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Table of contents

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From the Editors

We provide you with the second issue of JHPOR. As seen in the table of contents pharmacoeconomics, health policy and results of clinical trials are becoming increasingly important in shaping the health care system in Poland. The development of health technology assessment indicates that more and more work is devoted to the costs and cost-effectiveness of health technologies in Poland. It should be noted how important the comparative analysis of these phenomena with other countries is.

During the latest congress of ISPOR in Berlin we had the honor to participate in the Polish-Russian forum, which focused on common solutions for the reimbursement of medicines and medical devices in both countries. An in-depth analysis of the problem is presented in this issue. One of the articles refers to the role of a new type of health insurance, the so-called complementary health insurance. In our opinion this solution should be implemented into our health care system in the near future. The content of this JHPOR issue shows the enormous space for such publications in Poland. We encourage all stakeholders, especially members of the Polish Society of Pharmacoeconomics to publish in future editions of our Journal.

At the same time we hope you will find current issue interesting.

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The economics of vaccination

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Abstract

Since the end of the 18th century, vaccines against several infectious diseases have been developed. Having gone through a long process of technology improvements, traditional vaccination represents one of the most significant and cost-effective public health measures nowadays. Although many infectious diseases are vaccine-preventable, vaccines are generally still under-valued and under-utilized, resulting in a high burden of infectious diseases worldwide. Vaccination coverage rates are often used as a quality indicator of healthcare systems and are an important measure for reducing child mortality as outlined in Millennium Development Goal (MDG) number 4. However, there are challenges to deploying vaccinations as preventive measure to their full extent. For manufacturers, a high level of know-how is required as well as high upfront investments and fixed costs, which leads to there being only relatively few manufacturers for vaccines. At individual and societal level, there are problems of uncertainty and the phenomenon of time preference (for short-term benefits) when it comes to investigating the under-usage of vaccines. Despite these challenges, public health initiatives leading to higher vaccination coverage are likely to play an important role for controlling infectious diseases globally.

Key words: vaccination coverage, economics

Introduction

Immunization counts as a collective activity as vaccinations do not only reduce the incidence of a disease in those immunized but also indirectly protect susceptible individuals without vaccination (Brisson 2003) [1]. Therefore, increasing the immunization the coverage to a level of herd-immunity produces extra benefits or so-called positive externalities, and millions of infections can be avoided. Vaccinations are considered as one of the most significant public health interventions nowadays (Ehreth 2003a; 596 f.)[2].

The history of vaccines and immunization began with the development of the world's first vaccine for smallpox in the 1790s. During the last two centuries, effective vaccines for other relevant infectious diseases such as tuberculosis, rabies, diphtheria, measles, mumps and rubella have been developed. Technology improvements in the vaccine production lead to higher quality and safety (Stern and Markel 2005; 612) [3]. Overall, at least 26 diseases can be prevented, or their incidence reduced, by vaccination (Ehreth 2003b; 4107) [4]. Additionally, vaccinations are regarded as one of the most cost-effective health policy intervention (OECD 2011; 124) [5]. Being "cost-effective" is occasionally defined as "buying" a full year of healthy life at less than the per-capita gross domestic product of the country under study. In case of most vaccinations, the costs per healthy live-year saved are less than US$ 50 (Ehreth 2003a; 599) [2].

Global Burden of (infectious) Diseases

However, infectious diseases still count as a major threat to human life and health. In 2008, more than 8.7 million people died of infectious diseases worldwide; many of them were children under the age of five (WHO 2012a; 12) [6]. Globally, six infectious diseases are responsible for about 20 percent of total deaths (WHO 2008a; 11) [7]. In high-income countries, lower respiratory infections are the only infectious disease among the ten leading causes of death, being responsible for only four percent of mortality. Conversely, in low- and middle income countries, lower respiratory diseases represent the third

leading cause of death; diarrheal diseases, HIV/AIDS and tuberculosis are also among the ten leading causes of death (WHO 2008b)[8].

Considering child mortality, even 58 percent of under-five deaths were caused by infectious diseases (WHO 2012c) [9]. Children in developing countries face a higher mortality risk for infectious diseases; the chance of dying of a vaccine-preventable disease is 10-fold greater than for children in industrialized countries (Ehreth 2003b; 4107) [4]. With routine vaccination programs, nearly 1.5 million deaths of children younger than five years could have been prevented, which is equal to 17 percent of the under-five mortality (WHO 2012b) [10].

In order to take into account premature mortality, a metric considering both the frequency of death as well as the age at which death occurs has been devised, namely the years of life lost (YLL) (sometimes also referred to as potential years of life lost or PYLL) (WHO 2008b; 21)[8]. Infectious diseases mostly lead to deaths at younger age. Worldwide, more than 386 million life-years are saved annually because of vaccination programs (Ehreth 2003a; 599) [2].

The aforementioned infectious diseases carry various levels of severity causing different kinds of symptoms, and might lead to several disabling effects (WHO 2008b; 31) [8]. To account for disabling effects, the measure Years Lost due to Disability (YLD) has been developed. It considers of the number of years lived with a disability, the latter being weighted with a factor between 0 (perfect health) and 1 (death) to express the severity of the disability. YLD and YLL are subsequently added up to obtain Disability Adjusted Life Years, or DALYs (Van Lier et. al. 2007) [11]. One Disability-Adjusted Life Year is equivalent to one life year of full health lost. The DALY concept allows for comparisons between the burden of diseases which causes premature death but no disability, and diseases that are not fatal, but lead to severe, often long-standing, disabilities (WHO 2008b; 40)[8].

In low-income countries, six infectious diseases were responsible for 31.5 percent of the DALY burden in 2004, whereas there were no infectious diseases among the ten leading causes of DALY burden in high-income countries (WHO 2008b; 44) [8].

Looking at the leading 20 causes of burden of disease at global scale, infectious diseases – namely lower respiratory and diarrheal diseases, HIV/AIDS, tuberculosis, neonatal infections and malaria – accounted for about 21 percent of the DALY burden, which is equal to 326 million DALYs (WHO 2008b; 43)[8]. Based on the DALY burden of the source year 2004, approximately 200 million DALYs could be vaccine-preventable (authors' own estimates). Annually, vaccination programs already save more than 96 million DALYs worldwide (Ehreth 2003a; 599) [2].

Due to the tremendous effect, vaccinations have on mortality and morbidity burden from infectious diseases, vaccination coverage is often considered to be a quality-of-care indicator (OECD 2011) [5].

Production and Pricing

Economic factors play a key role in the development and use of vaccines throughout the world. However, there are many barriers that hinder the optimal use of vaccines, starting at the development and production phase and continuing in distribution as well as uptake phases (Milstien 2006) [12].

The production of novel vaccines requires a high level of know-how as well as investment costs for research and development. Fixed costs also play an important role in the manufacturing process as setting up production facilities will add to the upfront cost. Overall, vaccine production is a costly and high-risk enterprise, of comparatively modest economic value for the companies involved, taking the pharmaceutical market as a reference point. Vaccine products account for only two percent of the global pharmaceutical market, so relatively few suppliers feel attracted (GAVI) [13]. In addition, traditional vaccines are often products with a low margin, complex supply chain, short shelf-life, and single or limited (non-chronic) use. This, combined with the problem of uncertain demand when the product is available, further exacerbates the challenges to contain vaccine-preventable diseases (Milstein 2006) [12]. As a result, the number of major pharmaceutical companies producing traditional vaccines has gone down from over twenty in 1970 to four in 2005 (WTEC 2007)[14].

This reveals that many pharmaceutical manufacturers have not considered vaccinations to be a good business opportunity (Rappuoli 2002) [15]. Prices for the well-established traditional vaccines such

as measles, diphtheria, pertussis, tetanus, oral polio and BCG tend to decrease over time (Tracy 2005) [16]. Fixed costs make up a significant part of the total cost of vaccine production, but high demand for these vaccines – e.g. through uptake into routine immunization programs around the globe – leads to economies of scale. Thereby, fixed costs are "diluted" by the increasing volume, which lead to a growth of the total revenue to the manufacturers, who in turn can offer these vaccines at a lower price (Milstein 2006) [12]. Another reason for the sinking prices are technology improvements in vaccine production. Gains in productivity and efficiency achieved through the learning curve as the product matures are important. These effects also introduce the possibility of expanding the product portfolio by leaning towards economies of scope, creating new products which will again enter the cycle of innovation and maturation.

Challenges to prevention

In addition to the particular aspects on the manufacturing side, there are also elements at the individual and societal level that often hinder the widespread use of vaccines as a primary preventive measure. Vaccines, just as most other preventive actions, face fundamental challenges. In contrast to people seeking treatment for an acute illness, individuals contemplating getting immunized do not face morbidity pressure. Moreover, there is considerable uncertainty linked to the potential future benefits for the individual. An individual can only draw upon estimates about the risk of actually contracting the disease, typically derived from incidence data (with and without vaccination). The above, combined with the natural human preference for immediate benefits, often leads to an under-utilization of available vaccines. Another aspect contributing to this problem is the preference for short-term benefits not only at the individual, but also at the societal level. While the costs of policy programs geared towards an increase in immunization coverage will occur instantly, the benefits mostly arise in the long term. However, as political business cycles are often limited to a few years, there is a "risk" of such positive public health effects being reaped by a respective political successor. This predicament further reinforces the preference for short term benefits and frequently a focus on "repairing" rather than preventive medicine.

Conclusion

Infectious diseases are responsible for a high morbidity and mortality burden worldwide. Several vaccines can be used to avoid infections and the resulting illness. However, there are various challenges to developing, manufacturing and using vaccinations to their full extent.

Despite the aforementioned problems, the long term benefits of vaccination would still appear to outweigh any such challenges. Vaccinations had a tremendous impact on households and national economies so far, for example by eradicating polio and smallpox. The eradication of the latter alone resulted in global savings of over US$ 2 billion annually (Ehreth 2003b; 4105) [4]. Some vaccinations are considered to "pay for themselves": By adopting widespread use of the MMR vaccine, for example, US$ 3.94 - 4.91 were saved per dollar spent (Ehreth 2003b; 4114) [4]. Protecting a child against the most important infectious diseases can be reached by spending only US$ 30 on vaccines and administration (Ehreth 2003a; 599) [2]. These numbers show that relatively low spending levels can result in reducing mortality and morbidity from infectious diseases enormously. Therefore, vaccinations can contribute significantly to meet MDG 4, namely the reduction of child mortality by two-thirds until 2015. The value of vaccination programs lies in their low risks, but a high proven impact at global scale. By expanding immunization coverage, millions of lives can be saved.

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The organization of the health care system in the Russian Federation

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Abstract

This article is a part of the "Road Map ISPOR" and comprehensively describes health care system in the Russian Federation - including its funding, sources of financing, free medical care, and also the rules of mandatory medical insurance. It presents the organization of the health system at both local and national levels including the division of funding for programs and health care provided to specific groups of citizens. Functioning of the departmental health care financed from public funds is also described. Apart from the mandatory insurance, the article also outlines voluntary medical insurance. Finally it describes the decision-making structure and procedures in the health care system as well as organizations carrying out health technology assessment in Russia.

Key words: reimbursement, health economics, Russian Federation, health care system

Introduction

The interest in aspects of the health care, in particular, to the availability of drugs in Russia, primarily is interesting for health professionals: doctors, employees of pharmaceutical companies, but also for the patients themselves. The biggest controversy concerns drug reimbursement (for which, in the Russian language the term реимберсмент is used), and decision-making processes, whose aim is to incorporate drug reimbursement into funding from national budgets.

Up to now there has not been developed a unanimous system of reimbursement in the Russian Federation. There are only separate programs, and "subprograms" at both local and national levels, where drugs are included. These programs are implemented independently of one another lacking coordination and having different organizational forms. The criteria for selecting drugs to be reimbursed by the state budget are not clear. Furthermore, health technology assessment is only a recommended and not a mandatory procedure.

The subject matter is in demand – it is the matter of discussions of the associates of the Interregional Public Organization "The Society for Pharmacoeconomics" (MOOOFI) (the Russian Society of Pharmacoeconomics and Outcomes Research) at numerous conferences and meetings. For an in-depth examination of the specific organization of drug supply in the Russian Federation, MOOOFI became a participant in an international project on creating a worldwide ISPOR road map. Currently, 21 countries including Canada, Australia, the United States and most of the European Union members are involved in this project.

Accordingly to the protocol of ISPOR, the work was carried out in several stages. In January 2012 a first draft of the document was developed, which was then submitted to the review to chairmen of a few subsidiaries of the Russian branch of ISPOR (RSPOR). At this stage the development of the document was attended by:

• A.K. Hadzhidis - Doctor of Medicine, the chief clinical pharmacologist of Sankt Petersburg, the President of the St. Petersburg branch of RSPOR;

• T.L. Moroz - Doctor of Pharmaceutical Sciences, Professor of Pharmacy of Irkutsk State Institute of Improvement of Doctors, the President of Irkutsk branch of RSPOR;

• A. V. Baturin - Doctor of Medical Sciences, professor, Chairman of Clinical Pharmacology

Department of Stavropol State Medical Academy, President of Stavropol branch of RSPOR;

At the final stage the document was put forward to the experts who are the decision-makers in the field of medical insurance in the Russian Federation. In this phase the document have been worked on by:

• N.N. Vezikova - Doctor of Medicine, Head of the department of clinical pharmacology and therapeutic insurance at the Ministry of Health of the Republic of Karelia.

• E.N. Bochanova - Doctor of Medicine, Head of Department of the implementation of standards and quality management of health care and mandatory medical insurance, a clinical pharmacologist at the Ministry of Health of Krasnoyarsk region.

This article contains information about financing medical care as a whole. Aspects of financing the medical insurance for citizens of the Russian Federation were approached in a more detailed manner.

Financing health care

The Russian Federation (RF) consists of 83 federal entities [1]. According to the Federal State Statistics Service (ROSSTATA) for 2009 the total population of the RF amounted to 141.9 million people. Under the Constitution of the Russian Federation (art. 41) every Russian citizen has the right to be the beneficiary of health care and medical aid [2]. Medical care in state and local institutions is provided free of charge to citizens and financed from proper budget, insurance contributions and other sources.

However the declared rights of patients do not correspond to the reality. Patients with some rare diseases included in the “7 Diseases” program receive free treatment, while treatment of other rare diseases is not reimbursed. There are no clear criteria for the selection of a specific disease. The real number of patients with rare diseases has not been established. There is no register of the patients.

The sources of the health care funding are the following: federal budget, budgets of the RF entities, local budgets, mandatory health insurance contributions, funds coming from companies and citizens, funds received from natural and legal persons including charity contributions and other sources of funding which are allowed by the RF law.

Each year the Program of State Guarantees of Free Medical Care provided to Citizens of the Russian Federation (the “Program”), which specifies the types and conditions of providing medical care, standards of its extent and cost per unit of medical care provided, the standard of expenditure per patient, the arrangement of formulation and structure of medical care prices. It also provides criteria, quality and accessibility of medical care, provided within the state, free of charge to citizens of the Russian Federation.

Under the Program the state authorities of the entities of the Russian Federation shall develop and approve of the local programs to provide citizens with state guarantees of free medical care (including local programs of Mandatory Medical Insurance – MMI.

The state budget pays for the activities of state-level medical organizations: research and educational institutes, departmental health care institutions, the "7 Diseases" and the ONLS program, the number of highly specialized types of medical care, the priority national "Health". Project investment programs addressed to the whole nation (partial construction, repair of medical buildings, purchasing expensive equipment) and others.

Regional budgets pay for activities at the regional medical organizations, local investment programs (construction, repair of medical buildings, purchasing expensive equipment), local special purpose programs in the health care area, contributions to the Mandatory Medical Insurance on behalf of the unemployed, the implementation of local programs of the MMI exceeding the size of subsidies allocated from the State Fund budget to local funds.

The Mandatory Health Insurance System includes Federal Fund of the Mandatory Health Insurance (FFMHI), 84 Regional Mandatory Health Insurance Funds, 100 Insurance Medical Organizations (IMOs) and 261 branches of IMOs. All health insurance organizations provide financial access to health services under the RF Law No 326-FZ of November 29, 2010 “On Mandatory Health Insurance in the Russian Federation”. Insurance premiums amount to 97.6 % of funds. Until 2011 the main sources of revenues had been taxes, including the social tax in the part transferred to the accounts of the Federal Fund and contributions for mandatory health insurance of the

unemployed part of the population. Since 2011 the social tax has been transformed into insurance contributions in the MMI system paid by entities directly to Federal Fund in the amount of 5.1% of the salary [3].

It should be noted that an upper threshhold of the annual payment from which the deduction is realized in a given amount is set each year i.e. in 2012 – 512 000 rubles per year - after exceeding this sum the tax on the MMI is not charged. Under the Law No 212-FZ of 24 June 2009 certain amounts are not taxable insurance contrinutions, in particular unemployment benefits, compensation payments etc. [3].

All organizations offering medical insurance provide medical services under the Law "On mandatory medical insurance in the Russian Federation" No 326-FZ of 29 November 2010.

Departmental Medical Service: some citizens have access to the expanded list of medical services provided in the departmental medical services and funded from federal budget e.g. the Russian Railway Service, the Ministry of Interior Affairs, the Defense Ministry, the Federal Security Service, etc.. In several cases, medical care in departmental health services may be provided not only for the employees but for also their family members.

The System of Voluntary Health Insurance (VHI) includes a number of private insurance companies. Funding of VHI is funded partially from the employer's resources, and partially from the patient's resources. The list of medical services offered within VHI may differ significantly: in some cases it may be medical care only in emergency cases, in other cases certain types of inpatient and/or outpatient treatment are offered. Certain services in dental care may also be included in the VHI program.

At the request of the patient, he could fully fund medical assistance provided to him in state medical facilities (meaning medical care provided to the uninsured within the system of mandatory medical insurance).

Financing of medical insurance, state programs insuring separate groups of citizens

Insurance system consists of a two parts namely inpatient and outpatient.

When medical care is provided in hospitals in the state institutions, medicines should be available free of charge. There is a restricting formulary of medical institution, approved of by the regional program of state guarantees. Formulating Committee of a medical institution reviews the formulary not less frequently than once each year, which is annually approved of by the governing institutions managing such an entity.

Under the Regulation No 110 of the Minister of Health of the Russian Federation of 02.12.2007 "On prescribing medicines, medical devices and products for particular nutritional use" if there is a need to prescribe drugs which are not included in the territorial list of the most important and essential medicines, with adverse prognosis of the disease, presence of complications and/or co-existing diseases, or if there is a need to prescribe hazardous drugs as well as if there is intolerance to medicines which are in the local list of important and essential drugs, prescribing drugs is carried out by a medical committee and the decision is recorded in documents of the patient and medical journals of a medical committee.

Providing medical care in hospital medical insurance is possible:

1) With own resources of citizens through a network of retail pharmacies;

2) As a discount medical insurance of separate categories of citizens which is implemented by many treatment programs.

The Program of Additional Drug Supply (DLO) was launched in 2005 and 14.3 million people were surveyed, and the following from seven to eight million people continued to receive drugs within the regional programs. The extent of funding in 2005 amounted to 48.3 billion rubles. Since 2008 the Program has been functioning as two subprograms – ensuring the supply of vital and essential medicines (ONLS) and purchase of expensive drugs for the treatment of seven very expensive deseases ("7 Diseases" Program). Since 2008 funding the Program has been transferred to the regional level.

In 2010 the funding of DLO/ONLS Program amounted to 86.6 billion rubles, but it is almost two times smaller than the real needs. At the same time there was an outflow of patients from the Program for the past 5 years: in 2010 the number of patients decreased to 4.152 thousand people.

Thus about 70% of patients have chosen cash-for-benefits substitution instead of free drugs.

"7 Diseases" Program (Gaucher disease, multiple sclerosis, pituitary dwarfism, cystic fibrosis, hemophilia, chronic myelogenous leukemia and other hemoblastosis as well as state after organ and tissue transplantation) from 2008 to 2009 its funding amounted to 33 billions rubles per year. 44 billion and 45 billion rubles were spent in 2010 and 2011 respectively. 47 billions rubles are planned to be spent in 2012. The source of funding is the regional budget.

Regional programs of drug supply for certain categories of citizens who suffer from some diseases (Government Decree No 890), e.g. drug supply programs for patients with cancer in Moscow, St. Petersburg, the Republic of Tatarstan or the program for patients with psychiatric disorders in St. Petersburg. The total number of regional benefit recipients is 12 million, and the total amount of funding their drug supply from the regional budgets - about 19 billion rubles.

There are free programs for the medical insurance for patients with certain diseases: diabetes, tuberculosis, HIV infection - the so-called program "Prevention and preventing socially significant diseases", the vaccination program (National Immunization Scheme.) Currently, financing is carried out within the framework of public funds, by 2015 the financing obligation is planned to be transferred to the budgets of the entities of the Russian Federation.

Citizens of the Russian Federation have the right their expenses for medical care and drugs included in the list of medical care and expensive treatment in medical institutions to be reimbursed up to the level of the personal income tax i.e. 13%, The reimbursed amount depends on the income of a patient, so when turning to the local tax inspection office a citizen should submit information on annual income i.e. 2-NDFL form. The list of medical services and medicines to be reimbursed was approved by order No 201 of the Government of the Russian Federation of 19 March 2001.

To obtain reimbursement for purchased medicines and medical services a receipt of purchase and medical prescription with an official stamp, and a photocopy of the authorization of the healthcare institution. The reimbursement can be obtained not only for drugs purchased for the person but also for his or her children, parents and his or her partner.

Decision-makers on drug supply and relevant institutions influencing the process

National level

Duma is the lower house of the Federal Assembly - Parliament of the Russian Federation. The State Duma consists of 450 deputies. It adopts federal laws by a simple majority vote of all deputies unless otherwise provided by the Constitution of the Russian Federation.

Ministry of Health and Social Development is a federal executive authority which is in charge of working out a state policy as well as normative and legal regulations in the field of healthcare, social development, labor and protection of consumer rights.

Regional level

Ministries or Departments of Health coordinate certain regions of their own activities, providing medical and medical assistance to the population [6]. It also monitors the execution of the current legislation relating to the jurisdiction of the Department, public health, pharmacy and other institutions and enterprises, and other legal entities and individuals providing medical care services and access to medicines.

Decisions on programs are made by public officials. There are no transparent criteria of assessment.

Organizations of Health Technology Assessment (HTA)

Currently there is no official government agency for Health Technology Assessment in Russia. Several institutions such as Formulary Committee of the Russian Academy of Medical Sciences conducts clinical and economic analysis. Results are used as non-binding recommendations [7].

The level of medical organizations

Some hospitals conduct HTA and create hospital formularies, for example:

Central Clinical Hospital of the Russian Academy of Sciences, Moscow (multi-profile hospital of 600

beds including 18 therapeutic and surgical departments); Krasnoyarsk Regional Clinical Hospital (1270 beds, 17 therapeutic and surgical departments) and others.

Summary

As the result of the work a document which sets out the expert evaluation of health care financing system, carried out by major experts in this field in the Russian Federation has been prepared. Main provisions of health care financing, as a whole and in detail – ensuring access to medicines to patients are delineated in this article. The full version of the document in the English language will be posted within the international project " ISPOR road map" [9].

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Reimbursement of pharmaceuticals in the Czech Republic, Slovakia and Hungary – the update on reference pricing and risk sharing

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Abstract

There is a limited amount of published evidence, available to the international audience, on experiences from implementation of various initiatives within the field of pharmaceutical policies of the Czech Republic, Slovakia and Hungary. The reference pricing, both internal and external, has been introduced in the nineties of the 20th century in all countries of the Visegrad Group, however each country has developed its own local version. Hungary has the strongest experience related to the pharmaceutical risk sharing. Due to the economic crisis, the Hungarian health care system is under extremely strong pressure to keep pharmaceutical expenditures on a low level, which could possibly conflict with the appropriate provision of drugs. There is a well justified need for a more intensive exchange of experiences related to pharmaceutical pricing and reimbursement among the Visegrad Group countries - especially today, in the era of the global financial austerities.
Article contains current information on pharmaceutical reference pricing and risk sharing in Czech Republic, Slovakia and Hungary.

Key words: pharmaceutical policy, pharmaceutical pricing and reimbursement, reference pricing, risk sharing, Czech Republic, Slovakia, Hungary

Introduction

On 15th of February 1991, during a high-level meeting in Visegrad, Hungary, the Presidents of Poland (Lech Walesa) and the Czechoslovak Republic (Vaclav Havel) together with the Hungarian Prime Minister (Jozsef Antall) created a network of cooperation between their three neighboring countries. It was named the Visegrad Group and later, after the division of Czechoslovakia in 1994, the Visegrad Four or just simply V4. The idea of cooperation among countries of Central Europe (CE) could be closely linked to expectations, which had three other leaders, the Kings of Poland, Bohemia and Hungary, far back in time, in 1335. Those kings met exactly in the same place near today's Budapest in order to intensify cooperation and friendship between their states [1].

In June 2012 the Hungarian Journal for Healthcare Managers (IME) together with the Hungarian Health Economics Association (META) organized a big conference in Budapest on a vast array of current problems of health economics. Its title was quite self-explanatory: "Health economics, growing importance in scarcity". Large number of participants came mostly from Hungary and they included academics, professionals from fields of medicine, pharmacy, HTA and pharmaceutical policy, and industry representatives. From about 40 presentations and numerous posters, five lectures were clustered into one international session: "International reference pricing and individual price agreements in drug pricing". During that session the speakers analyzed problems of pharmaceutical policies in Hungary, the Czech Republic, Slovakia and Poland [2, 3, 4, 5]. The synthetic approach was also taken and all speakers, as well as the Hungarian audience, concluded that there are so many features and problems of the national health care systems, which are common to all four countries, that it would be unwise not to draw from the neighbor's experiences and to ignore lessons learned just behind the border.

There is much more evidence on pharmaceutical pricing and policy problems, published in English (being truly the "lingua Latina" of today's scientific world) and coming from countries, like the USA, the UK or even Australia - than evidence coming from countries of CE. Local environment, political culture, level of economic development and many other features and experiences of the CE

countries are often very different from those countries, which have been more extensively described in the scientific literature. It is also much easier to find the published evidence related to several far-away countries (in terms of either geography or important contexts influencing applicability of research conclusions), than to any country of the V4 Group. A "quick and dirty" test seems to be proving it. Exercise of typing into the Embase (date of testing: 29.08.2012) the search words "pharmaceutical", "reimbursement", combined by operator AND, and then adding alternatively the name of a given country, gives the following results: 348 records for the USA, 266 for the UK, 147 for Australia, 32 for the Czech Republic, 14 for Slovakia, 29 for Hungary and 28 for Poland. Many records relevant for the CE countries are available only in abstract forms, in the English language. Their full text versions turn out to be difficult to obtain and written in national languages. It seems that the old idea of cooperation among the CE countries, the same which gave rise to establishing the V4 Group more than 20 years ago, still waits for a more complete implementation, as it comes to the exchange of scientific knowledge and sharing evidence on health care policy developments. This paper presents some of the current problems of pharmaceutical pricing and reimbursement policy in CE and it utilizes lessons learned from the Budapest meeting of health economists.

The Czech Republic

Development of the current pharmaceutical pricing and reimbursement system in Czechia has been marked by four milestones [3]:

1. introduction of therapeutic groups in 1994,

2. generic substitution in 2007,

3. application of international reference pricing, using the EU lowest price as reference and introduction of provisional reimbursement in 2008,

4. introduction of electronic auctions and tight price regulations in 2012.

The Czech Republic regulates ex-factory prices of reimbursed pharmaceuticals and strives to achieve the lowest EU prices. For calculating the maximum price, the average price of the three lowest prices of a product in a basket of selected EU countries is being used. Since 2008, within framework of external (international) referencing, the lowest price of all drugs from therapeutic group, from the entire EU, has been used as a reference price for basic reimbursement. These processes in the Czech pharmaceutical pricing and reimbursement policy have been named "the double regulation". The internal and external referencing have been interrelated in the Czech Republic. Therapeutic groups (clusters) have been applied since 1994. There are more than 300 of them now and they differ in level of heterogeneity – from very low (e.g. ACE inhibitors) through intermediate (e.g. atypical antipsychotics) to very high (e.g. biological drugs like etanercept, infliximab, adalimumab, abatacept). The WHO system of ATC (Anatomical Therapeutic Chemical) classification of pharmaceuticals has been used in defining reference groups. There is a tendency to keep prices of drugs within therapeutic groups on a rather homogenous level, according to the rule that a surcharge rewarding superior, evidence-based benefits, in comparison to other drugs in the same group, should not exceed 30% above the basic reimbursement level within a group. About 60% of prescribed pharmaceuticals (measured by a number of packs sold) do not require co-payment higher than a small user fee introduced in 2008; slightly above EUR 1,00 [3, 6].

Besides the external and internal referencing, the application of HTA is considered one of the main pillars of the current drug reimbursement system in the Czech Republic. However, no specialized national HTA agency has been created so far. Instead, the State Institute of Drug Control serves as a hybrid institution responsible for simplified HTA application. The Ministry of Health is planning to implement new, more advanced HTA procedures in 2013, separating assessment from appraisal of health technologies. Risk sharing, which has been increasingly popular in many countries, over a span of recent years, has not been introduced yet into the Czech pharmaceutical reimbursement system [3].

Slovakia

The international reference pricing in Slovakia has been evolving. According to regulations of 2004 the ex-factory price could not exceed 110% of the average of the three lowest prices of the same drug sold across the EU. In practice, implementation of this rule was hampered by a poor access to relevant information and a weak political will. There was a noticeable impact of a relative

strength of the Slovak local currency (Slovakia entered the Euro zone on 01.01.2009), especially in 2005. Many drugs on the Slovak market between 2005 and 2007 had exceptionally high prices, as compared to countries of the EU. The pricing regulations were changed in 2008 and since then the price could not exceed the average of the six lowest prices of the same drug within the EU. Starting from 2012 the second lowest price within the EU has been used in order to set prices of drugs entering the Slovak market. The above regulations and recent changes have not influenced drug deliveries for the Slovak pharmaceutical market in a dramatic way. The impact of external reference pricing on the health care budget within last five years has been assessed positively [4].

The definition of reference group is narrow in Slovakia and it relates to drugs which contain the same active substance and are administered uniformly. Only in certain cases the health authorities (role of the Reimbursement Committee) may decide to create a separate reference group for pharmaceuticals having a different way of administration and a different amount of active substance per dose. The reimbursement from public sources is set as the maximum price for a standard daily dose in the reference group. Generic substitution has been in place since 2005, although in case of some active substances it has been prohibited, according to the list issued by the Minister of Health [7].

Application of HTA in pharmaceutical reimbursement decision-making is considered rather vague in Slovakia, although there have been on-going legislative changes, starting 2011, which should result in a stronger impact of HTA on the pharmaceutical reimbursement policy [8].

Hungary

Hungary regulates prices of reimbursed pharmaceuticals and setting them is being achieved through negotiations. Both external and internal referencing have been applied and the HTA has been used for new substances. The generic reference pricing was introduced in 1999 and in 2003 it was supplemented by the therapeutic referencing. Decisions on inclusion into drug groups were based on the ATC classification and the Defined Daily Doses of active ingredients [9]. The price of a new preparation cannot exceed the price from a group of selected countries. Starting 2007 the Hungarian government has been increasingly putting emphasis on fostering competition and refining the internal reference pricing. Introduction of more rigorous rules for excluding the most expensive products from competitive substance groups was a part of this new policy. Other pro-competitive measures have embraced liberalizing rules of ownership of pharmacies, increasing accountability of physicians in their prescribing behavior and more extensive use of information technologies in monitoring of the drug market [10].

The claw-back system is also in use and risk sharing, in the form of individual price-volume agreements on selected drugs, has been used since 2003. The partial repayments made by manufacturers are based on an agreed limit of a yearly volume of sales and the share of repayment changes progressively, depending on the level of overspending [10]. Outcome-based reimbursement schemes as a form of risk-sharing have become a part of a broader response to intrinsic problems of the Hungarian economy and the global crisis. As representatives of the National Health Insurance Fund Administration (in Hungarian: OEP) were reporting in 2009, the most important challenges related to design and implementation of those schemes were related to appropriate measurement of treatment outcomes, as well as both direct and indirect costs. Obtaining those data was necessary for calculation of expected payback and three main difficulties were identified with regard to this [11]:

1. low reliability of epidemiological data and general health outcome indicators,

2. frequent practices of subjecting the financing (DRG) data, through which indirect costs could be assessed, to profit-maximizing style of coding,

3. necessity to keep the administrative costs of these schemes on a reasonably low level.

