



Reengineering health care: questionable medical tests and procedures

Hanna Zowall et al.



**Availability of pneumococcal
vaccination in Europe**
Overview of funding mechanisms



**Reengineering health care:
questionable medical
tests and procedures**



Editor-in-Chief
Prof. Karina Jahnz-Rózyk

Dear colleagues

WE INVITE YOU TO READ PUBLICATIONS IN THE THIRD ISSUE OF JHPOR. WE PAID PARTICULAR ATTENTION TO THE FIRST TWO ARTICLES - ZOWALL ET AL (CMC GILL UNIVERSITY, MONTREAL, CANADA) AND MIKUDINA AND REDEKOP (ERASMUS UNIVERSITY, ROTTERDAM, THE NETHERLANDS). BOTH ARTICLES REFER TO THE VERY IMPORTANT, PREVIOUSLY UNAPPRECIATED SUBJECT OF CLINICAL EFFECTIVENESS, COMBINED WITH THE ECONOMIC EVALUATION OF DIAGNOSTIC TESTS.

It was pointed out by Mikudina and Redekop that medical technology assessment of medical devices and diagnostic tests in the early phases could help to make better decisions about further development, the regulatory and reimbursement strategy, and allocating public support for new technologies. In the Zowall et al publication the results of the U.S. scientific societies campaign titled „Choosing Wisely” are included. As a result of this campaign, a list of „Things Physicians and Patients Should Question” was created. It provides specific, evidence-based recommendations, so physician and patients can reach informed decisions about the appropriate level of care. We believe that in the near future efforts should be made to create a similar list based on the recommendations of Polish scientific societies established in Poland.

Also in this issue you will find a lot of interesting publications, relating to the reimbursement systems in different European countries, use of interesting pharmaco-economic analyses and of course the activities of the Polish Society of Pharmacoeconomics.

We wish you pleasant reading of our journal

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Karina Jahnz-Rozyk

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General Editorial Policies

Journal of Health Policy & Outcomes Research (JHPOR) is pre-reviewed, international scientific journal, publishing the work of an important contribution to the development of pharmacoeconomics and outcomes research in Poland and worldwide. The journal is issued under the auspices of the Polish Society of Pharmacoeconomics. The journal is published twice a year in electronic form, optionally in the paper version.

Topics of publications includes the following issues:

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Sanofi Group

Publisher

Fundacja Pro-Medicina
www.promedicina.pl

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Reengineering health care: questionable medical tests and procedures



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Keywords:
evidence-based
recommendations,
medical tests,
reengineering health
care

DOI: 10.7365/JHPOR.2013.3.1
JHPOR, 2013, 1, 4-25

ABSTRACT

Given current and future budgetary constraints, issues of what constitute appropriate level of care are becoming paramount. More evidence-based data are accumulated, identifying the appropriate use of medical tests and procedures becomes imperative. In the United States, the "Choosing Wisely" campaign is an initiative of the American Board of Internal Medicine Foundation to allow physicians to be leaders in better management of finite health care resources. As part of a campaign, each participating medical specialty society has created lists of "Things Physicians and Patients Should Question" that provide specific, evidence-based recommendations, so physicians and patients can reach informed decisions about the appropriate level of care. Here we provide the summary of the most important recommendations. The aim of this paper is to disseminate the information in order to stimulate discussions about the appropriateness of frequently ordered tests or treatments and about variations in patterns of care, and cost-effective ways of managing finite health care resources. Central to the best practice of medicine becomes comparative-effectiveness research, including long

term studies on clinical benefits and costs. Physicians must change practice patterns, through standard-of-practice guidelines, to practice in the most knowledge-based, least invasive, and less costly way. Physicians need to take a leadership role in teaching patients that more medicine is not better medicine, that costly efforts do not equal better health care. We need to explain to patients that new medical technology must be used with care and wisdom.

