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Economic Burden of Rare Diseases With Common Diseases as a Comorbidity in Poland

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Abstract

Purpose: Some of the common diseases are the comorbidities of rare diseases and they impose a considerable economic burden on the national health care system and economy. We examined the economic burden of a rare disease (tuberous sclerosis complex – TSC) in Poland and its comorbidities (common diseases – epilepsy and status epilepticus) while taking into account a sensitivity analysis.
Design/Methodology/Approach: This study is a prevalence-based top-down cost of illness study that analyzes the direct and indirect cost of TSC and its complications. The research was based on the data obtained from the National Health Fund (hereinafter referred to as "NFZ", which is the abbreviation of the source language name of the institution), Social Insurance Institution (hereinafter referred to as "ZUS", which is the abbreviation of the source language name of the institution), and Poland's Central Statistical Office (hereinafter referred to as "GUS", which is the abbreviation of the source language name of the institution) by using the human capital method.
Findings: The total cost of TSC and its complications in Poland, when taking the sensitivity analysis into account, amounts to EUR 2.2 million–EUR 3.4 million, which has a prevalence of indirect costs (61%–83% of the total costs). The conducted analysis indicates that the higher costs of common diseases result from insufficient financing for research of rare diseases which in many cases have common diseases as a comorbidity.
Research limitations/implications: The limitations of the research analysis result from the lack of registration of patients suffering from rare diseases in Poland and from the requirements for the billing codes in the documentation of NFZ and Polish health care providers. Therefore, the study includes a sensitivity analysis.
Originality/value: This is the first attempt to evaluate the total economic burden of TSC in Poland. The study indicates that the indirect costs of diseases are often overlooked in health care planning in Poland.

Keywords: burden of diseases, rare diseases, common diseases, complications, productivity losses.

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Ekonomiczne obciążenie chorobami rzadkimi ze współistniejącymi chorobami powszechnymi w Polsce

Streszczenie

Cel: niektóre z chorób powszechnych są chorobami współistniejącymi z chorobami rzadkimi i stanowią istotne obciążenie ekonomiczne dla systemu opieki zdrowotnej i gospodarki. W pracy przeanalizowano obciążenie ekonomiczne chorobą rzadką (stwardnienie guzowate; TSC) w Polsce i chorobami z nią współistniejącymi (choroby powszechne – epilepsja i stan padaczkowy), uwzględniając analizę wrażliwości.

Projekt/metodologia/podejście: badanie to jest badaniem kosztów choroby, które zostało przeprowadzone za pomocą metody opartej na rozpowszechnieniu choroby i wykorzystaniu tzw. podejścia z góry na dół. Przeanalizowano w nim bezpośrednie i pośrednie koszty TSC i jego powikłań. Analizę opracowano na podstawie danych Narodowego Funduszu Zdrowia (NFZ), Zakładu Ubezpieczeń Społecznych (ZUS) i Głównego Urzędu Statystycznego (GUS), wykorzystując metodę kapitału ludzkiego.

Wyniki: całkowity koszt TSC i jego powikłań w Polsce, biorąc pod uwagę analizę wrażliwości, wynosi 2,2–3,4 mln EUR, z przewagą kosztów pośrednich (61–83% kosztów całkowitych). Z przeprowadzonej analizy wynika, że wyższe koszty chorób powszechnych są rezultatem niewystarczającego finansowania badań nad chorobami rzadkimi, w przypadku których choroby powszechne stanowią często chorobę współistniejącą.

Ograniczenia/implikacje badawcze: ograniczenia badania wynikają z braku rejestrów pacjentów cierpiących na choroby rzadkie w Polsce oraz braku wymagań dotyczących kodów rozliczeniowych w dokumentacji NFZ i polskich świadczeniodawców. Z tego względu w badaniu przeprowadzono analizę wrażliwości.

Oryginalność/wartość: jest to pierwsze badanie, w którym przeprowadzono analizę całkowitego obciążenia ekonomicznego TSC w Polsce. Z badania wynika, że pośrednie koszty chorób często są nieuwzględniane w podejmowaniu decyzji w ramach planowania opieki zdrowotnej w Polsce.

Słowa kluczowe: obciążenie chorobami, choroby rzadkie, choroby powszechne, powikłania, utracona produktywność.