The news from Hungary in the middle of summer of 2012 were rather disturbing. The OEP reported to be running out of funds in its pharmaceutical budget, since 80% of it were spent by the beginning of August. The injection of the substantial sum of USD 316, 39 million into the healthcare system's financial bloodstream has been reported to be necessary. This would prevent a financial crash of the system but the OEP reserves have been reported to be only USD 185, 31 million. This situation has been posing a threat of drug shortages and hampering patient access to medicines [12].

The problems of keeping spending within limits of the drug budget coincide with efforts of the state authorities to combat the economic crisis, which started with a sharp slow-down of the economy in 2007 and was quickly followed by the deep recession. Pharmaceutical spending was reduced in order to diminish the country's budget deficit. The current problems on the drug market can be at least partially explained by preceding cuts, written into the so-called Szell Kalman Plan, accorting to which Hungary can retain EU subsidies. Besides pharmaceutical budget cuts, other measures undertaken from 2011 onwards have already been included [13]:

• increasing (from 12 to 20%) the mandatory levy which pharmaceutical companies have to pay on sales of reimbursed drugs,

• doubling of the registration fee for pharmaceutical representatives,

• introduction of blind tenders for reimbursed drugs,

• monitoring and assessment of drug effectiveness (introduction of a system based on registers),

• imposing prescribing by international non-proprietary name for some drugs.

• planning to introduce electronic prescriptions in 2013.

Conclusions

The pharmaceutical reference pricing has different forms but a well-grounded position within health care systems of the Czech Republic, Slovakia, Hungary and Poland. The risk-sharing between payers and pharmaceutical industry still remains a novel tool in the Visegrad Group countries. Geographical proximity, common history and many features of health care systems, which are shared by all V4 countries, call for a more intense exchange of experiences related to pharmaceutical pricing and reimbursement - especially today, in the era of the global financial austerities.

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Rola dodatkowych ubezpieczeń zdrowotnych nowego typu (ubezpieczeń komplementarnych) w bilansowaniu systemu ochrony zdrowia w Polsce

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Streszczenie

Deficyt, czyli dysproporcja między wielkością środków a zawartością koszyka świadczeń, jest podstawową chorobą systemu. System ochrony zdrowia nie może być ani efektywny, ani sprawiedliwy, jeśli koszyk świadczeń zawiera więcej technologii medycznych niż możliwe jest do sfinansowania ze środków zebranych ze składki.

Jednym ze sposobów radzenia sobie z dysproporcją pomiędzy zawartością koszyka gwarantowanego a wielkością środków publicznych na ochronę zdrowia jest wprowadzenie dodatkowych ubezpieczeń zdrowotnych nowego typu – ubezpieczeń komplementarnych.

Patrząc na trendy zmian w systemach opieki zdrowotnej, wydaje się, że wprowadzenie dodatkowych ubezpieczeń komplementarnych konkurujących świadczeniami z koszyka negatywnego ma największe znaczenie oraz, że rynek dodatkowych ubezpieczeń innego typu będzie ograniczony a być może nawet marginalny.

Słowa kluczowe: ubezpieczenia dodatkowe, koszyk świadczeń gwarantowanych, ubezpieczenia komplementarne

Abstract

The deficit understood as the disproportion between the amount of funds in health care and the content of the package is the fundamental disease of the system. The health care system cannot be either effective or fair if the benefits package includes more health technologies than it is possible to finance from the funds collected from the basic contribution.

A way of dealing with the disproportion between the content and size of guaranteed benefits package and amounts of public funding for health care is to introduce a new type of health insurance i.e. complementary insurance.

Analysing trends in health care systems, it appears that the introduction of additional health insurance competing by benefits outside of the guaranteed benefits package will prevail and the market of other types of additional health insurance may become limited and perhaps even marginal.

Key words: additional health insurance, basic benefit package, complementary health insurance

Nawet najlepiej rozwinięte i najbogatsze kraje przykładają wielką wagę do racjonalnego wydatkowania środków na ochronę zdrowia, gdyż na opiekę zdrowotną - szczególnie mając na względzie obecne tempo rozwoju medycyny - można wydać każdą ilość pieniędzy. Sprawne zarządzanie koszykiem świadczeń zdrowotnych ma zasadnicze znaczenie dla regulacji systemu ochrony zdrowia oraz funkcjonowania ubezpieczeń zdrowotnych. Skoro ochrona zdrowia jest obszarem wrażliwym społecznie, o ogromnym i rosnącym znaczeniu dla gospodarki, to prawidłowe określenie w systemie, a następnie sprawne zarządzanie koszykiem świadczeń, należy traktować bardzo poważnie, jako jedno z najważniejszych zadań państwa.

Prawidłowe określenie i sprawne zarządzanie koszykiem pozwalają na zapewnienie:

1. bezpieczeństwa zdrowotnego społeczeństwa oraz poczucia bezpieczeństwa obywateli,

2. sprawiedliwego[1] dostępu do świadczeń zdrowotnych finansowanych w ramach składki określonego rodzaju,

3. bezpieczeństwa budżetu oraz racjonalności i przejrzystości wydatków publicznych na ochronę zdrowia,

4. bezpieczeństwa budżetów rodzinnych oraz racjonalności wydatków prywatnych na ochronę zdrowia,

5. oraz spełnienie postulatów[2] suwerenności, solidarności i konkurencji, przy zapewnieniu efektywności systemu ochrony zdrowia.

[1]Sprawiedliwy dostęp do świadczeń finansowanych ze składki podstawowej, a więc w ramach koszyka świadczeń gwarantowanych, zależy w zasadniczym stopniu od władz państwowych; sprawiedliwy dostęp jest tu więc rozumiany, jako wywiązywanie się państwa ze złożonych społeczeństwu obietnic; skoro pojawia się obowiązek prawny nakładany przez Konstytucję RP i ustawy, to pojawia się równocześnie odpowiedzialność za wypełnienie tych zobowiązań.
[2]Zgodnie z pracami prof. Janosa Kornaia.

Zgodnie z ustawą koszykową w Polsce, co do zasady[3], zawartość poszczególnych części koszyka świadczeń gwarantowanych określana jest przez Ministra Zdrowia za pomocą stosownych rozporządzeń. Rozporządzenia te dotyczą m.in.: programów terapeutycznych, ambulatoryjnej opieki specjalistycznej, podstawowej opieki zdrowotnej, opieki szpitalnej, świadczeń wysokospecjalistycznych, szczepień obowiązkowych itp.

Mimo tego, że Ministerstwo Zdrowia ustala teoretyczną zawartość koszyka, to właściwie płatnik ma zasadniczy wpływ na jego finalny kształt i zapewnienie „gwarancji" dostępu do tego, co w rozporządzeniach około koszykowych zostało zapisane. Chcąc uniknąć przekroczeń budżetowych Prezes NFZ „urealnia" koszyk gwarantowany, bezpośrednio wpływając na jego ostateczną realizację. W Polsce pozycja monopsonisty – NFZ jest bardzo silna. W związku z tym przerzuca się obciążenia na świadczeniodawców oraz pośrednio, ogranicza dostęp chorych do świadczeń zdrowotnych, poprzez takie mechanizmy jak: konkurs ofert (konkurs to oczywiście bardzo przewrotna nazwa w warunkach monopsonu), limity, warunki kontraktowania świadczeń i faktyczne ograniczenie wielkości kontraktów w oparciu o budżety historyczne świadczeniodawców.

W przypadku gdy koszyk tworzony jest „ponad stan", czyli zawiera więcej świadczeń zdrowotnych niż płatnik jest w stanie sfinansować w ramach posiadanych środków, powstaje deficyt. Deficyt ten może prowadzić do:

1. zadłużania się płatnika,

2. zadłużania się świadczeniodawców,

3. **ograniczania dostępu do świadczeń teoretycznie „gwarantowanych",**

4. wszystkich powyższych w różnych konstelacjach i w różnych proporcjach.

Wraz z napływem nowych technologii medycznych, konkurujących o środki ze składki podstawowej oraz w przypadku, gdy środki na ochronę zdrowia i finansowanie świadczeń zdrowotnych nie rosną, dysproporcja pomiędzy wielkością tych środków, a zawartością koszyka stale się powiększa. Prowadzi to do pogłębienia deficytów, ograniczenia dostępności do podstawowych świadczeń zdrowotnych, również przez istotny wzrost współpłacenia, niezależnie od jego formy.

Deficyt, czyli dysproporcja między wielkością środków a zawartością koszyka świadczeń, jest podstawową chorobą systemu. Ograniczenia dostępu do świadczeń „gwarantowanych", niezależnie od charakteru tych ograniczeń, uderzają zwykle w najsłabszych. Prowadzą do przerzucenia kosztów diagnostyki i leczenia na budżety rodzinne, pogorszenia stanu zdrowia społeczeństwa, choćby z uwagi na to, że wiele osób nie skorzysta z opieki zdrowotnej w ogóle oraz wzrostu takich zjawisk patologicznych w relacji lekarz-pacjent, jak łapówkarstwo i korzystanie ze „znajomości". Zadłużanie się monopsonisty-płatnika w Polsce nie występuje, stąd deficyt prowadzi do przerzucania ciężaru zobowiązań na państwo. Zadłużanie się publicznych świadczeniodawców, niezależnie od tego, kto jest ich właścicielem i organem założycielskim, powoduje konieczność okresowych oddłużeń i wzrost długu publicznego.

Tak czy inaczej, im większy deficyt tym system jest bardziej niesprawiedliwy oraz tym bardziej nasilają się patologie. System ochrony zdrowia nie może być ani efektywny, ani sprawiedliwy, jeśli koszyk świadczeń zawiera więcej technologii medycznych niż możliwe jest do sfinansowania ze środków zebranych ze składki.

Funkcjonujący dziś system ochrony zdrowia w Polsce jest od dawna niewypłacalny, a dysproporcja między stale rosnącą zawartością koszyka świadczeń gwarantowanych a wielkością środków z podstawowej składki zdrowotnej jest coraz większa. Kolejek jest coraz więcej i są coraz dłuższe. Reglamentacja świadczeń zdrowotnych, nawet tych podstawowych, skutecznych i tanich (o bardzo korzystnym stosunku kosztu do uzyskiwanego efektu zdrowotnego) jest powszechna. Wprowadzane limity w ramach kontraktowania świadczeń z monopsonistą NFZ, prowadzą do ustawicznego zadłużania się świadczeniodawców. Prywatne środki w ochronie zdrowia poza dyspozycją NFZ sięgają już 30 40 mld zł rocznie, a korupcja i korzystanie z przywileju, czy znajomości są na porządku dziennym.

Zgodnie z przyjętymi założeniami, można wyróżnić 4 podstawowe sposoby radzenia sobie z dysproporcją pomiędzy zawartością koszyka gwarantowanego a wielkością środków publicznych na ochronę zdrowia:

[3]Wyjątki mogą przewidywać odrębne ustawy, tak np. ustawa z dnia 12 maja 2011 roku o refundacji leków, środków spożywczych specjalnego przeznaczenia żywieniowego i wyrobów medycznych (Dz.U. Nr 122, poz. 696), tzw. „ustawa refundacyjna".

1. Istotne zwiększenie wielkości podstawowej składki zdrowotnej, czyli podatku na ochronę zdrowia

2. Wprowadzenie wysokiego współpłacenia

3. Usunięcie z koszyka świadczeń gwarantowanych wielu technologii medycznych o niskiej opłacalności (relatywnie wysokim stosunku kosztu do uzyskiwanych korzyści zdrowotnych)

4. Wprowadzenie komplementarnych ubezpieczeń zdrowotnych

Dzięki wprowadzeniu komplementarnych ubezpieczeń zdrowotnych można osiągnąć kilka celów jednocześnie – można m.in.:

• poprawić efektywność wykorzystania środków prywatnych wydawanych na ochronę zdrowia[4];

• wprowadzić możliwość wyboru dodatkowego ubezpieczenia dla obywateli (postulat suwerenności Kornai'a);

• wprowadzić mechanizmy konkurencji, zarówno w obszarze płatników, jak też pobudzić konkurencję pomiędzy świadczeniodawcami (postulat konkurencji Kornai'a);

• zlikwidować lub ograniczyć szarą strefę w ochronie zdrowia;

• zwiększyć wielkość środków w systemie bez podnoszenia podatków;

• zwiększyć dostępność do świadczeń zdrowotnych w koszyku gwarantowanym, dla tych których stać jedynie na płacenie składki podstawowej oraz tych, którzy korzystają z bezpłatnej opieki zdrowotnej (utrzymanie postulatu solidarności Kornaia i zwiększenie efektywności systemu jako całości);

• zasadniczo ograniczyć reglamentację świadczeń gwarantowanych, korupcję i korzystanie z niepisanych "przywilejów" w ochronie zdrowia, przez likwidację dysproporcji pomiędzy wielkością środków ze składki podstawowej a zawartością koszyka gwarantowanego;

• Inne.

Poza dyskusją jest konieczność zapewnienia stabilności prawa, w przeciwnym razie rynek ubezpieczeń dodatkowych w Polsce nie będzie atrakcyjny dla poważnych inwestorów. Również dla funkcjonowania koszyka świadczeń gwarantowanych w systemie ochrony zdrowia, zasadnicze znaczenie ma określenie ram regulacyjnej roli państwa, względem rynku ubezpieczenia powszechnego, w relacji do ubezpieczeń komplementarnych. Konieczność racjonalnej regulacji z uwagi na wyjątkowe cechy rynku świadczeń zdrowotnych jest w dzisiejszym świecie poza dyskusją, biorąc pod uwagę, zarówno pozytywne przykłady regulacji w takich państwach jak Holandia czy Australia, jak też negatywne przykłady wybiórczej regulacji np. w Stanach Zjednoczonych

Dla rozwoju **dodatkowych ubezpieczeń komplementarnych konkurujących świadczeniami** spoza koszyka gwarantowanego, czyli dla rynku ubezpieczeń dodatkowych o największym potencjale, najważniejsze znaczenie ma określenie wielkości koszyka świadczeń gwarantowanych jako całości. Chcąc zachować proporcjonalną zawartość do wielkości środków ze składki podstawowej, koszyk świadczeń gwarantowanych w Polsce powinien być znacznie mniejszy niż dziś opisany rozporządzeniami koszykowymi lub wielkość środków na jego realizację musi zostać zwiększona.

Teoretycznie im większy koszyk gwarantowany, czyli im więcej pieniędzy publicznych na obowiązkowe ubezpieczenie zdrowotne, tym mniej miejsca na rynkową grę towarzystw ubezpieczeń komplementarnych oraz tworzenie przez te instytucje swoistych produktów ubezpieczeniowych obejmujących świadczenia zdrowotne nie finansowane ze składki podstawowej. Wielkość rynku ubezpieczeń komplementarnych koreluje bowiem bezpośrednio z wielkością i zawartością koszyka gwarantowanego. Innymi słowy im większa będzie liczba świadczeń i procedur, które pozostaną poza koszykiem gwarantowanym oraz im większa ich „atrakcyjność" dla klientów, tym większy będzie potencjalny rynek ubezpieczeń komplementarnych, i odwrotnie.

Dla rozwoju **dodatkowych ubezpieczeń komplementarnych** od współpłacenia istotne jest:

• wprowadzenie obowiązkowych, istotnych wartościowo dopłat do świadczeń częściowo gwarantowanych, czyli określenie świadczeń zdrowotnych, do których istotne wartościowo współpłacenie jest wymagane;

[4]Parafrazując wypowiedź Wiceministra Zdrowia Jakuba Szulca z konferencji pt. „Rola i miejsce ubezpieczeń zdrowotnych w finansowaniu systemów ochrony zdrowia", która odbyła się w października 2010 r. w Warszawie: „Wydatki z kieszeni pacjentów (out of pocket) na finansowanie świadczeń zdrowotnych opłacanych na zasadach fee-for-service to najgorszy sposób wykorzystania prywatnych pieniędzy. Za te same środki, ale wykorzystane w systemie ubezpieczeniowym można by kupić znacznie więcej świadczeń zdrowotnych."

Świadczenia częściowo gwarantowane to świadczenia zdrowotne tylko częściowo znajdujące się w koszyku gwarantowanym, a częściowo poza nim. Choć rozwiązanie takie jest teoretycznie uzasadnione i praktycznie możliwe do wprowadzenia, to nawet przy sprawnie funkcjonującej agencji taryf, zajmującej się wyceną świadczeń na rynku zdrowotnym, i tak nie należy oczekiwać, żeby liczba świadczeń częściowo gwarantowanych szybko stanowiła istotną systemowo pulę.

• wprowadzenie obowiązkowych, drobnych opłat do każdej wizyty u lekarza czy hospitalizacji

To rozwiązanie również wydaje się mało prawdopodobne. Po pierwsze nie rozwiązuje problemu dysproporcji środków i zawartości koszyka, gdyż środki zgromadzone z takiego współpłacenia są stosunkowo niewielkie. Po drugie takie współpłacenie, jak pokazał przykład Czech, jest bardzo wrażliwe społecznie i ryzykowne politycznie.

• wprowadzenie udziałów własnych, czyli istotnych wartościowo dopłat do pierwszej wizyty u lekarza lub pierwszej hospitalizacji w danym okresie czasu, ze współmierną redukcją wysokości składki ubezpieczeniowej (tak, jak to funkcjonuje w Australii)

Mechanizm ten zwiększa postulat suwerenności i konkurencyjność na rynku ubezpieczeń, jednak trudno a priori przewidzieć jego wpływ systemowy i powszechność stosowania. Zależą one od szczegółowych rozwiązań prawnych niezbędnych do wprowadzenia ubezpieczeń komplementarnych od współpłacenia i zachęt państwa do zbudowanie powszechności korzystania z udziału własnego.

Dodatkowe ubezpieczenia suplementarne dotyczą zakresu świadczeń zdrowotnych z koszyka gwarantowanego. Dotyczą albo wyższego standardu usług (np. hotelowego) albo ułatwień w dostępie do świadczeń deficytowych w ramach powszechnego ubezpieczenia zdrowotnego. W tym pierwszym przypadku obejmują wszystkie świadczenia lub część świadczeń z koszyka gwarantowanego. Ubezpieczenia suplementarne, które funkcjonują w Polsce, rozwijają się wolno i dotyczą głównie podwyższonego standardu usług oraz szybszego dostępu do ambulatoryjnych świadczeń deficytowych w systemie publicznym.

Im większa dysproporcja pomiędzy wielkością dostępnych środków finansowych ze składki podstawowej a zawartością koszyka świadczeń gwarantowanych, czyli im więcej i im dłuższe kolejki, im większa korupcja i im częstsze przypadki „świadczeń dla wybranych", tym większy popyt na ubezpieczenia suplementarne oraz tym większy rynek tych ubezpieczeń.

Warto w tym miejscu podkreślić, że ograniczenie zawartości koszyka nie może być zwykle dokonane samodzielnie przez **ubezpieczenia substytucyjne**, gdyż stanowienie zawartości koszyka „gwarantowanego" jest poza nimi - najczęściej zarządza jego zawartością Minister Zdrowia. Prywatne ubezpieczenia substytucyjne muszą oferować ten sam zakres świadczeń co ubezpieczenia powszechne, a więc są „na łasce i niełasce" tych, którzy decydują o zawartości koszyka gwarantowanego. Innymi słowy, rozwój ubezpieczeń substytucyjnych, które muszą oferować ten sam koszyk gwarantowany co obowiązkowe ubezpieczenie zdrowotne, uzależniony jest od możliwości prawnych, ale również od możliwości wpływu ubezpieczeń substytucyjnych na zawartość koszyka gwarantowanego. W przypadku braku wpływu lub złego zarządzania koszykiem świadczeń gwarantowanych ryzyko finansowe ubezpieczeń substytucyjnych jest nieprzewidywalne, a więc ten obszar biznesowy nie jest atrakcyjny dla inwestorów prywatnych.

Wielkość środków ze składki podstawowej nie będzie się prawdopodobnie w najbliższych 10 latach istotnie zmieniać. W związku z tym, obszar/rynek świadczeń zdrowotnych do konkurencji ubezpieczeń komplementarnych pozostanie stały, z tendencją do zwiększania się wraz z rejestracją nowych technologii medycznych (lekowych i nielekowych / profilaktycznych, terapeutycznych i diagnostycznych). Z całą pewnością można oczekiwać istotnego wzrostu popytu na ubezpieczenia dodatkowe w najbliższych latach. Należy też zauważyć, że ew. działania ograniczające możliwość wprowadzenia ubezpieczeń komplementarnych konkurujących świadczeniami nie będą w stanie realnie tego trendu zahamować.

Możliwych rozwiązań organizacyjnych w zakresie ubezpieczeń dodatkowych oraz możliwych rodzajów ryzyka, które podlega ubezpieczeniu dodatkowemu jest bardzo wiele. Widząc podstawowe trendy zmian w systemach opieki zdrowotnej na świecie (starzenie się społeczeństw, rozwój medycyny i coraz liczniejsze, nowe technologie medyczne, ograniczone środki w ramach składki podstawowej i kryzys ekonomiczny na świecie, wzrost oczekiwań społecznych względem możliwości leczniczych itd.) można stwierdzić, że dysproporcja pomiędzy zawartością koszyka świadczeń

gwarantowanych oraz możliwościami finansowymi podstawowego ubezpieczenia zdrowotnego jest już w wielu krajach dotkliwa i z pewnością będzie się dalej pogłębiać w najbliższych latach. Wydaje się więc, że wprowadzenie dodatkowych ubezpieczeń komplementarnych konkurujących świadczeniami z koszyka negatywnego ma największe znaczenie oraz że rynek dodatkowych ubezpieczeń innego typu będzie ograniczony a być może nawet marginalny.

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Economic evaluation of acute lymphoblastic leukaemia treatment with clofarabine (Evoltra®) combined with chemotherapy for children and adolescents in Poland

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Abstract

Background: To evaluate the cost-effectiveness of using clofarabine (Evoltra®) in combination chemotherapy (cyclophosphamide + etoposide) vs. nelarabine and IDA-FLAG protocol (idarubicin, fludarabine, cytarabine, GCSF - Granulocyte Colony Stimulating Factor) for the treatment of acute lymphoblastic leukaemia among children and adolescents who have relapsed or are refractory, after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response (as a third-line therapy for patients qualifying for hematopoietic stem cell transplantation), in the Polish setting.

Methods: The economic analysis was conducted on the basis of results of a systematic review. The cost analysis was carried out from the public payer (the National Health Fund) perspective in Poland, assuming that Evoltra® is financed from public funds within the chemotherapy catalogue. Direct medical costs were taken into account. Medical resources usage was determined on the basis of the results of a survey conducted in Polish centers specialized in haematology and children's oncology. The time horizon corresponds to the patients' life expectancy. Costs and health effects were discounted at 5% and 3.5% rate, respectively. The cost threshold for an additional quality-adjusted life year (QALY) is in line with the requirements of the Agency for Health Technology Assessment and amounts to PLN 99,543.

Results: Gaining an additional life year due to the use of clofarabine instead of nelarabine and IDA-FLAG protocol is associated with the cost from the public payer perspective PLN 27,529 and 26,046 respectively within the lifetime horizon. Cost of additional quality-adjusted life year (QALY) has been estimated at PLN 32,600 and 30,336 respectively. The results of probability sensitivity analysis confirmed stability of conclusions from the basic analysis.

Conclusions: Clofarabine (Evoltra®) used in combination chemotherapy for recurrent or refractory acute lymphoblastic leukaemia in children and adolescents is highly cost-effective therapeutic option in Poland compared with nelarabine and IDA-FLAG regimen.

Keywords: clofarabine, cost effectiveness analysis, cost utility analysis, acute lymphoblastic leukaemia, leukaemia treatment costs, hematopoietic stem cell transplantation

Introduction

Acute Lymphoblastic Leukaemia (ALL) is a cancer deriving from progenitor cells of the hematopoietic and lymphatic system [1]. The disease develops as a result of cancer cells proliferation in bone marrow and displacement of normal haematopoiesis or as a result of cancer cells accumulation in other organs outside bone marrow. In Poland, leukaemia account for 30% of all cancers among children, whereas acute lymphoblastic leukaemia account for 75%-80% of all forms of leukaemia among children aged less than 18 and approximately 20% of all types of leukaemia among adults [2,3]. Peak incidence occurs between age of 2 and 5 years.

Direct causes of acute lymphoblastic leukaemia are not fully known yet. Potential factors contributing to the development of the disease are: exposure to pathogenic agents, the influence of the environment and genetic predisposition [1,4,5]. In most patients non specific symptoms are reported (we-

akness, infection with fever and inflammatory lesions or even abscesses in the nasopharynx, loss of appetite) 2-6 weeks before the confirmed diagnosis [2].

Treatment leads to a complete remission in more than 95% of patients, however, approximately 20-30% of patients suffer from a relapse which remains the most frequent reason of a treatment failure and is associated with poor prognosis. Relapse of acute lymphoblastic leukaemia results from clones of the remaining leukemic blasts resistant to the first-line treatment. The blasts biological characteristics, including immunophenotype, might have a big impact upon selecting the right treatment strategy [4]. Thus relapse of acute lymphoblastic leukaemia poses a serious clinical problem. In Poland, the first relapse of ALL is diagnosed in 30–40 children every year.

In an acute lymphoblastic leukaemia therapy following the failure of all prior treatments for children and adolescents, clofarabine (Evoltra®), nelarabine and IDA-FLAG chemotherapy regimen (idarubicin, fludarabine, cytarabine and a granulocyte colony-stimulating factor (G% CSF)) are currently used in Poland.

According to the epidemiology data presented in reports of Oncology Center in Warsaw the incidence rate for lymphoid leukaemia (including lymphoblastic leukaemia) was 3.2/100,000 among boys aged up to 19 and 2.8/100,000 among girls aged up to 19 [6] in 2009 [6]. Based on the epidemiology data in Poland and around the word the disease is categorized as rare. Rare diseases are often life-threatening or chronically debilitating, constituting a serious health problem for the society and are considered a priority in EU health and scientific research programs [7,8]. Usually there is no effective treatment, but screening for early diagnosis, followed by suitable care, can improve quality of life and life expectancy.

Medicinal products used in rare diseases are commonly referred to as orphan drugs.

On February 2, 2002, Evoltra® was labeled as an orphan medical product used for treatment of acute lymphoblastic leukaemia in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response [9].

The aim of this analysis is to evaluate the cost effectiveness of using clofarabine (Evoltra®) in combination chemotherapy (cyclophosphamide + etoposide) vs. nelarabine and IDA-FLAG protocol (idarubicin, fludarabine, cytarabine, G-CSF) for recurrent and refractory acute lymphoblastic leukaemia among children and adolescents, after receiving at least two prior standard lines and in case there are no other options enabling to predict a long-term response (as a third-line therapy, used among patients qualified for hematopoietic stem cell transplantation), given the Polish market conditions.

The cost-effectiveness evaluation of clofarabine includes most common therapeutic scheme in Poland, i.e. clofarabine combination treatment according to the Locatelli's scheme which encompasses clofarabine (a dose of 40 mg/m2), cyclophosphamide (400 mg/m2) and etoposide (150 mg/m2), used for 5 consecutive days as an intravenous infusion [10]. Locatelli's scheme is recommended by the Polish (Polish Union of Oncology 2011) and international (National Cancer Institute 2012) guidelines for clinical practices for patients when there is no response to acute lymphoblastic leukaemia relapse treatment among children and adolescents [11,12].

Materials

The economic assessment was based upon a clinical effectiveness analysis using a systematic review approach. As part of the clinical effectiveness analysis, after reviewing medical databases, studies were qualified for analyses based on their subject matter and reliability. Then clinical effectiveness and safety results were combined with each other for individual methods of handling patients from the group analysed. The evaluation of clinical data credibility was carried out pursuant to the principles of Evidence-Based Medicine (EBM) [13].

Clofarabine's clinical effectiveness assessment was carried out in comparison to the reimbursed technologies:

• chemotherapy according to IDA-FLAG protocol - for T-cell and B-cell lymphoblastic leukaemia;

as well as compared to:

• nelarabine which may be considered a comparator for clofarabine only in case of T-cell acute lymphoblastic leukaemia due to its registered indication for treatment of patients with T-cell acute

lymphoblastic leukaemia (T-ALL) and a T-cell lymphoblastic lymphoma.

Methods

Research techniques

Based on the results of the systematic review, a cost effectiveness analysis and a cost utility analysis were performed for using clofarabine in combination chemotherapy (cyclophosphamide + etoposide) vs. nelarabine and IDA-FLAG.

The results of a systematic review indicated lack of studies directly comparing clofarabine with any alternative therapy in the analysed indication and lack of clinical studies concerning the use of clofarabine compared with other drugs which might potentially be used as a common comparator for an indirect comparison (clinical studies for the clofarabine found while examining medical databases were without clinical control group).

Given the above, and due to the fact that clofarabine is an orphan drug it was not possible to conduct a standard direct or indirect comparison, a clinical analysis was carried out using an indirect comparison without adjustment towards a common comparator (the so-called "naïve" indirect comparison). Pursuant to the Minister of Health's Ordinance of April 2, 2012, the analysis includes a list of data from separate clinical studies for clofarabine, nelarabine and chemotherapy according to IDA-FLAG protocol, compared against a natural course of the disease (understood as lack of causal treatment, i.e. applying placebo or the best available palliative care) [14].

The economic analysis comprises the following assessment:

• A list of health results and the costs of using comparable methods as part of the so-called "naïve" indirect comparison

• A calculation of cost-effectiveness and cost-utility ratios for the technology and optional technologies.

Within the cost effectiveness and cost utility analysis the costs per life year gained (LYG) and quality adjusted life year (QALY) gained were calculated in case of replacing nelarabine or IDA-FLAG with clofarabine (Evoltra®), in children and adolescents with recurrent or refractory acute lymphoblastic leukaemia after using at least two standard treatment cycles (as part of the third-line therapy), over a lifetime horizon, from the public payer perspective in Poland.

The description and assumptions of the model

The model assumes that a patient treated for recurrent or refractory acute lymphoblastic leukaemia among children and adolescents, after using at least two previous standard treatments and in case there are no other options enabling the prediction of a long-term response within the third line of therapy, receives clofarabine (Evoltra®) in combination with chemotherapy, nelarabine or IDA-FLAG. Using clofarabine, nelarabine or IDA-FLAG within the third course of therapy of acute lymphoblastic leukaemia may result in a complete remission (CR), a partial remission (PR), a complete remission without platelet recovery (CRp) or no objectively verified response (NoR). After the use of clofarabine, nelarabine or IDA-FLAG regimen, the patient may have received the hematopoietic stem-cell transplantation (HSCT). With regard to patients who received clofarabine, nelarabine or chemotherapy according to IDA-FLAG protocol within the third course of therapy of acute lymphoblastic leukaemia and then received HSCT and lived for over 2 years after the transplantation, the life expectancy after HSCT was based upon the expectancy for a person from the general population of Poland, with the same age as the patient. Patients who received clofarabine, nelarabine or IDA-FLAG within the third course of therapy of acute lymphoblastic leukaemia and then were subject to HSCT were considered to live over 2 years, 1-2- years, or up to 1 year. Survival of the patients either those who were subjected to HSCT or were not subjected to HSCT was based on the studies: clofarabine, nelarabine and IDA-FLAG [10,15,16,17,18,19,20]. Based on study only one patient with ALL that received IDA-FLAG had CR and HSCT and survived 2 months (the decision tree Figure 3. for IDA-FLAG treatment reflects the patients disease course from the study [20]).

A simulation was conducted using a decision-tree with time horizon determined at the level of life expectancy of a patient from the analysed population. The scheme of the decision model trees considered in the analysis is shown in the figures (Figure 1, Figure 2, Figure 3).