INTRODUCTION

As many countries focus on ways to provide safer, higher-quality care to patients at affordable prices, the rational use of health care resources is an issue of considerable concern¹⁻⁵. Given the fast pace of technological change, the use of many routine medical tests becomes questionable, as newer and perhaps "better", but usually more expensive tests become available. As more evidence-based data are accumulated, identifying the appropriate use of medical tests becomes imperative. In many jurisdictions, where the majority of health care services are publicly provided, there is no room for delivering duplicative or unnecessary care. Given current and future budgetary constraints, moves away from fee-for-service towards pay-for-performance arrange-

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.

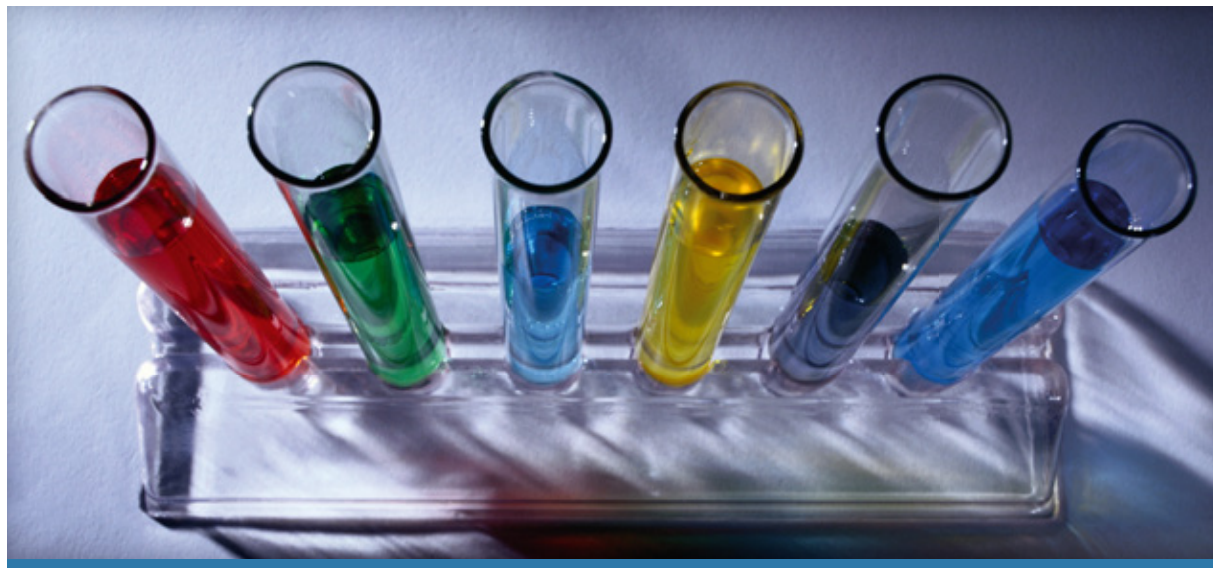
ments, issues of what constitute appropriate level of care are becoming paramount. It is important to provide health care, supported by evidence-based data that is not duplicative, and is truly necessary, where clinical benefits outweigh harm. Many experts agree that in the United States, health care delivery contains waste, with some stating that as much as 30 percent of care delivered is duplicative or unnecessary, and may not improve patients' health³⁻⁴. The aim of this paper is disseminate the information in order to stimulate discussions about the appropriateness of frequently ordered tests or treatments and to encourage discussions about variations in patterns of care, and cost-effective ways of managing finite health care resources.

U.S. CHOOSING WISELY CAMPAIGN SPONSORED BY AMERICAN BOARD OF INTERNAL MEDICINE FOUNDATION

In the United States, the "Choosing Wisely" campaign is an initiative of the American Board of Internal Medicine (ABIM) Foundation⁶. It is part of a continuous effort to allow physicians to be leaders in better management of finite health care resources. While meeting the needs of individual patients, physicians are required to provide health care that is based on cost-effective management of limited clinical resources. Since

1999, the ABIM Foundation has worked toward its mission of advancing medical professionalism into clinical policy and practice. "Choosing Wisely" is intended to help physicians and patients engage in conversations about the appropriate use of tests and procedures and support physician efforts to help patients make smart and effective care choices. As part of "Choosing Wisely", each participating medical specialty society has created lists of "Things Physicians and Patients Should Question" that provide specific, evidence-based practice, so physicians and patients can reach informed decisions about the appropriate care based on the patients' individual situation.