1. Introduction

Rare diseases are an economic challenge for all countries worldwide and are currently on a top-priority list of the European Union. According to the nomenclature of the European Union, a rare disease is any disease affecting fewer than 1 person in a population of 2,000 (Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:en:PDF; accessed: 30/07/2019).

It should be emphasized here that the majority of rare diseases are complex and multiorgan diseases. Their economic burden tends to be underestimated due to the fact that the relevant cost-related issues are partly omitted. It should be emphasized that rare diseases are often accompanied by multiple comorbidities.

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The term comorbidity was first used by Feinstein in 1970. He used this term to address the diagnostic implications and functional effects of comorbid conditions on the patient (Feinstein, 1970). Interestingly, until recently, the terms 'comorbidity' and 'multimorbidity' tended to be used interchangeably. However, nowadays, the term comorbidity should only be used when referring to a specific condition index or to specific combinations of different conditions. In the case of multimorbidity, any condition can be included (Smith et al., 2016).

Taking into account the comorbidities of rare diseases in Poland, they pose a serious threat to people's health, as is the case in any other country. Health is an important factor influencing the quality of human capital. Becker, for instance, pointed out health as a component of human capital resources. His empirical research, however, focused on education instead (Becker, 1993). A theoretical basis of the perception of health as an integral part of human capital was developed by Grossman, who created the model of demand for health (Grossman, 1972). According to this model, health is a consumption asset and investment asset: as a consumption asset, it has a direct impact on the formation of the utility function, while as capital, it determines the amount of time available for market and non-market activities. An increased investment in health reduces the amount of time that cannot be spent on either market or non-market activities, and the monetary value of this potential time loss is the amount of return from an investment in health.

An estimation of the influence of rare diseases on the economy and health care expenditures is complicated due to the multifaceted nature of the issue. The total costs can be divided into medical and non-medical or direct and indirect costs. Indirect costs are not directly related with medical treatment. They include the costs of years of life lost due to premature death (mortality costs) and the value of activity days lost due to short-term and long-term disability (morbidity costs due to short-term disability – sickness absence and due to long-term disability – work incapacity).

It should be emphasized that, in addition to the costs associated with disease treatment, the treatment of immediate and distant future complications caused by rare diseases should also be taken into consideration. For instance, patients suffering from diabetes are at a high risk of serious cardio- or cerebrovascular problems, neuropathy, and/or microvascular complications (nephropathy, retinopathy), which lead to a rise in the total costs of illness and significantly lower the patient's quality of life. The increased risks of disability, inability to work, and premature death are also important. The productivity loss caused directly by the diseases or by disease-related complications constitutes a substantial economic burden.

It is noteworthy that, apart from the epidemiological evidence demonstrating the burden of rare diseases, the existing literature is lacking in evidence on the economic impact of those diseases. In 2015, a multinational

cost of illness study (BURQOL-RD) evaluated the burden of 10 rare diseases in Europe (Angelis, Tordrup, & Kanavos, 2015). However, the total annual costs (including indirect costs) have been estimated only in the case of five diseases (i.e. cystic fibrosis, hemophilia, juvenile idiopathic arthritis, scleroderma, histiocytosis). It must be stressed that the reported costs vary depending on the data source used, type of assessment, and scope of the analysis. The methodologies differ in terms of the methods of calculating the direct and indirect costs and, therefore, the methodological variations prevent any detailed comparison between the conditions. Although the results of different studies either cannot be compared or the comparison is problematic and unreliable, all of these five rare diseases are associated with significant economic burden, both direct and indirect. An analysis of the cystic fibrosis costs, which was conducted in Denmark (Nielsen & Gyrd-Hansen, 2002), showed a per patient average total cost (direct and indirect) ranging from EUR 16,307 at the ages 1–9 to EUR 68,331 at the ages 30–39. The indirect costs of cystic fibrosis have been estimated in the US based on incapacity to work, disability, and premature death. The annual indirect costs amounted to EUR 8,814 and comprise 37% of the total costs (Pauly, 1983). The indirect costs associated with hemophilia estimated in Sweden in the case of on-demand and prophylactic treatment equal EUR 37,582 and EUR 15,716, respectively (Carlsson et al., 2006). These costs constitute 47% and 11% of the total costs. In the costs of a juvenile idiopathic arthritis study conducted in Germany, the mean annual total cost is estimated between EUR 4,143 per patient (Minden et al., 2004) and EUR 29,613 per patient (Minden et al., 2009). In the same study, the authors reported indirect costs at EUR 274 per patient annually. This cost constitutes 0.9% of the total costs. The indirect costs associated with scleroderma were estimated in Hungary and totaled EUR 6,742 per patient, of which 98% is productivity loss by disability pensioners and 2% is sick leave (Minier et al., 2010). The total annual average cost of treatment for patients with histiocytosis syndrome (e.g. Niemann-Pick disease) was estimated at EUR 49,947 per patient (Imrie et al., 2009). It comprised direct medical costs (46.2% of the total costs), direct non-medical costs (24.1% of the total costs), and indirect costs (29.7% of the total costs).

