Pharmacoeconomics of Bronchial Asthma

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Introduction: Pharmacoeconomics (PE) treats the problems of pharmacotherapy policy, drug marketing and reimbursement and clinical trials. It guides policy makers for effective health resources utilization and determines the profitability of the new drugs on the basis of their price, efficacy and benefits for society.

Types of health costs and pharmacoeconomic analyses: In the current review the main types of health costs are discussed. The main PE analyses with their advantages and disadvantages are presented.

Pharmacoeconomic of bronchial asthma: The main aspects of PE of bronchial asthma are available in the current review. The costs of health services (direct and indirect), the educational programs and asthma medications in different countries are discussed. Recently published data showed correlation between asthma cost and disease severity, control, social status and therapy adherence.

Conclusion: PE analyses provide the benefit of making cost consistent decisions in the field of asthma care. This review adds more data on the cost of current asthma treatment worldwide and in Bulgaria.

INTRODUCTION AND SHORT HISTORICAL REVIEW OF PHARMACOECONOMICS

Economics of health (EH) is a subdiscipline of economics, which studies the main economics principles of public health and health care systems. In EH both methods of economics and medicine are used. Analysis of EH typically assumes that the primary role of the publicly funded healthcare is to maximize population health. In recent years there has been rapid development of EH due to the enormous health costs and their continuous increase. Worldwide, the number of pharmacoeconomic (PE) analyses increases. In Bulgaria the same tendency is observed but with a slight delay. The highest number of PE analyses in Bulgaria were performed and published in 2003.

Pharmacoeconomics (PE) is a part of EH which applies its methods in the area of medical drugs and products. Development of PE started during the eighties of the 20th century. One of the first scientific studies on PE was the fundamental “Economics of Health” by H. Klarman, published in 1965. In Bulgaria the first PE analysis was published in 1995-1997 with a focus on pharmacotherapy of socially significant diseases.

PE deals with the problems of pharmacotherapy policy, drug marketing, reimbursement and clinical trials. The costs and results in PE analysis should be expressed as quantity when comparing at least two drugs. If the PE analysis concludes that some of the drugs, health programs or medical interventions are economically unprofitable, the resources should be directed to more profitable aspects.

The results of a PE analysis should be applied when assessing the health care system of a country. The principles and methods of PE analysis are universal but it is not possible to transfer the results and recommendations from one country to another. Some authors suggest alternative approaches when the data for PE analysis is collected from sites in different countries and the term ‘locally applicable’ for such approaches is introduced. Thom H et al. proposed a test method for similarity and identity with which the costs and/or health consequences for patients in two states could be compared.

In the present review we discuss the analysis of health costs, main definitions and types of analysis. PE analyses, concerning direct and indirect costs, different inhaled medications and educational programs for patients with bronchial asthma, are presented.
TYPES OF COSTS

The analysis of health costs is a complex, multifunctional process, which is determined by the different health costs and the unique features of the disease (course of the disease and duration of the treatment).1

Usually health costs are divided in the following groups, described in details below.

Direct health costs: the utilized resources, directly spent on medical services1,2,5; they can be directly calculated (hospitalizations, drugs, medical supplies, consultations, laboratory and imaging tests, rehabilitation and preventing programs)1,2,5;

Indirect costs include all incomes and benefits, which have been missed due to temporary or permanent disability, the economic loss when people take care of a family member with disability and reduced work effectiveness when there is a disease or disability1,5.

Unmeasured costs assess and measure pain, depression and loss of quality of life and are not expressed in monetary units directly but they are added to the PE analyses.2,5

Common costs include all costs for the production of a drug.1

Permanent costs are unchanged (permanent) for a short period of time (usually one year).1 They do not depend on the production quantity (employees’ salaries, rents).1

Variable costs: depend on the quantity of the production (for example cost for materials).1

Health costs are impacted by different conditions (comorbidities, socioeconomic status (confounding), complicated natural histories (reverse causality) and self-reported health status (measurement error). Usually, studies estimate the correlations between healthcare costs and health conditions but generally they cannot identify causal relationships.10

TYPES OF PE ANALYSES

The most common types of PE analyses are presented below.