The resulting list is intended to stimulate discussion about the appropriateness of frequently ordered tests or treatments. This concept was originally piloted by the US National Physicians Alliance, who through the ABIM Foundation created a list for physicians to use in their practices to promote more effective use of health care resources. The "Top 5" lists in primary care study was published in Archives of Internal Medicine, 2011¹¹. The list included tests and procedure of questionable value in three medical specialties: Family Medicine, Internal Medicine and Pediatrics. Briefly, panels of experts evaluated the current pattern of care and reviewed them according to evidence-based data. The new,



updated and enlarged list prepared by 25 leading physician specialty societies in the United States, representing over 725,000 physicians, was released in February 2013⁶. Each medical specialty society identified major tests or procedures that are commonly performed, but whose use should be questioned. For each recommendation the data sources were compiled. Here, selected recommendations are cited. The full list is provided at www.choosingwisely.org.

SELECTED LIST OF TESTS AND PROCEDURES FOR PHYSICIANS AND PATIENTS TO QUESTION (QUOTED FROM WWW.CHOOSINGWISELY.ORG)

American Academy of Family Physicians

Don't routinely prescribe antibiotics for acute mild-to-moderate sinusitis unless symptoms last for seven or more days, or symptoms worsen after initial clinical improvement.

Symptoms must include discolored nasal secretions and facial or dental tenderness when touched. Most sinusitis in the ambulatory setting is due to a viral infection that will resolve on its own. Despite consistent recommendations to the contrary, antibiotics are prescribed in more than 80 percent of outpatient visits for acute sinusitis. Sinusitis accounts for 16 million office visits and \$5.8 billion in annual health care costs.

Don't perform Pap smears on women younger than 21 or who have had a hysterectomy for non-cancer disease.

Most observed abnormalities in adolescents regress spontaneously, therefore Pap smears for this age group can lead to unnecessary anxiety, additional testing and cost. Pap smears are not helpful in women after hysterectomy (for non-cancer disease) and there is little evidence for improved outcomes.

Don't schedule elective, non-medically indicated inductions of labor or Cesarean deliveries before 39 weeks, 0 days gestational age.

Delivery prior to 39 weeks, 0 days has been shown to be associated with an increased risk of learning disabilities and a potential increase in morbidity and mortality. There are clear medical indications for delivery prior to 39 weeks and 0 days based on maternal and/or fetal conditions. A mature fetal lung test, in the absence of appropriate clinical criteria, is not an indication for delivery.

Avoid elective, non-medically indicated inductions of labor between 39 weeks, 0 days and 41 weeks, 0 days unless the cervix is deemed favorable.

Ideally, labor should start on its own initiative whenever possible. Higher Cesarean delivery rates result from inductions of labor when the cervix is unfavorable. Health care clinicians should discuss the risks and benefits with their patients before considering inductions of labor without medical indications.

Don't screen for carotid artery stenosis (CAS) in asymptomatic adult patients.

There is good evidence that for adult patients with no symptoms of carotid artery stenosis, the harms of screening outweigh the benefits. Screening could lead to non-indicated surgeries that result in serious harms, including death, stroke and myocardial infarction.

Don't screen women older than 65 years of age for cervical cancer who have had adequate prior screening and are not otherwise at high risk for cervical cancer.

There is adequate evidence that screening women older than 65 years of age for cervical cancer who have had adequate prior screening and are not otherwise at high risk provides little to no benefit.

Don't screen women younger than 30 years of age for cervical cancer with human papilloma virus (HPV) testing, alone or in combination with cytology.

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.

There is adequate evidence that the harms of HPV testing, alone or in combination with cytology, in women younger than 30 years of age are moderate. The harms include more frequent testing and invasive diagnostic procedures such as colposcopy and cervical biopsy. Abnormal screening test results are also associated with psychological harms, anxiety and distress.

Don't use dual-energy x-ray absorptiometry (DEXA) screening for osteoporosis in women younger than 65 or men younger than 70 with no risk factors.