It must be stressed here that, in the case of scleroderma, the indirect costs constitute 216% of the direct costs. In all the other conditions where evidence is available, the indirect costs amount to less than the direct costs. Moreover, none of the aforementioned studies provided a comprehensive view of the total costs of rare diseases, which include the direct and indirect costs of the diseases and their complications. Therefore, the present paper attempts to fill that gap by presenting estimates of the economic impact of a selected disease and its complications – tuberous sclerosis (TSC)

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with epilepsy and status epilepticus complications. This illness was chosen because it poses a serious threat to the health of Polish people due to the high risk of complications. It is a multisystem disorder characterized by hamartomatous growths that may affect the brain, skin, retina, heart, kidneys, and lungs, which is due to a mutation in either TSC1 or TSC2 (Jóźwiak et al., 2019). TSC is characterized by high rates of neurological and neuropsychiatric abnormalities. According to Polish neurologists, epilepsy affects 70% to 90% of patients suffering from TSC and is one of the most devastating comorbidities (Jóźwiak et al., 2011). The first clinical seizures usually appear between the 4th and 6th month of life. Different types of seizures may be present and coexist in the course of TSC, with infantile spasms, which occur in approximately 30–60% of patients, being the most destructive ones.

2. Analysis Limitations

There are some crucial limitations of the research analysis that should be taken into consideration. The first one is connected with the profile of the TSC disease. It is a highly variable multi-system disease. Any system in the body can be affected and health care providers may report health services data connected with the comorbidity to NFZ as a result. In the case of an adult suffering from tuberous sclerosis and epilepsy, health care providers typically report that the patient's disease is epilepsy. The classic TSC diagnostic triad of seizures, intellectual disability, and facial angiofibromas occur in less than one-third of patients with TSC. Even though its treatment is only symptomatic, an early diagnosis is crucial to prevent long-term organ system damage (Schwartz et al., 2007).

The second limitation of the research analysis results from the lack of the registration of Poles suffering from rare diseases, including TSC. Therefore, the data on the number of people suffering from TSC can be obtained mainly from NFZ. Taking into account the reporting process that health care providers use to report health services data to NFZ, data concerning rare diseases are underestimated.

The last and most important limitation of the analysis is connected with the requirements for the billing codes in the documentation of health care providers and the payer (NFZ) in Poland. Health care providers are not obliged to report full ICD10 codes (of more than three characters), which means that the incidence of TSC and its complications (epilepsy) is understated. According to the NFZ data, epileptics account for only 45% of patients with TSC, while specialists claim it could even be 70–90%.

In view of the above-mentioned limitations of the research analysis, the study included a sensitivity analysis.

3. Methods

3.1. Design

This study is a prevalence-based top-down cost of illness study, which analyzes the direct and indirect cost of TSC and its complications. Prevalence is defined as all patients suffering from TSC and its complications and who were alive on December 31, 2016. The resources used for TSC were identified based on TSC being the first diagnosis for resource consumption. In addition, we estimated the costs of TSC complications. It was decided to analyze Epilepsy (G40) and Status epilepticus (G41) as the TSC-related complication crucial for the study (Kotulska et al., 2014).

The research was based on the data obtained from the National Health Fund (NFZ), the Social Insurance Institution (ZUS), and Poland's Central Statistical Office (GUS).

