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# HOW MUCH IS THE COST OF MULTIPLE SCLEROSIS – SYSTEMATIC LITERATURE REVIEW

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## ABSTRACT

In Poland, a data on MS costs is lacking. **AIM.** The systematic review of cost of illness studies was conducted to estimate the average annual cost of MS patient and its breakdown.
**MATERIAL AND METHODS.** The PubMed database was searched for relevant literature. Following search criteria were used: "multiple sclerosis", „costs", „cost of illness" and „disease burden". Articles written in English including total costs published 2002-2012 were included. In total 17 studies were classified. The costs were re-calculated into USD Purchasing Power Parity (PPP). The available approach from the literature was used for the cost breakdown presentation.
**RESULTS.** The average patient was 47 years old with EDSS equals 4 and 13 years from the date of diagnosis. The average annual cost was 41 133 US$ PPP. The direct costs did not exceed 70% of total costs in any study. The pharmaceutical expenses were one of the most important contributors to the direct costs. Only 40% of patients were active on the labor market what translated into the loss of productivity and consequently an increase in total costs.
**CONCLUSIONS.** The preformed systematic review revealed that multiple sclerosis imposes a huge economic burden on the healthcare system and society. It happens due to productivity loss and caregiver burden.

**Key words***: multiple sclerosis, systematic review, cost of illness*

## INTRODUCTION

Growing health needs have been putting healthcare budgets under increasing pressure all over the world. For this reason new methods of rationalising access to health services are being searched for. In order to be able to achieve optimal allocation of limited healthcare resources it is necessary to determine which groups of diseases incur the highest costs and which health services are indispensable in the treatment of particular groups of patients.

Clinical trials do not always provide an answer as to how healthcare resources should be allocated across different disease areas. This is caused by artificial circumstances in which patient is placed within a clinical trial as well as a limited follow up. In some cases the analysis of the consumption of resources during a clinical trial may not reflect actual clinical practice either. The necessary detailed assessment of the patient's medical condition during the trial may lead to administering more diagnostic tests and doctor's visits and thus incurring the so-called protocol driven costs. In such situations a cost of illness study may be conducted with alternative options, which can be grouped into two following approaches:

1. Primary – aggregation of data on the consumption of resources obtained via questionnaires and databases – the so called cost-of-illness (CoI) studies
2. Secondary – review of available publications or reports.

The present paper qualifies as the secondary approach. The cost of multiple sclerosis (MS) treatment was chosen here for analysis. MS is an autoimmunological disorder caused by a mechanism of autoaggression (1). Epidemiological data show that the prevalence of the disease ranges between 10 and 216 per 100 000 people (2). It is estimated that in the EU countries and Switzerland, Iceland and Norway there are approximately 470 000 people suffering from the disease (3). In Poland there are approximately 40 000 patients with the disease according to experts' data. Despite the fact that the existing innovative methods of treatment reduce the impact of the disease on the health of the patient, MS still remains an incurable disease.

According to the available data, MS is one of the most costly nuerological diseases (4). This is mainly due to the fact that it starts manifesting itself at a young age leading thus to significant social costs. The average onset of first symptoms of the disease is 29 years of age (2). Multiple sclerosis compromises physical and mental ability and in this way limits the professional activity of patients early in their adult lives.

There is a scarcity of data on the total cost of MS in Poland. While a cost-of-illness study was conducted over seven years ago, it did not cover patients treated with the new innovative therapies involving beta interferon, glatiramer acetate, natalizumab and fingolimod (6). This has led the author of the present paper to choose the second approach for the MS costs assessment, which is the review of the scientific literature on the subject. The aim of this review is to determine the average annual cost of MS and define its main components. The conclusions resulting from this study are intended to be the basis for recommendations for future researchers of the topic who would like to conduct an active MS cost study in Poland.

A cost-of illness study may be pursued from the perspective of the budgetholder of services or society (7). In the former approach only the healthcare budget expenditures are taken into account while the latter one takes note also of all other consequences of the disease, including the costs resulting from the loss of capacity to work.

The available knowledge on the subject demonstrates that the indirect costs rank high on the list of all MS-related expenses. For this reason the author decided to review the studies that were conducted from the social perspective.

## MATERIALS AND METHODS

A systematic review of scientific literature was carried out with the use of the Pubmed database. The keywords searched for were 'multiple sclerosis' in conjunction with 'costs', 'cost of illness' or 'disease burden'. Only English-speaking papers presenting the total cost of the disease that appeared between 2002 and 2012 were included in the analysis. 130 publications were found based on the keyword search but only 29 of them met the above criteria. A further 12 articles from this group were excluded from the study: seven of them did not collect data according to the bottom-up approach i.e. did not collect information on using different health services from the perspective of the patient but rather a top-down approach, in which data on the costs of MS was extracted from a total value concerning expenses on various diseases. In addition, three papers were excluded in which the total costs were not broken down into individual costs and two papers in which there was no data on indirect costs and treatment with modern therapies.