DEXA is not cost effective in younger, low-risk patients, but is cost effective in older patients.

Don't order annual electrocardiograms (EKGs) or any other cardiac screening for low-risk patients without symptoms.

There is little evidence that detection of coronary artery stenosis in asymptomatic patients at low risk for coronary heart disease improves health outcomes. False-positive tests are likely to lead to harm through unnecessary invasive procedures, over-treatment and misdiagnosis. Potential harms of this routine annual screening exceed the potential benefit.

American College of Physicians

Don't obtain imaging studies in patients with non-specific low back pain.

In patients with back pain that cannot be attributed to a specific disease or spinal abnormality following a history and physical examination (e.g., non-specific low back pain), imaging with plain radiography, computed tomography (CT) scan, or magnetic resonance imaging (MRI) does not improve patient outcomes.

Don't obtain screening exercise electrocardiogram testing in individuals who are asymptomatic and at low risk for coronary heart disease.

In asymptomatic individuals at low risk for coronary heart disease (10-year risk <10%) screening for coronary heart disease with exercise electrocardiography does not improve patient outcomes.

In the evaluation of simple syncope and a normal neurological examination, don't obtain brain imaging studies (CT or MRI).

In patients with witnessed syncope but with no suggestion of seizure and no report of other neurologic symptoms or signs, the likelihood of a central nervous system (CNS) cause of the event is extremely low and patient outcomes are not improved with brain imaging studies.

In patients with low pretest probability of venous thromboembolism (VTE), obtain a high-sensitive D-dimer measurement as the initial diagnostic test; don't obtain imaging studies as the initial diagnostic test.

In patients with low pretest probability of VTE as defined by the Wells prediction rules, a negative high-sensitivity D-dimer measurement effectively excludes VTE and the need for further imaging studies.

The American College of Obstetricians and Gynecologists

Don't perform routine annual cervical cytology screening (Pap tests) in women 30–65 years of age.

In average risk women, annual cervical cytology screening has been shown to offer no advantage over screening performed at 3-year intervals. However, a well-woman visit should occur annually for patients with their health care practitioner to discuss concerns and problems, and have appropriate screening with consideration of a pelvic examination.

Don't treat patients who have mild dysplasia of less than two years in duration.

Mild dysplasia (Cervical Intraepithelial Neoplasia [CIN 1]) is associated with the presence of the HPV, which does not require treatment in average risk women. Most women with CIN 1 on biopsy have a transient HPV infection that will usually clear in less than 12 months and, therefore, does not require treatment.

Don't screen for ovarian cancer in asymptomatic women at average risk.

In population studies, there is only fair evidence that screening of asymptomatic women with serum CA-125 level and/or transvaginal ultrasound can detect ovarian cancer at an earlier stage than it can be detected in the absence of screening. Because of the low prevalence of ovarian cancer and the invasive nature of the interventions required after a positive screening test, the potential harms of screening outweigh the potential benefits.

American Academy of Pediatrics

Antibiotics should not be used for apparent viral respiratory illnesses (sinusitis, pharyngitis, bronchitis).

Although overall antibiotic prescription rates for children have fallen, they still remain alarmingly high. Unnecessary medication use for viral respiratory illnesses can lead to antibiotic resistance and contributes to higher health care costs and the risks of adverse events.

Cough and cold medicines should not be prescribed or recommended for respiratory illnesses in children under four years of age.

Research has shown these products offer little benefit to young children and can have potentially serious side effects. Many cough and cold products for children have more than one ingredient, increasing the chance of accidental overdose if combined with another product.

CT scans are not necessary in the immediate evaluation of minor head injuries; clinical observation/Pediatric Emergency Care Applied Research Network (PECARN) criteria should be used to determine whether imaging is indicated.

Minor head injuries occur commonly in children and adolescents. Approximately 50% of children who visit hospital emergency departments with a head injury are given a CT scan, many of which may be unnecessary. Unnecessary exposure to x-rays poses considerable danger to children including increasing the lifetime risk of cancer because a child's brain tissue is more sensitive to ionizing radiation. Unnecessary CT scans impose undue costs to the health care system. Clinical observation prior to CT decision-making for children with minor head injuries is an effective approach.