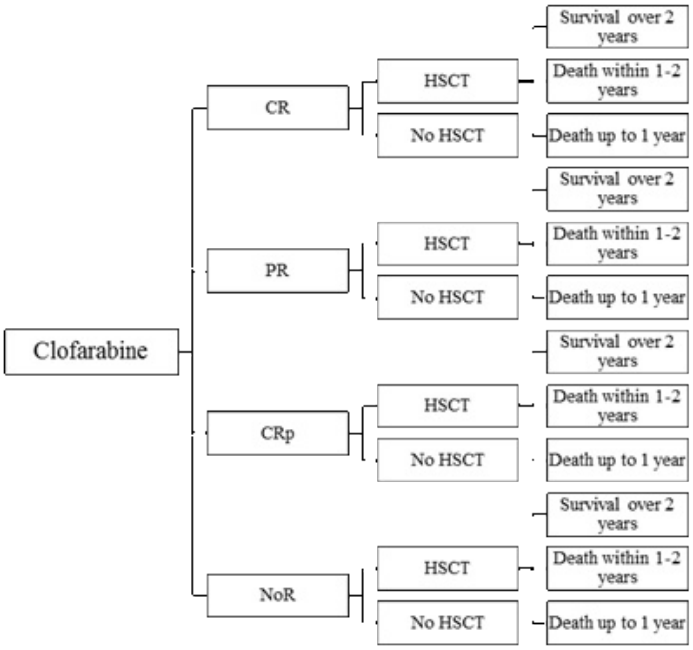

Figure 1. Decision model tree for clofarabine

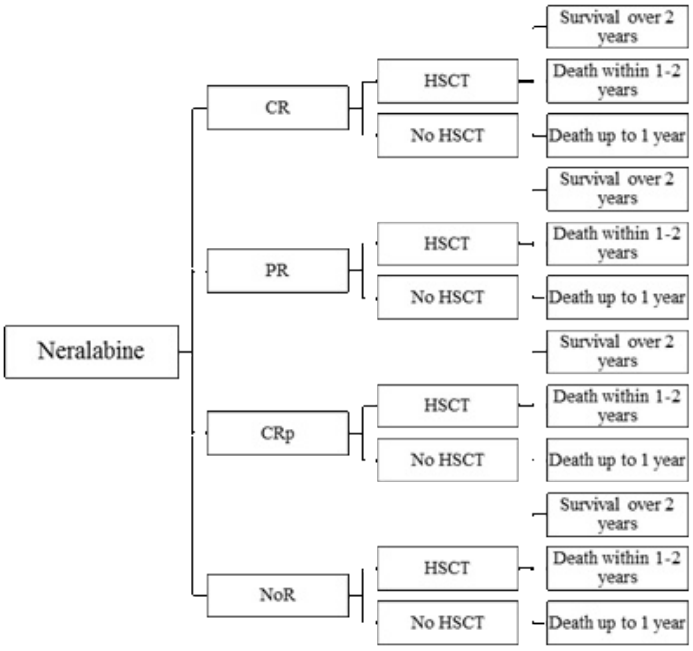

Figure 2. Decision model tree for nelarabine

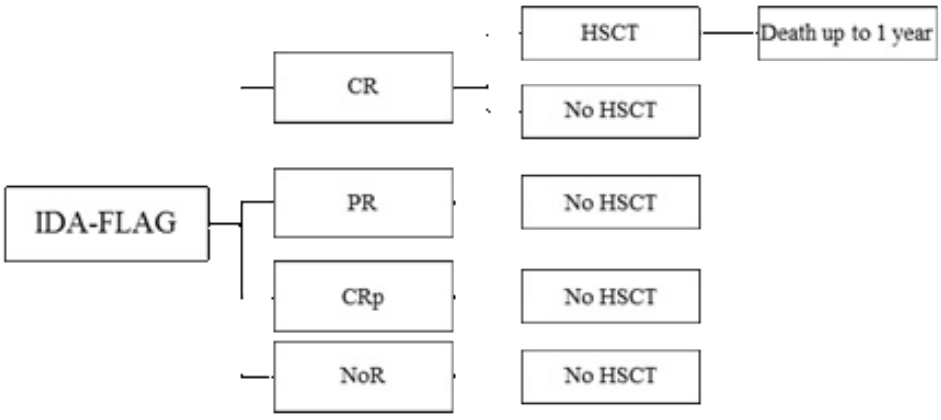

Figure 3. Decision model tree for IDA-FLAG protocol

Clinical data

The probabilities and data sources for the occurrence of a response to treatment, the probability of receiving HSCT and the general survival after HSCT following the application of the schemes are shown in Table 1.

Table 1. Health response for clofarabine combination therapy, nelarabine, IDA-FLAG

Parameter		Mean	Lower Confidence Interval [LCI]	Upper Confidence Interval [UCI]	Source
% of patients with treatment response					
Clofarabine combination therapy	CR	52.00%	32.82%	70.88%	[10]
	PR	8.00%	1.03%	21.12%	
	CRp	4.00%	0.11%	14.25%	
Nelarabine	CR	12.82%	4.41%	24.80%	[15, 19]
	PR	2.56%	0.07%	9.25%	
	CRp	10.26%	2.94%	21.38%	
IDA-FLAG	CR	22.22%	3.19%	52.65%	[20]
	PR	11.11%	0.32%	36.94%	
	CRp	0.00%	-	-	
% of patients who underwent HSCT					
Clofarabine combination therapy	CR	53.85%	27.67%	78.91%	[10]
	PR	0.00%	-	-	
	CRp	0.00%	-	-	
	NoR	0.00%	-	-	
Nelarabine	CR	60.00%	19.41%	93.24%	[15, 16, 17, 18, 19]
	PR	100.00%	-	-	
	CRp	25.00%	0.84%	70.76%	
	NoR	10.34%	2.27%	23.50%	
IDA-FLAG		Individual patient data from the study [20]: HSCT was conducted in one patient with CR			
Survival after HSCT					

Clofarabine combination therapy	< 1 year	57.14%	22.28%	88.19%	[10]
	Between 1 and 2 year	0.00%	0.00%	0.00%	
Parameter	**Mean**	**0.00%**	**Lower Confidence Interval [LCI]**	**Upper Confidence Interval [UCI]**	**Source**
therapy	> 2 years	42.86%	-	-	
Nelarabine	< 1 year	75.00%	29.24%	99.16%	[15, 16, 17, 18, 19]
	Between 1 and 2 year	25.00%	0.84%	70.76%	
	> 2 years	0.00%	-	-	
	Patients lost from observations	7.69%	1.66%	17.75%	[*]
IDA-FLAG		Individual patient data from the study [20]; one patient survived after HSCT 2 months from transplantation.			

* The proportion of patients lost from observation and alive at the latest visit was tested as the potential proportion of patients surviving longer than 2 years after HSCT.

Table 2. Adverse events

Parameter		**Mean**	**LCI**	**UCI**	**Source**
Clofarabine combination therapy (*)	Febrile neutropenia	8.0%	1.0%	21.1%	[10]
	Neutropenia	0.0%	-	-	[10]
	Sepsis and bacteraemia	32.0%	15.6%	51.1%	[10]
	Respiratory distress	4.0%	0.1%	14.2%	[10]
	Hepatic dysfunction and/or hyperbilirubinemia	24.0%	9.8%	42.2%	[10]
	Central nervous system dysfunctions	4.0%	0.1%	14.2%	[10]
	Mucositis	12.0%	2.7%	27.0%	[10]
Nelarabine	Central nervous system dysfunctions	9.8%	5.3%	15.3%	[15]

IDA-FLAG	Febrile neutropenia	92.0%	78.9%	99.0%	Due to lack of individual patient data from the study [20] aggregated data for Acute Myeloid Leukaemia and Acute Lymphoblastic Leukaemia were included
	Mucositis	32.0%	15.6%	51.1%	

(*) In the analysis it was assumed that adverse events presented in the publication [10] correspond respectively to: febrile neutropenia correspond to metabolic/laboratory treatment related toxicity, sepsis and bacteraemia correspond to infections, respiratory distress correspond to lung, hepatic dysfunction and/or hyperbilirubinemia correspond to hepatic.

The analysis includes adverse events (grade ≥ 3) influencing quality of life and generating treatment costs from the public payer perspective (febrile neutropenia, neutropenia, sepsis and bacteraemia, respiratory distress, hepatic dysfunction, central nervous system dysfunctions and mucositis). The probability of occurrence of these events is presented in Table 2.

Utility data

The occurrence of a neoplastic disease and then oncology treatment is related with lower quality of life. Due to lack of available data on the quality of life of patients from the analysed population, values of utility coefficients were determined based on the results of a questionnaire conducted in 4 centers specialized in children's haematology and oncology. The experts were asked to assess the quality of life on the scale 0-1 with respect to patient clinical state. The results of the survey regarding quality of life are shown in Table 3.

Costs

Cost analysis was carried out from the public payer perspective, assuming that Evoltra® was financed from public funds within the Catalogue of Chemotherapy Drugs [21].

The following cost categories important from the public payer perspective, were identified:

• Clofarabine costs (Evoltra®), cyclophosphamide and etoposide chemotherapy, nelarabine, IDA-FLAG chemotherapy (idarubicin, G-CSF, fludarabine, cytarabine), antiemetics and costs of pharmacotherapy administration;

Table 3. Patients' quality of life

Patient clinical state		Quality of life	LCI	UCI
Patient received palliative care		0.26	0.12	0.43
Patient received clofarabine (or other treatment), lack of HSCT		0.34	0.18	0.53
Patient received clofarabine (or other treatment) and HSCT and survived less than 1 year after HSCT		0.48	0.31	0.65
Treated with clofarabine, and surviving in:	1 year from HSCT	0.80	0.38	0.99
	2 years from HSCT	0.85	0.55	0.99
	next years	0.88	0.64	0.99

• Costs of a hematopoietic stem cell transplantation (HSCT) and related complications;

• Costs of treating adverse events in the third-line therapy of acute lymphoblastic leukaemia;

• Costs of the patient's condition monitoring after treatment;

• Costs of the best supporting care (BSC).

Costs are listed in Table 4.

Costs relevant for August 2012 were implemented to the analysis. While identifying medical resources used in the treatment of patients from the analysed population, the results of a survey conducted among clinical experts from medical centers specialized in children's haematology and oncology in Poland were considered.

Discounting of health effects and costs was taken into consideration with the yearly discount rate of 3.5% for health effects and 5.0% for costs.

The cost utility threshold in Poland, according to the requirements of the Agency for Health Technology Assessment, was estimated at PLN 99,543 (three times the expected GDP per capita per year).

Sensitivity analysis

A deterministic and probabilistic sensitivity analysis for the results of the economic analysis were conducted. The probabilistic sensitivity analysis indicate the probability of cost effectiveness of using clofarabine in comparison to nelarabine and IDA-FLAG, with regard to the cost effectiveness threshold at a level of PLN 99,543.

Results

The analysis was based on systematic review of clinical trials. The study demonstrated that treatment with clofarabine combined with chemotherapy (cyclophosphamide and etoposide), based on the Locatelli protocol, leads to good treatment results in patients with acute (recurrent and refractory) lymphoblastic leukaemia [10]. The improvement of response rate was also demonstrated in studies for nelarabine (treatment of T-cell ALL) and IDA-FLAG protocol [15,16,17,18,19,20]. Good response rate in these patients, increases the probability for a hematopoietic stem cell transplantation leading to long term survival.

The results of costs-consequences analysis for clofarabine in combination therapy, nelarabine and IDA-FLAG in lifetime horizon and from the public payer perspective are presented in Table 5. The table summarize the results in terms of life years, quality adjusted life years and cost categories important from the public payer (National Health Fund, NHF) perspective for each analysed therapy. Clofarabine combination therapy brings 3.61 life years (LY) and 2.83 quality adjusted life years (QALY) with total cost equal to 178,120 PLN in the lifetime horizon. Nelarabine therapy brings 0.46 LY and 0.17 QALY with total cost equal to 91,404 PLN in the lifetime horizon while IDA-FLAG brings 0.64 LY and 0.28 QALY with total cost equal to 100,764 PLN.

The results of the analysis indicated that using clofarabine in combination therapy in patients from the analysed population is associated with higher costs but with better health outcomes with regard to nelarabine and IDA-FLAG.

Incremental cost effectiveness ratio (ICER) and incremental cost utility ratio (ICUR) are presented in Table 6.

Gaining an additional life year resulting from the use of clofarabine in combination chemotherapy (cyclophosphamide + etoposide) in place of nelarabine and IDA-FLAG is associated with the cost of PLN 27,529 and 26,046 respectively, for the public payer in the lifetime horizon. Gaining an additional quality-adjusted life year (QALY) costs PLN 32,600 and 30,336 respectively.

As part of the deterministic sensitivity analysis for the economic analysis evaluating the use of clofarabine in combination therapy, 3 parameters most influencing results of the analysis were identified: the probability of surviving less than a year after a transplantation following the use of clofarabine in combination treatment, the probability of surviving less than a year after a transplantation following the use of nelarabine and the life expectancy of a patient who lived for over 2 years after HSCT. A change to other parameters covered in the deterministic sensitivity analysis does not result in different conclusions from the basic analysis when it comes to the cost utility assessment of using clofarabine in combination therapy instead of nelarabine or IDA-FLAG.

The results of the probabilistic sensitivity analysis (Table 7) indicate that the probability of cost-effectiveness of using Evoltra® in combination therapy, with a cost-effectiveness threshold of PLN

Table 4. Costs important from the public payer perspective

	Parameter	Mean	LCI	UCI	Source
Total cost of drug (1 cycle)	Clofarabine	5,307 PLN	3,649 PLN	7,271 PLN	Questionnaire study
	Nelarabine	5,265 PLN	3,616 PLN	7,219 PLN	
	IDA-FLAG	3,120 PLN	-	-	
Monitoring cost per cycle		858 PLN	735 PLN	991 PLN	Questionnaire study
Best supportive care (BSC) – yearly cost		9,251 PLN	8,098 PLN	10,481 PLN	Questionnaire study
Adverse events	Febrile neutropenia	11,197 PLN	9,595 PLN	12,922 PLN	Questionnaire study
	Neutropenia	10,443 PLN	8,127 PLN	13,046 PLN	
	Sepsis and bacteraemia	6,266 PLN	4,438 PLN	8,404 PLN	
	Respiratory distress	11,880 PLN	8,207 PLN	16,223 PLN	
	Hepatic dysfunction and/or hyperbilirubinemia	3,016 PLN	3,016 PLN	3,016 PLN	
	Central nervous system dysfunctions	1,300 PLN	1,012 PLN	1,623 PLN	
	Mucositis	1,508 PLN	1,406 PLN	1,607 PLN	
GVHD		19,240 PLN	-	-	Questionnaire study
Costs of HSCT and complications of HSCT	Cost HSCT	206,950 PLN	184,066 PLN	231,155 PLN	Questionnaire study
	Serious adverse events	3,860 PLN	1,991 PLN	6,337 PLN	
	Infection complications treatment	4,297 PLN	2,427 PLN	6,691 PLN	
	Non infections complications treatment	1,400 PLN	513 PLN	2,725 PLN	
	Prevention of the disease - GVHD	7,995 PLN	-	-	
	Other	776 PLN	-	-	

Table 5. Costs-consequences analysis for the basic scenario, results per 1 patient

Endpoint		Clofarabine	Nelarabine	IDA-FLAG
Life years		3.61	0.46	0.64
Quality adjusted life years		2.83	0.17	0.28
Cost categories important from the NHF perspective	Cost of Evoltra®	102,611PLN	0 PLN	0 PLN
	Other drugs cost	399 PLN	29,847 PLN	61,261 PLN
	Drug administration costs	5,730 PLN	9,161 PLN	4,493 PLN
	Monitoring costs	927 PLN	1,493 PLN	1,236 PLN
	Adverse events costs	4,333 PLN	127 PLN	10,784 PLN
	HSCT costs	62,617 PLN	48,125 PLN	21,809 PLN
	BSC costs	1,503 PLN	2,652 PLN	1,182 PLN
Total cost from payer perspective		178,120 PLN	91,404 PLN	100,764 PLN
Cost effectiveness ratio (CER)		49,341 PLN	198,705 PLN	157,443 PLN
Cost utility ratio (CUR)		62,940 PLN	537,673 PLN	359,870 PLN

Table 6. Incremental results of the basic analysis

	Difference in:	vs. nelarabine	vs. IDA-FLAG
Clofarabine in combination therapy	Life years gained	3.15	2.97
	Quality adjusted life years gained	2.66	2.55
	Public payer perspective cost	86,715 PLN	77,356 PLN
	ICER from public payer perspective	27,529 PLN	26,046 PLN
	ICUR from public payer perspective	32,600 PLN	30,336 PLN

Table 7. Probabilistic sensitivity analysis results - the probability of cost-effectiveness of the clofarabine

Condition	Comparator	Probability of cost-effectiveness of clofarabine in combination therapy
Probability that ICER<99 543	Nelarabine	97.1%
	IDA-FLAG	96.5%
Probability that ICUR<99 543	Nelarabine	95.2%
	IDA-FLAG	95.3%

99,543 for a life-year gained (LYG) from the public payer perspective is equal to:

• 97.1% in comparison to nelarabine

• 96.5% in comparison to IDA-FLAG.

The probability of cost-effectiveness of using Evoltra® in combination therapy, with a cost-effectiveness threshold of PLN 99,543 for a quality adjusted life year (QALY) gained from the public payer perspective is equal to:

• 95.2% in comparison to nelarabine

• 95.3% in comparison to IDA-FLAG.

Discussion

Acute lymphoblastic leukaemia is a rare disease which, according to the definition by the European Union, means that its morbidity does not exceed 5 cases per 10 thousand persons.

In case of drugs for rare diseases (which are defined as orphan drugs), a simplified registration procedure is applied – clofarabine was registered in a special course in the United States and the European Union on the basis of phase II studies. This is due to the fact that there is no other effective medical therapy which might be applied in patients when two previous therapies have failed or in patients who are resistant to standard chemotherapy. So far patients might have been offered IDA-FLAG chemotherapy protocol, nelarabine (in case of T-cell acute lymphoblastic leukaemia) or palliative care aimed at alleviation of disease symptoms in the last few months before death.

The limitations of the analysis are related with the character of the health problem (orphan drug used in rare disease) and restrictions of the clinical studies based on which the analysis was conducted. The studies found in the systematic review and included in the analysis were characterized by low quality resulting from lack of control group, small patient size and related with it wide range of variability of parameters. Despite the limitation of the studies, these are the most reliable and available clinical trials assessing the use of clofarabine combination therapy, nelarabine and IDA-FLAG protocol in the analysed disease. Also the limitations of the analysis result from lack of data on patient quality of life from the analysed population which made it necessary to conduct a survey.

At present, the main therapeutic goal in case of acute lymphoblastic leukaemia (ALL) in children and adolescents is to get remission of the disease and then to perform a hematopoietic stem cell transplantation which may result in recovery and long-term survival. Remission that enables HSCT for patients with refractory or recurrent acute lymphoblastic leukaemia with a poor prognosis can be obtained as a result of treatment with clofarabine, which is a significant breakthrough for these patients.

In spite of adverse events reported in clinical studies, the safety profile of Evoltra seems to be acceptable for acute lymphoblastic leukaemia, in particular among the population of patients who are often subjected to frequent and exhausting cycles

of chemotherapy. It also needs to be mentioned that in 40% of patients who have been treated with clofarabine in combination with chemotherapy at a lower dose, i.e. 40 mg/m2 of body surface area (Locatelli protocol), no adverse reactions were reported [10]. For patients receiving Locatelli regimen, no case of the most severe complication of transplantation i.e. Graft-Versus-Host Disease (GvHD) was reported.

Therapy with clofarabine provides patients with refractory or recurrent acute lymphoblastic leukaemia, with two previous unsuccessful chemotherapies, a chance to become cured when there are no other therapeutic alternatives left. Therefore, although some patients treated with clofarabine may not respond to the therapy, it is recommended to use this medicinal product as an agent which may allow proceeding to the next stage of the therapy, i.e. HSCT, which is deemed to be curative therapy.

The analysed clinical trial allowed demonstrating that treatment with clofarabine combined with chemotherapy (cyclophosphamide and etoposide), based on the Locatelli protocol, leads to better treatment results in patients with acute (recurrent and refractory) lymphoblastic leukaemia [10]. This combination with clofarabine results in good response in these patients, thus increasing the probability for a hematopoietic stem cell transplantation leading to long term survival.

The analysis showed treatment with Evoltra® of the analysed disease under Polish conditions is highly cost-effective from the public payer perspective compared with reimbursed optional therapies (nelarabine, IDA-FLAG). Gaining an additional life-year by using clofarabine in combination with chemotherapy (cyclophosphamide + etoposide) instead of nelarabine and IDA-FLAG regimen is equal to PLN 27,529 and 26,046 respectively, in lifetime horizon from the public payer perspective. Gain of an additional quality-adjusted life-year (QALY) is estimated at PLN 32,600 and 30,336 respectively. It is far below the cost effectiveness threshold of PLN 99,543. The cost-effectiveness analysis for orphan drugs such as clofarabine might be conducted on the basis of non-standard criteria and might allow accepting the cost of an additional life-year in perfect health higher than the standard cost effectiveness threshold of PLN 99,543. The triple value of GDP per capita, i.e. 99,543, for a therapeutic effect (LYG or QALY gained) is a threshold recommended by WHO in case of standard cost-effectiveness analyses which do not cover rare diseases. In United Kingdom, the cost effectiveness threshold for products which are used in rare diseases is GBP 200-300k, i.e. 10 times more than the cost effectiveness threshold for "standard" medications – ones that are not defined as orphan drugs [23].

Treatment with clofarabine (Evoltra) can considerably increase the survival of patients especially those that undergo HSCT, which in case of neoplastic condition is, apart from quality of life, a key indicator of therapy effectiveness.

Conclusions

The economic analysis demonstrated that the use of clofarabine (Evoltra) in combination with cyclophosphamide and etoposide in Poland is cost-effective when compared to nelarabine and IDA-FLAG in lifetime horizon in recurrent and refractory acute lymphoblastic leukaemia among children and adolescents, after receiving at least two prior standard lines and in patients where other options that predict a long-term response are limited.

Disclosures

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Economic and social burden of cystic fibrosis in Poland. Estimates based on patients - reported data

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Abstract

Cystic fibrosis (CF) is a genetic disease inherited as an autosomal recessive disorder. With an incidence of 1:2500 to 1:3000 in white race population it can be regarded as the most common rare disease. Taking into account clinical characteristics of patients, CF may place a substantial burden on a population both from social and economic point of view. The aim of the study was to estimate the cost of CF treatment in Poland with a special emphasis on outpatient treatment. Selected medical and social aspects were also investigated. Survey study was conducted on the sample of 100 children and adolescents patients. Indirect costs linked to lost productivity and a cost of care could be 4 fold higher then direct costs. Medication and diet costs are main components of direct costs. Life satisfaction is deteriorated in the vast majority of studied CF patients.

Key words: cystic fibrosis, costs, Poland, health economics, burden of disease, patient-reported costs

Introduction

Cystic fibrosis (CF) is a genetic disease inherited as an autosomal recessive disorder. The incidence of this disease in white race population varies from 1:2500 to 1:3000, but carriers of this genetic defect are many more - about 1 in 20 people (5%) [1]. A cause of the disease is a mutation of a gene responsible for synthesis of membrane chloride channel CFTR (cystic fibrosis transmembrane conductance regulator) which is located on the long arm of chromosome 7 [2]. There were identified about 1600 different mutations of the cystic fibrosis gene till September 2011. The mutation causes lesion of the transport of sodium and water by the cells of exocrine glands, which affects especially the respiratory and digestive system [3,4]. Most of the patients develop multi-organ dysfunctions, but the quality and life expectancy is usually determined by the changes in the respiratory system [5,6]. Treatment of the disease is mainly supportive care and consists of diet (including fat-soluble vitamins supplementation [7]), pancreatic enzymes supplementation, physiotherapy [8,9,10,11,12]. Exacerbation of a broncho-pulmonary disease (one of CF's complication) usually needs inclusion of antibiotic, bronchodilators and mucolytic therapy.

Materials and Methods

The aim of the study was to estimate the cost of cystic fibrosis (CF) treatment in Poland with a special emphasis on outpatient treatment. Selected medical and social aspects were also investigated including estimation of indirect costs. The inclusion criteria were: patients with diagnosed cystic fibrosis, aged 1-18 years old, treated in the two biggest paediatric centres in Warsaw, providing treatment for all Polish citizens.

Data on costs of main resource groups used in CF treatment were obtained from a survey study from patients or/ and their care-givers. Information was collected with a use of specifically designed, standardised and validated questionnaire during face to face interviews. Individual personal data were blinded, information about age and gender was further processed. Medical aspects covered: date of the disease diagnosis, parents' first reaction to diagnosis, main symptoms and influence on life quality of life.

As far as economics of CF outpatient treatment is concerned, methods of exacerbations' treatment and management were investigated, coupled with drugs, special diet, specialized equipment, health care professionals' consultations and self- education costs. Different sources of financing including state payer- the National Health Fund, social security funding and non- governmental organisations support was investigated, all from patients perspectives.

Direct non- medical costs covering hotel costs and transportation were also taken into account.

Productivity cost of productive and non- productive population being a consequence of care of an ill person was calculated with both working time and leisure time in focus. Influence of CF on working abilities of parents was also studied. Average earning lost in Mazovia district was used in calculations.

Alternative education opportunities for ill children were also looked upon.

Data collected in this study from the sample of 100 patients and their families were extrapolated to the whole CF population stored in the national patient register. Based on that, a total cost of outpatient treatment of CF in Poland was estimated.

Study group

Survey study was conducted on the sample of 100 patients, of which 43 were female.

The questionnaire was answered either by patients or parents of children treated in two Warsaw hospitals: the Institute of Mother and Child and Children's Memorial Health Institute. The study was conducted from 30th October 2010 to28th February 2011. Most of the patients were between 11 and 18 years old.

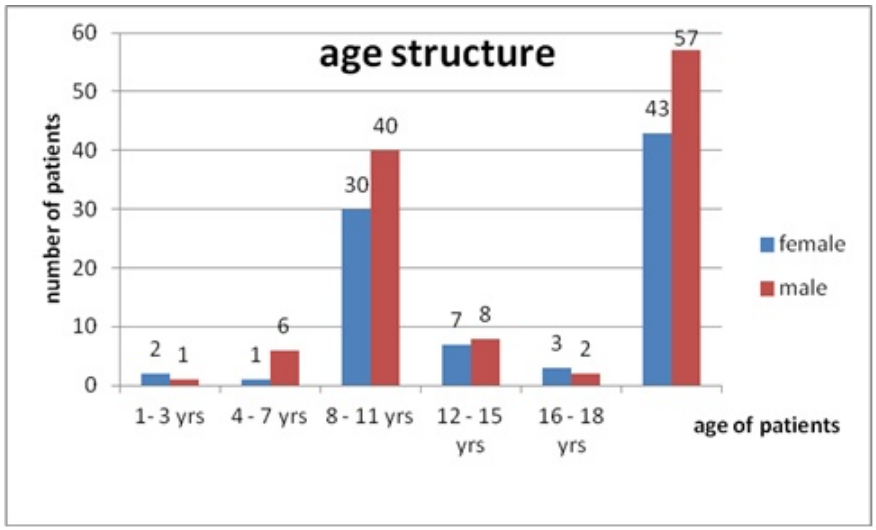

Figure 1. The age structure of patients enrolled

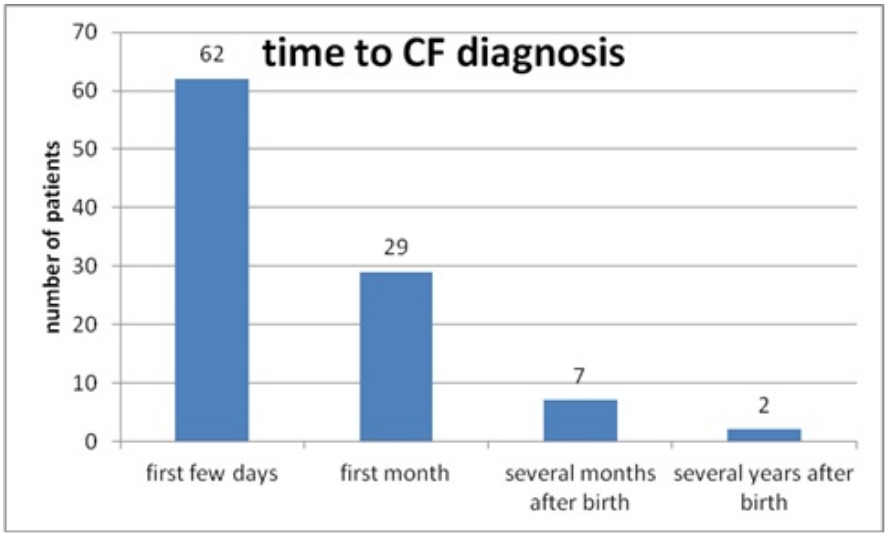

Figure 2. Time to first CF diagnosis in enrolled group of patients
The data was not divided by gender.

Results

Collected data indicates that first diagnosis of CF in this study group was made in 91% of patients within first month of life (fig.2).

Cost of CF treatment

According to the results of the survey all of patients experiencing exacerbations of the disease used pharmacotherapy and physiotherapy.

The expenses on prescription drugs from parents'/care-takers' perspective ("out of pocket") are presented below (fig.3).

The survey results were not presented by age and gender - differences, if any, relating to these aspects could not be reported.

Another identified, significant cost from parents' perspective concerned a special diet. The level of monthly expenditure on food supplements ranged from 100 to 1800 PLN (fig.4).

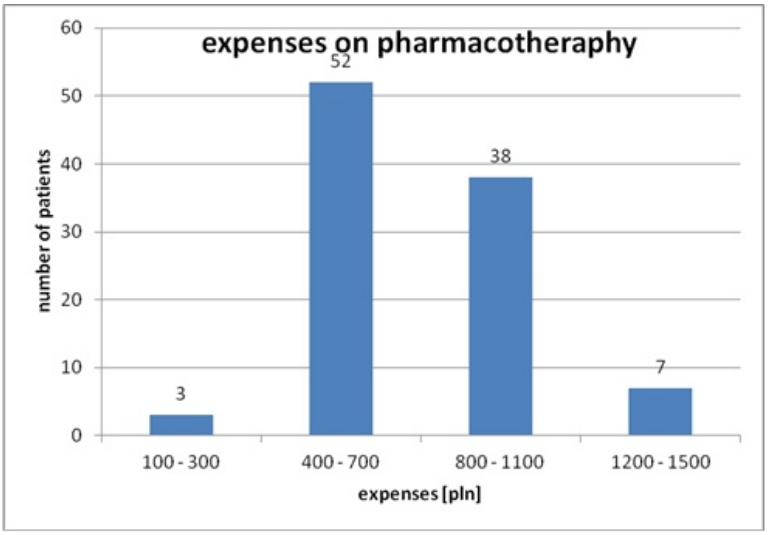

Figure 3. Annual expenses on pharmacotherapy from caretakers' perspective

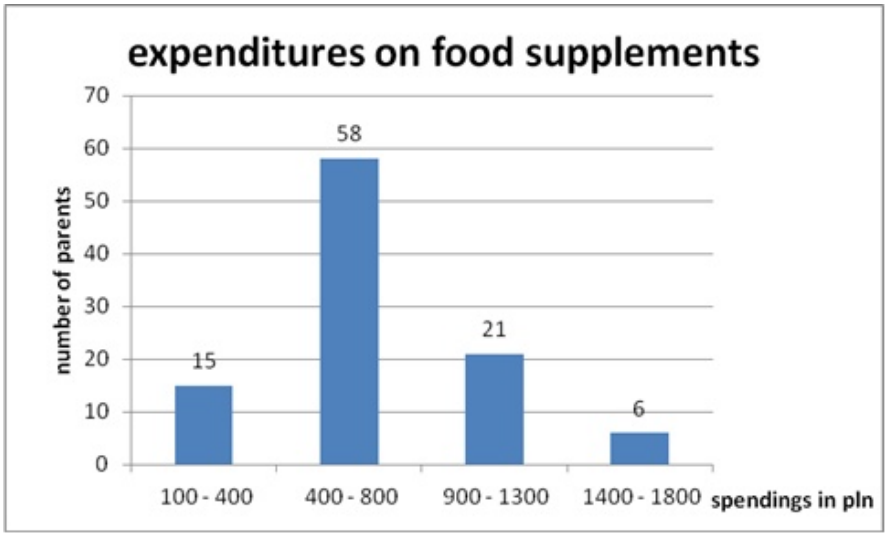

Figure 4. Monthly expenditures on food supplements

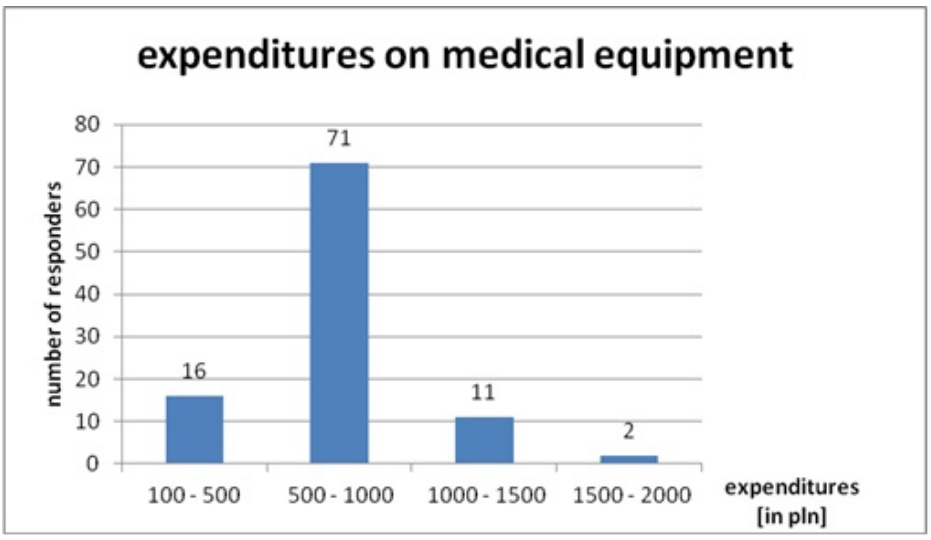

Figure 5. Annual expenditures on medical equipment

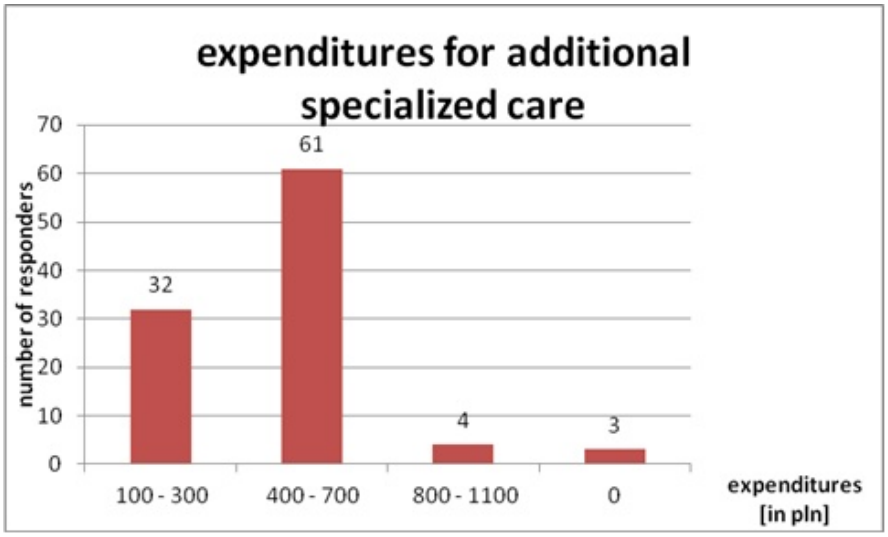

Figure 6. Annual expenditures for additional specialized care

The next cost group from the survey concerned medical equipment. Responders indicated that the annual spending on medical equipment range from 100 to 2000 PLN (fig.5).

