivers are mostly middle aged people with a lot of other responsibilities. Sometimes, they even give up their jobs in order to help their loved ones. Furthermore, besides losing their regular income, they often lose their relationship, free time and eventually, they end up in social isolation. This consequently affects their health as well. They usually have sleep problems and behavioural disorders<sup>22</sup>. As research studies<sup>23-27</sup> confirm the life of these caregivers is seriously modified by physical, emotional, financial and social overload.

Nowadays, there exist research studies, such as Van Durme, Macq, Jeanmart, & Gobert, (2011)<sup>28</sup>, which provide assessment scales that identify the above mentioned negative impacts of caregiving on the caregiver's life and suggest timely interventions to reduce burden. These interventions might include different types of help. The most radical, on the one hand, for family caregivers, mainly spouses<sup>26</sup>, is institutionalization, but on the other hand, it results in great relief after some time. Daily centres, secondary caregivers coming to AD patients' homes or psychological therapies via the Internet can be also a timely solution to reduce burden of family caregivers.

#### Discussion

Thus, each national government (see Table 3), including the Czech Republic, should develop its strategic plan on dealing with all aspects (economic, political, and social) of Alzheimer's disease. These governments worldwide could follow the core principles for the advancement of the clinical delivery of care and scientific understanding of AD and related disorders which were set at the War Invitational Summit in the USA in 2012. These principles focus on the following needs<sup>29</sup>:

- integrate, but not duplicate services, resources, and research, including building on existing infrastructure where appropriate (e.g., resources available across different institutes such as the National Institutes of Health or Centres for Disease Control);
- shift resources and care delivery to the community and home, providing *one stop shopping* that incorporates both medical and social interventions along with research and training to improve the lives of people with AD and their families;
- increase awareness among the public, health care providers, and policy makers;
- deliver cost effective diagnostics, treatments and services;
- engage patients, family caregivers, and advocacy groups in the decision-making process;
- focus on affected persons and their families across the trajectory of AD disease; this requires a better understanding of the natural history of the disease and effects of multi-morbidity;
- focus on drug development and biomarker research towards the aim of reducing the incidence and progression of dementia; and
- ensure that dementia is a priority across all segments of societies and governments both nationally and internationally.

Table 3. An overview of countries with or without a functioning national strategic plan for AD

Countries with a national plan	Countries with a national plan under preparation	Countries with a different plan	Countries without any plan
Belgium, Denmark, Finland, France, Luxembourg, Netherlands, Norway, Greece, Sweden, Switzerland, Great Britain	Bulgaria, Czech Republic, Ireland, Italy, Cyprus, Portugal, Austria, Slovenia	Spain	Croatia, Iceland, Germany, Poland, Rumania, Turkey

Source: own processing according to<sup>38</sup>

In order to meet the above described needs and to overcome certain barriers (e.g., underfunding, a lack of validated therapeutic targets and animal models, or a lack of technical infrastructure in areas such as bioinformatics and gene expression), co-investment by public and private sector stakeholders is needed. In addition, a clear consensus among the experts in industry and academia is a must<sup>30–32</sup>.

As Karran (2012)<sup>33</sup> states at an example of UK, governments should establish a national dementia research strategy, with long-term, protected funding, and a lasting commitment to dementia research since there has been a crisis in the development of novel drugs for AD patients<sup>32</sup>. In fact, as Cummings, Morstorf and Zhong (2014) claim, no new treatments have been approved for AD since 2003<sup>34</sup>.

Nowadays, as it has been already mentioned, there are only four core drugs which have been successfully clinically tested and publically used for AD treatment. Those are: the cholinesterase inhibitors (ChEI) donepezil, rivastigmine and galantamine for mild to moderate AD, and memantine (an NMDA receptor antagonist), and they can accommodate moderate to severe AD. In addition, all these four compounds have proved to considerably improve patients' reported outcomes, that is, cognition, memory, communication and the ability to perform daily activities, which undoubtedly affect health-related quality of life (QoL). Therefore substantial improvements in drug discovery and clinical development methods are needed (cf. Schneider et al., 2014)<sup>35</sup>.

Furthermore, researchers claim there must be the collaborative efforts of the research, clinical, pharmaceutical, and regulatory communities, as well as policy makers, to identify barriers and solutions at each stage of drug development. There also exists share recognition of the complexity of the disease, the likelihood that multiple treatments are required at different stages of this disease and that more than one drug is needed. For example, several novel strategies for AD treatment are proposed – vaccination and immunization, use of modulators of secretases or use of statins (cf. Zemek et al., 2014; or Korabecny et al., 2014)<sup>36, 37</sup>.

## Conclusion

The literature review and conducted comparisons show that the detection of AD patients in the initial stage of the outbreak of this disease is very desirable from an economic point of view because the costs of the day care in comparison with the institutionalization care are much lower<sup>7</sup>. Therefore, as it has been stated several times above, there is an urgent call for the development of novel drugs and a well-functioning national strategic plan which could significantly contribute to the cost cuts in the first phases of this disease, but which would also substantially reduce caregivers' burden and contribute to the improvement of AD patients' lives.

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