The approach used in the analysis of the studies was the one proposed by Zhu in a systematic review of publications on the costs of lupus erythematosus (8). This approach involves obtaining data such as the year of the study, population size, gender, average age, average duration of the disease and employment status.

The stage of disease advancement has been defined using the most popular model, which is Kurtzke's Expanded Disability Status Scale (EDSS) with a rating of 0 to 10. In EDSS the early stage of MS is defined as having a rating of below 3.5, intermediate stage – 4–7, and advanced stage – $\geq$7.5 (5).

In order to achieve comparability of results across the studies under analysis the expenses described in the studies were broken down into the same categories. The methodology used for the analysis was the one proposed by *Kobelt* et al. for the analysis of the cost of MS in Europie (9). The direct costs were thus divided into outpatient care, inpatient care, medication, tests and procedures and orthopaedic aids. The sources of indirect costs identified were productivity loss and informal care.

## RESULTS

The final analysis included two studies from each of the following countries: the UK (10, 11) Germany (12, 13) and Spain (14, 15) and single studies from Austria (16), Switzerland (17), Sweden (18), Norway (19), Denmark (20), Italy (21), Belgium (22), the Czech Republic (23), the USA (24), the Netherlands (25) and Australia (26).

All studies were retrospective and were based on a questionnaire. Only the Danish study used data on the consumption of healthcare resources stored in a patient register (20). In most cases the follow up period did not extend beyond 3 months. Only questions concerning inpatient care covered usually 12 months.

The number of patients differed significantly across studies. The largest number of subjects were analysed in the study by *Jennum* et al. from Denmark (2) – 10 849 and the smallest number was covered by the study by *Taylor* (26) – 100. The profile of the average subject as far as their age and duration of the disease are concerned differed to a large extent between the studies (table 1). The average patient was 47 year old and the actual ages ranged between 38 and 54. The mean duration of the disease was 13 years and it ranged between 7 and 19. The mean EDSS rating was 4. The systematic review covered six studies involving patients in the early stage of MS and seven studies involving patients in the inter-

Table I. Characteristics of included studies

| | Author/year | Country | No of subjects | Women, % of total | mean age | mean disease duration | mean EDSS | % of employed | absentism % of resp | early retirenmet due to MS | % patients on MS treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Taylor B, 2007 | Australia | 100 | 0.67 | 49 | 10 | - | 0.28 | - | 0.02 | - |
| 2 | Kobelt G,2006 | Austria | 1,019 | 0.70 | 50 | 15 | 4.4 | 0.30 | 0.25 | - | - |
| 3 | Kobelt G, 2006 | Belgium | 799 | 0.68 | 48 | 13 | 3.9 | 0.40 | 0.60 | 0.33 | 0.50 |
| 4 | Dusankova,2012 | Czech Rep | 909 | 0.73 | 41 | 8 | 3.4 | 0.42 | - | 0.47 | 0.41 |
| 5 | Jennum, 2012 | Denmark | 10,849 | 0.66 | 48 | - | - | 0.39 | - | - | - |
| 6 | Reese , 2011 | Germany | 144 | 0.68 | 42 | 7 | 3.5 | 0.52 | 0.17 | 0.35 | 0.60 |
| 7 | Kobelt G,2006 | Germany | 2,973 | 0.72 | 45 | 13 | 3.8 | 0.41 | 0.11 | 0.37 | 0.50 |
| 8 | Kobelt G,2006 | Italy | 921 | 0.66 | 46 | 12 | 4.6 | 0.42 | 0.53 | 0.33 | 0.43 |
| 9 | Kobelt G, 2006 | Netherlands | 1,549 | 0.69 | 47 | 10 | 3.9 | 0.38 | - | 0.42 | 0.35 |
| 10 | Svendsen, 2012 | Norway | 526 | 0.65 | 38 | - | 4.3 | 0.34 | 0.14 | 0.50 | 0.25 |
| 11 | Kobelt G,2006 | Spain | 1,848 | 0.64 | 45 | 11 | 4.5 | 0.30 | 0.05 | - | 0.52 |
| 12 | Casado, 2006 | Spain, Catalonia | 200 | 0.65 | 42 | 12 | 2.7 | - | - | - | 0.68 |
| 13 | Berg J, 2006 | Sweden | 1,339 | 0.73 | 53 | 14 | 5.1 | 0.40 | 0.25 | 0.36 | 0.43 |
| 14 | Kobelt G,2006 | Switzerland | 1,101 | 0.64 | 53 | 17 | 5 | 0.35 | 0.05 | 0.36 | 0.38 |
| 15 | Kobelt G,2006 | UK | 2,048 | 0.75 | 51 | 19 | 5.1 | 0.28 | 0.12 | 0.43 | 0.21 |
| 16 | McCrone, 2008 | UK | 1,942 | 0.72 | 54 | 15 | - | 0.18 | 0.08 | - | 0.37 |
| 17 | Kobelt G,2006 | USA | 1,909 | 0.76 | 49 | 13 | - | 0.40 | - | 0,31 | 0.94 |
| | | **Average** | **1,767** | **0.69** | **47** | **13** | **4** | **0.36** | **0.21** | **0.36** | **0.47** |