Majority of responders indicated the need for additional specialized care (97 % of responders).

These included, among others, paid doctor's and psychologist's advices. These annual costs ranged from 0 to 1100 PLN (fig. 6).

From parents' perspective travel expenses appear to be significant. These were understood as the cost of commuting to health centers and accommodation in hotels (fig.7).

All of parents indicated that they were constantly improving their knowledge about CF. On textbooks, brochures etc. most of the parents spent from 20 to 50 PLN monthly (62 % of responders), all the rest did not spend money as they made use of internet resources.

91 % of parents due to high cost of care benefited from foundations, both care and rehabilitation allowance. These additional sources of funding reduced expenses by 50% (decelerated by 53 % of responders), more than 50 % (27 % of responders) or less than 50 % (11 % of declarations).

Additionally data concerning time spent on child's care was collected (fig.8).

According to gathered data, due to CF all children required care from parents. The vast majority of children requires at least 4 hours of parents' care per day (declared by 98% of the study group). That was probably the main reason of reducing a number of working hours by at least one of the parents (declared by 87 % in the study group, fig.9).

These data indicate that 83% of parents need to reduce working hours significantly (understood as a reduction of at least 4 hours per day). In 13 % of cases parents were able to manage the child's care without reducing working time.

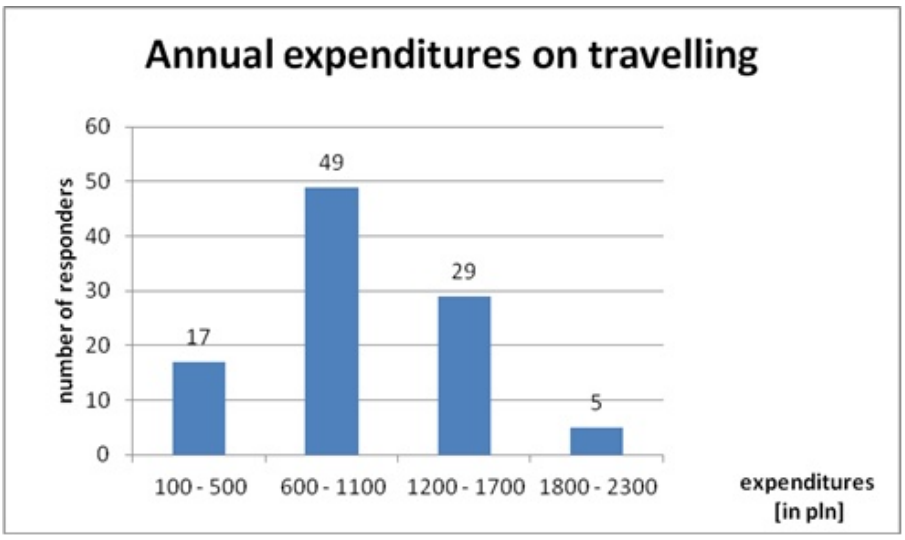

Figure 7. Annual expenditures on traveling from responders' perspective

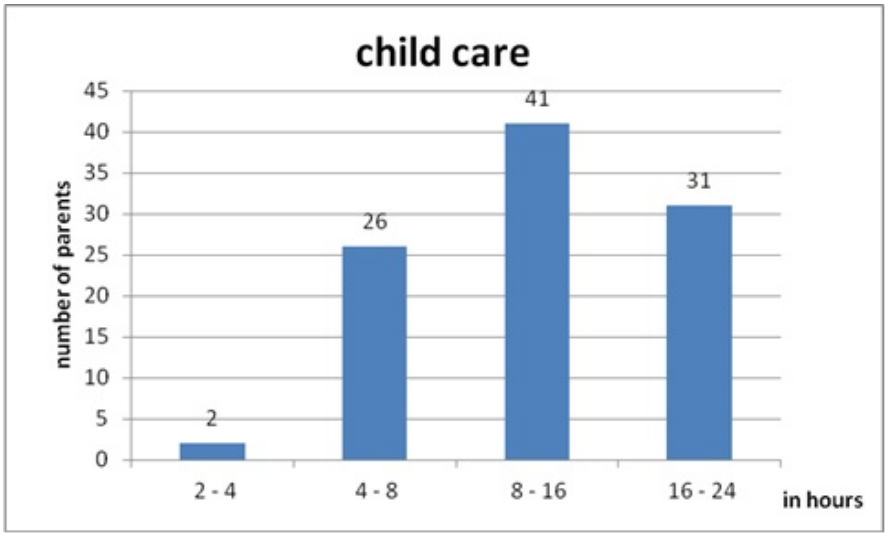

Figure 8. Time spent on child's care per day

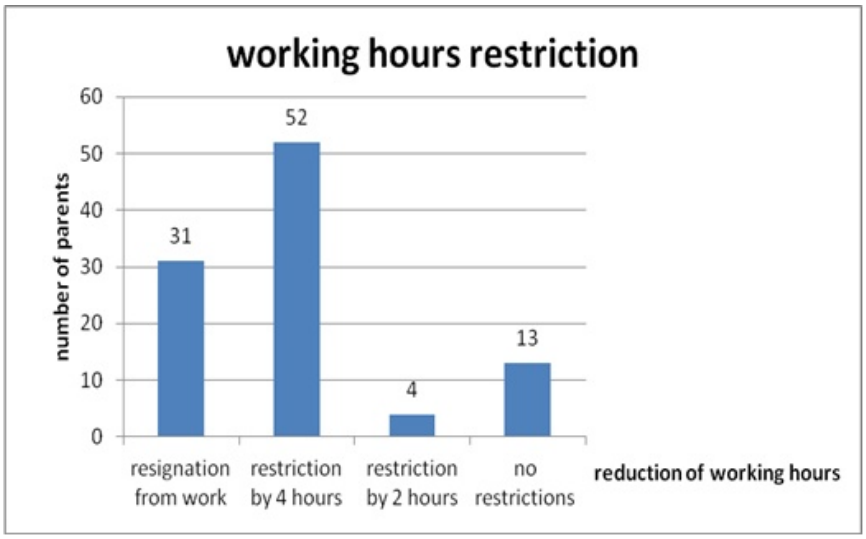

Figure 9. Working hours restrictions caused by providing care to a child

Quality of life

According to the survey's data, 91 % of responders assessed that the quality of life of children suffering from CF deteriorated. Only 3 % assessed that the quality of life was not worsened (fig.10).

The expenditures presented below were aggregated to present an average cost of CF in Poland from patient's /caregiver's perspective (fig.11).

Discussion and Conclusions

In the study group time to first diagnosis differs from other scientific reports indicating that in Poland the average age of patients when being CF diagnosed is between 3.5 to 5 years [13]. It may indicate that the severity of CF in investigated population was greater than in the whole CF population observed in the national patient register. The consequence might be that costs calculated in this study were overestimated.

The age structure of the patient groups in this study is characterized by an overwhelming majority of patients aged 11-18 years, who constituted 70% of the study population - both male and female. This in comparison with data from a survey pointing out that in 91% of patients diagnosis of CF was raised within first month of age, may indicate that during first decade of life it comes to a significant deterioration in the health status of people with CF in Poland. It may point out to urgent need to strengthen patient care from the very moment of diagnosis. Due to absence of information, in the presented results of the study, on the severity of CF in the studied population this hypothesis is difficult to be verified.

Presented results indicate a significant reduction of average patient's age when the diagnosis of CF is made from about 3-5 years to one month. This may indicate the effectiveness of the screening program for CF introduced in Poland in stages from September 2000.

In Poland the average annual cost of treating a child with CF aged 1-18 years from the perspective of a caretaker was estimated to be 108 948 pln. That cost is mainly composed of indirect expenditures.

While presented structure of medical expenses incurred by parents is reliable, the level of the National Health Found spending should be treated with caution. Verification of these data should be the next step in the process of estimating the costs of treating CF in Poland. The calculations based on national or hospital registries should also provide more accurate and reliable data on a real resources consumption level. Such an approach would assure external validation of the results obtained in this study.

Figure 10. QoL deterioration

cost category		
indirect	child care	58250
	decrease in productivity	30624
	total	**88874**
direct - medical	medicines	8 970
	diet supplements	8550
	medical equipment	753
	additional specialized care	789
direct non-medical	education	22
	transportation	990
	total	**20074**
total		**108984**

Figure 11. Annual average cost per patient [in PLN] of CF in Poland

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Stage III/IV Melanoma in Poland: epidemiology, standard of care and treatment related costs

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Abstract

Objectives: Melanoma is the most serious type of skin cancer. New methods offering significant benefits for advanced melanoma treatment are needed and in order to assess their cost-effectiveness reliable data on epidemiology, standard of care, adverse events and costs are required. The aim of this project was to collect such information using surveys in Poland.

Methods: A questionnaire focused on the disease characteristics, treatment patterns, health care resources utilization and costs among melanoma patients (stage III/IV) was designed.

Direct medical costs from Polish Public Payer perspective (National Health Found) were computed using data from the survey.

Results: Increase in incidence and mortality rates due to melanoma in subsequent years is observed.

Regardless of the disease stage about ¾ of the patients had a surgical procedure in the past. Among melanoma patients receiving best supportive care, 77.5% received one and 15% received two chemotherapy schemes.

Total yearly cost (including drugs costs, resources used) for 1st, 2nd and 3rd line therapy is respectively 6 522.99 PLN, 12 627.25 PLN and 9 267.39 PLN.

Conclusions: An increase in incidence and mortality rates of melanoma in subsequent years is expected. Costs related to advanced melanoma treatment compared to other oncological indications seem to be moderate. This reflects lack of major advances in melanoma treatment for many years with a steady, high mortality and short survival of patients with advanced disease.

Key words: epidemiology, standard of care, costs of stage III/IV melanoma treatment in Poland

Background and objectives

Melanoma is the most serious type of skin cancer. It is derived from melanocytes localized mainly (90% of cases) in the skin. Rarely it may occur as primary unknown, or localized in mucous membrane of the mouth and genitals or in the eyeball [1]. Being diagnosed at an early stage is curable in many cases (by simple surgical excision). However, at later stages of the disease it is considered fatal and long-term survival relate to few patients [2].

Over the past few decades, a constant, dynamic increase in the incidence of melanoma is observed and the continuation of this trend will cause an increase of morbidity [3]. Therefore, new methods of treatment that may offer significant benefits in treating patients with advanced melanoma are compiled and analysed. In order to assess their cost-effectiveness via pharmacoeconomic modelling data on epidemiology, current standard of care, adverse events and costs are needed. The aim of this study was to collect such information using surveys in major centres in Poland.

Methodology

The results are presented in substantially separate areas (epidemiology, patient care, medical expenses, adverse events) based on the available data. When performing a survey it is always a problem how to standardise the available data and how to handle the missing information, if present. In this study, the following general rules have been applied.

In case when the data were given in several questionnaires, the arithmetic mean was calculated. If the values given by the respondents differed significantly from each other, the range of values was presented in brackets.

The survey included the most important centres in Poland, and the results should be treated as opinions of respondents, not as a result of quantitative estimates of each centre. Due to that reason statistical analysis was not performed. In case the respondents were asked for a structure of patients, and the categories did not sum to 100%, it was assumed a mistake and corrected for – i.e. the percentages were scaled up or down. This scaling was not performed however, if the highlighted categories did not have to be separate or deplete the population, e.g. in determining the percentage of patients who performed various diagnostic procedures.

All the cases in which no answer was given were not included into the analysis. The final analysis was based on a smaller number of surveys then.

In some cases the information could be deduced from answers to several questions in the survey (e.g. in the area relating to standards of care and cost). In this case, the aggregation of data was performed, in effort to select the most reliable and accurate information.

Data sources

This paper presents the results of the analysis of data provided in a survey regarding the standard practice of melanoma treatment in Poland. The survey was conducted in four centres in Poland with slightly different clinical approach to melanoma patients:

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D. Dept. of Diagnostics and Immunology of Cancer, the Great Poland Cancer Centre; Poznan, Poland (Zakład Diagnostyki i Immunologii Nowotworów, Wielkopolskie Centrum Onkologii, Poznań, Polska).

A questionnaire was designed and implemented in MS Excel. The survey questions encompassed: the disease characteristics, current treatment patterns, health care resources utilization and costs among patients diagnosed with melanoma (stage III/IV).

The survey consisted of four sections:

- Epidemiology - included, among others, information on the prevalence of melanoma, severity degree, the presence of BRAF mutation and incidence rates, morbidity and mortality.

• Standards of treatment - included information about the 1st, 2nd and 3rd line of treatment used in each centre, including dosage, frequency of administration and the percentage of patients treated. This section also contained information about the frequency of surgery or palliative radiotherapy.

• Resources costs –in this section costs of melanoma treatment in different lines were included, with special attention paid to costs of performed procedures / diagnostic tests, drugs and the resources used for drugs administration. All information related to the resources used in melanoma treatment was the basis for the final costs calculations which were based on public payer available cost data (NHF).

• Adverse events - a summary of the standards and the cost of adverse events (taking into account the degree of toxicity) occurring during treatment of melanoma.

Cost evaluation

Resources costs and standard of care data for melanoma patients were divided into three therapy lines, and information such as treatment scheme, drug cost and performed diagnostic procedures were collected. The costs of adverse events associated with therapy were also obtained.

Direct medical costs were computed using the data from the presented survey and the unit costs from the Public Payer in Poland (the National Health Found, NHF) [9,10,11,12].

Results

The survey was distributed in four hospitals in Poland covering the majority of advanced melanoma patients being treated; therefore the results can be regarded as a reliable estimate of the current situation in Poland.

Epidemiology

Incidence and mortality rate:

Year	1998	2002	2003	2004	2005	2006	2007	2008	2009	2010
Incidence rate (per 100,000)	4.00	5.21	5.61	5.73	6.26	6.35	6.69	7.06	7.94	8.80
Mortality rate (per 100,000)	2.70	2.30	2.88	2.82	2.80	3.04	3.14	3.27	3.27	3.67

This data indicate a noticeable increase in the incidence and mortality rates in subsequent years. The incidence rate doubles its value about every 10 years. Using a linear trend extrapolation, it is expected that the incidence and mortality rate for year 2012 will amount to about 8.85 and 3.57 respectively (per 100,000).

The prevalence rate for year 2008 is equal to 17.3 per 100,000 inhabitants.

Patients with melanoma stage I and II represent a total of 70% of all patients (respectively 30% and 40%). Roughly 25% of patients are those with stage III, and 5% with stage IV at the time of diagnosis. The proportion of patients with resectable melanoma amounts to 80%. 15% patients have an unresectable stage III melanoma and the remaining 5% are patients – unresectable stage IV.

Standard care for unresectable / metastatic patients:

Since the time of introduction to the clinical practice BRAF-inhibitors, in patients with unresectable disease, the test for the presence of BRAF mutation has been a routinely performed and a positive result of this study has been obtained in 45% of cases.

Among all melanoma patients (regardless the stage), more than ¾ had a surgical procedure in the past. At a certain stage of treatment, palliative surgery is performed in about 14% of patients with non-resectable melanoma. In approximately 21.5% cases, palliative radiotherapy is used along or as a combination with the surgery. All patients with brain and painful bone metastasis received palliative radiotherapy as a standard of care.

Only in the Dept. of Soft Tissue/Bone Sarcoma and Melanoma, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw,

Poland in selected cases with melanoma in transit – the electrochemotherapy was performed.

In cases qualified to the systemic palliative therapy, 77.5% patients received one and 15% - two chemotherapy lines together with best supportive care (BSC). Approximately 49.75% of patients who underwent 1st line and 89% of patients after 2nd line therapy received BSC instead of next line treatment.

1st line therapy:

	Treatment scheme (drug name)	% of patients treated	Dosage (mg/m^2 per 3 weeks)	Treatment duration (weeks)
1.	DTIC (dacarbazine)	70 (5 - 100)	1 265.63 (937,5 – 2 000)	18.5 (8 – 24)
2.	DDP (cisplatin)	30 (25 - 95)	70 (60 – 80)	21 (18 – 24)
	DTIC		850 (800 – 900)	
	VBL (vinblastine)		6.9 (4,8 – 9)	

2nd line therapy:

	Treatment scheme (drug name)	% of patients treated	Dosage (mg/m2 per 3 weeks)	Treatment duration (weeks)
1.	BLEO (bleomycin)	33.33	33.75	24
	DTIC		900	
	VCR (vincristine)		9	
2.	Carboplatin	24.56	300	21
	Paclitaxel		150	
3.	DTIC	16.67	1000	15
4.	DDP	16.67	56.25	20
	Paclitaxel		202.5	
5.	DDP	8.77	80	18
	DTIC		800	
	VBL		4.8	

Approximately 7.5% of these patients did not receive chemotherapy due to poor clinical condition or lack of informed consent.

Treatment scheme

According to clinical experts, about 88.5% (39.5%, 13%) receive 1st line (2nd line, 3rd line) of chemotherapy at one point of their treatment.

3rd line therapy:

	Treatment scheme (drug name)	% of patients treated	Dosage (mg/m2 per 3 weeks)	Treatment duration (weeks)
1.	Carboplatin	50	300	17.5
	Paclitaxel		150	
2.	Paclitaxel	50	300	5

Treatment schemes used in melanoma treatment in Poland (including the percentage of patients applying a particular treatment, average dose and duration of treatment) are presented below.

Melanoma treatment costs

The drug costs were based on data from treatment schemes for each therapy line (see standard care for patients) and on the drug pricing data from the Public Payer in Poland (NHF). When calculating the cost, it was assumed that no patient receives a dose greater than the maximum refunded value.

The costs of resources used for drug administration were calculated by setting the average number (per year) of performances of various resources (one-day hospitalization, overnight hospitalization or ambulatory visit) and their unit cost.

The costs of medical procedures were calculated by estimating the percentage of patients in whom a procedure is used, the frequency of performances (per year) and their unit cost, according to NHF. The following diagnostic procedures were included in estimating: CT scan (computed tomography), X-ray, USG (ultrasonography), laboratory test, MRI, Bone Scintigraphy.

Treatment costs:

	Drug costs (PLN)	Cost of resources used for drug administration (PLN)	Costs of medical procedures (PLN)	Total yearly cost (PLN)
1st line	1 488.14	3 060.72	1 974.13	6 522.99
2nd line	4 361.12	6 292.00	1 974.13	12 627.25
3rd line	2 821.26	4 472.00	1 974.13	9 267.39
TOTAL COST	8 670.52	13 824.72	5 922.39	28 417.63

All costs associated with melanoma treatment in Poland are presented below.

The patient's body surface area was taken as 1.7 m2.

Adverse events costs

The following costs are presented for adverse events that occur most frequently concomitantly/after therapy with DTIC (according to BRIM-3 study [4]). It is expected that in the case of politherapy with DTIC and different drugs, adverse events are similar (although the frequency of particular actions may differ).

Discussion

Data collected from four experts practicing at the leading Polish oncological centres in Poland reviled that in Poland, the treatment of melanoma patients is based on the recommendation of the European Society of Medical Oncology and the Polish Oncological Union.

Adverse event (grade*)	Cost of pharmacotherapy (PLN)	Cost of medical procedures (PLN)	Total cost (PLN)
Arthralgia (grade 3)	113.27	356.65	469.92
Fatigue (grade 3)	n.a.	n.a.	n.a.
Nausea (grade 3)	n.a.	2 860.00	2 860.00
Diarrhea (grade 3)	n.a.	2 860.00	2 860.00
Headache (grade 3)	56.95	142.66	199.61
Vomiting (grade 3)	n.a.	2 860.00	2 860.00
Neutropenia (grade 3)	n.a.	n.a.	n.a.
Neutropenia (grade 4)	1 767.29	4 004.00	5 771.29

* Grade according to Common Terminology Criteria for Adverse Events, CTCAE, version 4.0 [5]
** Cost of medical resources includes: hospitalization, ambulatory visit or skin lesion removal (with histological observation)

Based on data from the Polish Cancer Registry the incidence of melanoma is increasing each year. This is in line with the observed in other European countries trend of incidence of melanoma skin cancer. This phenomenon is linked to specific behaviour: e.g. winter holidays, sun seeking as well, as to improved rates of diagnosis resulting from better detection of melanoma. The risk factors are also acute, irregular and excessive exposure to the sun, mainly during childhood, and the increasing usage of sun beds. Melanoma is more frequent among people in the higher socioeconomic groups and among northern European populations. This is probably due to their higher excessive intermittent exposure to UV radiation combined with a light skin type [6].

The total yearly cost (including cost of drugs, resources used for drugs administration and medical procedures) for the 1st, 2nd and 3rdline therapy is respectively 6 522.99 PLN, 12 627.25 PLN and 9 267.39 PLN.

The highest costs of adverse events are observed for neutropenia grade 4 (5 771.29 PLN).

Recently the new groups of medication have been approved by the FDA to treat patients with late-stage melanoma stage IV or unresectable stage III: ipilimumab in March 2011 and vemurafenib in August 17, 2011. The mechanism of action of ipilimumab is blockade of the CTLA-4 inhibitory signal, and allowing the CTL cells to destroy the cancer cells [7]. BRAF inhibitors such as vemurafenib and dabrafenib produce tumor shrinkage, progression-free and survival time benefits in large proportion of patients. The side effects related to the new drugs are different than those of classical chemotherapy. Ipilimumab treatment has been associated with severe immunological adverse effects due to T cell activation. The most common side effects of BRAF pathway inhibitors are: hyperkeratosis, pyrexia, arthralgia and palmar-plantar erythrodysaesthesia syndrome. Other skin-related toxicities of interest included photosensitivity and squamous cell carcinoma/keratoacanthoma.

Due to high unmet medical need for effective treatment of melanoma Health Technology Assessment (HTA) agencies in some countries already started the assessment of cost – effectiveness for new drugs. Recently in UK NICE have issued a Final Appraisal Determination document with a positive approach to targeted melanoma therapy with vemurafenib, a BRAF inhibitor [8]. Such decisions by HTA agencies will make innovative treatment available for patients.

Conclusions

Increase in the incidence and mortality rates of melanoma in subsequent years is expected;

The drug most commonly used in 1st and 2nd line melanoma treatment is dacarbazine (alone or as a component of a multidrug therapy);

Paclitaxel is the most commonly used medication in case of progression on therapy with dacarbazine.

The overall costs related to advanced melanoma treatment seem to be moderate, compared to other oncological indications. On the other hand, this situation reflects lack of major advances in this treatment for many years with a steady, high mortality and short survival of patients with advanced disease.

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Clinical effectiveness and cost-utility analysis of sunitinib for the treatment of pancreatic neuroendocrine tumors

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Abstract

Background: The objective of this review is to assess the clinical effectiveness and cost–utility of sunitinib and best supportive care (BSC) versus placebo and best supportive care in the treatment of patients with unresectable or metastatic well-differentiated pancreatic neuroendocrine tumors with disease progression.

Methods: Assessment of the clinical effectiveness of the interventions was conducted in accordance with the principles of systematic review, based on the Cochrane Collaboration guidelines (Cochrane Reviewer's Handbook) and the guidelines of the Polish Agency for Health Technology Assessment (AOTM). The Markov model constructed in TreeAge Pro 2009 was used in the cost-utility analysis. The time horizon covered the period from the beginning of the treatment until the patient's death (lifetime horizon). Quality adjusted years (QALY) were used as the measure of effectiveness and the results were presented as incremental cost-utility. CUA was conducted from the perspective of the public payer for health services (Polish National Health Fund, PNHF) and from the patient's and PNHF's perspective.

Results: As the result of the systematic search, one primary randomized clinical trial satisfying the inclusion criteria was found (Raymond 2011). The results of the present analysis clearly prove that sunitinib administered in a 37.5 mg dose is an effective and safe therapy in the treatment of patients with unresectable or metastatic well-differentiated pancreatic neuroendocrine tumors with disease progression. The cost of gaining an additional QALY by replacing placebo+BSC with sunitinib+BSC is PLN 84,214 /PLN 84,296 (€20,441/€20,461) from PNHF/PNHF+patient perspective.

Conclusion: Sunitinib is a more costly and a more effective therapy than BSC.

Key words: Sunitinib, Systematic review, Cost-Utility, Antineoplastic Agents; Neuroendocrine Tumors; Pancreatic Neoplasms

Introduction

Pancreatic neuroendocrine tumors (pNETs) are uncommon tumors originating from highly specialized cells of the diffuse endocrine system. Those malignancies represent only 4% of all neuroendocrine tumors (NETs), of which over half are hormonally inactive tumors. PNETs belong to gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Up to 70% of all NETs are localized in the digestive system. The incidence of GEP-NETs has been estimated at 2.5 cases per 100 000, of which 10% are tumors of the pancreas, and 1/3 are clinically assessed as malignant [1].

Data published between 2008 and 2010 reports that pancreatic NETs are rarely occurring neoplasms of this organ constituting approximately 2% - 10%. The incidence of pets is estimated at 4 – 12 cases per million per year [2, 3]. The peak incidence of pets is found in the fifth decade of life, with slight female predominance [3]. It is worth noting that most patients with pNETs (around 65%) have unresectable or metastatic disease at diagnosis [4].

It should be emphasized that rare diseases, such as the analyzed one, have been recognized as a priority area in public health in the European Union and given fundamental importance in European Union programs for health and scientific research. The assessment of a medical technology in reference to orphan drugs is a challenging issue in view of the frequent lack of comparative medicines and the small quantity of scientific reports due to the difficulties of conducting reliable studies on a small population.

Sunitinib malate (Sutent®), an oral multitargeted tyrosine-kinase inhibitor, is designed to inhibit: platelet-derived growth factor receptors (PDGFR-α and PDGFR-β), vascular endothelial growth factor receptors (VEGFR1, VEGFR2, VEGFR3), the stem cell factor receptor (KIT), fms-like tyrosine kinase 3 (FLT3), colony-stimulating factor-1 receptor (CSF-1R) and glial cell line derived neurotrophic factor receptor (RET). Thus, the analyzed drug influences cell growth, angiogenesis and tumor proliferation with metastases [5].

In the European Union (EU), sunitinib is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumor (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance, for the treatment of advanced/metastatic renal cell carcinoma (MRCC), and for the treatment of unresectable or metastatic well-differentiated pancreatic neuroendocrine tumors with disease progression. Sunitinib received marketing authorization in the United States on 26 January 2006 and in Europe on 19 July 2006 [5].

The therapy with multitargeted tyrosine-kinase inhibitor – sunitinib in the treatment of pNETs has already been recommended and reimbursed in such European countries as Great Britain, Switzerland, the Netherlands, France, and Finland.

The objective of this review is to comprehensively present clinical effectiveness and cost-utility (CUA) of sunitinib given as a support of best supportive care (SUN+BSC) in the treatment of patients with unresectable or metastatic well-differentiated pancreatic neuroendocrine tumors with disease progression. The survey was conducted in accordance with the Cochrane Collaboration guidelines [6] and the Polish Agency for Health Technology Assessment (AOTM) recommendations [7]. The systematic review and CUA were conducted on the basis of a published high reliability randomized controlled trial (RCT) conducted in a double-blind manner.

Decision problem (PICOS)

The decision problem was formulated in accordance with the PICOS pattern (population, intervention, comparator, outcomes, study design):

Population: adults with unresectable or metastatic well-differentiated pancreatic neuroendocrine tumors with disease progression;

Intervention: sunitinib administered orally at a dose of 37.5 mg per day (continuous regimen) in combination with best supportive care (SUN+BSC);

Comparator: placebo and best supportive care (PL+BSC);

Outcome: progression free survival (PFS), overall survival (OS), objective tumor response (complete response, partial response, stable response, progressive disease), objective response rate (ORR), quality of life, death, adverse events, quality adjusted life years (QALY);

Study design: head-to-head RCT trials conducted in parallel groups.

Clinical effectiveness analysis of Sunitinib for the treatment of pNETs

Search strategy

The search strategy was designed by two independent authors. Terminology from scientific papers as well as from Medline Thesaurus (Mesh) was included. Boolean Operator (OR) was used to combine the search sets. Trials were identified by searching electronic databases such as: Medline via PubMed, Cochrane Library, EmBase, and CRD. To find additional primary studies that comply with the inclusion criteria, references of identified secondary literature were searched. Clinical Trial

Registry - ClinicalTrials.gov was also screened. Terms used in the search strategy included, among others, phrases such as “sutent”, “sunitinib”, “sunitinib malate” and adequate synonyms. The search was conducted in March 2012.

At the stage of designing the search strategy, no restrictions regarding disease classification, alternative intervention and evaluated outcomes were adopted due to the possibility of lowering the sensitivity of the searching process applied. Also, no limitations were applied regarding publication type, which allowed identification of secondary and observational studies covering additional information in respect of practical efficacy and safety over a long period of time.

A two-step eligibility and selection process was used. The selection of relevant abstracts and full-text articles was prepared independently by two reviewers. Firstly, the reviewers independently screened all titles and abstracts to determine whether an article met the general inclusion criteria. Secondly, two reviewers independently assessed the full-text studies using predefined inclusion and exclusion criteria. The reference lists of identified articles were then examined for additional publications. Only published trials were included into the review. Data from abstracts or conference posters were accepted for inclusion into the analysis if those provided additional information to the full text published version.

Both authors independently extracted methodological data and outcomes; disagreements were resolved by discussion.

Selection criteria

The systematic review was performed in accordance with Evidence Based Medicine, contributions of the Cochrane Collaboration (Cochrane Reviewer’s Handbook) [6] and the guidelines of the Polish Agency for Health Technology Assessment [7]. The clinical question was formulated in accordance with the PICOS scheme (population, intervention, comparator, outcomes, study design). The primary endpoint analyzed in the included clinical trial was progression free survival defined as the time from randomization to the first evidence of progression or death due to any cause. Secondary efficacy endpoints included overall survival, objective response rate, time to tumor response, duration of response, safety, and patient-reported outcomes. Tumor response was assessed by investigators with the use of RECIST. Confirmed responses were those that persisted on repeat imaging 4 weeks or more after initial documentation. Safety analysis involved: discontinuation of the study, total adverse events, serious adverse events, and other adverse events. Safety assessments included documentation of adverse events with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. The self-administered European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30, version 3.0) was used to measure patient-reported outcomes.