3.2. Direct Costs

The direct costs assessed in the research, in the case of TSC, include medical care (i.e. outpatient consultations, hospitalization) without drug reimbursement. They are calculated from the payer's perspective on the basis of the data acquired from NFZ. Due to the marginal share of co-payments in the public health care system, the costs calculated from the payer's perspective are a good estimate of the social cost of the disease. Due to the lack of data, the intangible costs and costs of informal care have been omitted.

In the case of complications, the calculation of direct costs was also carried out on the basis of the data obtained from NFZ. These costs do not include the costs of Primary Health Care (PHC) and drug reimbursement. The data were extracted by NFZ in two stages. First, patients with primary and comorbid TSC diagnosis (i.e. Q85.1) were selected. Then, episodes containing primary or TSC-related comorbidity (G40 and G41) were identified for these patients. The direct costs of complications were calculated using etiological fractions (EF) in order to estimate what share of the comorbidities costs is attributable to TSC. The impact of the complications of the diseases analyzed on the health care system and economy was, therefore, based on the attributable risk methodology (Walter, 1976).

We used an attributable risk methodology that is based on population etiological fractions. The methodology involves calculating population attributable risk (population attributable fraction). The concept of population attributable fraction was first proposed by Mort Levin in 1953 (Levin, 1953). The attributable risk is the maximum estimate of the proportion of the incidence of disease that would be prevented if a given risk factor were eliminated. A formula for the attributable fraction proposed by Levin is dependent on generally accessible estimates regarding the prevalence of the risk factor in the population and the relative risk of developing the

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disease among those with, versus those without, the risk factor (Rosen, 2013). Levin's original formula, published in 1953, is:

$$AF = \frac{p(RR-1)}{p(RR-1)+1},$$

where: P is the underlying prevalence of the risk factor in the population and RR is a relative risk. The relative risk is the risk of contracting a disease in an exposed population divided by the risk of contracting the disease in an unexposed population.

It should be noted here that Levin's formula is unbiased in the absence of confounding and is valid only for the unadjusted risk ratio. An alternate formulation of the attributable fraction (AF/EF) was offered by Olli Miettinen in 1974 (Miettinen, 1974). In Miettinen's opinion, the proportion of a given disease attributable to a particular etiologic factor is dependent not only on the risk of the disease among people with this factor relative to those without it but also on the frequency of this factor in the population from which the cases arise. Miettinen's original formula is based on case distribution and adjusted risk:

$$EF = CF_1 \frac{SMR_1 - 1}{SMR_1},$$

where: CF_1 is the case fraction in the higher-risk category of the risk indicator (proportion of cases with the marker of increased risk), SMR_1 is the standardized morbidity (mortality) ratio. There is an adjustment that is required for generality in the formula based on case distribution. This adjustment is simply connected with using SMR_1 in place of RR in Levin's formula. Therefore, Miettinen' formula can be written in the following way: $EF = CF_1 \frac{P_c(RR_{adj}-1)}{RR_{adj}}$, where: P_c is the proportion of cases exposed to risk factor (the prevalence of exposure among the cases) and RR_{adj} is the adjusted relative risk.

It must be stressed here that the population attributable fraction/etiological fraction is widely used in the costs of illness studies in order to quantify the contribution of different risk factors (e.g. unhealthy lifestyle, comorbidities) to disease burden. Such studies have been extensively conducted in the case of common diseases, e.g. diabetes. In 2008, Cosgrove et al. estimated the total population fraction of diabetes cases attributable to depression at 4% (Cosgrove, Sargeant, & Griffin, 2008). Etiological fractions have also been used to describe the proportion of type 2 diabetes cases due to obesity and sugar intake. In the case of obesity (i.e. median of body mass index >/= 24.8), the proportion of type 2 diabetes cases is 82.5% (Wang, Rimm, Stampfer, & Hu, 2005). The proportion of diabetes cases

attributable to sugar-sweetened beverages is 8.7% in the United States (Imamura et al., 2015). Recently, population attributable fractions have been used to quantify the contribution of risk factors to infectious disease burden, e.g. the contribution of malnutrition to childhood infections. The population attributable fraction of rotavirus cases attributable to malnutrition is 6% (Paynter, 2016).