Cost analysis is an economic analysis of the costs for one particular disease.2 The decisions are taken on the basis of absolute costs.2 Smith et al. defined the ‘high-cost asthmatic patients’ as those that have poor asthma control, severer asthma forms, predominantly elderly people and Caucasian.11

Cost-minimization analysis is a method in which two alternative programs with completely identical therapeutic results are compared.1 It requires very precise calculation of the costs.2

Cost-effect analysis is based on the results from two alternative programs/therapeutic drugs.1 The results are presented with natural or physiological index (saved life years, reduced blood pressure).1

In this analysis the researcher could use the final results (saved life years, days free of asthma attacks) or the preliminary results (patients treated successfully, newly diagnosed cases).1

Cost-effectiveness analysis is applied when the health programs results are not compatible and comparable. It allows only their effectiveness to be analyzed.1 Measuring units are QALYs (quality-adjusted life years), HYEs (healthy-years equivalent) or DALYs (disability-adjusted life years)1, EuroQol (European quality of life scale).12,13

Cost-benefit analysis is used to compare the results from health care programs expressed in monetary units or other comparable units. This analysis is usually applied to assess indirect costs.1 There are difficulties in calculating the costs of reduction of suffering, pain, the price of one saved life or the loss of a relative.2

PE analyses could have some limitations. Due to the limited data from randomized clinical trials, data from uncontrolled trials is used. There could also be poor study design or statistical processing or the studied groups of patients might not be corresponding because the investigator is not blinded. Discordance could arise between the aims, results, conclusions and recommendations and it is not possible a therapeutic effect of the drug to be demonstrated.14

PE OF BRONCHIAL ASTHMA

Cost of asthma

L. Antonicelli et al. calculated the direct costs for treatment of asthmatic patients in Italy for a seven month period in 1999. The authors estimated total costs of asthma per patient per year to be €1,260 and 52% of those costs were due to indirect costs. Patients with severe persistent asthma generated higher than the average annual costs for their treatment (€1,535).15 When an analysis of the direct costs was performed, the patient therapy compliance16 and the control of the disease17 were important for correct calculation of the direct costs. The authors also assessed the days lost of work due to illness for students and housewives. The authors emphasized that including the days lost of work due to illness would reveal the true indirect costs, which could be twice more than the initially calculated.15

Weiss et al. analyzed the costs, generated by pa-
patients with bronchial asthma in USA between 1985 and 1990. The cost of illness related to asthma in 1990 was estimated to be $6.2 billion and one-sixth of that sum was due to indirect costs. Emergency room visits, hospitalization and death were responsible for 43% of the asthma economic weight. In their further research Weiss et al. followed up patients with bronchial asthma and found that the total cost of asthma in 1994 was $10.7 billion. The tendencies they noticed were: hospital inpatient costs decreased (compared to initial one), because of shorter lengths of stay and decreased total number of admissions; drugs were the largest proportion of direct medical expenditures (in comparison with 1985, when hospital charges were the largest proportion); the largest component of indirect costs that was increased was loss of work.

Sadatsafavi et al. calculated that when asthma is well controlled and there were no absences from work, CAD$184.8 (CAD$ - Canadian dollars) weekly could be saved. Brandt et al. found that in the USA, from 36% to 38% of the indirect costs for asthma treatment of children were due to absence from school. Birnbaum et al. calculated that for asthmatic patients the generated cost due to partial or full disability was up to three times higher than for healthy volunteers ($14,827 vs. $5280 respectively). The authors matched 3387 USA asthmatic patients, who were followed up for two years (1996 to 1998). For asthmatic employees the medical cost and the expenditures for workdays lost (due to absenteeism or disability) were almost equal (about 40-43%). It was found that concomitant respiratory diseases increase the usage of health care services and the health cost. For example patients with asthma/COPD overlap have higher utilization of any service type than patients with only COPD or asthma.

Kerkhof et al. determined another high cost phenotype of asthma. Patients with severe, uncontrolled, eosinophilic asthma generated four times higher costs, compared to general population of asthmatics. Patients with severe refractory asthma also generated high annual mean treatment costs (between £2912 (SD £2212) and £4217 (SD £2449)). Hospital treatment is another factor, which leads to high health cost. Stanford et al. calculated that the costs for manage asthma attack in Emergency Department were £234.48 per patient, but in case of hospitalization the costs increased up to £3,102.53 per patient. In another study, asthmatic patients were followed-up for receiving primary or secondary care 60 days after discharging from hospital. Authors found no difference between the costs or the risk of readmission between both groups, but more appropriate treatment was observed in patients who received secondary care.