Quality assessment

Quality assessment criteria included number of sites, randomization, presence of information concerning allocation concealment, blinding, and intention-to-treat (ITT) analysis. The validity of the clinical trial meeting the inclusion criteria for the analysis was determined with the use of the Jadad scale [8].

Statistical analysis

In the statistical analysis of dichotomous parameters, the Odds Ratio (OR) obtained in the compared groups was calculated. The Relative Risk (RR), the ratio of risk in the intervention group to the ratio of risk in the control group, was used as an effect measure. For variables of the "time to" (time to event) type, the hazard ratio (HR) was specified. In addition, as a measure of efficacy, the number needed to treat (NNT) was also calculated for the outcomes with significantly different overall effects. Mean Differences (MD) were calculated for continuous variables. All treatment effects were calculated within a 95% Confidence Interval (95% CI).

In the analysis of probability of rare events (in the case where at least in one of the groups there were events with a rate of occurrence of 0 or close to 0), calculations were performed using the Peto or Mantel-Haenszel methods.

All calculations were performed using the StatsDirect® 2.6.8 statistical package. A two-sided P-value of < 0.05 was considered significant.

Results

11 052 publications were identified (Pubmed: 2178, Embase: 8320, Cochrane: 99, CRD: 42, clinicaltrials.gov: 408, other: 5) of which 117 publications were analyzed in full-text version. As a result of a systematic search, one primary randomized clinical trial (phase III trial) satisfying the inclusion criteria was found (Raymond 2011) [4, 9, 10]. In addition, three conference reports [11, 12, 13], which contain updated results of Raymond 2011 study, were found and included into the analysis. Search results are demonstrated in Figure 1.

The study Raymond 2011 included in the analysis was a multicentre, double-blind, randomized controlled trial (subtype II A). The Jadad scale [8] was used in the process of assessing the reliability of studies. The reliability of Raymond 2011 study is high and corresponds to 5 out of 5 points on the Jadad scale. The detailed characteristic of the included study are presented in Table 1.

Patients with well-differentiated pancreatic neuroendocrine tumors were randomized into two groups receiving sunitinib (86 patients) or placebo (85 patients). All patients received best supportive care. Concurrent treatment with somatostatin analogs was permitted. Dose interruption and/or dose modification were permitted for toxicity. Treatment continued until death, progression of disease, or unacceptable toxicity. Patients with disease progression, while receiving placebo, could enter an open-label sunitinib extension protocol (NCT00443534 or NCT00428220).

Baseline characteristics were similar between the two study groups. Approximately 90% of patients in each treatment group had previously received surgery for pNETs. 66% (57/86) of sunitinib patients and 61% (72/85) of placebo patients had received previous systemic chemotherapy. The median duration of treatment in the phase III trial was 4.6 and 3.7 months in the sunitinib and placebo groups. Efficacy assessments were performed in the intent-to-treat population.

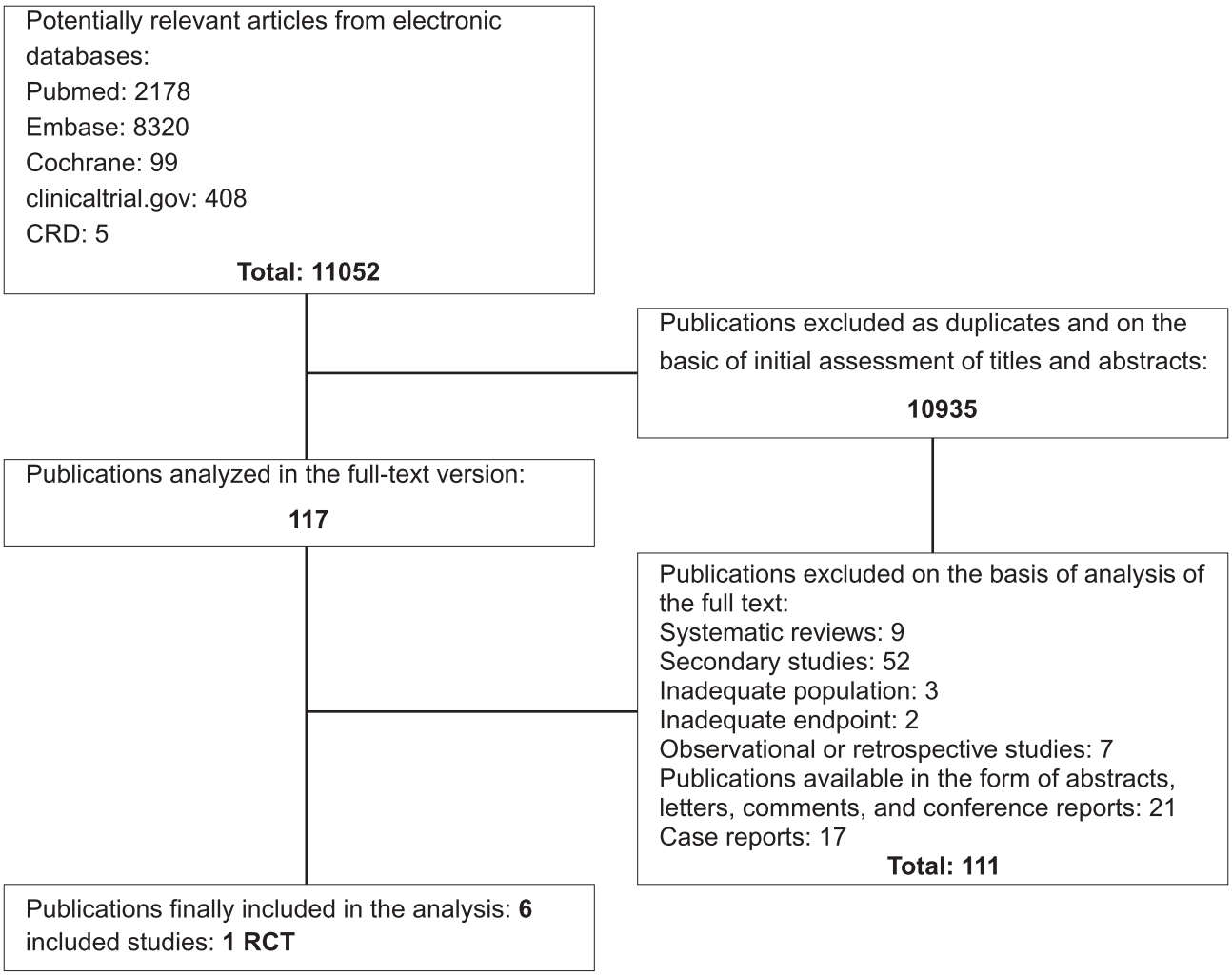

Figure 1. Diagram describing the results of the articles search and studies selection (in accordance with QUOROM [15])
Date of the systematic search: 02 – 05.03.2012

Table 1. Characteristics of studies included in the analysis

Study	Type of study	Number of centers	Inclusion criteria	Intervention	Endpoints	Jadad score
Raymond 2011 **Sponsor**: Pfizer	RCT, double blind	42	(1) histological or cytological proven diagnosis of well-differentiated pancreatic islet tumor (according to WHO 2000 classification) locally-advanced or metastatic disease; 2) disease not amenable to surgery; 3) documented disease progression within the previous 12 months as assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) with disease progression; 4) one or more measurable target lesions; 5) an Eastern Cooperative Oncology Group performance status of 0 or 1; 6) adequate organ function.	**SUN+BSC***: once-daily oral sunitinib at dose of 37.5 mg per day + best supportive care [N = 86]; **PL+BSC***: matching placebo (1 placebo capsule identical to sunitinib per day) plus best supportive care [N = 85]; Treatment continued until death, progression of disease, unacceptable toxicity. Patients with disease progression while receiving placebo could enter an open-label sunitinib extension protocol (NCT00443534 or NCT00428220).	progression free survival, overall survival, objective tumor response, safety (deaths, discontinuations of the study, total adverse events, serious adverse events and other adverse events), quality of life.	5

*Before the trial, during the trial, or both patients could receive somatostatin analogs at the investigator's discretion

It was shown that the use of sunitinib plus BSC results in statistically significant higher clinical efficacy in respect of progression free survival (PFS), overall survival (OS) and objective response rate in comparison with the control group (placebo plus BSC). The median PFS (HR = 0.42; 95% CI, 0.26; 0.65) was over two fold greater in sunitinib treated patients (11.4 months) than in the placebo group (5.5 months). At the data cut-off point, 9 deaths (10%) were reported in the sunitinib group compared with 21 deaths (25%) in the placebo group (HR = 0.40; 95% CI, 0.18 to 0.86). Detailed data on the analyzed endpoints is shown in Table 2. The objective response rate was 9.3% in the sunitinib group versus 0% in the placebo group (Figure 2). Among the eight patients who achieved a tumor response (as assessed by RECIST) with sunitinib, two had a complete response and the remainder had partial responses; only one responder developed progressive disease before the trial was terminated. The time to tumor response ranged from 0.8 to 11.1 months (median 3.1 months) and responses lasted from 0.9 to > 15.0 months. The remaining sunitinib and placebo recipients had stable disease (63% vs 60%), progressive disease (14% vs 27%), or could not be evaluated (14% vs 13%) (Figure 2).

Health-related quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life questionnaire but the value of the results was limited by low patient numbers. There was no indication that treatment with sunitinib produced a significant deterioration in quality of life (Figure 3).

Sunitinib is a safe and well-tolerated therapy (Table 3). In the course of the analysis, statistically significant differences in favor of sunitinib plus BSC were indicated in the case of total death, discontinuation from the study due to progression or relapse and total serious adverse events. The most frequent adverse events in the sunitinib group were diarrhea, nausea, vomiting, asthenia and fatigue. In most cases, the analyzed adverse events were of low severity grade.

The Raymond 2011 study was closed prematurely, after the independent data and safety monitoring committee observed more serious events and death in the placebo group as well as a difference in PFS favoring sunitinib. A significant number of patients in the placebo arm crossed over to active treatment at progression or at early termination of the trial.

Crossover is common and unavoidable for ethical reasons, but leads to an underestimation of true clinical gain in OS with standard statistical analyses (intention-to-treat). Adjusting for crossover bias with the Rank Preserving Structural Failure Time (RPSFT) model amplified this effect: HR = 0.18

Table 2. Efficacy results for progression free survival (PFS) and overall survival (OS)

Outcome	Number of patients in SUN+BSC group	Number of patients in PL+BSC group	Number with events	Median, months (95 % CI)	Hazard ratio (95 % CI), p-value
Data cut-off point: 15 April 2009*					
PFS	86	85	SUN+BSC: 30 PL+BSC: 51	SUN+BSC: 11.4 (7.4; 19.8) PL+BSC: 5.5 (3.6; 7.4)	0.42 (0.26; 0.65), p = 0.000118
OS	86	85	SUN+BSC: 9 PL+BSC: 21	Not reached	0.40 (0.18 0.86) p = 0.02
OS (model RPSFT^)	-	-	-	-	0.18 (0.06; 0.68)
Data cut-off point: June 2010**					
OS	86	85	SUN+BSC: 34 PL+BSC: 39	SUN+BSC: 30.5 (20.6; NA) PL+BSC: 24.4 (16.3; NA)	0.737 (0.465; 1.168) p = 0.1926
OS (model RPSFT^)	-	-	-	-	0.499 (0.351; 0.947) p = 0.0035

*Raymond 2011 and Ishak 2011 [9, 10]
**Valle 2011 [11]
^Model RPSFT (rank-preserving structural failure time) is a non-parametric model that produces a randomization-based effect estimator assuming that treatment with the investigational drug extends survival time uniformly for all patients. Assuming this model is correct, survival times can be calculated for all patients had they received placebo. For patients who crossed over, the time on treatment after crossover is adjusted to reflect what would have happened if they had stayed on placebo. Due to randomization, the distribution of the calculated survival times should be the same in both groups. The model has been recognized by health technology assessment bodies (e.g., the National Institute of Clinical Excellence in the UK, and Tandvårds-och läkemedelsförmånsverket in Sweden).

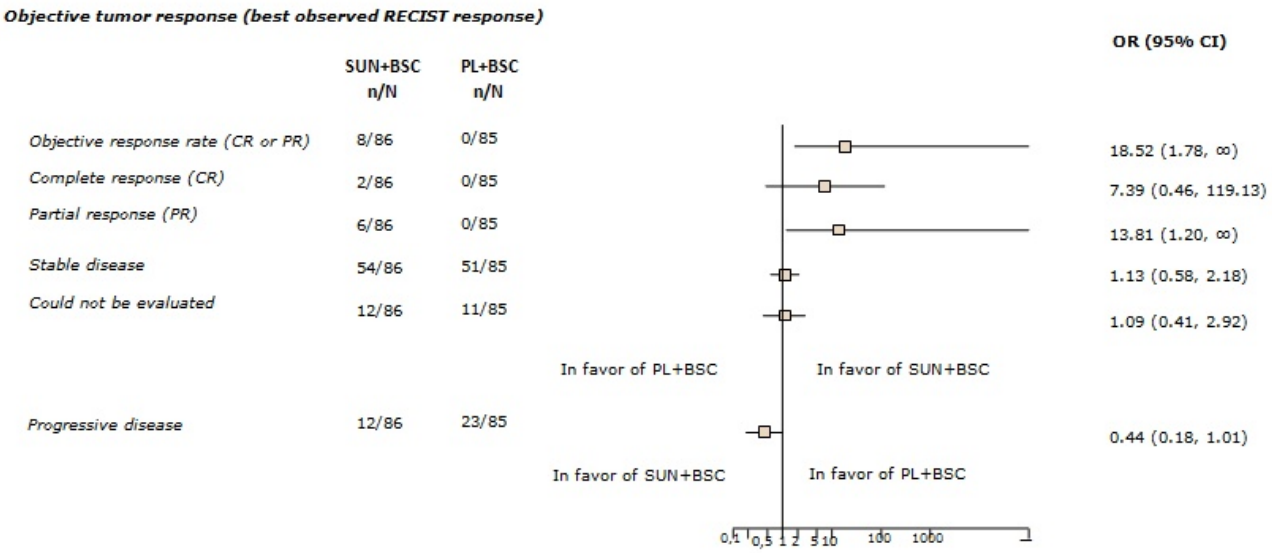

Figure 2. Objective tumor response (RECIST) – odds ratio (95% CI)

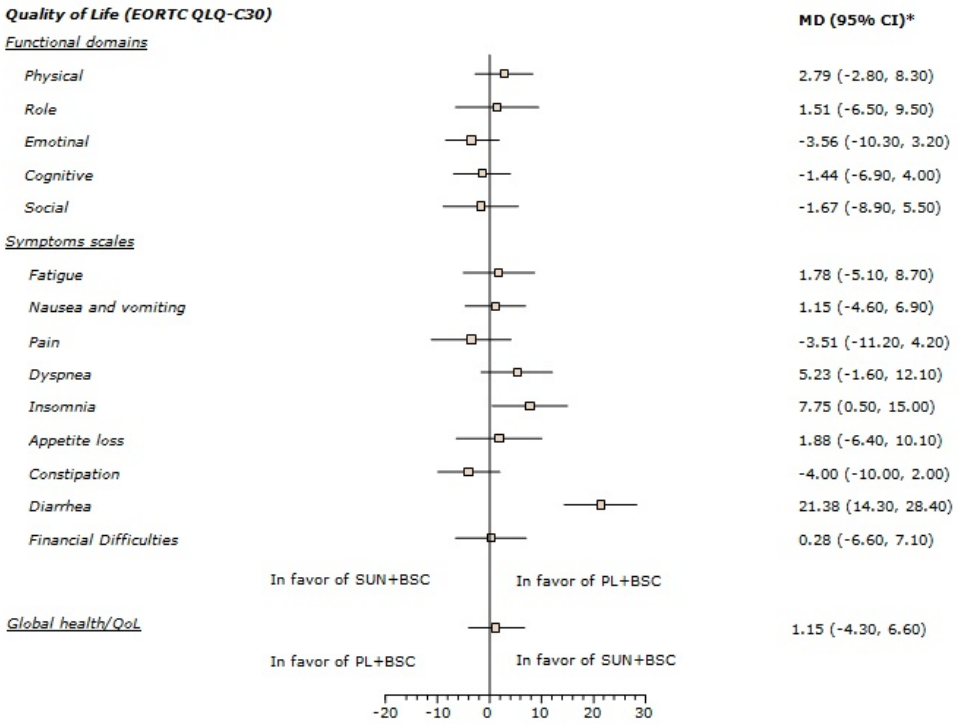

Figure 3. Quality of Life (EORTCQLQ-C30)

(95% CI: 0.06; 0.68); that is an 82% reduction in the risk of death with sunitinib compared placebo (Table 2).

A limitation of applying the RPSFT method to this study includes the relatively small size, however, findings provide a clear direction for the effect of crossover and the RPSFT result may provide a possible upper bound on the true effect size.

Updated OS and an estimate of the effect of sunitinib on OS by adjusting for treatment crossover was described in the poster Valle 2011. As of June 2010, median OS had been reached with 34 deaths in the sunitinib group and 39 deaths in the placebo group. Median follow-up time was 26.0 months. Updated ITT analysis of OS demonstrated a 6.1 month improvement in median OS in the sunitinib arm when compared with the placebo arm (HR = 0.737, 95% CI: 0.465; 1.168).

However, due to crossover, it could be underestimated and it did not reach statistical significance. When data were analyzed using the RPSFT model, OS reached statistical significance: HR = 0.499 (95% CI: 0.351; 0.947), that is a 50% reduction in the risk of death with sunitinib (Table 2).

Cost-utility analysis of Sunitinib for the treatment of pNETs

Analytical technique

In order to evaluate the profitability of well-differentiated pancreatic neuroendocrine tumors treatment using sunitinib (Sutent®) in combination with BSC in comparison to standard therapies reimbursed in Poland, a cost-utility analysis (CUA) was performed using the Markov decision model constructed in TreeAge Pro 2009. As the measure of effectiveness, QALY was used and the result was presented as incremental cost-utility ratio (ICUR). ICUR expresses the cost of gaining one additional unit of QALY in case of replacing BSC with sunitinib plus BSC. Additionally, a one-way sensitive analysis was performed to estimate the influence of fundamental, uncertain parameters (connected with costs, effects, methods or assumptions) on the results and conclusions. Furthermore, the best and the worst case scenarios were considered as multivariate analyses.

Table 3. Safety results (deaths, discontinuations, serious adverse events, common adverse events)

Outcome	Intervention	N	n (%)	OR (95% CI)	NNT (95% CI)
Total deaths*	**SUN+BSC**	86	9 (10.5)	0.36 (0.13; 0.89)	8 (4; 35)
	PL+BSC	85	21 (24.7)		
Discontinued from the study due to adverse event	**SUN+BSC**	86	15 (17.44*)	2.35 (0.84; 7.20)	-
	PL+BSC	85	7 (8.24*)		
Discontinuation from the study due to progression or relapse	**SUN+BSC**	86	19 (22.0)	0.23 (0.11; 0.47)	4 (3; 6)
	PL+BSC	85	47 (55.0)		
Discontinuation from the study due to death	**SUN+BSC**	86	1 (1.16*)	0.32 (0.01; 4.12)	-
	PL+BSC	85	3 (3.53*)		
Total serious adverse events	**SUN+BSC**	83	22 (26.5)	0.51 (0.25; 1.03)	-
	PL+BSC	82	34 (41.5)		
Diarrhea^	**SUN+BSC**	83	49 (59)	2.25 (1.15; 4.41)	5 (3; 22)
	PL+BSC	82	32 (39)		
Nausea^	**SUN+BSC**	83	37 (45)	1.94 (0.97; 3.90)	-
	PL+BSC	82	24 (29)		
Asthenia^	**SUN+BSC**	83	28 (34)	1.39 (0.68; 2.87)	-
	PL+BSC	82	22 (27)		
Vomiting^	**SUN+BSC**	83	28 (34)	1.16 (0.57; 2.36)	-
	PL+BSC	82	25 (30)		
Fatigue^	**SUN+BSC**	83	27 (32)	1.31 (0.64; 2.72)	-
	PL+BSC	82	22 (27)		
Hair-color changes^	**SUN+BSC**	83	24 (29)	32.95 (5.01; 1371.21)	4 (3; 6)
	PL+BSC	82	1 (1)		
Neutropenia^	**SUN+BSC**	83	24 (29)	10.71 (3.00; 57.44)	4 (3; 7)
	PL+BSC	82	3 (4)		

Outcome	Intervention	N	n (%)	OR (95% CI)	NNT (95% CI)
Abdominal pain^	SUN+BSC	83	23 (28)	0.83 (0.40; 1.70)	-
	PL+BSC	82	26 (32)		
Hypertension^	SUN+BSC	83	22 (26)	7.03 (2.20; 29.24)	5 (4; 9)
	PL+BSC	82	4 (5)		
Palmar-plantar erythrodysesthesia^	SUN+BSC	83	19 (23)	11.88 (2.67; 107.60)	5 (4; 9)
	PL+BSC	82	2 (2)		
Anorexia^	SUN+BSC	83	18 (22)	1.06 (0.47; 2.40)	-
	PL+BSC	82	17 (21)		
Stomatitis^	SUN+BSC	83	18 (22)	11.08 (2.48; 100.74)	6 (4; 10)
	PL+BSC	82	2 (2)		
Dysgeusia^	SUN+BSC	83	17 (20)	8.82 (1.92; 81.35)	7 (4; 15)
	PL+BSC	82	4 (5)		
Epistaxis^	SUN+BSC	83	17 (20)	8.82 (1.92; 81.35)	7 (4; 15)
	PL+BSC	82	4 (5)		
Headache^	SUN+BSC	83	15 (18)	1.42 (0.56; 3.68)	-
	PL+BSC	82	11 (10)		
Insomnia^	SUN+BSC	83	15 (18)	1.59 (0.61; 4.23)	-
	PL+BSC	82	10 (12)		
Rash^	SUN+BSC	83	15 (18)	4.30 (1.28; 18.51)	8 (5; 27)
	PL+BSC	82	4 (5)		
Thrombocytopenia^	SUN+BSC	83	14 (17)	3.96 (1.16; 17.16)	9 (5; 38)
	PL+BSC	82	4 (5)		
Mucosal inflammation^	SUN+BSC	83	13 (16)	2.35 (0.78; 7.94)	-
	PL+BSC	82	6 (7)		

Outcome	Intervention	N	n (%)	OR (95% CI)	NNT (95% CI)
Weight loss^	**SUN+BSC**	83	13 (16)	1.51 (0.55; 4.25)	-
	PL+BSC	82	9 (11)		
Constipation^	**SUN+BSC**	83	12 (14)	0.70 (0.28; 1.71)	-
	PL+BSC	82	16 (20)		
Back pain^	**SUN+BSC**	83	10 (12)	0.67 (0.25; 1.74)	-
	PL+BSC	82	14 (17)		

*At the data cut-off point: April 15, 2009;
^Adverse events were defined on the basis of National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Events listed are those of any grade that occurred in more than 15% of patients in either group

Perspective

CUA analysis was conducted from the perspective of the public payer for health services (Polish National Health Fund, PNHF) and from the patient and PNHF perspective.

Time horizon

The time horizon covered the period from the beginning of treatment until the patient's death (lifetime horizon).

Model structure

The model structure was based on the data from the clinical trial Raymond 2011 [9], analysis of the course of the disease, and medical expert opinion.

In the Markov decision model, the following states, which are important from economic or clinical point of view, were taken into consideration: "initial state", "disease progression" and "death". All patients entered the model in the "initial state" and were treated with either sunitinib plus BSC or placebo plus BCS. In the "initial state", after the end of the cycle, a transition to the following states: "initial state", "disease progression" and "death" is possible. The "disease progression" state can be followed after the end of the cycle by the "disease progression" or "death" state. The "Death" is the terminal (absorbing) state.

The length of the model cycle, corresponding to the frequency of health state changes in patients, is four weeks. A discount rate of 5% for costs and 3.5% for benefits was used.

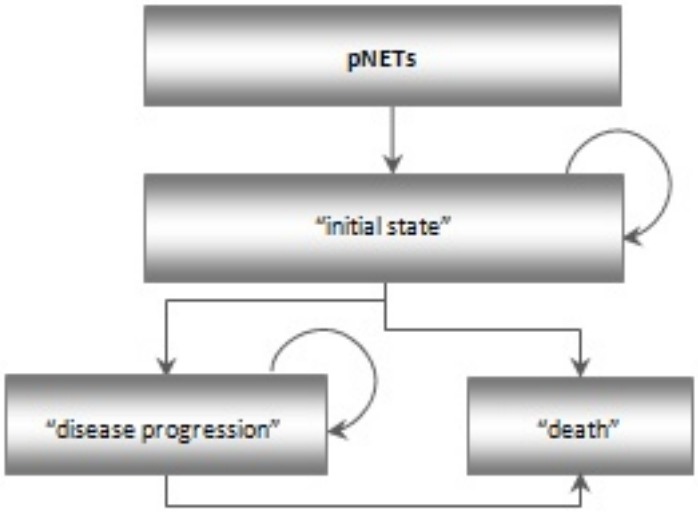

Figure 4. Structure of the model

Assumption and model parameters

Clinical data were taken from the main phase III clinical trial (Raymond 2011 [9]). Data on progression-free survival and overall survival were extrapolated using a Weibull method and included the use of RPSFT method to allow for crossover between the arms of the clinical trial. The base case included events occurring in the extension period of the clinical study, after un-blinding had occurred. This revealed an improved OS benefit (HR=0.18; 95% CI: 0.06–0.68) [10].

Patients in any state of the model (with the exception of the "death" state, which is an absorbing state) are exposed to the risk of progression, which increases as the disease progresses.

Utilities for the health states before ("initial state") and after progression were based on a conversion of the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire responses from the clinical study Raymond 2011 into utility values. The "initial state" utility value was 0.73 and the progression utility value was 0.596 [9, 14].

Table 4. Summary of model parameters - effectiveness and utilities

Parameters	SUN+BSC	PL+BSC
The shape parameter for OS	1.63	-
The scale parameter for OS	40.04	-
The shape parameter for PFS	0.79	1.16
The scale parameter for PFS	19.89	6.31
Utility "initial state"	0.730	0.730
Utility "disease progression"	0.596	0.596
P_death (1 cycle)*	0.000000	0.000000
P_ death (2 cycle)*	0.002440	0.013481
P_ death (3 cycle)*	0.012963	0.069753
P_ death (4 cycle)*	0.028187	0.151328
P_ death (5 cycle)*	0.046766	0.244331
P_ death (6 cycle)*	0.067822	0.339491
P_ progression (1 cycle)*	0.000000	0.000000
P_ progression (2 cycle)*	0.087465	0.097843
P_ progression (3 cycle)*	0.137352	0.162067
P_ progression (4 cycle)*	0.172810	0.193011
P_ progression (5 cycle)*	0.198695	0.200967
P_ progression (6 cycle)*	0.217514	0.194445

Table 4 shows clinical parameters (effectiveness and utilities) used in the model.

Following that, direct medical costs were included: sunitinib, the administration of the drug, diagnostic and monitoring, somatostatin analogs, BSC, severe adverse events (AEs) and palliative care. Only the cost of grade 3 and 4 AEs were considered. Prices were evaluated on the basis of Polish National Health Fund regulations applicable in 2012.

Median duration of drug use, which takes into account discontinuation due to an AE, disease progression and death, was used to estimate the cost of sunitinib and somatostatin analogs. The assumption that patients continue sunitinib treatment until the next disease progression was tested in a sensitivity analysis.

In the analysis, compliance at 91.3% in the group receiving sunitinib was included (estimated as the proportion of administered doses relative to the number of planned doses at 37.5 mg daily) [9].

Costs of terminal care (hospice at home within the last week of life) are associated with the "death" state.

Cost parameters used in the model are shown in Table 5.

Results

Cost-utility analysis

Results of a cost-utility analysis of sunitinib plus BSC in the treatment of patients with unresectable or metastatic well-differentiated pancreatic neuroendocrine tumors with disease progression were presented in Table 6.

Table 5. Summary of model parameters - costs

Parameters	PNHF [PLN]		PNHF+patient [PLN]	
	SUN+BSC	PL+BSC	SUN+BSC	PL+BSC
Cost of sunitinib /per cycle	17,302.80	-	17,302.80	-
Compliance	0.913	-	0.913	-
Cost of administration of the sunitinib	104.00	-	104.00	-
Cost of diagnostic and monitoring:				
Computerized Tomography (CT scan)	389.70 (every 2 months for the first six months, and then every 3 months until progression)	-	389.70 (every 2 months for the first six months, and then every 3 months until progression)	-
Specialist advise (1st type)	34.90 (every 4 weeks, or every 3 months in patients responding to treatment)	-	34.90 (every 4 weeks, or every 3 months in patients responding to treatment)	-
Comprehensive advice (1st type)	59.82 (in the first cycle)	-	59.82 (in the first cycle)	-
Cost of monitoring	34.90 (once every three months after the end of the program)	34.90 (once every three months)	34.90 (once every three months after the end of the program)	34.90 (once every three months)
Cost of somatostatin analogues	6,166.09	5,424.89	6,166.09	5,424.89
Cost of BSC	43.38		49.86	
Cost of severe adverse events	393.85	18.03	394.78	18.15
Cost of palliative care *	1,501.64		1,501.64	

* the cost of palliative care will be added during the last week of life

Table 6. The results of the cost-utility analysis for a life time horizon

Parameters	SUN+BSC	PL+BSC
PNHF perspective		
Total costs [PLN]	89,688.63	7,095.85
Incremental cost [PLN]	82,592.78	
Total health effects [QALY]	1.44	0.46
Incremental health effects [QALY]	0.98	
ICUR [PLN/QALY]	**84,213.78**	
PNHF+patient perspective		
Total costs [PLN]	89,821.83	7,148.58
Incremental cost [PLN]	82,673.25	
Total health effects [QALY]	1.44	0.46
Incremental health effects [QALY]	0.98	
ICUR [PLN/QALY]	**84,295.83**	

The incremental cost-utility ratio (ICUR) for the comparison of sunitinib+BSC with BSC was determined from the following formula:

$$ICUR=(Cost_{SUN+BSC} - Cost_{BCS})/(Effect_{SUN+BSC} - Effect_{BSC})$$

The cost of gaining an additional QALY by replacing placebo+BSC with sunitinib+BSC is PLN 84,214 /PLN 84,296 (€20,441/€20,461) from PNHF/PNHF+patient perspective. The cost-utility analysis proved that SUN+BSC is more expensive but more effective than BSC alone in the treatment of patients with unresectable or metastatic well-differentiated pancreatic neuroendocrine tumors with disease progression.

The results obtained are below the acceptability threshold in Poland (which is about PLN 99,543 (€24,162)). The 2011 weighted average exchange rate of Polish National Bank was €1 = PLN 4.1198.

Sensitivity analysis

In order to investigate the influence of key parameter changes and the settings of the model on the results of the cost-utility analysis, one-way and multi-way sensitivity analyses were performed. A sensitivity analysis for the comparison SUN+BSC vs BSC showed robustness of the results (confirmed that SUN+BSC remains more expensive, but still more effective than BSC). The results were the most sensitive to:

•sunitinib was continued until disease progression (ICUR PLN 254,372.88 per QALY/ PLN 254,454.93 per QALY from PNHF/PNHF+patient perspective);

•minimal median duration of sunitinib use (ICUR PLN 16,239.56 per QALY/ PLN 16,321.61 per QALY from PNHF/PNHF+patient perspective);

•maximal median duration of sunitinib use (ICUR PLN 239,474.98 per QALY/ PLN 239,557.03 per QALY from PNHF/PNHF+patient perspective).

Discussion

The aim of this publication was to evaluate the clinical and cost effectiveness of sunitinib and best supportive care in the treatment of patients with unresectable or metastatic well-differentiated pancreatic neuroendocrine tumors with disease progression on the basis of a systematic literature review.

When assessing the restrictions of this systematic review and CUA features, PICOS predefined inclusion criteria and the quality of input data available, as well as the scope of the analysis in respect of an explicit decision problem, should be considered.