There is a lack of costs of illness studies with the etiological fraction calculus in the field of rare diseases. It is noteworthy that there was only one risk factor (i.e. TSC) amenable to intervention in our research. Therefore, we used Levin's unadjusted equation: $\frac{p(R-1)}{p(R-1)+1}$, where P stands for the prevalence rate of TSC among the patients treated in Poland, and R is a relative risk of suffering from a given complication among those with TSC (Hogan, Dall, & Nikolov, 2003).

3.3. Indirect Costs

The indirect costs assessed in the research include the costs of productivity loss due to premature death, work absence, or inability to work. The indirect costs were estimated using the data from ZUS and GUS. While estimating the indirect costs, the human capital method was used. In this methodology, the gross wages (including employee benefits) are used to estimate the productivity costs (either due to absenteeism or premature death). There is an assumption that wages are a proxy measure of employee output (Brinbaum, 2005). It is important to note that the human capital approach has been widely used in the literature to estimate the lost productivity costs of morbidity and/or mortality for communicable and non-communicable diseases, e.g. malaria (Alonso et al., 2019) and cancer (Hanly & Sharp, 2014).

The costs of lost productivity due to sickness absence were calculated with the use of the ZUS data (i.e. the number of workdays missed due to sickness caused by diseases) and the average daily gross wage in the economy.

The analysis of the indirect costs also involves lost productivity due to work incapacity (disability). These costs are incurred due to inactivity in the labor market and the collection of social security benefits. They were calculated on the basis of the ZUS data concerning the volume of social security benefits transferred, along with the GUS data on the average gross salary in the economy. These data were corrected by subtracting the volume of benefits transferred to the not working age groups from the total volume of social security transferred. This calculation relied on data on the employment rate in the labor force.

Productivity lost as a result of premature death was also included in the analysis. A calculation of those costs was carried out on the basis of the data acquired from GUS. These data included the number of deaths due to TSC

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and its comorbidities (epilepsy and status epilepticus) divided by the age and sex as well as Poland's average gross monthly wages.

The indirect costs of complications were calculated using etiological fractions (EF), as in the case of direct costs.

3.4. Sensitivity Analysis

In our study, we applied point estimates of EF for TSC complications. As variables used to calculate EF are subject to uncertainty, we provided limits to the direct and indirect costs resulting from adjusting the Relative Risk and Prevalence Rate. It is worth emphasizing that, according to the NFZ data, epilepsy affects 45% of patients with TSC. However, as aforementioned, according to Polish neurologists, epilepsy affects 70% to 90% of patients suffering from TSC. Therefore, the Relative Risk of 80% has also been applied. With regard to the Prevalence Rate, we used the data from the European Tuberous Sclerosis Complex Association – a birth incidence of approximately 1 in every 6,000 (http://www.e-tsc.eu/; accessed: 30/07/2019).

4. Results

4.1. TSC Costs

In 2016, the costs of the health care services provided in relation to TSC amounted to EUR 226,100.49.

The indirect costs of the analyzed disease amounted to EUR 345,286.71. In the structure of those costs, there is a prevalence of the productivity lost due to work incapacity – 81.4% of the total costs.

4.2. Costs of TSC Complications – EF Standard

The NFZ database has made it possible to extract the costs of treatment for TSC-related complications. Calculated etiological fractions for people diagnosed with TSC, on the basis of NFZ data, are presented in Table 1.

Diseases	EF
Epilepsy (G40)	0.0007
Status Epilepticus (G41)	0.0002

Tab. 1. Calculated attributable risks for TSC-related complications in Poland in 2016. Source: The author's elaboration on the basis of the NFZ data.

In 2016, the costs of health care services provided in relation to complications of TSC (without the costs of drugs and PHC) amounted to EUR 761.26.90. The indirect costs of the complications of the disease analyzed amounted to EUR 125,715.17.

4.3. TSC Costs and Its Complications – EF Standard

In 2016, the total costs of TSC and its complications amounted to EUR 773,229.27 (Table 2). These costs constitute 0.004% of the total costs of non-communicable diseases. In the structure of these costs, there is a prevalence of indirect costs (Figure 1).

	TSC	Complications of TSC	Total costs of TSC and its complications
	Total	Total	Total
DIRECT – total	226.1	76.1	302.2
INDIRECT – total	345.3	125.7	471.0
TOTAL	571.4	201.8	773.2

Tab. 2. The values of the costs related to TSC and its complications in Poland in 2016 (in EUR thousands). Source: The author's elaboration on the basis of the ZUS, NFZ, and GUS data.