Zillich et al. recruited 1000 asthma patients in Kentucky. They analyzed the asthma severity, quality of life and willingness to pay. The disease severity was assessed by a spirometry test (the objective method) and by a multiple choice questionnaire (subjective method). Willingness to pay was significantly related to both objective and subjective assessment of disease severity. As the severity increased, the willingness to pay went up. Castaldi et al. found controversial results. In their study, patients with obstructive pulmonary diseases (COPD or asthma), who had higher out-of-pocket inhaler costs, were more risky for nonadherence to inhaler therapy.

Godard et al. quantified the impact of disease severity on costs in a cohort of 318 French asthmatic patients, who were followed-up prospectively for 1 year. Asthma was classified as intermittent, mild persistent, moderate persistent and severe persistent. All of the following parameters: mean direct cost for goods and services, the use and cost of bronchodilators and corticosteroids, indirect cost of days lost from work and poor quality of life (QoL) increased significantly according to disease severity. Mean age, body weight, asthma duration, low forced expiratory volume in one second and inhaled corticosteroid prescriptions also significantly correlated with disease severity.

For Ayres et al. a matter of interest was the burden of occupational asthma in UK. The new cases of occupational asthma were about 209 patients, who generated medical costs between £25.3 and 27.3 million annually. Total costs for treatment of occupational asthma in UK were estimated about £70 and 100 million. About 49% of these costs were paid by the patient, 48% by the government and 3% by the employer.

Costs of educational programs

Kauppinen et al. carried out their study in Finland between September 1991 and February 1993. They recruited 162 consecutive new asthmatic patients, aged 18-76, who were randomized into an intervention group (IG=80 patients) or a control group (CG=82 patients). Patients from IG were educated on asthma self-management by physicians and respiratory nurses. Forced expiratory volume in 1 sec and peak expiratory flow were significantly higher in the IG. The risk for sickness day was less in the
IG and among patients who used the PEF meter. There was no statistically significant difference in costs, although there was a consistent tendency for lower costs for patients in the intensive program. Later the Ministry of Social Affairs and Health in Finland set up a national program for a 10 year period (1994–2004) to improve asthma care, to reduce the costs, to implement new knowledge, with focus on primary care. In the final program report the experts concluded that there was a reduction: in the number of hospital days (with 69%), number of asthmatic patients who received disability pension (with 83%), decreasing of the total costs per patient per year (with 36%).

A similar educational program was conducted in Denmark by Søndergaard et al. It consisted of information about the disease, its therapy and correct inhalation technique. The total costs for planning, implementation and evaluation of the program were £14074. The number of days lost through sickness decreased in the patient education group, corresponding to a £4528. These patients also had improvement in the quality of life. The idea of educational programs for patients with bronchial asthma was upgraded with the launching of the Danish National Database for Asthma (DNDA) in 2016. The aims of the register were to collect data for all patients treated for asthma, monitoring asthma occurrence, the quality of diagnosis and management.

Ivanov et al. followed-up 505 asthma patients with different disease severity for one year, providing patients with an educational program: brochures, individualized written instructions, verbal instructions. They found that applying the program led to 1.5 reduction of the overall asthma cost. The direct cost was reduced by 1.3 while the indirect one by 4.3. The main factors contributing to this were reductions in exacerbations, hospitalizations, emergency department visits and work absences. On the other hand the low treatment adherence increased the cost per patient by 1.6.

The educational programs and some other programs are summarized in Table 1.

**PE analyses performed to assess different asthma inhaled medications.**

Salmeterol/fluticasone combination (SFC) was compared to fluticasone propionate (FP) mono therapy in asthma patients. The patients on SFC treatment had higher number of successfully controlled weeks and higher mean weekly direct treatment costs compared to patient with FP treatment.

Another cost-effectiveness analysis was performed based on effectiveness and resource-utilization data. Patients (n=2143) in 16 countries were randomised to SMART (Symbicort Maintenance and Reliever Therapy) or SFC. Treatment with SMART resulted in significantly fewer severe exacerbations per patient per year. Investigators found that the reduction in mean total cost per exacerbation avoided was lower, but not statistically significant. In the systemic review performed by Bahadori et al., it was claimed that the SMART strategy was found to be a significantly less costly treatment option than SFC ($1,416 versus $1,590).