Neuroimaging (CT, MRI) is not necessary in a child with simple febrile seizure.

CT scanning is associated with radiation exposure that may escalate future cancer risk. MRI also is associated with risks from required sedation and high cost. The literature does not support the use of skull films in the evaluation of a child with a febrile seizure. Clinicians evaluating infants or young children after a simple febrile seizure should direct their attention toward identifying the cause of the child's fever.

CT scans are not necessary in the routine evaluation of abdominal pain.

Utilization of CT imaging in the emergency department evaluation of children with abdominal pain is increasing. The increased lifetime risk for cancer due to excess radiation exposure is of special concern given the acute sensitivity of children's organs. There also is the potential for radiation overdose with inappropriate CT protocols.



American College of Cardiology (ACC)

Don't perform stress cardiac imaging or advanced non-invasive imaging in the initial evaluation of patients without cardiac symptoms unless high-risk markers are present.

Asymptomatic, low-risk patients account for up to 45 percent of unnecessary "screening." Testing should be performed only when the following findings are present: diabetes in patients older than 40-years-old; peripheral arterial disease; or greater than 2 percent yearly risk for coronary heart disease events.

Don't perform annual stress cardiac imaging or advanced non-invasive imaging as part of routine follow-up in asymptomatic patients.

Performing stress cardiac imaging or advanced non-invasive imaging in patients without symptoms on a serial or scheduled pattern (e.g., every one to two years or at a heart procedure anniversary) rarely results in any meaningful change in patient management. This practice may, in fact, lead to unnecessary invasive procedures and excess radiation exposure without any proven impact on patients' outcomes. An exception to this rule would be for patients more than five years after a bypass operation.

Don't perform stress cardiac imaging or advanced non-invasive imaging as a pre-operative assessment in patients scheduled to undergo low-risk non-cardiac surgery.

Non-invasive testing is not useful for patients undergoing low-risk non-cardiac surgery (e.g., cataract removal). These types of tests do not change the patient's clinical management or outcomes and will result in increased costs.

Don't perform echocardiography as routine follow-up for mild, asymptomatic native valve disease in adult patients with no change in signs or symptoms.

Patients with native valve disease usually have years without symptoms before the onset of deterioration. An echocardiogram is not recommended yearly unless there is a change in clinical status.

Don't perform stenting of non-culprit lesions during percutaneous coronary intervention (PCI) for uncomplicated hemodynamically stable ST-segment elevation myocardial infarction (STEMI).

Stent placement in a noninfarct artery during primary PCI for STEMI in a hemodynamically stable patient may lead to increased mortality and complications. While potentially beneficial in patients with hemodynamic compromise, intervention beyond the culprit lesion during primary PCI has not demonstrated benefit in clinical trials to date.

American Society of Nuclear Cardiology

Don't perform cardiac imaging for patients who are at low risk.

Chest pain patients at low risk of cardiac death and myocardial infarction (based on history, physical exam, electrocardiograms and cardiac biomarkers) do not merit stress radionuclide myocardial perfusion imaging or stress echocardiography as an initial testing strategy if they have a normal electrocardiogram (without baseline ST-abnormalities, left ventricular hypertrophy, pre-excitation, bundle branch block, intra-ventricular conduction delay, paced rhythm or on digoxin therapy) and are able to exercise.

Use methods to reduce radiation exposure in cardiac imaging, whenever possible, including not performing such tests when limited benefits are likely.

The key step to reduce or eliminate radiation exposure is appropriate selection of any test or procedure for a specific person, in keeping with medical society recommendations, such as appropriate use

criteria. Health care providers should incorporate new methodologies in cardiac imaging to reduce patient exposure to radiation while maintaining high-quality test results.

Don't perform radionuclide imaging as part of routine follow-up in asymptomatic patients.