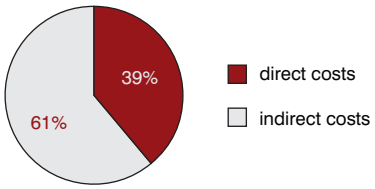

Fig. 1. Structure of the total costs of TSC and comorbidities. Source: The author's elaboration on the basis of the ZUS, NFZ, and GUS data.

Analyzing the data shown in Table 2, we can observe that, in the structure of the total costs of TSC and in the case of the costs of complications, there is a prevalence of indirect costs (60% and 62%, respectively).

4.4. Sensitivity Analysis – Costs of TSC Complications

The sensitivity analysis conducted (Tables 3 and 4) revealed the very high elasticity of direct and indirect costs with respect to the Prevalence Rate and Relative Risk.

Variable	Model value	Sensitivity value
Prevalence Rate	76.1	206.5
Prevalence Rate and Relative Risk	76.1	344.1

Tab. 3. Sensitivity analysis for TSC complications' direct costs (in EUR thousands). Source: The author's elaboration on the basis of the NFZ and epidemiological data.

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Variable	Model value	Sensitivity value
Prevalence Rate	125.7	1,508
Prevalence Rate and Relative Risk	125.7	2,514

Tab. 4. Sensitivity analysis for TSC complications' indirect costs (in EUR thousands). Source: The author's elaboration on the basis of the ZUS, GUS, and epidemiological data.

The analysis shows that a 35% increase in the value of the Prevalence Rate results in a 171% and 1,099% increase in the direct and indirect costs, respectively. The values of the direct and indirect costs calculated for a higher Prevalence Rate and higher Relative Risk (by 35% and 45%, respectively) are 352% and 1,899% higher compared with the model values.

It should be emphasized that there is a high domination of indirect costs in the structure of the total costs of TSC and comorbidities (Figures 2 and 3).

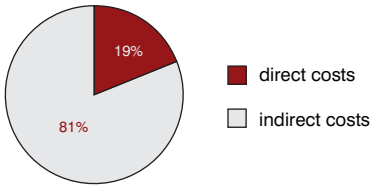

Fig. 2. Structure of the total costs of TSC and comorbidities (P = 0.00016). Source: The author's elaboration on the basis of the ZUS, NFZ, and GUS data.

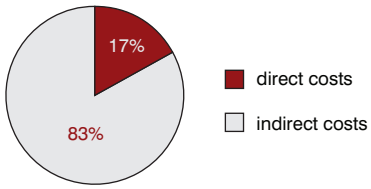

Fig. 3. Structure of the total costs of TSC and comorbidities (P = 0.00016 + relative risk of epilepsy and status epilepticus among patients with TSC = 80%). Source: The author's elaboration on the basis of the ZUS, NFZ, and GUS data.

It is noteworthy that the costs of disease-related complications are much higher than those of the disease itself. The total costs of TSC amounted to EUR 571,300. The total costs of TSC complications amounted to EUR 1.7–2.8 million, taking into account the sensitivity analysis. This high prevalence of the costs of TSC complications is mainly connected with the problem of drug-resistant epilepsy.

4.5. Epilepsy and Status Epilepticus Costs

The total cost of epilepsy and status epilepticus in Poland amounts to EUR 333 million. In the structure of these costs, there is a prevalence of indirect costs (Table 5). However, it is important to point out here that the direct costs do not include the costs of primary care and drug reimbursement.

	Epilepsy	Status Epilepticus	Total cost of epilepsy and status epilepticus
	Total	Total	Total
DIRECT – total without drug reimbursement and GPs	41,530	2,060	43,590
INDIRECT – total	282,500	6,990	289,490
TOTAL without drug reimbursement and GPs	324,030	9,050	333,080

Tab. 5. The values of the costs related to epilepsy and status epilepticus in Poland in 2016 (in EUR thousands). Source: The author's elaboration on the basis of the ZUS, NFZ, and GUS data.