A retrospective economic analysis was performed to determine the cost-effectiveness of omalizumab, which is an expensive medication. The incremental cost-effectiveness ratios showed that the cost to achieve an additional successfully controlled day was $523, and the daily cost to achieve at least a 0.5-point increase in Asthma Quality of Life Questionnaire score was $378 in 2003 dollars. From a PE standpoint, omalizumab would be better used in allergic asthmatic patients, non-smokers, with frequent hospitalizations and increased risk of emergency health care and with poorly controlled symptoms despite maximal therapy, given the high cost and modest efficacy of this agent. Some authors emphasize on the fact that the final cost of the therapy with omalizumab depends on the dosage, which varies according to patient’s weight and IgE level.

A large systematic review was conducted between 1990 and Jan 2008 that provided data on the costs of asthma medications. The studies that contained primary clinical data evaluating the cost of asthma treatment were 307, but only 49 of them met the inclusion criteria. In three of the studies there was a cost-benefit due to the introduction of ICS therapy. This therapy brought about significant decreases in health care utilization and asthma-related costs.

The results of the three studies indicated that LABA (particularly formoterol) achieved significant improvements in effectiveness, less use of reliever and maintenance medication, and reduced resource utilization, with only a limited increase in health care costs compared to SABA.

**CONCLUSION**

The present review of the PE of bronchial asthma shows that the direct and indirect cost have equal burden, sometimes with slight predominance of the indirect cost. The highest percentage of the direct cost was used for medications. Absenteeism from
Table 1. Educational programs of different countries compared by year of study, number of enrolled patients, cost, and clinical benefits

<table>
<thead>
<tr>
<th>Authors</th>
<th>Aim of the program</th>
<th>Country, year</th>
<th>Number of patients</th>
<th>Cost</th>
<th>Clinical effects/benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kauppinen et al.</td>
<td>Aim: Asthma self-management education</td>
<td>Finland, 1991-1993</td>
<td>162</td>
<td>Tendency for lower, but</td>
<td>FEV1% and PEF were significantly higher in the IG. Less risk for a sickness day in the IG.</td>
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<td></td>
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<td></td>
<td>insignificant cost for</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>patients in the IG.</td>
<td></td>
</tr>
<tr>
<td>*National program.</td>
<td>Aim:</td>
<td>Finland, 1994-2004</td>
<td>NA</td>
<td>NA</td>
<td>Reduction:</td>
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<td></td>
<td>- improve asthma care;</td>
<td></td>
<td></td>
<td></td>
<td>- of the number of hospital days (by 69%);</td>
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<td></td>
<td>- reduce the cost;</td>
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<td></td>
<td></td>
<td>- of the number of asthmatic patients receiving disability pension (by 83%);</td>
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<td></td>
<td>- implementation of new knowledge, (focus on primary care);</td>
<td></td>
<td></td>
<td></td>
<td>- of the total cost per patient per year (by 6%).</td>
</tr>
<tr>
<td>Søndergaard B. et al</td>
<td>Aim: To inform asthmatic patients about the disease, its therapy and correct</td>
<td>Denmark, 1992</td>
<td>NA</td>
<td>NA</td>
<td>Improved the quality of life and health status.</td>
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<td></td>
<td>inhalation technique.</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>*Danish National Database for Asthma (DNDA)</td>
<td>Aim:</td>
<td>Denmark, 2016</td>
<td>NA</td>
<td>NA</td>
<td>Data and monitoring of:</td>
</tr>
<tr>
<td></td>
<td>- collecting data of all patients treated for asthma;</td>
<td></td>
<td></td>
<td></td>
<td>- annual asthma control visits;</td>
</tr>
<tr>
<td></td>
<td>- monitoring asthma management, occurrence, quality of diagnosis;</td>
<td></td>
<td></td>
<td></td>
<td>- appropriate pharmacological treatment;</td>
</tr>
<tr>
<td>Ivanov Y et al.</td>
<td>Aim: To provide patients with an educational program:</td>
<td>Bulgaria, 1999</td>
<td>505</td>
<td>Implementing the program led to 1.5-fold reduction of the overall asthma cost. The direct cost was reduced by 1.3 and the indirect cost by 4.3. The low treatment adherence increased the cost per patient by 1.6.</td>
<td>Reduction of exacerbations, hospitalizations, emergency department visits and work absences.</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Aim</td>
<td>Location</td>
<td>Year</td>
<td>Group Size</td>
<td>Findings</td>
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<tr>
<td>Urek M et al.</td>
<td>Patients with moderate persistent asthma were given: individual verbal instructions; written information; asthma classes;</td>
<td>Croatia, 2005</td>
<td>60</td>
<td>Individual verbal instructions lead to better asthma control and quality of life.40</td>
<td></td>
</tr>
<tr>
<td>Felix et al.</td>
<td>To analyze some features of patients with asthma before and after educational intervention.</td>
<td>Brazil, 2018</td>
<td>39</td>
<td>In the educational group (29 patients) a significant improvement was found in: asthma control, quality of life and FEV1%, decreased cough, sputum eosinophils, and depression levels.41</td>
<td></td>
</tr>
<tr>
<td>Gomez et al.</td>
<td>To evaluate the cost and savings of the asthma intervention of a state-funded healthy homes program.</td>
<td>USA, 2017</td>
<td>more than 2000</td>
<td>Patients with more poorly controlled asthma had higher benefits from the health services.42</td>
<td></td>
</tr>
<tr>
<td>Boulet LP et al.</td>
<td>Asses the effect of educational program in primary care on patient outcomes and healthcare use.</td>
<td>Canada, 2015</td>
<td>124</td>
<td>The educational program results in: improvements in patient asthma outcomes; reduction of unscheduled visits, decreasing of antibiotic treatments related to respiratory problems by &gt; 50%; significant decrease was observed of total number of oral corticosteroid treatment.43</td>
<td></td>
</tr>
<tr>
<td>Ozturk AB et al.</td>
<td>To study the correlation between asthma self-management knowledge and short-term asthma control in older adults.</td>
<td>Turkey, 2015</td>
<td>82</td>
<td>- 48% of the patients had limited asthma knowledge; no significant association between patients’ asthma knowledge and asthma control level.44</td>
<td></td>
</tr>
<tr>
<td>Elbanna R et al.</td>
<td>Improvement of asthma control in all patients in family health care units.</td>
<td>Egypt, 2016</td>
<td>84</td>
<td>- significant improvement in the level of asthma knowledge, asthma control; fewer visits to the emergency room, hospitalization and referral to specialist.45</td>
<td></td>
</tr>
</tbody>
</table>
Implementation of educational program and assessment of asthma control after the program.