Performing stress radionuclide imaging in patients without symptoms on a serial or scheduled pattern (e.g., every one to two years or at a heart procedure anniversary) rarely results in any meaningful change in patient management. This practice may lead to unnecessary invasive procedures and excess radiation exposure without any proven impact on patients' outcomes. An exception to this rule would be for patients more than five years after a bypass operation.

American College of Radiology

Don't do imaging for uncomplicated headache.

Imaging headache patients absent specific risk factors for structural disease is not likely to change management or improve outcome. Those patients with a significant likelihood of structural disease requiring immediate attention are detected by clinical screens that have been validated in many settings. Many studies and clinical practice guidelines concur. Also, incidental findings lead to additional medical procedures and expense that do not improve patient well-being.

Don't image for suspected pulmonary embolism (PE) without moderate or high pre-test probability of PE.

While deep vein thrombosis (DVT) and PE are relatively common clinically, they are rare in the absence of elevated blood d-Dimer levels and certain specific risk factors. Imaging, particularly CT pulmonary angiography, is a rapid, accurate and widely available test, but has limited value in patients who are very unlikely, based on serum and clinical criteria, to have significant value.

Imaging is helpful to confirm or exclude PE only for such patients, not for patients with low pre-test probability of PE.

Avoid admission or preoperative chest x-rays for ambulatory patients with unremarkable history and physical exam.

Performing routine admission or preoperative chest x-rays is not recommended for ambulatory patients without specific reasons suggested by the history and/or physical examination findings. Only 2 percent of such images lead to a change in management. Obtaining a chest radiograph is reasonable if acute cardiopulmonary disease is suspected or there is a history of chronic stable cardiopulmonary disease in a patient older than age 70 who has not had chest radiography within six months.

Don't do CT for the evaluation of suspected appendicitis in children until after ultrasound has been considered as an option.

Although CT is accurate in the evaluation of suspected appendicitis in the pediatric population, ultrasound is nearly as good in experienced hands. Since ultrasound will reduce radiation exposure, ultrasound is the preferred initial consideration for imaging examination in children. If the results of the ultrasound exam are equivocal, it may be followed by CT. This approach is cost-effective, reduces potential radiation risks and has excellent accuracy, with reported sensitivity and specificity of 94 percent.

Don't recommend follow-up imaging for clinically inconsequential adnexal cysts.

Simple cysts and hemorrhagic cysts in women of reproductive age are almost always physiologic. Small simple cysts in postmenopausal women are common, and clinically inconsequential. Ovarian cancer, while typically cystic, does not arise from these benign-appearing cysts. After a good quality ultrasound in women of reproductive age, don't recommend follow-up for a classic corpus luteum or simple cyst.

Society of Hospital Medicine

Don't place, or leave in place, urinary catheters for incontinence or convenience or monitoring of output for non-critically ill patients (acceptable indications: critical illness, obstruction, hospice, perioperatively for <2days urologic procedures:use weights instead to monitor diuresis).

Catheter Associated Urinary Tract Infections (CAUTIs) are the most frequently occurring health care acquired infection (HAI). Use of urinary catheters for incontinence or convenience without proper indication or specified optimal duration of use increases the likelihood of infection and is commonly associated with greater morbidity, mortality and health care costs. Published guidelines suggest that hospitals and long-term care facilities should develop, maintain and promulgate policies and procedures for recommended catheter insertion indications, insertion and maintenance techniques, discontinuation strategies and replacement indications.

Don't prescribe medications for stress ulcer prophylaxis to medical inpatients unless at high risk for GI complications.

According to published guidelines, medications for stress ulcer prophylaxis are not recommended for adult patients in non-intensive care unit (ICU) settings. Histamine-2 receptor antagonists (H2RAs) and proton-pump inhibitors (PPIs), commonly used to treat stress ulcers, are associated with adverse drug events and increased medication costs, and commonly enhance susceptibility to community-acquired nosocomial pneumonia and *Clostridium difficile*. Adherence to therapeutic guidelines will aid health care providers in reducing treatment of patients without clinically important risk factors for gastrointestinal bleeding.

Avoid transfusions of red blood cells for arbitrary hemoglobin or hematocrit thresholds and in the absence of symptoms of active coronary disease, heart failure or stroke.