Source: based on own preparation

Tabela II. Mean annual cost per MS patient in US$ PPP

| | Author/year | Country | Total cost (US$ PPP) | Direct costs | | | | | | Indirect costs | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Total | Out-patient visits | Inpatient visits | MS drugs | Tests, procedures | Aids, adaptation | Total | Productivity loss | Informal care |
| 1 | Kobelt G,2006 | UK | 49,055 | 0.18 | 0.06 | 0.06 | 0.05 | 0.00 | 0.02 | 0.81 | 0.34 | 0.48 |
| 2 | Jennum, 2012 | Denmark | 13,921 | 0.24 | 0.02 | 0.16 | 0.05 | - | - | 0.76 | 0.76 | - |
| 3 | McCrone, 2008 | UK | 37,221 | 0.32 | 0.11 | 0.03 | 0.08 | 0.00 | 0.10 | 0.68 | 0.37 | 0.31 |
| 4 | Kobelt G,2006 | Italy | 49,171 | 0.33 | 0.05 | 0.07 | 0.12 | 0.02 | 0.07 | 0.67 | 0.30 | 0.37 |
| 5 | Svendsen, 2012 | Norway | 53,813 | 0.39 | 0.05 | 0.10 | 0.07 | - | 0.17 | 0.61 | 0.61 | - |
| 6 | Kobelt G, 2006 | Netherlands | 35,027 | 0.42 | 0.06 | 0.05 | 0.16 | 0.01 | 0.14 | 0.58 | 0.46 | 0.12 |
| 7 | Kobelt G,2006 | Spain | 46,467 | 0.44 | 0.07 | 0.08 | 0.21 | 0.00 | 0.08 | 0.56 | 0.26 | 0.30 |
| 8 | Casado, 2006 | Spain, Catalonia | 33,711 | 0.44 | 0.01 | 0.00 | 0.37 | 0.01 | 0.05 | 0.57 | 0.36 | 0.21 |
| 9 | Kobelt G,2006 | Switzerland | 44,790 | 0.47 | 0.05 | 0.06 | 0.15 | 0.01 | 0.20 | 0.53 | 0.38 | 0.15 |
| 10 | Kobelt G,2006 | Austria | 47,412 | 0.48 | 0.13 | 0.11 | 0.18 | - | 0.06 | 0.52 | 0.36 | 0.16 |
| 11 | Reese , 2011 | Germany | 49,998 | 0.50 | 0.08 | 0.08 | 0.22 | 0.08 | 0.04 | 0.50 | 0.40 | 0.10 |
| 12 | Kobelt G,2006 | Germany | 51,645 | 0.52 | 0.02 | 0.08 | 0.37 | - | 0.05 | 0.48 | 0.48 | - |
| 13 | Kobelt G,2006 | USA | 47,215 | 0.53 | 0.03 | 0.03 | 0.40 | 0.02 | 0.06 | 0.47 | 0.37 | 0.10 |
| 14 | Dusankova,2012 | Czech Rep | 24,568 | 0.54 | 0.02 | 0.03 | 0.39 | 0.02 | 0.08 | 0.46 | 0.37 | 0.09 |
| 15 | Berg J, 2006 | Sweden | 54,600 | 0.60 | 0.06 | 0.10 | 0.13 | 0.00 | 0.31 | 0.40 | 0.32 | 0.08 |
| 16 | Kobelt G, 2006 | Belgium | 37,751 | 0.67 | 0.07 | 0.14 | 0.35 | 0.01 | 0.10 | 0.33 | 0.33 | - |
| 17 | Taylor B, 2007 | Australia | 22,891 | 0.70 | 0.18 | 0.05 | 0.28 | 0.05 | 0.14 | 0.30 | 0.14 | 0.16 |
| | | **Average** | **41,133** | **0.46** | **0.06** | **0.07** | **0.21** | **0.02** | **0.10** | **0.54** | **0.39** | **0.15** |

Source: based on own preparation

mediate stage of the disease. In four studies the mean EDSS was not provided.