IG: intensive group; FEV1%: percent of the predicted forced expiratory volume in 1 second; PEF: peak expiratory flow; NA: not applicable

work/school was the main reason for high indirect cost. The number of hospitalizations of asthmatic patients (and costs for hospital treatment) has been reduced. Published data shows that asthma cost correlates not only with asthma severity, control, social status and therapy adherence, but also with asthma phenotype. The highest healthcare cost burden is due to patients with severe uncontrolled eosinophilic asthma and severe refractory asthma. Recently performed PE analyses of occupational asthma exposed its real and significant treatment cost.

In most of the countries educational programs for asthmatic patients started in the early 1990s and later were transformed into national comprehensive programs. In Bulgaria, not only were the PE analysis performed later (1999), but also there is no updated information available today. Still there is no integrated register to follow up and manage asthmatic patients in Bulgaria.

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Pharmacoeconomics of Bronchial Asthma


Фармакоэкономика бронхиальной астмы

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Ключевые слова: фармакоэкономика, стоимость, астма

Введение: Фармакоэкономика (ФЭ) рассматривает вопросы фармакотерапевтической политики, рынка лекарственных средств и возмещения расходов, а также клинических испытаний. Она направляет внимание специалистов, разрабатывающих подходы, на эффективное использование ресурсов здравоохранения и определяет экономическую эффективность новых лекарств на основе их стоимости, эффективности и выгод для общества.

Типы затрат на здравоохранение и фармакоэкономический анализ: В этом обзоре рассматриваются основные виды расходов на здравоохранение. Представлены основные анализы ФЭ, их преимущества и недостатки.

Фармакоэкономика бронхиальной астмы: Основные аспекты ФЭ при бронхиальной астме доступны в настоящем исследовании. Обсуждается стоимость медицинских услуг (прямых и косвенных), образовательных программ и лекарств от астмы в разных странах. Недавно опубликованные данные показали корреляцию между расходами на лечение астмы и тяжестью заболевания, контролем, социальным статусом и соблюдением режима лечения.

Заключение: Анализ ФЭ обеспечивает преимущество принимать решения в соответствии с расходами на текущее лечение астмы во всём мире и в Болгарии.