It must be stressed that epilepsy is often associated with neuropsychiatric comorbidities, which markedly decrease the quality of life of the patients and their families. Approximately 30% of children with epilepsy have autism and/or intellectual or developmental disabilities (Brooks-Kayal et al., 2013). Among TSC patients, the prevalence of mental retardation is about 50%. The early onset of epilepsy, especially manifested by infantile spasms, is critically associated with severe forms of mental retardation.

5. Challenges of Financing Innovative Treatment Solutions

Poland is one of the last countries in the European Union that have failed to adopt a national strategy for rare diseases. Orphan drugs and technologies are among the most expensive solutions to develop and market. Some disease entities relate to only a few or a few dozen people in any country. Developing an effective drug requires huge expenses – on average, it takes 15 years to introduce a drug to the market and it can sometimes cost well over one billion US dollars. If manufacturers do not derive profits from the development of new medicines, and the billions invested in laboratory research do not generate returns, it is hard to expect the development of any new drugs for rare diseases. That is why the European Commission calls for the implementation of the National Plan and the creation of a coherent system of financing such drugs, so that the patients have a chance to obtain

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treatments, and manufacturers have reasons to develop them (Commission of the European Communities, https://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf; accessed: 30/07/2019).

It is important to emphasize that the Agency for Health Technology Assessment (AOTMiT), which evaluates reimbursement claims, remains the sore point. The economic factor is one of the main decision criteria. AOTMiT calculates the threshold of profitability. Therefore, orphan drugs have to compete with drugs for common diseases. One of the conditions that makes it impossible to arrive at a favorable decision is exceeding the threshold of profitability. This value amounts to three times the gross domestic product per individual citizen per one quality-adjusted life-year (QALY).

In most cases, there is no effective treatment. However, it should be noted that early diagnosis and proper care may contribute to improving the patient's life quality and expectancy. It also relates to the patients suffering from comorbidities of rare diseases. Antiepileptic treatment before the onset of seizures in the case of infants suffering from TSC is a case in point. In 2011, Polish neurologists from the Children's Memorial Health Institute in Warsaw applied an innovative epilepsy control method in the form of preventive antiepileptic treatment (vigabatrin). The administration of Sabril (vigabatrin) in patients aged up to 24 months prevented the development of epilepsy in 90% of children suffering from TSC. The studies conducted by the pediatric neurologists indicate that the introduction of antiepileptic treatment before seizures reduces the severity of epilepsy and the risk of intellectual disability in children suffering from TSC (Jóźwiak et al., 2011). The Polish Ministry of Health refused to finance the Sabril-based (vigabatrin-based) preventive treatment for 3 years. Finally, in July 2014, it agreed to finance the Sabril-based (vigabatrin-based) preventive treatment as a reimbursed off-label use.

6. Conclusion

6.1. Economic Burden

This is the first attempt to evaluate the total economic burden of TSC in Poland. The total costs of TSC and TSC complications amounted to EUR 2.2–3.4 million, when taking into account the sensitivity analysis. These costs constitute 0.01–0.02% of the total costs of non-communicable diseases. It should be emphasized that compared with the economic burden of rare diseases estimated within the BURQOL-RD project, the economic burden of TSC and its complications is lower. However, the share of indirect costs in the total costs in the case of TSC and its complications are much higher than in the case of five rare diseases within the BURQOL-RD project.

The study shows that a significant share of the total costs (61%–83%) of TSC and epilepsy and status epilepticus as complications of TSC is constituted by indirect costs. Generally, the indirect costs of diseases are often overlooked in health care planning in Poland.

The use of health care resources should be planned not only to cut the direct costs of treatment but also to consider the social impact of the disease, through effective treatment to minimize the indirect costs. The results of this study show that the indirect costs can be higher than the direct costs and, therefore, cannot be ignored in health care decision-making processes.

The indirect costs of diseases are only occasionally included in the economic analysis. This is mainly due to the lack of formal requirements for the inclusion of these costs in the cost accounting process. Usually, there are no clear guidelines that would enable a reliable assessment of the social burden associated with the indirect costs. In Poland, according to the guidelines for the assessment of medical technologies issued by AOTMiT, the perspective of the payer for health benefits is privileged. Furthermore, if necessary, an analysis can be conducted that addresses the social perspective (Andrałojć, 2016). Similar guidelines have also been implemented in Slovakia and the Baltic states.