In order to facilitate the comparison between the studies the cost of MS was converted to USD PPP. OECD data served as the basis for the conversion (27). The mean cost for one patient from studies under analysis was calculated as 41 133 USD PPP (table 2). The lowest costs were recorded in Denmark, the Czech Republic and Australia, the highest - Norway, Germany and Sweden. Productivity loss occupied the highest proportion of both indirect and total costs (Table 2). One of the main components of direct costs was MS drugs expenses. Orthopaedic aids and adaptation measures were the second largest contributors to direct costs. Tests and procedures were the least significant component of the direct costs.

In none of the countries did the direct costs exceed 70% of the total expenses. In ten cases they were lower than 50%, which was the case in England, Denmark, Spain, Italy, Switzerland, Norway and the Netherlands where the direct costs constituted the majority of the total costs. This was due to the loss of productivity. Lack of employment generated more costs than informal care. It was the case in all countries except for Italy where this proportion was exactly the opposite. All studies apart from those conducted in Germany demonstrated a tendency for the costs to grow as the disease advances.

## DISCUSSION

The literature review has revealed that MS is a disease that requires extensive expenditure at an average annual level of over 41 133 USD PPP. Indirect costs were a significant contributor to the total costs. The influence of lack of employment on the profile of MS costs is not surprising considering the early age of patients affected by this chronic disease. This is a well-identified problem in the literature (28).

As the average patient included in the studies was of working age, it is especially important to note that fewer than 52% of patients were professionally active. This figure is comparable with the one concerning the proportion of patients receiving ill-health pension benefits. In addition, it is important to mention that as many as every fifth professionally active subject revealed that they were on a sick leave at the time of the study.

The observation concerning the influence of the disease on patients' functional abilities requires special attention in the future CoI studies on MS market in Poland. Preformed descriptive analysis does not provide any basis for determining to what extent the loss of work activity was responsible for the increase in the total costs of the disease. It was interesting to observe that in countries where the share of medication expenditure in total costs was higher the percentage spent on costs of informal care was lower. This is another important aspect to be taken into account by experts intending to research the cost of MS in Poland.

## CONCLUSION

The systematic review conducted has not provided an answer to the question whether there is any relationship between the stage of the disease and its cost. The variability of data observed does not constitute suitable ground for establishing any correlation between the total treatment expenses and the proportion of patients treated.

In addition, it may be suspected that the expenditure figures in this paper are underestimated. There are two reasons for this: firstly, it is the result of the adoption of prevalence based approach, in which the focus is on the mean annual cost calculated per patient. It is important to note, however, that MS generates significant costs at the diagnosis stage of the disease. As a consequence, adopting an incidence based approach, i.e. an attempt to determine the total cost of the disease across the whole life of a patient could lead to different final conclusions.

Secondly, the patients are customarily divided into groups based on the disease progression. It is assumed that on average 50% of patients are in the early stage of the disease (EDSS $\leq$3.5), 25% are in the intermediate stage (EDSS 4–7) and 5% of patients suffer from very advanced SM (EDSS $\geq$7.5) (3).The present review included mainly those studies that involved patients from the first two categories. The costs would certainly have been different had the patients with longer time since diagnosis been included in the review as well. Statistical distribution of patients ranked according to the stage of their condition should definitely be another issue taken into account by researchers who wish to pursue empirical studies on the topic.

Given that the access to innovative treatments in Poland is still limited, one can question applicability of results the above review to the Polish circumstances. Data published in 2011 by the European Multiple Sclerosis Platform (EMSP) show that only 7% of Polish patients affected by SM receive medication that modifies the course of the disease while in the majority of European states this figure is not less than 30–40%, reaching 50% in Slovakia or 70% in Germany, Austria, Switzerland and Lithuania (29). As for the access to medication and therapy Poland ranks among the bottom three countries and is followed by Bosnia and Herzegovina and Belarus. This certainly is a factor in the size and structure of the cost of multiple sclerosis. It is worth remembering, however, that the methodology employed by EMSP is not fully clear. When researching the costs of the disease, considering the nature of special therapeutic schemes in

Poland, it is definitely worth to try to address the issue of determining the actual number of patients treated with the use of modern methods and reflect the proportion of such patients while qualifying subjects for the study.

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