Pursuant to the assumption of the decision problem, the analyzed population are adult patients with unresectable or metastatic well-differentiated pancreatic neuroendocrine tumors with disease progression. Therefore, studies which assessed patients below 18 years-of-age or with diseases such as gastrointestinal stromal tumor, metastatic renal cell carcinoma and other were excluded.

Pursuant to the Summary of Product Characteristic of Sutent® [5], sunitinib in the indication specified above should be given in the dose of 37.5 mg once a day, orally (continuous regimen). Therefore, all clinical trials assessing sunitinib given in the dose of 12.5 mg/d, 25 mg/d or 50 mg/d were excluded from this analysis.

Authors of this systematic review did not include in the main analysis publications available only in the form of abstracts or conferences reports due to the absence of a possibility of carrying out an assessment of reliability of this type of survey. The review covered all found randomized studies satisfying the predefined analysis inclusion criteria.

The comparator of the intervention assessed should be a valid practice [7]. Authors of the report consulted the selection of the comparator with a medical expert. Based on information about unresectable or metastatic well-differentiated pancreatic neuroendocrine tumors with disease progression treatment standards in Poland and the opinion of the medical expert, best supportive care was considered as the proper comparator for the intervention assessed.

To sum up, the systematic review and cost-utility analysis of sunitinib is consistent with the assumptions presented in the analysis of the decision-making problem. Population included in the analysis is consistent with the population included in the Summary of Product Characteristic of Sutent® [1]. The treatment period and chosen endpoints seems to be justified and sufficient to fully prove the efficacy of the intervention assessed.

Following the search of publications, one primary randomized clinical trial (phase III) was found (subtype II A) to satisfy the inclusion criteria for the analysis [4, 9, 10, 11, 12, 13]. The study directly compared the clinical effectiveness of sunitinib and BSC versus placebo and BSC in the treatment of patients with unresectable or metastatic well-differentiated pancreatic neuroendocrine tumors with disease progression.

Sunitinib together with BSC in the treatment of patients with unresectable or metastatic well-differentiated pancreatic neuroendocrine tumors with disease progression provides higher clinical efficacy and a comparable safety profile against BSC. Statistically significant differences to the benefit of sunitinib were found in respect of main endpoints: progression free survival and overall survival as well as the objective response rate. This clinical effectiveness analysis also showed statistically significant effects of sunitinib regarding the amount of total deaths and discontinuation from the study due to progression or relapse.

Inclusion of patients in the studies is based on clearly defined criteria, which are often rigorous. Such criteria must be examined before extrapolating studies results on to the general population. For this reason, it is essential to assess the similarity between the population surveyed and the target population, taking into account the clinical and demographic features of patients. The trial population (Raymond 2011) was relatively well-balanced, unselected, with demographic characteristics and treatment history that are typical for patients with advanced pNETs. On the other hand, rigorous criteria of including patients into the analyzed clinical trial (Raymond 2011) decreased the possibility of incorporating the results obtained into everyday clinical practice.

The QALY parameter was the measure of effectiveness in the CUA, which was calculated on the basis of modeling conducted using TreeAge Pro 2009. Similarly to the majority of economic analyses concerning profitability of other cancer treatment, a Markov model was implemented. The economic

model predicted a gain of 0.98 QALYs from 0.46 QALYs in the BSC arm to 1.44 with sunitinib. This is a very substantial increase for those patients.

Results of the cost-utility analysis proved that a therapy containing SUN+BSC is more expensive and more effective than BSC alone. Treatment with the use of Sutent® leads to extending overall survival (OS) as well as time to progression (TTP).

According to the recommendations of the consultation board of the Agency for Health Technology Assessment in Poland concerning the threshold of medical technologies profitability, sunitinib therapy with BSC in the treatment of pNETs is a cost effective strategy in comparison with BSC alone when the measure of effectiveness is QALY. ICUR is below the acceptability threshold in Poland (which is about PLN 99,543).

At present, patients with unresectable or metastatic well-differentiated pancreatic neuroendocrine tumors with disease progression do not have any other effective treatment option. A positive reimbursement decision for sunitinib will increase the possibilities of treatment in this group of patients.

Conclusions

These analyses suggest a survival advantage and further support the clinical benefit of sunitinib for adult patients with progressive unresectable or metastatic well-differentiated pancreatic NETs.

The results of the present clinical effectiveness analysis clearly prove that sunitinib administered in a 37.5 mg dose is an effective and safe therapy in the treatment of patients with unresectable or metastatic well-differentiated pancreatic neuroendocrine tumors with disease progression. Sunitinib in combination with BSC prolongs overall survival and time to next progression.

The reimbursement of sunitinib would bring benefits to patients for whom there is currently no other effective treatment option. Compared with BSC, sunitinib treatment in patients with advanced pNETs improved effectiveness in terms of QALYs gained and the ICUR was within the range of what is considered cost-effective in Poland.

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Opioids, history still present. Policy issues in implementing the drug treatment of pain

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Abstract

In the history of medicine and pharmacy issues of treatment or prevention of pain disorders have been discussed since ancient times to the present. Opioids are a class of drugs controlled in the manufacturing, distribution, their use is specified by a certain health policy, medicine, pharmaceutical economics and rationalization of treatment within the competence of the ministries of health. The treatment of chronic pain management in both origin cancer and non-malignant forms provides solutions to ensure the relative balance in all aspects of the policy of balance, or balancing the risk factors associated with the use of opioids as controlled drugs in health care.
In the analysis of a variety of sources, including the evaluation of the Polish pharmaceutical market, particularly during the legislative process of the Reimbursement Act, it seems an important challenge for state drug policy makers to balance the controlled drugs market (including opioids).

Key words: opioids, pain management, health policy for the treatment with opioid drugs, pharmaceutical legislation

The healing properties of opioids have been known to mankind for centuries. Poppy, due to the possibility of using both petals of flowers and seeds became a major source of these substances. Parts of the plant are used in the treatment of various diseases and ailments. In order to know the qualities and characteristics of opioid as a medicine with special properties better it is worth presenting the brief history of their use.

Poppy as the main component of herbal mixtures, called species pectorales already in ancient times, was identified as an excellent source of soothing coughs and ailments of the heart muscle [1]. The positive effects of it, especially in children drew the attention of the botanist Ignacy Czerwiakowski [2]. Chomel, on the other hand, discovered properties of poppy seeds, relieving pain caused by colic [3].

Positive impact of the substance on complaints was evident not only among circles of folk rymedicine. The use of the poppy by pharmacists confirmed in his work Józef Celiński who rysaid "In pharmacies [poppy leafs] are used for infusion, tincture and syrup" [4]. A record of the use of opioids in the form of herbs also appears in J. Trapp's "Farmakognozyi" [5].

Poppy properties described by the researchers had their origin in opium - the substance harvested as milk poppy from immature green pericarp head of plants. Medicinal syrups and alcoholic tincture of the dried pouch were prepared. High quality of Polish opium was emphasized due to the morphine content of 12-13% [6] Apart from morphine more than 20 other alkaloids were detected in opium. Its derivatives, such as papaverine (spasmolytic) and codeine (antitussive) [7] have also been used in medicine.

Romuald Świerzbiński delivered a lot of important information on the effects of morphine in his publication of 1857. The author classified morphine as a drug to reduce pain and as a muscle relaxant. Effects of the substance on the circulatory system in the form of acceleration of pulse and breath, increase of temperature and pressure were found. In 1933, Jan Muszyński by analyzing a number of the formulations prepared on the basis of opium (including Extractum Opii, Opii crocata), identified narcotic substances as exclusive in medicine.

Opium was widely used over the next centuries. It has been often used as a antidiarrheal and diuretic. However the most well-known and appreciated were its pain-relieving and hypnotic properties. There were also documented cases of the use of opium in the treatment of alcoholism [8] and mental illnesses. The drug also demonstrated to be

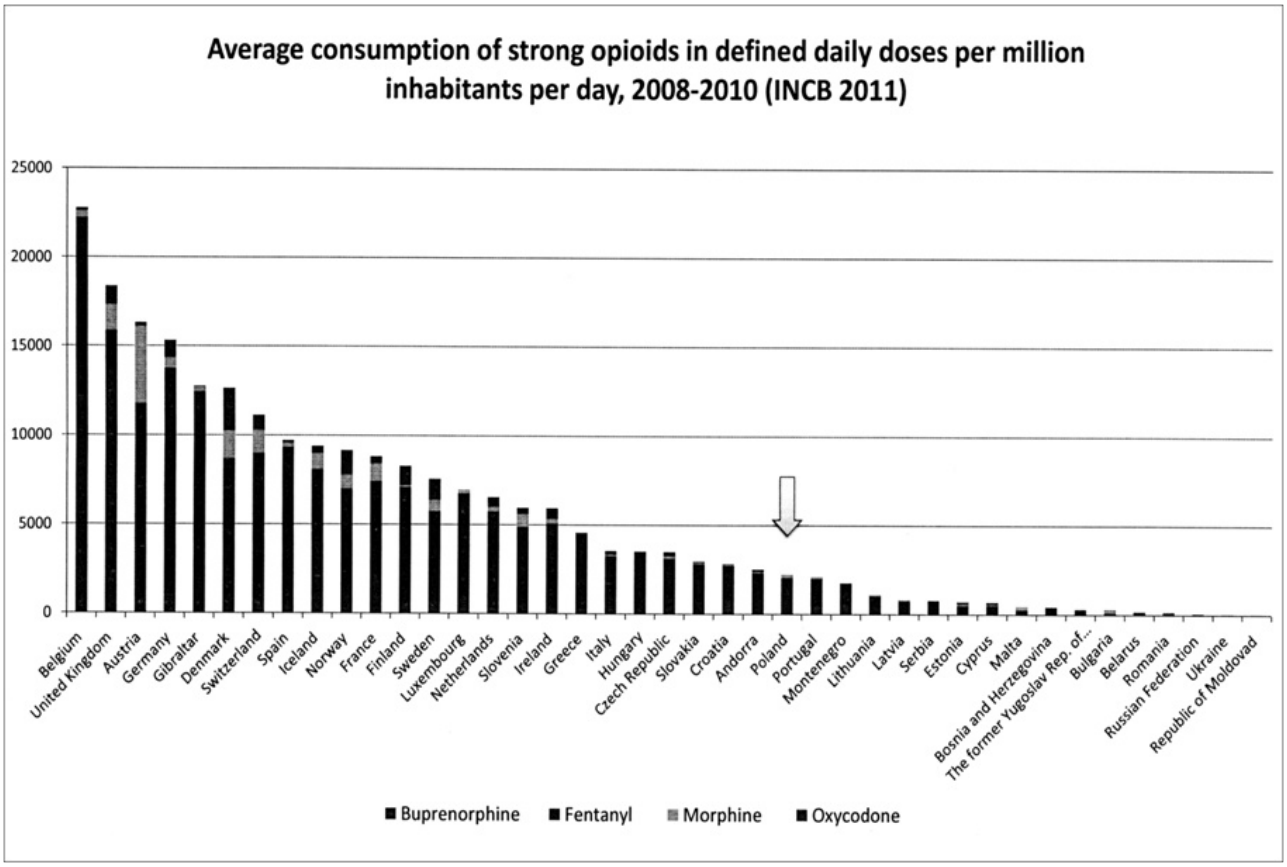
effective in dealing with people in hysteria or having trouble with insomnia. It was used during surgeries, childbirth, intestinal parasite control and treatment of malaria. It turned out to be known and appreciated as a detoxifying aid in cases of poisoning. Medical calendars of the following years provide accurate descriptions of a wide range of indications for the use of opium in the treatment of various disorders.

Despite the passage of time, progress in technology and medicine, opioids continue to play an important role in pharmacotherapy. Today's focus is primarily on the use of analgesic properties of these substances. Opioid analgesics are mainly based on the treatment of cancer pain. Ever more frequently they are also helpful in relieving chronic (moderate and severe) non-malignant pain. The problem of use of "heavy opiates' in daily doses in individual European countries is illustrated in the graph below on basis of data -2008-2010 INCB.

Cases of significant reduction of pain in patients with chronic non-cancer pain, continuing a long-term opioid therapy were confirmed by analysis of the Cochrane Collaboration [9].

From the beginning of the medical use of opioids both researchers and doctors have tried to determine and analyze the safety of opioid preparations., Leopold Lafontaine, the surgeon living in the nineteenth century stated that the administration of opium to children can be deadly toxic [10]. Similarly spoke Jan Biegański: „decoction of poppy puts to sleep (...), which in general badly affects health of children (...) and sometimes baby is put to sleep forever" [1]. It was feared that the inadequate doses of the drug can poison, which was also reflected in "Calendar for year 1921" containing descriptions of the treatment of excessive consumption of opioids [11].

Currently concerns relate mainly to the likelihood of opioid dependence. Physicians providing treatment direct their efforts to build an appropriate dosing regimen and careful monitoring of the progress, effectiveness and side effects of treatment implemented. Systematic review of the literature data show that less than 0.5% of patients with a negative history of substance abuse, committed an abuse of prescription pharmaceuticals while taking opioid analgesics [12]. This information is also confirmed by the study of Cochrane Collaboration which showed that only 0.27% of patients participating in the experiments with symptoms of dependence were observed [9].



The commonness of chronic non-malignant pain (every fifth European adult suffers from it, more frequently - the elderly) led scientists to begin the development of the research on pain and methods of management of it [13]. A group of experts in the field of pain was inter alia set up for this purpose - OPENMinds (Opioids and Pain European Network of Minds). This group with the publication of the " White Book" in 2005 and 2011 obliged European governments the to make policy changes into the treatment of pain and access to opioid drugs. The following are the key topics of the above publication.

Special attention was paid to the problem of pain in people with cancer. Study of European Pain in Cancer (EPIC) found that more than half of the above patients exhibit pain. Furthermore it was found that nearly 80% of patients experience chronic pain with the development of the disease. The research led to the following conclusions: about one third of patients were not treated at the time of the study, and 20% had never applied analgesics prescribed drugs. Only one in twenty patients was treated for pain with the help of a specialist [14].

International organizations such as the World Health Organization (WHO) and Human Rights Watch have qualified the access to pain treatment as one of the fundamental human and patient rights. Ensuring patient access to the highest quality of pain management systems came under the responsibility of national governments. Directives, adopted by the European Parliament, regulate international health care and patients' rights to obtain the reimbursement in of the country of residence for health care received abroad [15].

As mentioned before, the pain has not been treated properly in most countries. The reasons for this situation are considered to be the low-quality and standard of prevention of pain and treatment conducted and marginalization of the problem of the chronic pain. According to the Declaration of Montreal as obstacles in gaining access to optimal health care system is inter alia lack of qualified medical personnel in the treatment of pain, a low level of scientific research on pain, limited access to opioids and other drugs used for pain [16]. According to the Achieving Balance in National Opioids Control 2011 guidelines, governments have a two-pronged obligation in the case of controlled drugs (such as opioids): firstly to ensure the availability of substances to be used for medical purposes and secondly they should protect patients against abuse of drugs and addiction to them [17].

The subject of controlled drugs carries a lot of problematic issues, such as the availability of these substances, affordability of them and above all, the control. The implementation of the policy related to this group of medications requires the support to governments and societies. According to WHO, this policy should be characterized by the effort to achieve a balance between the access, use of drugs and their abuse. The distribution and migration of opioids are subject to international laws and national drug control policies of individual countries. The government is burdened with the responsibility for balancing the risk of use of drug with an appropriate (optimal) access to treatment. Members of OPENMinds mark out a few areas of government policies aimed at improvement and development of the management of the treatment of chronic pain (of cancer and non-malignant origin).

These are the following issues:

1. prioritizing the treatment of pain;

2. raising the level of knowledge and skills of health staff through cooperation with national educational institutions;

3. creation or maintenance of interdisciplinary outpatient clinics for the diagnosis and treatment of pain;

4. ensuring the availability of analgesics (including opioids);

5. improvement in pain prevention by promoting and funding research on the nature of pain;

6. the establishment of appropriate facilities (resources) to achieve the proper level of safeguard for services.

To enable the achievement of the accepted goal of balanced levels of use, the World Health Organization has developed sui generis guide ("Ensuring the balance of national policies on the controlled substances: Recommendations for the availability and accessibility of the controlled medicines") in the form of recommendations for the optimization of the drug policy under control. Individual instructions can be grouped according to the aspect discussed.

The recommendations emphasize the importance of the rules, especially in the process of implementation, execution and development of the controlled drugs policy. The very first two recommendations concern legislation issues. According to the first of them, the drug control policy should be based on the necessary information about their use in the medical and research purposes. In accordance with article 2 of the Single Convention on Narcotic Drugs and article 5 of the Convention on Psychotropic Substances, governments should recognize the need for controlled drugs for the treatment of pain and for scientific purposes and take care of appropriate access to these substances. It seems important to improve the state laws to adopt international regulations. Recommendation nr 2 describes in detail the role of the heads of states and governments as to this issue. The obligation of governments to respect the law on the control over resources as well as other standards relating to human rights was emphasized. Human rights coupled with patients' rights require the access to drugs (including opioids), under the right to health. Already in 2005 the World Health Assembly and the Economic and Social Council of the United Nations called the countries to follow international treaties in order to ensure access to and the use of opioid therapies. The guidelines contained in article 4 of the Uniform Convention are similar in tone: "The parties shall adopt such legislative and administrative measures which they consider necessary ... to limit the collection, production, distribution ..., ... the use and possession of drugs exclusively for medical and scientific purposes." Article 12 of the International Covenant on Economic, Social and Cultural Rights (ICESCR) raises such an issue as the right to access to the appropriate treatment of conditions ensuring the use of essential drugs, and also increases the importance of a balanced therapy with monitored drugs.

Recommendation no 7 indicates a major role of planning of the pharmaceutical policy in terms of availability and affordability of the controlled drugs. It justifies the need to include the issue of controlled drugs in the national control system and public health policy. Policy plans allow to lay down the appropriate target, the implementation of access to medicines, and monitoring of the fulfillment of obligations for states imposed by international conventions on the use of both narcotic drugs and patients' rights. The importance of including the subject in policy plans affordability of drugs for scientific as well as medicinal purposes was emphasized. It is extremely important to include points associated with the availability of opioid analgesics as well as an integrated system of palliative care, especially in patients with cancer origin pain, in the program. The task of the government is to create the essential drugs list (based on the WHO List of Essential Medicines) - controlled drugs necessary to meet the immediate (medical) needs of the society. The policy carried out by governments should also include the strategy for optimal and rational use of the above mentioned drugs. An important issue is the distribution of reliable information on controlled drugs (social campaigns, leaflets).

International human rights law also imposes the obligation to respect the principle of non-discrimination on the availability of controlled drugs and the prevention of addictions of their use on the government. Drug policies lead by individual countries should take such actions which would ensure equal access to medicines for each group of people, regardless of economic, ethnic factors, etc. Each patient should have same rights to the use of drugs in therapies. The situation of patients using opioid analgesics is special, particularly with HIV positive patients, prisoners and opioid addicts. In many countries, these patients are still in some way discriminated – the access to controlled drugs in these cases is difficult or intentionally restricted. According to article 2 of the Universal Declaration of Human Rights, there is no reason to split patients into different groups of non-medical criteria, "every man has all the rights and freedom (...), regardless of race, color, sex, language, religion (...) or any other status, do not also make a difference depending on the political, jurisdictional or international status of the country or territory to which a person belongs (...) ".

Procedures related to the legislation should not regulate the issues relating to the use of controlled drugs too strictly. The task of government is to establish appropriate regulations, to optimize the use of drugs. Under the article 23 of the Convention on Psychotropic Substances it is permitted and acceptable to use more precise (tighter) control measures, if such measures are dictated by the need to protect public health. It seems important to verify the usefulness of legal norms in contribution to the protection of the public health. Situations

in which the accepted legal rules constitute a barrier to accessibility (affordability) of drugs, but do not affect the reduction of their abuse, should be avoided. Keeping records of opioid-dependent patients, the detail of which can contribute to the difficulty of obtaining the drug for patients from more than one source may serve as an example of this type of the phenomenon... Other barriers such as affordability of medicines are due to the use in some countries, severe penalties for any errors or problems with prescriptions (drug release) of drugs under control. The effect of such legislation may be refraining from releasing such medicines by health care professionals.

These elements of the strategy (policy) of the controlled drugs constitute specific challenges for the governments of Europe, but it is worth making an effort to improve the current situation. There are also expectations that investments in these spaces of activities will bring measurable economic tangible benefits to individual countries due to the reduction of the indirect costs of the chronic pain, including productivity lost and informal care.

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Opinion of patients on analgesics drugs used in the process of self-medication

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Abstract

The surveyed group was divided by age, education, place of purchase of the medicine, place of residence. The study surveyed the understanding of a medicine leaflet. 97% of respondents buy analgesics from a pharmacy, 9 % in a hypermarket and 5% in a grocery store, 4% at a petrol station.
Education defines the comprehension of a leaflet. 79% with the tertiary education people understand the leaflet and 38% with the primary education people understand the leaflet.
Overall men do not read medicine leaflets and most frequently misuse medicines.
The education, sex and place of residence have an important influence on the purchase and the way of medicine administration by patients in Poland.

Key words: Analgesics drugs, self-medication, Poland

Introduction

Medicines available without a prescription from a healthcare professional are used not only by elderly and middle-aged people but also by the young and occasionally by children. However, the mode of application of the analgesic drugs of this kind leaves a lot to be desired. The majority of the patients do not read information leaflets; moreover, they purchase medicines in non-pharmacy outlets, frequently on recommendation of a non-expert or under the influence of advertisements. [1, 2, 3].

This study presents an analysis of the mode of usage of the analgesic drugs and of the knowledge of this kind of medicines demonstrated by their users. This information serves as the basis to determine the degree of risk which results from the usage of the OTC drugs. One of the goals of the study is also to examine the patients' attitude to the analgesic drugs available without the doctor's prescription.

Methods

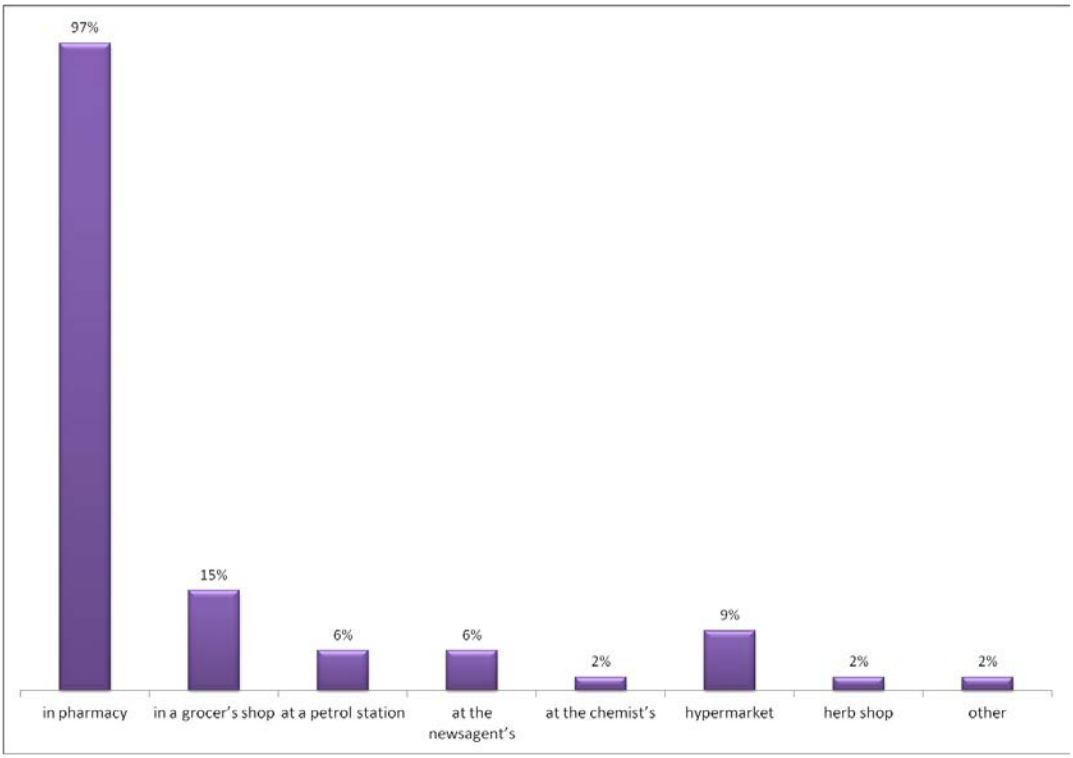
Research material consists of the data collected by means of a proprietary questionnaire addressed to adults. The survey research was conducted between February and April 2011. The research material comprises the information collected during the survey and included in the questionnaire either by the researcher during a direct conversation with a patient or by a respondent himself/herself. The survey was conducted among the patients of the Lublin clinics and among the users of the Facebook social networking service and of the www.insomnia.pl forum. The research tool was a questionnaire, independently developed for the purposes of this study. The respondents were able to choose multiple answers to many of the questions. The data collected during the research have been subjected to a statistical predicate analysis in the MS Excel 2007 program.

363 people aged 18 to 85 took part in the research. There were 227 female and 136 male respondents. 21 participants had primary education, 136 secondary education, 65 incomplete higher education and 138 higher education. The great majority of the respondents - 138 - were the inhabitants of the cities with population above 100 thousand people; 80 participants of the survey inhabited the cities with the population under 100 thousand people and 99 lived in the country.

Results and discussion

Respondents were asked about their preferred point of purchase of the analgesic drugs. Pharmacy turned out to be the most frequently chosen point of purchase of the OTC analgesics from a pharmacy. The definite majority of the respondents, as many as 97 %, declared that this is the place where they buy medicaments. The second and third most popular options were respectively a grocer's shop – 15% and a hypermarket – 9 %. A considerably smaller number of patients purchased medicines at the petrol stations – 6% and at a newsagent's – 6%. The chemist's and herb shops options were marked by 2% of the respondents each.

The analysis of the respondents' answers shows that the patients' education plays a large part in their choice of the point of purchase of the examined medicines. 75% of the respondents with primary or secondary education chose the pharmacy as their sole point of purchase. Only 25 % opted for other retail outlets. The respondents with higher or incomplete higher education declared that they purchase drugs in pharmacy – 55%, but also in the pharmacies combined with non-pharmacy outlets – 45%. There was also a visible difference in the choice of the point of purchase between various age categories. In comparison with the elderly young people more frequently buy medicines outside the pharmacy. In the 18-29 age category 61% of the questioned purchase medicines in pharmacy only. In the 30-45 age category this proportion increases to 72% and in the categories 46-59 and over 60 it amounts to 87% and 89% respectively. Such results may be explained by the fact that young people more often use the Internet and other sources of information to choose the medicine and the method of treatment on their own; it is also likely that they have better knowledge of various medicines than the old people. The elderly tend to rely on the knowledge of pharmacists and doctors to a greater extent, which they themselves mentioned when completing the questionnaire. It is possible that this fact caused such a considerable difference as far as the choice of the point of purchase is concerned. Having taken into account the gender as the factor influencing the choice of the point of purchase of the OTC analgesic drugs it was concluded that 74% women opted for the pharmacy as the only point of purchase. Men tend to buy medicines outside the pharmacy, so the proportion of the patients buying drugs in pharmacy only is smaller among the male respondents, amounting to 67%.



Picture 1. Point of purchase of the OTC analgesic drugs

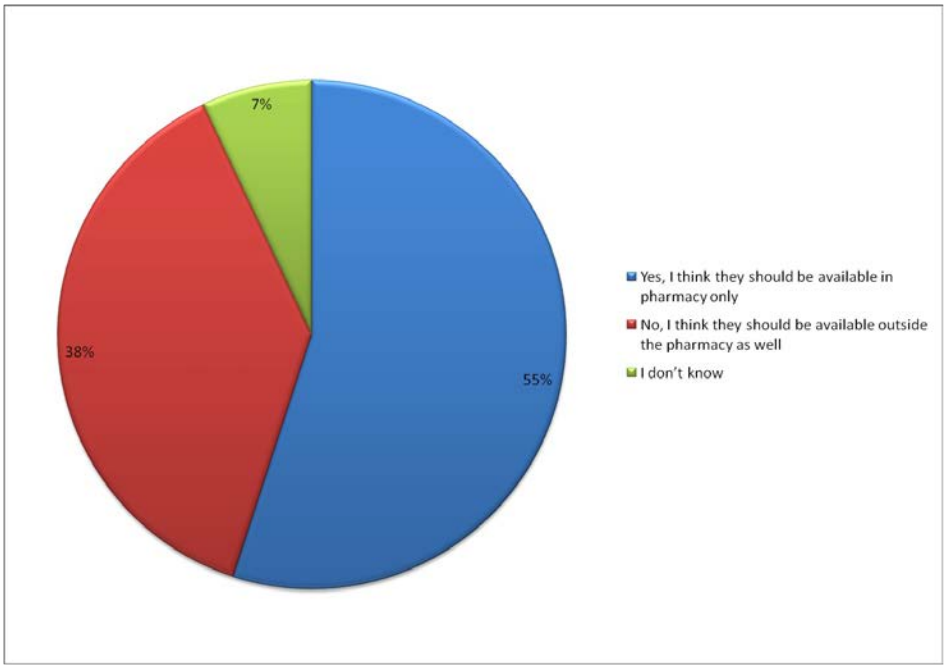
Table 1. Understanding of information leaflet by the respondents, depending on the level of education [in %]

	Education Primary	Education Secondary	Education Higher - incomplete	Education Higher
Yes	38	65	73	79
No	33	14	13	7
I don't know	29	21	14	14

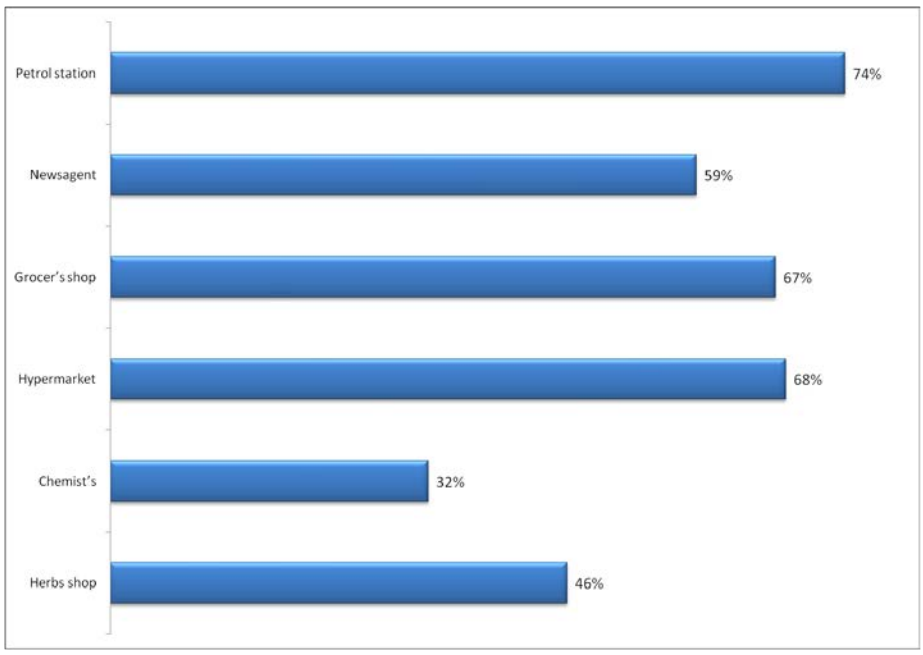
Only 38% of the questioned people with primary education declare that the contents of the leaflet are comprehensible. In the group of respondents with secondary education this proportion increases to as many as 65%. The understanding of the leaflet causes the least problems to the people with incomplete higher or higher education (73% and 79% respectively). Most likely it results from the fact that the larger knowledge of the better educated people positively influences their level of competence in self-medication. Therefore such people understand the contents of the leaflet better and it is clearer to them than to the lower-educated.

When asked a question concerning the availability of the medicines outside the pharmacy 55% of the respondents expressed the belief that drugs should not be available in other retail outlets. During the survey some of them drew attention to the overuse of OTC drugs by the Polish society and the necessity of putting some restrictions to non-pharmacy sales. 38% of the surveyed were of different opinion; they would like to have an option of buying medicines outside the pharmacy. They argued that such a possibility was necessary in case someone is in emergency. 7% of the respondents had no opinion on this subject.

Those patients who expressed the wish to buy medicines outside the pharmacy were additionally asked to indicate their preferred alternative points of purchase. Many of them ticked all the possible answers or the majority of them. However, the most frequent answer was a petrol station – 74%. Almost as many respondents opted for a hypermarket – 68% and a grocer's shop – 67%. The next option chosen was a newsagent – 59%. The least popular answers were a herbs shop at 46% and the chemist's – 46%.