In Hungary and the Czech Republic, a "by case" approach to HTA is applied, while in the UK, according to the National Institute for Health and Clinical Excellence's guidelines (NICE), the role of social perspective has been greatly reduced. By contrast, a broad perspective, including the social aspects, constitutes a basis for any pharmacoeconomic analysis in Sweden, France, and the Netherlands (International Society for Pharmacoeconomics and Outcomes Research, https://tools.ispor.org/PEguidelines/countrydet.asp?c=21&t=1 (accessed: 7/30/2019); https://tools.ispor.org/PEguidelines/countrydet.asp?c=22&t=1 (accessed: 7/30/2019); https://tools.ispor.org/PEguidelines/countrydet.asp?c=8&t=1 (accessed: 7/30/2019)).

In the United Sates, the indirect costs are monitored regularly and estimated for 15 diseases – leading causes of death in the past year. In the report of the Institute of Medicine for 1998, it is recommended that, in the process of setting priorities, the National Institutes of Health (NIH) should strengthen their analysis and use of health data, such as the burdens and costs of diseases (Rosenberg, 1998). Therefore, it is clear that NIH, the Institute of Medicine, and the US Congress recognize the importance of the cost of illness estimates in setting research priorities (Rice, 2000).

In the process of the assessment of national health expenditures, countries should seek to include the real costs of illnesses and disabilities. It would provide reliable evidence for establishing and conducting health policies based on proof and facilitate international comparisons.

What is more, it is necessary to redefine the costs in the evaluation of allocative efficiency. A redefinition of the costs (data) to assess the allocative efficiency of health expenditures is shown in Figure 4.

https://doi.org/10.7172/1644-9584.89.6

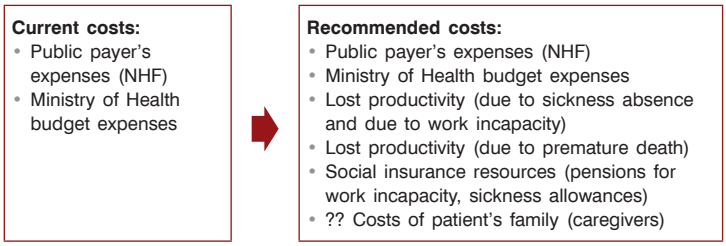

Fig. 4. Redefinition of the costs in the evaluation of allocative efficiency. Source: The author's elaboration.

In the country where the income level of a public payer is closely linked with the domestic economic situation, it is vital to analyze the health care expenditures of all the institutions involved in the functioning of health care. This analysis should, therefore, also evaluate the cost of burdening the society and economy with diseases and scrutinize the availability of innovative solutions.

6.2. Economic Burden – Common and Rare Diseases

In 2016, the total costs of epilepsy and epilepticus status amounted to EUR 333 million. In the same year, the total costs of TSC amounted to EUR 571,300. This juxtaposition proves that the higher costs of common diseases result from insufficient financing of rare diseases that, in many cases, have common diseases as the comorbidity (e.g. TSC and epilepsy).

6.3. Cost-Effectiveness Analysis (Health Technology Assessment)

In Poland, for the cost-effectiveness analysis of interventions within the health care sector, a threefold gross domestic product (GDP) per capita threshold has been implemented. It has been applied in line with the World Health Organization (WHO) suggestions of twofold to threefold GDP per capita. It is a threshold for the cost-effectiveness of interventions within the health care sector.

As aforementioned in the section connected with the challenges of financing innovative treatment solutions, a drug is deemed cost-effective by AOTMiT if the cost per QALY estimates are lower than threefold the GDP per capita. Services that exceed threefold GDP per capita are viewed as economically unattractive. According to the opinions of experts from the Commission on Macroeconomics and Health at the World Health Organization, a fixed cost-effectiveness threshold should never be used as a stand-alone criterion for decision-making. Moreover, the use of the most common threshold – threefold per capita GDP per DALY averted – in national funding decisions or for setting the price or reimbursement value of a new drug or other intervention must be avoided. The Norwegian

Committee on Priority Setting has suggested differentiating thresholds across the different categories of potential health loss (Ottersen et al., 2016). It is also advisable to introduce similar solutions in Poland. There should be a different threshold in the case of common and rare diseases.

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