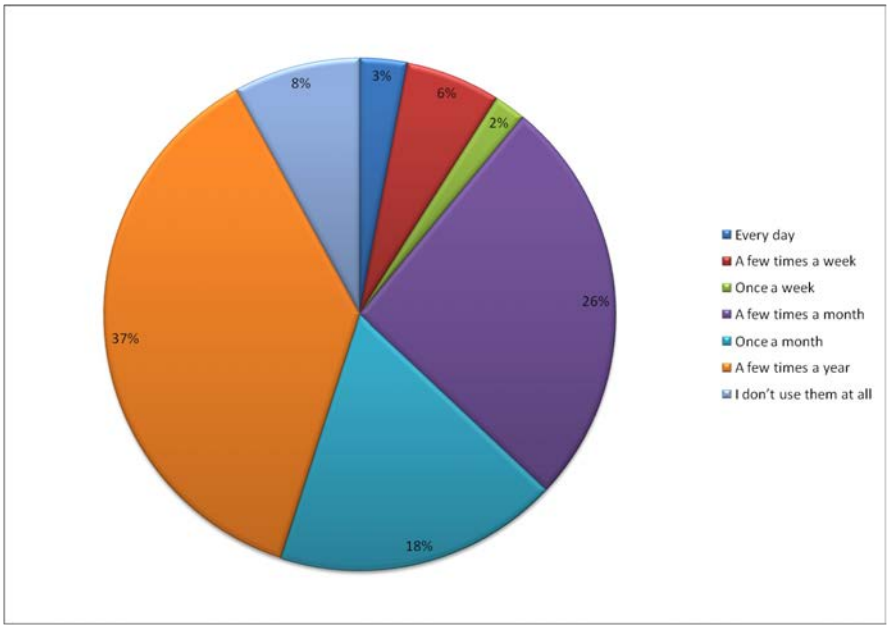
Picture 2. The respondents' opinion on possible points of purchase of the analysed group of drugs



Picture 3. Preferred points of purchase of the medicines outside the pharmacy

After the analysis of the data in terms of the gender factor it turned out that men were more willing to purchase medicines outside the pharmacy. 46% of them believed that non-prescription drugs should be available in this manner. In the group of female respondents the proportion of such answers was smaller and amounted to 33% only. In both groups there was a similar proportion – 7% – of people who did not have any opinion on this subject. The analysis in terms of age showed that the younger patients, particularly from the 18-29 age category (49%) would prefer the medicines to be sold in pharmacies only. In the 30-45 and 46-59 age categories the proportion of such answers was slightly different and amounted to 58% and 54% respectively. The majority of respondents from the 60+ category supported the idea of pharmacy-limited sale of drugs – the proportion of such answers amounted to as much as 82%.

As a part of the study the respondents were also asked how often they used the non-prescription analgesic drugs.



Picture 4. Frequency of non-prescription analgesic drugs application

When asked about the frequency of application of the non-prescription analgesic drugs most respondents – 37% – answered "a few times a year". Almost as many respondents – 29% use such drugs once a month, and 25% – a few times a month. The clear minority of the surveyed, 2% use them once a week. 6% of the patients apply these drugs a few times a week and 3% every day. The survey showed that the respondents who most frequently used analgesic drugs usually preferred the medicines containing paracetamol. Their application was sometimes controversial; for instance one of the patients used the "Apap noc" ("Apap night") painkiller as a hypnotic drug every day.

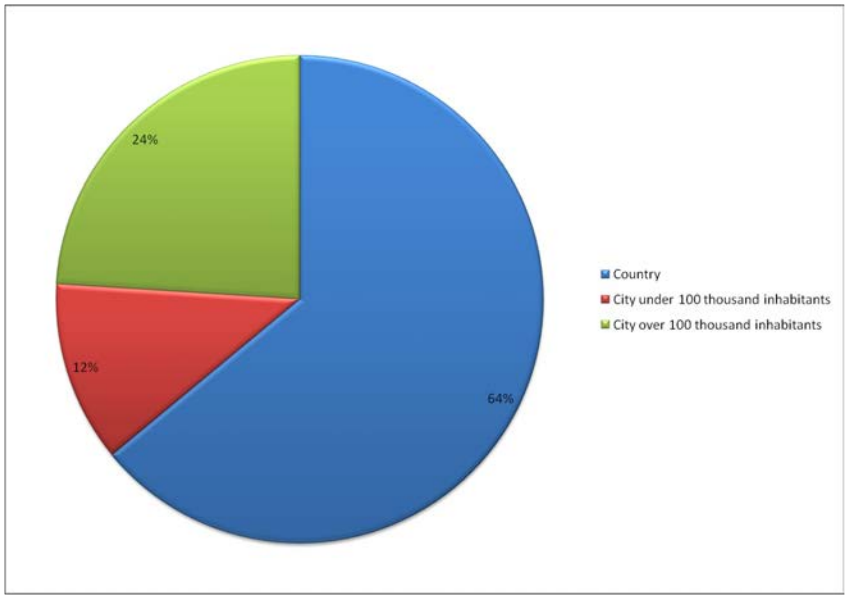
Most of the patients who chose the "every day", "a few times a week" or "once a week" options, which attest to the frequent use of medicines, lived in the country (64%) or in small towns (12 %). Only 24% of such respondents are the inhabitants of the cities over 100 thousand.

The large majority of the respondents who applied medicines so frequently were the people with primary (12%) or secondary (15%) education. In the group of respondents with incomplete higher and higher education those proportions amounted to 4% and 8% respectively. In the group of people, who use analgesics every day, there was only one person with higher education. What is interesting, more than half of the frequent users declared that the information contained in the leaflets were comprehensible and exhausting – and it is made clear in the leaflets that the analgesic medicines should not be used for period longer than 5 days. It is possible that some of these people used analgesic drugs due to chronic pain and had previously consulted their doctor.

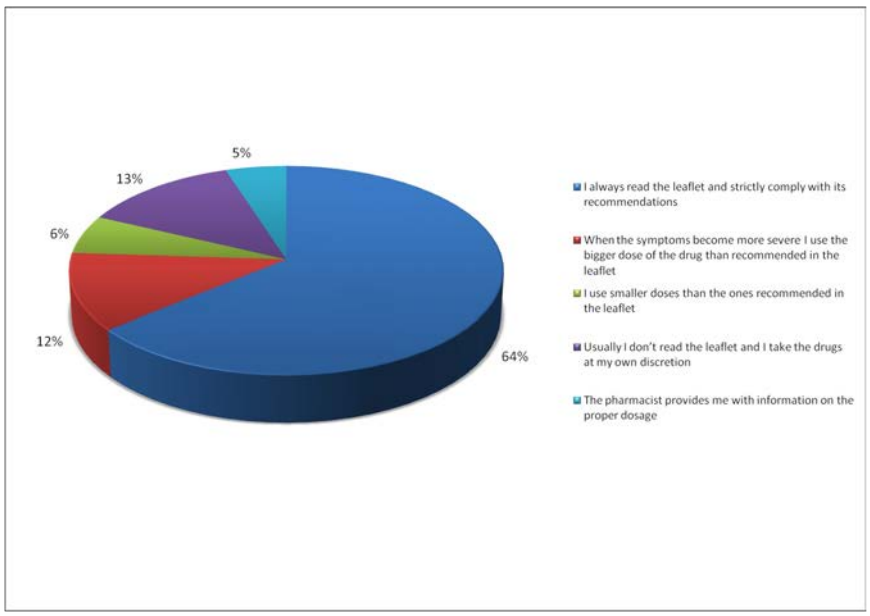
The usage of medicines among men differs from the usage among women and is generally lower. The female respondents much more often gave the answers which attested to higher frequency of drug application, such as „everyday" – 3% (male respondents -1%), "a few times a week" – 7% (male respondents – 4%), "once a week" – 4% (male respondents – 0%). In all likelihood the increased usage of medicines by women results from the application of the analgesics due to, among others, menstruation pains.

After analysing the frequency of usage of the analgesic OTC drugs in various age categories it turned out the patients from the older age groups took them more often. None of the respondents in the 18-29 age categories admitted to using analgesic medicaments every day. However, in the following age categories the proportion of respondents who do so gradually increases. In the 30-35 age category it amounts to 1%, but in the 46-59 age group it is 4% and in the 60+ age category – 16%. Similar numbers appear when it comes to using the analgesics a few times a week. Most of the younger people (18-29 years old) use those medicines a few times a year (41%) or once a month (26%).

At the next stage of the research the respondents were asked about their typical behaviour in the process of drugs application and about the dosage of the analgesic drugs.



Picture 5. Place of residence of the respondents who most frequently apply the analgesic drugs from the OTC group



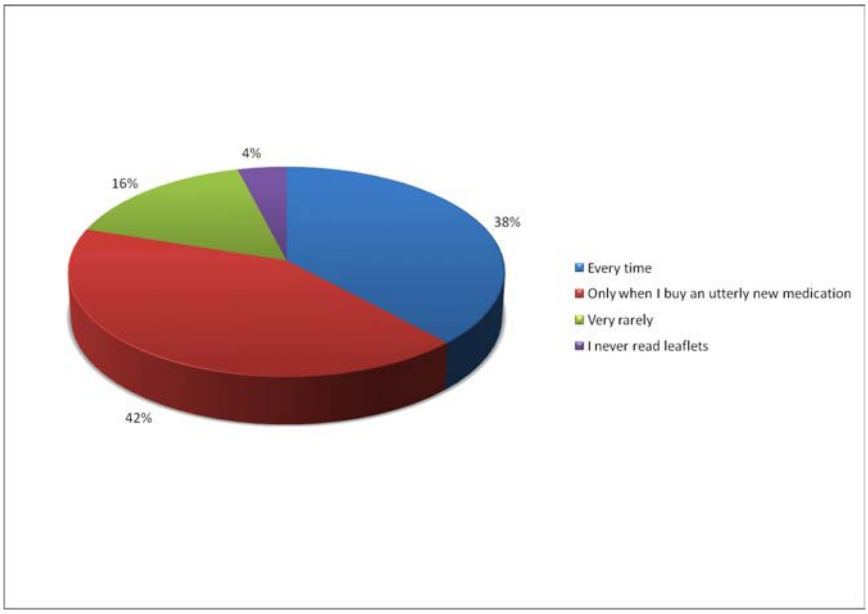
Picture 6. Dosage of the analgesic drugs

The majority of the respondents, as many as 64%, go by recommendations mentioned in a information leaflet attached to a medicament and strictly follow its instructions; 6% read the leaflet, but take smaller drug doses than recommended, and 12% take larger doses when the symptoms become more severe. The proportion of the people who do not read the leaflet and use the drug at their own discretion amounts to 13%. The pharmacist as the source of information on the proper dosage plays the least important part and only 5% of the respondents admitted to following his recommendations.

The analysis of the data has proven that men use the analgesic drugs in a more carefree way. Only 57% of the male respondents read the leaflet and strictly follow its recommendations, while in case of female respondents this proportion amounts to 67%. Men more often answered that they apply the drug at their own discretion – such an answer was ticked by 16% of the surveyed. Only 12% of women gave such an answer. The tendency to overuse drugs when the illness symptoms (high fever, acute pain) become more severe is similar in case of both sexes and amounts to 12% in case of the female respondents and 13% for the male respondents. The pharmacist recommendations are followed by 7% of men and 4% of women.

The analysis of the collected data in terms of age has shown that in all age categories there is a similar proportion of people who do not follow the leaflet instructions concerning the dosage and apply the medications at their own discretion instead; it oscillates between 15 and 16%. Most people who strictly comply with the leaflet instructions can be found in the 30-45 age category – as many as 70%. When the illness symptoms become more severe the majority of people use larger doses than those recommended in the leaflet; the proportion of such people in the respective age categories amounts to: 18-29 years – 15%, 30-45 years – 10% and 46-59 years – 15%. In the group of people over 60 years of age only 3% of the respondents apply higher doses than those recommended by the leaflet. However, the proportion of people who use lower doses than recommended is the highest in this age category (18%). The representatives of this group most frequently follow the pharmacist's advice – 8%. In the remaining groups the proportion of such people oscillates between 3 and 5%.

The analysis has proven that the groups of respondents who are most cautious when applying the medicines are paradoxically the people with the lowest education level. Only 5% of them apply the medicines at their own discretion and the same proportion of people from this group use higher drug doses when the illness symptoms become more severe. A pharmacist's role in the process of treatment turns out to be much more important in this group than in the case of the other ones – as many as 14% of the respondents rely on his/her knowledge. As far as the groups of people with secondary, incomplete higher and higher education are concerned the results turn out to be similar



Picture 7. Leaflet reading frequency among the respondents

to one another. There are considerably more respondents who do not read the leaflets at all – from 12 to 16% of the surveyed. Only 4%-6% of them use lower doses than the ones recommended by the leaflet. Similarly, rather few of them consult the pharmacist in regard to the proper drug dosage – 4% to 5%. The highest proportion of people who strictly follow the leaflet recommendations can be found among the respondents with higher education – 68%.

Only 38% of the respondents read leaflets every time and 42% read them only when they buy an utterly new medicine. 16% admitted to reading such information very rarely; 4% do not do it al. all.

The analysis of the data in terms of education has shown that the people with primary or secondary education read the leaflets most often – in 48-50% of cases. The proportion of people who do so in the groups of respondents with higher or incomplete higher education amounts to 23% and 32% respectively. There is also a visible difference as far as the number of people who read the leaflets only when buying a new drug is concerned. This number is considerably higher in the group of people with higher education – 49% and incomplete higher education – 52%. The proportion of such respondents in the groups with primary or secondary education amounts to 33% and 31% respectively. The proportion of people who do not read leaflets at all is similar in all of the groups and it oscillates between 3 and 5%. The same applies to the number of people who read leaflets occasionally – the proportion oscillates between 14 and 20%.

The male respondents read the leaflets definitely less frequently than the female ones; moreover, 7 % of them do not read them at all and 20% do it just occasionally. Only 2% of the female respondents never read leaflets and 14% do it rarely.

The group most varied in terms of the leaflet reading frequency turn out to be the people over 60 years of age. In this age category the proportion of people who read the leaflets every time is the highest, amounting to 58%, however, there are also most people who never do that – 11% of the group. In comparison, in the 46-59 age category the proportion of people who never read leaflets amounts to 1% and in the 30-45 category – 0%. The results presented by the chart 92 are equally disturbing; it shows that 20% of the respondents from the 18-29 age category very rarely read the leaflets and 5% of them do not do it at all. What is more, only 28% of them read the leaflets every time when buying the drug – this is the lowest result among all the groups.

Self-medication is one of the elements of the healthcare system, which is important both from the point of view of the patient and of the state. The increasing access of patients to medicines results in the reduction of the doctors' workload, as they have fewer visits in cases of minor ailments, which the patients are able to diagnose on their own. Consequently, self-treatment creates

one of the possibilities of saving the public finances and at the same time it enables the patients to consciously take responsibility for their own health [4, 5, 6, 7].

This study has presented the behaviours of the Polish patients and the meaning of the independent application of drugs available without prescription in the Polish healthcare system. It can easily be noticed that the mode of application of analgesic drugs by the survey respondents leaves a lot to be desired. A one-time slight overdose of medicament or linking it with alcohol would obviously not influence the patient's state of health to a considerable extent[1]. However, if he or she does it quite often and in addition does not read the leaflets and buys the medicament in the non-pharmacy outlets; negative effects on health can be expected [8, 9]. For these reason the inflow of information on drug overdoses, overuse and polypharmacy is an incitement to perform an assessment of the knowledge of our society in the field of self-treatment.

Conclusions

The results of the research give ground to the following conclusions:

1. A pharmacy is the main point of purchase of the drugs, however, in the group of young and better educated people it is less frequently the priority choice. Pharmacist's help in regard to drug dosage has the greatest importance for people with primary education.

2. The analysis of the survey results in terms of gender has shown that the men, even though these are the women who use the analgesics more often, are more vulnerable to discomforts caused by improper use of such drugs. Men more often than women buy medicines outside the pharmacy and less frequently read leaflets. Besides, they tend to use the medications at their own discretion more frequently. Such a combination is very dangerous, because if the patient uses drugs in an improper way there is no person who could inform him about this. Moreover, the patient cannot realise this himself as he does not consult the leaflet.

3. After the analysis of the various age categories it turns out that drugs are most often applied by the people over 60 years of age and this age category is the most vulnerable to drug-related dangers. People from this group most frequently tend to take several medicines containing the same substance. It shall be remembered that the liver competence is lower in older people than in the younger ones. It is nevertheless comforting to notice that the elderly prefer to purchase medicines in the pharmacy, where they can obtain proper advice concerning their application. It is important, as in the 60 plus age category there is the highest proportion of people who never read drugs information leaflets. On the other hand, similar danger exists among the young people. What is more, in comparison with the elderly many more of them prefer to buy drugs outside the pharmacy, and as a result they do not get professional advice. Quite a large proportion of people from this group use higher drug doses than recommended by the leaflet when the illness symptoms become more severe.

4. The analysis of he survey results in terms of education has proven that it is the most differentiating factor as far as the use of the analgesic OTC drugs is concerned. A large part of the people with primary or secondary education do not understand the content of the information leaflets. Their preferred point of purchase is a pharmacy and they more frequently consult the pharmacist than the people with higher education. People with higher education more often apply the drugs at their own discretion and tend to overuse them when the illness symptoms become more severe. Moreover, they read the leaflets less frequently than the lower-educated people. However, the leaflets are more comprehensible to them, which minimizes the treatment-related risk.

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Optimization of effects and medical costs in the system of medical care for the heavy users patient group

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Abstract

The paper concerns the optimization of effects and medical costs in the process of providing medical services with the Health Care System. The idea of optimization relies on the use of the opportunity to steer the demand for medical services by different segments of potential patients. For this purpose the most important patient groups were identified from the perspective of effects and medical costs. A special attention was paid to the groups of patients of the HEAVY USERS (HU) and the LIGHTHEARTED USERS (LU) types – the so called „carefree" patients. The paper contains the concept of the method identifying HU type and LU types patients. Patients of these groups generate relatively high medical costs. The costs are usually unjustified (the losses of the HCS) additionally leading to the decrease of medical and social effects of medical care. Identification and classification of the groups of patients further enables the use of the application of adequately selected clinical paths and the medical intervention system.

Key words: heavy user N and H types, lighthearted user, clinical path, living space, life pattern, heavy users patterns, lighthearted users pattern, heavy users pattern, classification and identification of heavy users and lighthearted users

Introduction

Constant medical progress and related ever higher costs are generated by the application of ever more novel and more effective diagnostics and therapeutic methods, changes in the age structure of the population (the extension of average life expectancy) or higher expectations of the patients' life quality cause constant pressure to increase expenditure on the health care system (HCS). On the other hand limited financial resources of public payers result in the situation in which there are no worldwide public HCSs which are able to satisfy health care needs of their all citizens to the full extent. In the light of this, the optimum redistribution of the available resources of the HCS to be used in the best possible manner is becoming a burning issue. One of the sources of generating high costs in the HCS what is indicated in ever more numerous scientific papers is the population of patients described as heavy users. This is a heterogeneous group of patients whose common attribute is the consumption of significant resources of the HCS. Among them one can distinguish persons who in case of a serious disease tend to, usually periodically, increase the demand for the HCS resources (so called N type heavy users) and persons for whom there is no justified, from the medical perspective, need to frequently use the system resources (H type heavy users).

The scale of the phenomenon is not precisely known. In the worldwide publications in which the phenomenon of occurrence of the heavy user patients was examined taking into account the example of Emergency Departments (ED) show that the population may constitute between 0,2% and 11% of patients using the services of ED at the same time generating between 1,9% and 32% of all visits. The problem of heavy user patients in Poland is still less well-known however ever more interest in the phenomenon is being observed. The analyses conducted in the companies offering private outpatient medical care in Poland at the same time clearly point out the existence of the said group of patients – the group of 1,5% most expensive patients generated 10% of medical costs (and 4% of patients generate 20% of medical costs respectively):

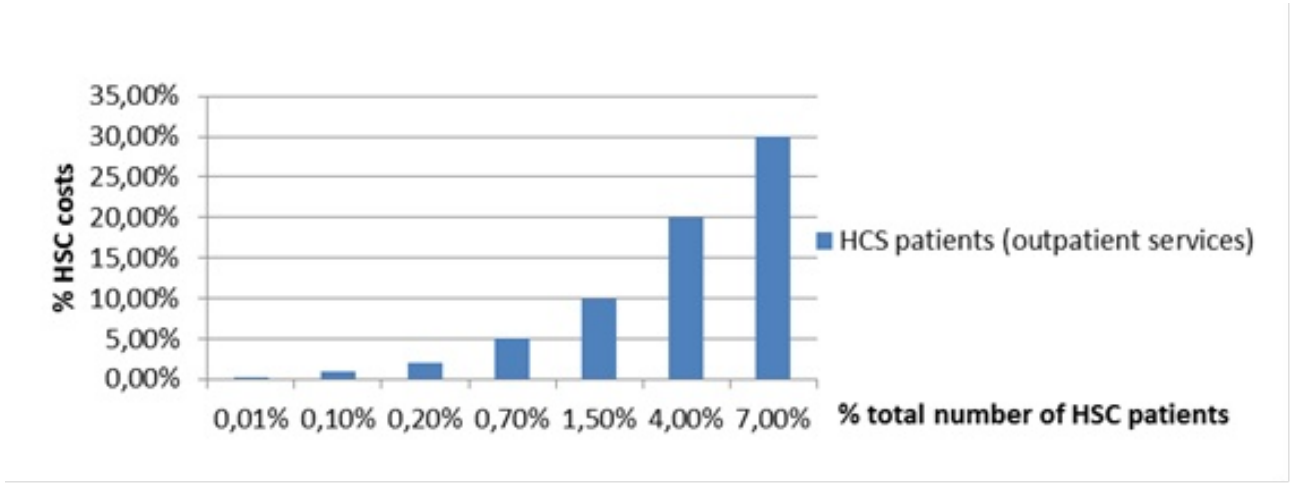

Figure 1. Consumption of medical resources by heavy users

The aim of the analysis is the attempt to identify the patient group of so called heavy users, identification of common and differentiating attributes of the selected subgroups (H and N types of heavy users). Limited resources of each and every HCS, including the financial ones, require the rationalization of the health care expenses borne.

One of the ways of achieving the goal is the optimization of the clinical paths management proposed to individual identified patient groups included in heavy users type. To identify heavy user patients the author's survey model was developed aiming at the analysis of the identified subgroups of heavy users (N and H types) which is based on broadly understood algorithms of the pattern identification [1, 12]. To achieve it so called the living space, disease patters, health patterns and patters of respective subgroups of heavy users were identified.

The group of patients described as heavy users is not homogeneous. Among them two main subgroups may be distinguished:

N type heavy users – patients who in case of being affected by a serious disease (usually periodically) increase the demand for the HCS resources. After some time the manner of using the HCS resources usually returns to the level from before the disease or remains at a higher level. This group entails patients with chronic diseases. Due to similar behavior patterns the patient group is periodically included in the N type heavy users.

H type heavy users – persons who do not seem to have a justified, from the medical perspective, need for frequent use of the HCS resources. In this group of patients the vast majority is constituted of persons with psychosocial problems with frequent co-morbidity of chronic diseases [6]. Periodical increased use of the HCS resources is observed with the patients. In case of the constantly increased use of the HCS resources the behavior pattern of the patients is similar to patients with chronic diseases.

The division of heavy user (N and H types) patients is not entirely unequivocal (dichotomous) due to the possibility of the occurrence of mixed situations particularly in the group of patients characteristic for H type heavy users. The survey results indicated that for the heavy users group certain characteristic attributes may be distinguished as common e.g. in case of frequent seeking help in Emergency Departments was observed that previous number of visits, previous psychiatric treatment, being lonely and the feeling of loneliness predisposes to remain a heavy user [7]. Another characteristic which is noticed by the researchers in Poland and which is aimed at helping to identify heavy user patients is the observation of a big number of different diagnoses (according to ICD-10) assigned to individual patients.

In case of some patients using private outpatient care in Poland the number of diagnoses according to ICD-10 has amounted to dozens within the last 12 months. In the population of the patients ca 1,5-2,0% of them uses medical consultations at least 26 times per year i.e. every two weeks on average. Among patients covered by private outpatient care in Poland almost 6% of diagnoses are Z00 and Z01 according to ICD-10 (General examination without any diseases and the diagnosis of a disease and another special examination without any ailment and the diagnosis of the disease respectively).

Table 1. Characteristics of H and N type heavy users

Characteristic attributes	H type heavy user	N type heavy user
Frequency of using HCS resources	high	
Effectiveness of using HCS resources	usually low	
Time of demand for increased HCS resources	usually long, periodic	usually shorter, irregular
Diagnosis of disorder	usually psychosocial less frequently organic	usually organic
General health / additional medical examination	within the normal range	usually some irregularities are found
Occurrence of significant disease risks	average at most	increased
Number of diagnoses according to ICD-10	usually high	low
Number of specialist consultations within the last 12 months	usually high	close to the average in the population

The analysis of the available data allows to point premises enabling identifying heavy user patients.

The occurrence of the above mentioned characteristic attributes allows only for preliminary diagnosis in the context of identifying heavy users of individual types. The division does not have to be, as mentioned above, entirely dichotomous. „Mixed cases" combining those two types are possible. A mixed case is a special H type heavy user case. It requires special approach in proposing further treatment. The initial characteristic of heavy users may be summed up as follows:

Heavy users N type (HU N type)

Due to inter alia complex health issues and the way of the organization of delivering health care the patients as a rule use health care resources intensively for some time with no satisfying effects for them in a short time. In the period the description of their behavior is the reflection of the behavior of the so called „classic" heavy user (H type). After some time in this group of patients, contrary to H type heavy users, return to behavior typical for the period preceding the health care problem or permanent increase of the demand for medical care services (the diagnosis of a chronic disease) is observed. The health needs of patients have been met (the disorder has been property diagnosed and proper treatment has been introduced) or after some time they have realized that the health care system is not capable of coping with their health problems (the attitude of resignation).

H type heavy users (HU H type)

This group of patients intensively uses medical care, most frequently in the aspect of a few diseases in a significantly longer period of time (the so called regular patient). These patients require an entirely different path of treatment. The characteristic attribute of the patient group is relatively good health most often confirmed by correct (within the normal range) results of additional examinations. On the whole physicians easily recognize such attitudes. There is a certain danger of the risk of overlooking a disease due to the reduced alertness of a physician to an ailment reported by a patient.

A strict division between heavy users of H type and N type is difficult to draw and burdened with a significant risk of a medical error (in particular the so called mixed case). Clear diagnosis is frequently difficult what causes the process of medical care (including treatment) to be significantly prolonged. It is detrimental both in case of N and H types. In the range of large populations of patients covered by HCS care the phenomenon poses a significant health, economic and social problem. Designing a tool to guarantee a proper diagnosis would be a big opportunity to effectively treat both groups of patients and secondly to efficiently

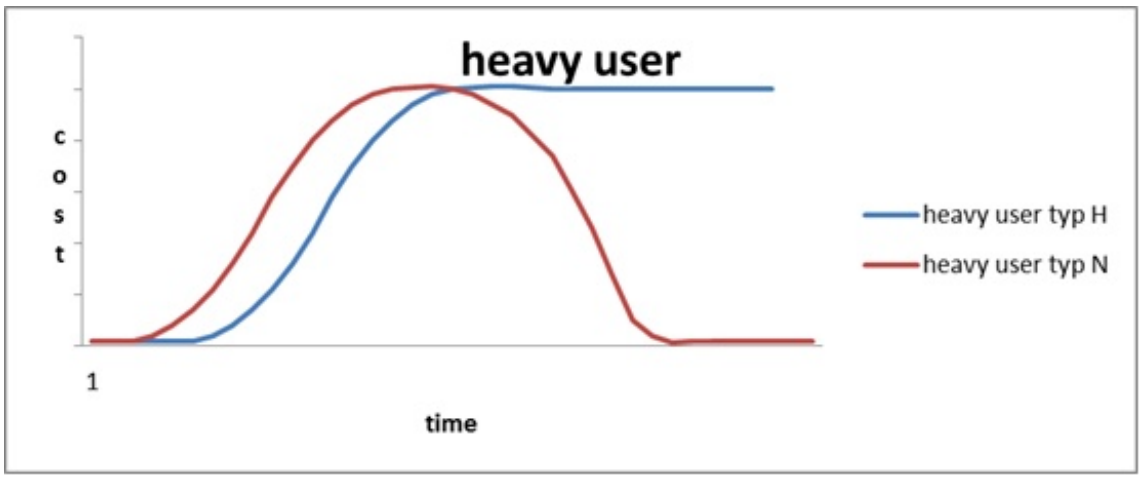

Figure 2. Typical characteristics of costs for heavy users

distribute public resources for medical care. The social dimension to shorten the time to remain a HU (shortening the time of the societal exclusion due to the disease) is of the essence as well. In Figure 2. typical characteristics of costs for both HU types are presented.

In the first phase of observation both patient groups are difficult to differentiate solely based on this characteristic. After a certain time an „observable difference" appears which may be a premise for the final finding. The two above mentioned patient groups generate relatively high social treatment costs. While the fact is fully justified in the case of N type heavy users inasmuch additional costs generated by H type heavy users are not justified. A significant group of HU H type in the overall patient population may limit the access to medical services of other patients to a considerable extent. Precise identification and classification of the patient groups to propose optimum clinical paths is a critical problem. The process may be realized based on definitions of respective classification attributes of individual patient groups having the aspect of measurability. The process is a typical process of detection of individual elements of the fixed population.

Detection of heavy users – the diagnostic process allowing to precisely detect the group of patients complying with the criteria of the heavy users definition. The scheme of the detections presented in Figure 3.

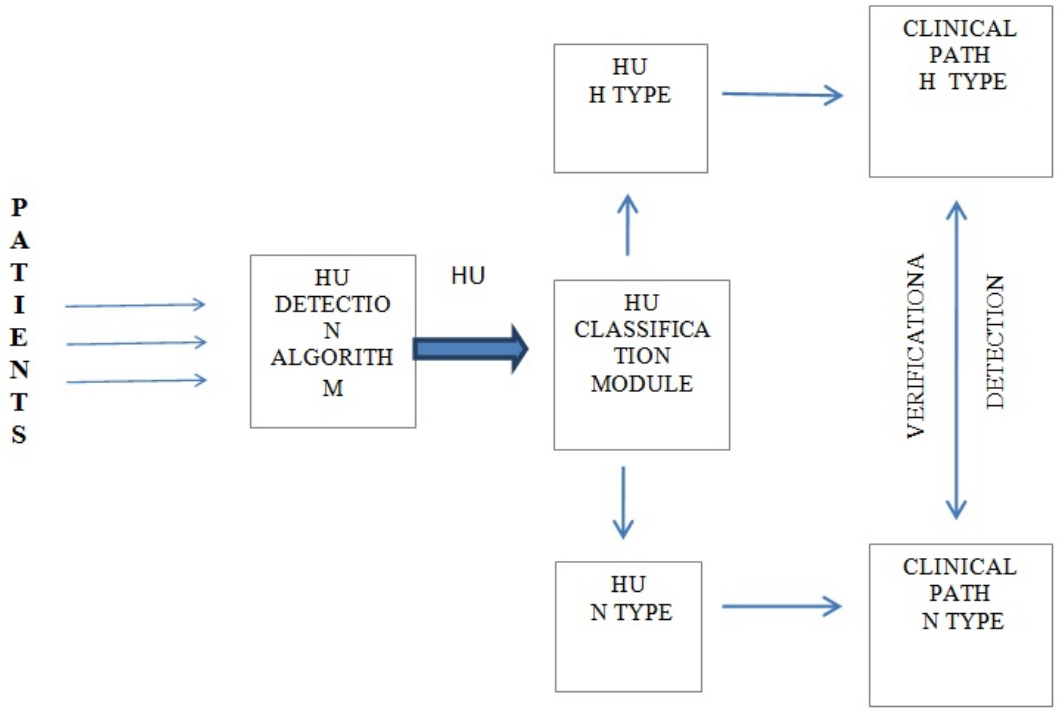

Figure 3. General scheme of the heavy users detection and classification process

Depending on the period of the patients „existing" in the „state of heavy users" disproportionately high costs connected with ineffective functioning of the health care system are generated. Shortening the time of the patients existing in the heavy users state through the recommendation of specific and adequate as well as more effective way approaching the correct diagnosis and treatment to them should give in effect the decrease of costs related to the functioning of the health care system as a whole:

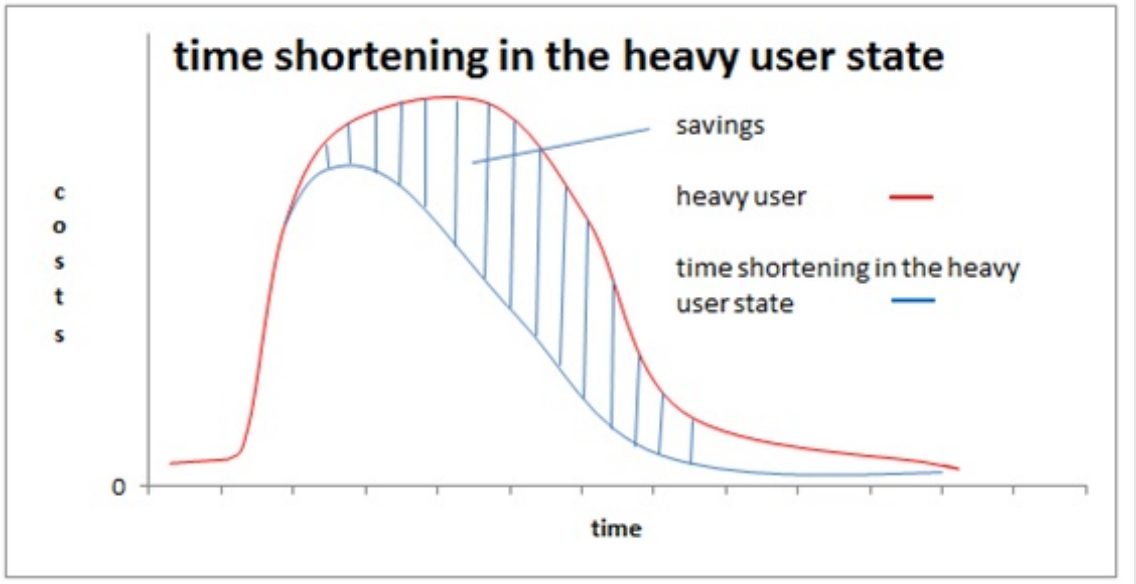

Figure 4. Modification of the cost characteristics through adjusting a clinical path

To achieve this goal, it is essential to identify patients out of the population covered with the health care of the patients whose profile corresponds to a patient falling into the heavy users category. Initial designation of the patients may rely on the analysis of parameters of the cost curve. A more effective and precise method is the identification of those patients with pattern recognition algorithms [1, 3, 12]. It is required to define health patterns, diseases patterns and patterns of N and H type heavy users respectively in the so called life space [12]. Such an approach offers a very helpful support of the diagnostic process based on the results of additional examinations enabling the construction of merit indicators [4]. The idea of identification algorithms and the classification of heavy users is to define objective, complex indicator of a patient's state of health understood as property defined „distance" from the pattern of a patient's health with respect to a corresponding sex and age group and some characteristic of the closest disease threat [1, 2, 3, 4, 12]. These two characteristics, except for the very simple characteristic illustrating the intensity (costliness) of the use of HCS resources allow for the creation of the so called space of identification which enables to identify potential N and H types of HU [4]. In this space the sought patterns of N and H type HU are easy to be built. Each patient, on the basis of their features on the medical examination results is possible to be placed in the space setting respective merit indicators [4]. Having a sufficient patient data base („treatment history") one can precisely calibrate the said model describing the sought threshold values of the necessary indicators. This can be done though a computer simulation with the use of patient data base and experts' findings. After the detection stage is carried out and then the classification of respective subgroups of heavy users, the patient will be offered a individualized clinical path, which in case of N type heavy users will be aimed at proper diagnosis in the shortest possible time. The matter which requires an in-depth analysis, with the involvement of experts from various fields including ethics is the manner of further procedure towards H type heavy user patients. These patients have to be covered with a dedicated program with the emphasis on frequent non-somatic disorders. It appears essential to work out a socially acceptable strategy of cost reduction for the treatment of the population of the patients including special medical and organizational procedures. Introduction of the detection system and further classification of heavy user type patients should cause the obtainment of medical, social and economic bene-

fits. Medical benefits encompass faster accurate diagnosis in case of N type heavy user patients, coverage with the dedicated care program for H type heavy user patients to a big extent aimed at frequent occurrence of psychosocial problems arising in the group. The implementation of the system is justified from the social and economic perspectives. In the longer time horizon it should result in more rational utilization of HCS resources what should be reflected in the availability of HCS resources to a bigger patient group. Not without significance is the optimization of expenditure incurred for HCS. A separate and very important issue from the perspective of the optimization of global patient treatment costs and economic and social effects of health care is so called "the light-hearted patient" issue.

Light-hearted patient is a patient who temporarily (frequently in a very long time) does not generate any health care costs. This group encompasses patients who chronically (due to different reasons) avoid contacts with health care.

This group is not homogeneous either. Patients of the group sooner or later generate very high treatment and social costs connected with the too-late diagnosis of a disease. The problem of detection and classification of this patient group arises. The issue of "light-hearted user" patient type is as important as the issue of "heavy user" patient type. The joint solution of this complex issue may lead to substantial effects of the optimization of HCS activity. The key issue is the problem of heavy user patient type the solution of which creates an opportunity to significantly decrease the number of light-hearted patients with the same capacity of HCS budget. A simplified model of the detection space and the classification of patients-users of HCS is presented below. The model presents the opportunity to detect previously discussed patient class and adjust proper strategies of medical treatment (proper clinical paths or other medical interventions).

Mathematical detection space model

A simplified model of the detection process and classification of patient population is presented below. X symbol stands for a class (population) of patients identified with the variable $x \in X$ (x – patient identification number e.g. PESEL). The X class *de facto* is the patient database and $x \in X$ is a respective e-health x patient record. On the basis of data contained in the X base any models describing the patient's health (life spaces), health threat, disease detection, diagnostic, clinical paths, special attribute patient group detection spaces, etc. may be built [1,4,5,12]. To optimize the functioning of the HCS, a model of detection model of the patient group significant in the area of costs and treatment effects will be presented. The detection (and then classification) the $x \in X$ patient requires the definition of respective qualification attributes which are important from the perspective of the classification aim. The attributes may be in particular:

- general indicator of the patient's health d(x) [1, 12]

- indicator of the resources (costs) consumption HCS n(x) [3]

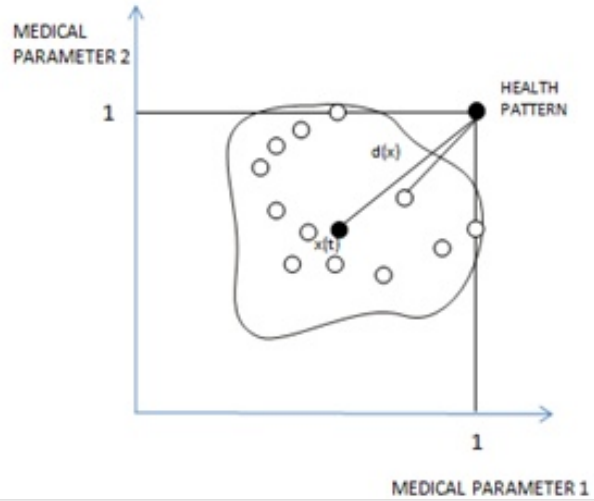

Figure 5. Standardized health space

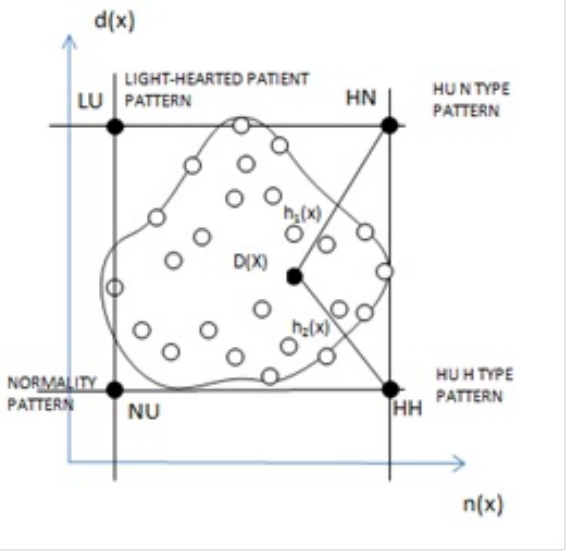

Figure 6. Detection space

- indicator of the present disease threat to a patient g(x) [1]

- indicator of range of patient treatment h(x)

In more precise models there is a possibility to define many more other qualification attributes. The indicator of the patient's general health pattern is generally understood as "distance" of the patient's health from the pattern of a patient's health (for a specified age and sex of the patient) [1]. The indicator of the HCS resources consumption may be defined as a number of medical consultations (examinations) in a specified time unit or directly as a cost [5]. The indicators of the disease threat are defined by analogy as the distance of the patient's health from the patterns of respective disease units [12]. The indicator of the range of patient's treatment is generally defined as the quotient of number of different specialists visited in a time unit against the total number of medical consultations.

In Figures 5 and 6 the simplest cases of the so called life space are presented and the detection space covering only two attributes due to presentation reasons [1, 12]. The detection space D(X) presented in Figure 6. is a class of "pictures" of x X patients in terms of classification attributes adopted in the model. Defining respective relationships of the patient's health specificity (such as: 'normality", "light-heartedness", H type "nuisance", N type "nuisance" as Pareto relations it is easy to define patterns: normality, light-heartedness, H type and N type "nuisances" as so called an end to the class D(X) [12]. These are respectively marked in Figure 6. points: HH, HN, LU, NU. They may be interpreted as pictures of virtual, standard patients of respective classes.

Introduced relations allow for additional comparison of pictures of patients in different aspects as well as for definition classes of patients of particularly important attributes in the optimization process such as: the class of "the most hypochondriac" patients, the class of patients where there are no other as hypochondriac as them, the class of patients where there are no other as light-heartened as them in the population etc [1, 12]. The D(X) space enables defining and examining many other distance characteristics very valuable for the detection and classification of respective patient groups in Figure 6. exemplary distances of the picture of a selected x patient from HU N type pattern and from HU H type were marked.

Conclusions

Extremely high rate of information technology of the medical care offers an enormous opportunity to build the so called Computer Systems of Medical Decisions Support. Patient data bases created in many countries (based on so called e-health records and computer-interpretable clinical paths enable complex optimization of medical care management processes in particular the support of the medical diagnostics and treatment processes [1,12]. These systems allow for an enormous opportunity of rationalization (optimization) of the structure of the demand for medical services through the possibility of detection (identification) of individual classes of HCS users and later the opportunity to adjust corresponding clinical paths to the specificity of the groups. The presented version of space detection model simplified for the purpose of the limited space in this work may be a very useful tool of versatile analysis of the medical services consumption structure offered by HCS primarily a tool of support to optimization of medical care processes. The model after corresponding calibration and simulations will allow to designate corresponding patient groups for optimal medical care through offering properly designed clinical paths for these patient groups and the system of proper medical intervention as well as organizational and legal processes of health prevention as well as global health policy making. The following step may be the construction of patients' behavior simulator based on the presented model of the space detection which would allow for examination (and optimization) of the effects of health policy implemented at different levels of management.

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Towards an effective access into Polish national health data – just a step away from a wealth of information

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Abstract

Background: Public health institutions (National Health Fund -NFZ, Social Insurance - ZUS, National Institute of Hygiene - PZH) gather population-based, real-time, extensive set of data, characterizing the health status and behaviour of individual patients in relation to health care resources spending pattern. The accessibility of the data for scientific purposes would be a significant step towards optimization of expenditure and assimilation of innovation. Furthermore, improved availability of pharmacoepidemiological and health-related data has been set as one of the strategic goals of The Section of Epidemiology and Cost of Illness of Polish Pharmacoeconomics Society - PTFE.

Methods: To show the value of widely-available comprehensive data analysis platform, and to initiate a debate addressing this issue. Non-systematic review of relevant papers dealing with the problem in question has been conducted with special focus on available Polish studies.

Results: A few general areas are characterized by a direct link between effective data availability and practical measures taken to optimize expenditure and rationalize innovation assimilation, namely: availability of comprehensive multi-perspective burden of illness studies, accurate identification of complex health care demands through description of co-morbidity patterns, continuous monitoring of treatment patterns enabling the detection of irregularities and implementation of treatment-optimizing mechanisms, as well as the identification of associated phenomena which affect expected treatment effectiveness (compliance) in order to design comprehensive solutions addressed for specific subpopulations of patients. Major obstacles significantly restricting the utilization of data from Polish health care system include: lack of direct link between reported expenditure and covered population in available sources, lack of unique drug record within the system, complex decision-making process leading to merging different public sources into one comprehensive picture.

Conclusion: Data collected by public health institutions represent a valuable source of information enabling real-time monitoring of population health status: co-morbidity patterns, burden of illness, compliance, and therapeutic patterns. Analyses based on a comprehensive and actual data will help to define health priorities, allowing the appropriate allocation of financial resources in order to achieve the desired effects with regards to public expenditure and dynamic access to innovations.

Key words: Pharmacoepidemiology, Quality of Health Care, Data Mining,

Introduction

Recent experiences, Polish but also those considered long-term in nature originated from other countries, clearly indicate that the databases managed by public health institutions (National Health Fund - NFZ, National Institute of Hygiene - PZH, Social Insurance - ZUS) are a valuable source of strategic information. Analyses using the data collected by the public institutions include the whole population, not only a predefined group of patients, as is usually the case in the surveys.

According to the Act on Healthcare Services Financed from the Public Funds, the National Health Fund has the right to process personal data of insured persons with the focus on monitoring the patients' state of health and the needs of the insured for health care services, medications, and medical devices [1]. Different projects conducted within the framework of PZH, especially the Hospital Morbidity Project, constitute a complementary set of data, which allow building a clearer picture of epidemiological changes and evolving health care needs. ZUS possesses the missing piece of the puzzle as it manages the data concerned with social spending linked with sick leaves and the cost of rehabilitation, as well as the data on the long-term economic consequences reflected by the disability pension.

Structured access to the reimbursement and health care utilization data can deliver more precise assessment of disease burden and help to identify patterns of co-morbidity and behavioural factors (compliance), which play an important role in disease management. This knowledge can lead to better setting of health priorities, indicating the most cost-effective area of health care investment as well as monitoring the impact of changes in public health.

On the level of individual patient, real life data can be confronted with the guidelines for the treatment of specific disease entities. It has the potential to result in clinical practice optimization through training or updating procedure standards in the light of scientific evidence. Potentially desired effect in the field of public health can be linked with improved allocation of funds in the health care system. Effective utilization of the content by identifying and streamlining the rules for access may be an additional stimulus supporting the efforts to optimize health care.

The scope of drug use undergoes constant change therefore systematic observations should be fundamental to studying this process, allowing for improving the quality of drug prescription and setting priorities to the rational allocation of resources in health care.

The Section of Epidemiology and Cost of Illness of Polish Pharmacoeconomics Society has set a number of goals with respect to its activities, especially on improving the availability of epidemiological and cost data. This could be performed through “dynamization” of channels of access to National Health Fund and Social Insurance data. This paper is intended to initiate a debate addressing this access by showing the value of building such comprehensive data analysis platform.

Review of literature

Non-systematic review of relevant papers has been conducted with special focus on available Polish studies.

International experience

Norwegian Prescription Database (NorPD), created in 2004, is a perfect example of a database in which data on drug consumption are collected and processed [2, 3]. NorPD provides health care decision-makers with direct access to current data. Its main purpose is to study drug consumption and changes in trends over time, thus ensuring the ongoing monitoring of the patients' state of health. Data provided by NorPD were used, among other things, to describe the use of antimicrobial therapy in primary health care in Norway, taking into account the age and gender of the patients [4]. The available data allowed to identify the patients with the highest level of antibiotics consumption and to detect differences between individual groups with regard to different variables. Access to data enables the health care system to fast track changes in trends in antibiotic consumption and identifies "habits" in drug prescriptions.

A number of other examples of international databases that allow collecting and using data for the purposes of the health care decision-makers are presented in Table 1. These solutions facilitate continuous monitoring and improving the quality of medical services. The value of facilitating access to national public health resources is evident in cost of illness studies conducted in different national settings. They are normally

carried out using various data sources, namely survey data, epidemiological data from disease registers, and public and private institutions data, such as the payer's data, social security offices data, IMS Health, etc.

It is possible to create a database of this type in Poland, allowing for continuous and ongoing monitoring of patient's state of health, involving the data which, according to the Ministry of Health regulations and the president of the National Health Fund, must be sent to the payer by the health care providers [8, 9].

Polish experience

Reliable monitoring of changes in health care system may be crucial in optimizing the allocation of financial resources in health care services and the availability of drugs and medical devices. Access to the data collected by the National Health Fund in Poland has been a significant base for a number of studies and analyses, which are considered an important source of current knowledge on the demographic structure of patients, changes in health trends and in the cost of treatment.

Currently, NHF is reporting the precise number of packages sold by EAN codes for outpatient use as well as cumulative drug spending in hospital setting [10]. On the other hand, until now the majority of available local cost of illness analysis has been primarily obtained based on epidemiological data from dedicated disease registers, data obtained from the patients surveyed or from the individual health service providers. Lack of a direct link between reported spending and covered population imposes significant restrictions on interpretability of these data.

Cost of rheumatoid arthritis in Poland in the period 2003 – 2007

A major study, Professor Jacek Ruszkowski's report entitled "The actual economic cost of illness in Poland" demonstrates the possibility of using the data on the patients' state of health in Poland [11]. The analysis was designed to evaluate the real cost of rheumatoid arthritis (RA) in the period 2003-2007. The direct costs were mainly assessed based on the data obtained from the NHF, while the indirect costs were calculated by evaluating the expenditure of the Social Insurance Institution. In addition, the assessment of productivity loss due to rheumatoid arthritis was performed.

The difficulty of calculating the actual cost of illness in Poland is due to the problem of availability of data (or complete lack of access to it); the problem of identifying the costs makes the study even more important. Prof. Ruszkowski's study fills the gap with respect to reliable estimates on total, direct, and indirect cost of illness incurred by Polish economy. Until now, only the expenditure related to diagnosing and treating the disease (direct costs) has been estimated, while the expenditure on social security (indirect costs), shown by the report to be substantially higher than the costs of RA treatment, has not been analysed. Therefore, access to National Health Fund and Social Insurance Institution data has enabled the execution of a comprehensive assessment of the costs associated with the onset of RA; furthermore, it helped to determine the economic losses incurred as a result of the loss of productivity of those unable to work due to RA.

Rationalization of antibiotic therapy in Opole Voivodeship

An analysis of regional antibiotic consumption, educational campaign for doctors and their patients, and the implementation of the guidelines for rational antibiotic therapy were carried out within the framework of Programme for Rational Antibiotic Therapy in the Primary Health Care in Opole Voivodeship, which was launched in 2007 [12, 13].

The complete data stored by NHF concerning antibiotics prescribed to patients by primary care doctors was analysed. The only limitation was the lack of data concerning the indications for the use of antibiotics. The average number of antibiotic therapies per patient in different age groups were considered the main indicator. The results of the study indicated a need to implement an efficient intervention system across the whole region that would help to monitor and rationalize the habits of primary care doctors concerning the prescribed antibiotics. In order to optimize antibiotic treatment, a number of training sessions for family doctors have been conducted, including an analysis of the guidelines for the use of antibiotics in the treatment of respiratory diseases as compared to the course of antibiotic treatment, which was prescribed by the doctor and registered in the system.

Table 1. Examples of drug databases (NorPD [2], DNPR [5], Register of Medicinal Product Statistics [6], NPDUIS [7])

Norway	Norwegian Prescription Database (NorPD) [2] Aim: • Collecting and processing data on inpatient hospitalizations, mental health, and outpatient care • A tool for mapping and monitoring trends • A source of research on drug consumption • Providing the employees of the health care system with the possibility of continuous monitoring of expenditure and expense planning. Data used: • Number of users, the distribution by gender, age, or county/health area • Number of users per 1000 inhabitants • Population base by gender, age, or county or health area • Turnover by value (pharmacy retail price in NOK) • Turnover by dose (DDD - defined daily dose).
Denmark	Danish National Patient Register (DNPR) [5] • Two types of data: administrative and clinical data • Administrative data: includes the patient identification number (CPR number), municipality, ward, time and date of admission, information about the circumstances that led to being admitted to hospital • Clinical data includes: diagnostic and surgical procedures.
	Register of Medicinal Product Statistics [6] Aim: • Gathering data on drug sales in Denmark with a statistical tool - medstat.dk. Data used: • The share of prescription medicines sold to individuals in total sales • Number of users, age, gender • ATC code, reporting errors and omissions, etc., selling over-the-counter medicines and prescription medicines • Region, sales volumes, DDD • Eligible for reimbursement/reimbursed, year.
Canada	National Prescription Drug Utilization Information System (NPDUIS) [7] Aim: • Data gathering and providing decision-makers with information and insights about the changes in trends in prices, consumption, and costs. Data used: • Data on costs and payment information with regard to prescription medicines • Data Form identifying which drugs are eligible for public drug programmes in Canada. • Data on medicinal products.

The tangible results of the Programme for Rational Antibiotic Therapy in the Primary Health Care in Opole Voivodeship were seen as early as in the second month of programme duration. They consisted of 16% decrease in the number of antibiotic courses prescribed by the doctors who took part in this training as compared to an overall 8.76% decrease in this parameter in the group of physicians who did not undergo training; also, there were changes with respect to the identity of prescribed antibiotics.

The analysis of the NHF data for Lubuskie Voivodeship

Analysis of antibiotic consumption

The study based on data from Lubuskie branch of NHF and the Central Statistical Office (CSO) was included to emphasize the implication and importance of the data collected by the public payer [14]. The aim of the study was to analyse the use of antibiotics (ATC J01) in outpatient population (> 1 million). The relationship between the level of antibiotic sales, patients' age, and the season of the year was analysed. In addition, an attempt was made to identify the group of patients with recurrent bacterial infections. The unique nature of available data allowed for the creation of a tool, i.e. a map, showing the increase in disease relapse associated with the use of antimicrobial therapy.

Analysis of compliance in patients treated with statins

The aim of the analysis was to assess the phenomenon of compliance (non-adherence to a recommended course of treatment) in patients treated with statins [15]. In this analysis, the information reported to the Lubuskie branch of the National Health Fund, concerning the number of prescriptions for reimbursed drugs dispensed in the period 2002–2005, was used as a source of data. The analysis database included 21 million records (documenting each dispensation of medication at a pharmacy) for 800 000 patients. The main indicators used to describe this phenomenon included the value of medication possession ratio (MPR) of patients and the percentage of patients achieving a minimal level of compliance guaranteeing satisfactory clinical effects. The analysis demonstrated significant irregularities in the context of adherence to the recommended course of treatment in the population of Lubuskie Voivodeship: the average value of MPR in the analysed population was 55.8%, and only 12% of the population showed a continuity of medication use. Authors of the analysis concluded that noncompliance might be the main cause of limited effectiveness in the group of patients treated with statins. They also emphasized the role of education, which plays a crucial role in improving the general health and in reducing the costs of treating cardiovascular incidents.

Chemotherapy costs in Poland (2004 - 2009)

Tkacz study (2010) is one of the analyses that utilize the data obtained from NHF to determine the population in selected therapeutic area, the cost of treatment, age structure, and changes in the availability of cancer treatment in Poland [16]. The study was designed to evaluate the value of the data collected by the National Health Fund; an analysis of their limitations and potential. Between 2004 and 2009 in Poland, NHF recorded the data regarding public funding of chemotherapy in 169 733 women and 150 307 men. The analysis of NHF data showed an increase in costs significantly exceeding the trend resulting from an increase in the number of patients. The analysis of the age structure of patients indicated the age range of the largest group of beneficiaries and helped to determine the differences between the voivodeships in the field of oncology treatment, allowing for detection of a strong migration trend in patients. This study confirms that the data collected by the National Health Fund is a valuable source of information that plays an important role in allotment of financial resources.

Potential benefits of effective access

Identifying patterns of co-morbidity

Scientific literature abounds in research on identifying the patterns of co-morbidity. To the best of the authors' knowledge, the results of the analysis of co-morbidity based on the National Health Fund data have not been published to date. However, as a result of the importance assigned to this issue, reference was made to the study carried out in Germany. One of the issues discussed in the context of the analysis of data on drug consumption is co-morbidity (≥ 2 units

of disease) in the elderly. According to the results of population-based study conducted in Germany (KORA-Age Study) on a group of patients aged 65-94 years (N = 4.127), four co-morbidity patterns were distinguished. Information related to 13 chronic conditions was collected through questionnaires and telephone calls [17]. The most frequently reported conditions were hypertension (57.9%), eye disease (38.1%), and heart disease (25.8%). The analysis showed that co-morbidity concerned 58.6% of the elderly; furthermore, 44% of them manifested at least one of the following patterns: 1) cardiovascular and metabolic diseases; 2) joint, liver, lung, and eye disease; 3) psychiatric and neurological disorders; 4) gastrointestinal diseases and tumours.

Monitoring of medication use

An example of the benefits associated with drug usage analysis is presented in the report prepared for WHO [18]. The report provides data such as: estimation of the number of patients exposed to the drug; estimation of drug consumption for a selected time horizon (e.g. one year, or a comparison of a few years, setting trends), for a specific area (at the level of hospital, city, voivodeship, country, or a comparison of a selected voivodeship vs. data from across the country) or for demographically diverse groups (e.g. gender, age); estimation e.g. on the basis of epidemiological data available for the selected disease entity, the extent to which the medication technology is properly used (or abused). Moreover, such analyses allow for comparison of observed data with current treatment guidelines for a specific disease entity in order to detect irregularities and to implement mechanisms to optimize treatment.

Cost of illness analysis

Limited resources in health care require optimal allocation of financial resources. The world standard for prioritizing the objectives is the estimation of the costs and burdens involved in disease management. In Poland, such an evaluation is usually prepared based on the data obtained from the patients' surveys, individual health service providers, or, rarely, from disease registers. The previously discussed examples of international analyses are increasingly based on the data provided by public institutions, including payers, which, because of its completeness and relevance is a reliable source of data that can be used for the calculation of the costs associated with a specific disease entity.

Compliance analysis

Data collected by NHF payer is a key source of data on drug use and the problems associated with their effectiveness, including non-compliance. The analysis discussed previously, which was based on the data from the Lubuskie branch of the National Health Fund, showed the scale of the phenomenon, thus indicating the need to implement measures such as education programmes [15]. Despite some limitations of the analysis based on data reported to the National Health Fund pharmacy, its usefulness in detecting abnormalities related to therapeutic adherence is obvious.

Therapy optimization in the context of the current guidelines

Research on the consumption of medications may be useful for assessing the relationship between the doctor's instructions and the clinical practice. It may also help in evaluating whether a medicinal product may be misused, by establishing if the patients take increasing doses of the drug or if the medication is excessively re-prescribed. Monitoring enables detecting the abnormalities in drug consumption and allows for implementation of remedial programmes. In Poland, such activities were undertaken by the National Program of Protection of Antibiotics [19]. This group monitors the use of antibiotics by cooperating with the National Health Fund and by analysing antibiotic consumption as well as the structure of consumption of various classes of drugs. These analyses constitute the basis for designing interventions and evaluating their effectiveness, contributing to significant changes in the amount of prescribed drugs and their proper selection.

Conclusions

Data being collected by the public health institutions constitute a valuable source of information. NHF and ZUS data possess crucial importance, because they enable real-time monitoring of the state of the population (in terms of selected parameters). Analyses based on a comprehensive and current data will help determine the present situation and set health priorities, allowing the appropriate allocation of financial resources

that will ensure the desired effect in the field of public expenditure.

The limitations of the studies on drug consumption based solely on the pharmaceutical data transferred to NHF should not be ignored. One of the major limitations to consider is the ambiguity related to the indications for which the drug was prescribed. Studies reporting the phenomenon of compliance should take into consideration the fact that dispensing a prescribed medication is not always equivalent to taking the medication. Utilization of complementary sources of information that deliver diagnosis and clinical outcome data may increase the reliability of the studies. In the case of assessment of the costs of illness, analysis should be supplemented by data collected by Social Insurance Institution, associated with reduced productivity of citizens: disability pension, social pension, rehabilitation and sickness benefits.

An important issue in the context of the potential of data reported to NHF is the evaluation of its quality. One of the studies mentioned previously demonstrates the usefulness and high quality of NHF data [16]. The aim of this analysis was to assess the value of the data in terms of the number of patients in each age group. The authors emphasize that: "(…) the data collected by the National Health Fund may be a valuable source of information on population, its age structure and the cost of inpatient chemotherapy. This information is of special importance because of its relevance, the state of the population in terms of those parameters can be displayed with a few weeks delay."

Achieving effective platform of access to databases managed by public health institutions seems to go beyond the "good will" of these institutions. It could be considered as a “must” for the system intended on achieving a fundamental step towards optimizing spending and, concurrently, stimulating access to health care inventions.

Conflict of interests: This document has been voluntarily created for the Polish Pharmaeconomics Society. Anna Zapalska is a partner and Zygmunt Podolec is an owner of the analytical/research companies. Dominik Dziurda and Dagmara Tronczyńska are the employees of a pharmaceutical company. The authors declare that there is no conflict of interest with regards to the topics addressed in the paper.

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Polish Pharmacoeconomic Society activities review

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The Polish Pharmacoeconomic Society Sections during the second half of 2012 continue its initially planned activities.

- Epidemiology and cost of disease – The main focus of the Diseases' Epidemiology and Costs Section was the methodology and analysis of public data sources (NHF, GUS). The ultimate objective for 2012 was to define and formalize the process of getting access to these sources for scientific purposes. Apart from defining the process, the other objective is to conduct a targeted analysis in the selected disease area regarding e.g. co-morbidity, compliance, indirect costs. After discussions within the Section the process is currently consulted with the decision making bodies.

- Health Technology Assessment – The Section members continue the review of the official HTA guidelines issued in 2009 by AHTAPol in order to provide constructive comments on that document.

- The Health Related Quality of Life section (HRQoL) – Section members are currently working on a dictionary of quality of life and utility related terms. At the first meeting the methodology was discussed and agreed by all Section members. As the first step there a search for English terms was made. Based on the final list each member was assigned the corresponding list of terms to be translated into Polish. At regular meetings the consecutive parts of translations are reviewed and final versions are agreed.

- The Therapeutic Programs and Pharmaceutical Care section (TPPC),

According to the scheduled program meetings Section members continued the discussion regarding the necessary requirements in relation to HTA assessment for biosimilars.

In Poland, as in many other countries, a mandatory assessment of HTA was introduced as part of the reimbursement process. The need to prepare the HTA dossier in accordance with the Guidelines of the Agency for Health Technology Assessment applies to all applications for reimbursement of new technologies, both drug and non-drug.

At the time of registration of biosimilar drugs a question arises regarding what the decision-making process should look like. What will the criteria to fulfill be in case of biosimilar drugs applying for funding? The process should be defined for different reimbursement options in Poland. It was discussed that the HTA process is to assess not only the cost-effectiveness of the new technologies and the impact on the payer's budget, but also to evaluate the efficacy and safety compared to standard therapy used. Therefore, bearing in mind the interests of the patient and in order to allocate public funds which are spent in the health sector in the best possible way it seems to be reasonable if biosimilar drugs were subject to the same formalities, including a full assessment of HTA. Examples from other countries were discussed at the meetings and e.g., in Australia, an experienced HTA country, the PBAC agency's guidelines, dedicated to how to prepare documentation for reimbursement in 2008, mentioned biosimilar drugs as an item that should be included in the next edition of the guidelines.

The Section's conclusion was that it is recommended that AHTAPol should also consider this topic in the process of updating the HTA Guidelines, which, after the introduction of the new reimbursement Act from January 2012 is mandatory.

The other important topic discussed at the Section meetings were the competences of the pharmacist in pharmaceutical care.

The results of the yearly work of each section will be presented at the next General Meeting, scheduled for December 2012.

At this General Meeting the elections of a new Board of Polish Pharmacoeconomic Society are also planned.

It is important to mention the significant event which is the 10th International Anniversary Conference of the Polish Pharmacoeconomic Society. It will take place in Warsaw, 5th-7th December 2012.

The main subject of the conference is "Pharmacoeconomics in Poland - summing up the decade". It will be a unique opportunity to exchange experience with specialists from different countries participating in the event. Among others there are plenary sessions, the ISPOR dedicated session and additional educational workshops planned.