The American Association of Blood banks (AABB) recommends adhering to a restrictive transfusion strategy (7 to 8 g/dL) in hospitalized, stable patients. The AABB suggests that transfusion decisions be influenced by symptoms as well as hemoglobin concentration. According to a National Institutes of Health Consensus Conference, no single criterion should be used as an indication for red cell component therapy. Instead, multiple factors related to the patient's clinical status and oxygen delivery should be considered.

Don't order continuous telemetry monitoring outside of the ICU without using a protocol that governs continuation.

Telemetric monitoring is of limited utility or measurable benefit in low risk cardiac chest pain patients with normal electrocardiogram. Published guidelines provide clear indications for the use of telemetric monitoring in patients which are contingent upon frequency, severity, duration and conditions under which the symptoms occur. Inappropriate use of telemetric monitoring is likely to increase cost of care and produce false positives potentially resulting in errors in patient management.

Don't perform repetitive complete blood count (CBC) and chemistry testing in the face of clinical and lab stability.

Hospitalized patients frequently have considerable volumes of blood drawn (phlebotomy) for diagnostic testing during short periods of time. Phlebotomy is highly associated with changes in hemoglobin and hematocrit levels for patients and can contribute to anemia. This anemia, in turn, may have significant consequences, especially for patients with cardiorespiratory diseases. Additionally, reducing the frequency of daily unnecessary phlebotomy can result in significant cost savings for hospitals.

Don't order chest radiographs in children with uncomplicated asthma or bronchiolitis.

NATIONAL GUIDELINES
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National guidelines articulate a reliance on physical examination and patient history for diagnosis of asthma and bronchiolitis in the pediatric population. Multiple studies have established limited clinical utility of chest radiographs for patients with asthma or bronchiolitis. Omission of the use of chest radiography will reduce costs, but not compromise diagnostic accuracy and care.

Don't routinely use bronchodilators in children with bronchiolitis.

Published guidelines do not advocate the routine use of bronchodilators in patients with bronchiolitis. Comprehensive reviews of the literature have demonstrated that the use of bronchodilators in children admitted to the hospital with bronchiolitis has no effect on any important outcomes. There is limited demonstration of clear impact of bronchodilator therapy upon the course of disease. Additionally, providers should consider the potential impact of adverse events upon the patient.

Don't use systemic corticosteroids in children under 2 years of age with an uncomplicated lower respiratory tract infection.

Published guidelines recommend that corticosteroid medications not be used routinely in the management of bronchiolitis. Furthermore, additional studies in patients with other viral lower respiratory tract infections have failed to demonstrate any benefits.

Don't treat gastroesophageal reflux in infants routinely with acid suppression therapy.

Antireflux therapy has been demonstrated to have no effect in reducing the symptoms of gastroesophageal reflux disease (GERD) in children. Concerns regarding the use of proton-pump inhibitor therapy in infants include an inability to definitively diagnose pediatric patients according to the established criteria of GERD, lack of documented efficacy of acid suppression therapy in infants and the po-

tential adverse effects associated with acid suppression therapy.

Don't use continuous pulse oximetry routinely in children with acute respiratory illness unless they are on supplemental oxygen.

The utility of continuous pulse oximetry in pediatric patients with acute respiratory illness is not well established. Use of continuous pulse oximetry has been previously associated with increased admission rates and increased length of stay. The clinical benefit of pulse oximetry is not validated or well documented.



American Geriatrics Society

Don't use antipsychotics as first choice to treat behavioral and psychological symptoms of dementia.

People with dementia often exhibit aggression, resistance to care and other challenging or disruptive behaviors. In such instances, antipsychotic medicines are often prescribed, but they provide limited benefit and can cause serious harm, including stroke and premature death. Use of these drugs should be limited to cases where non-pharmacologic measures have failed and patients pose an imminent threat to themselves or others. Identifying and addressing causes of behavior change can make drug treatment unnecessary.

Avoid using medications to achieve hemoglobin A1c < 7.5% in most adults age 65 and older; moderate control is generally better.

There is no evidence that using medications to achieve tight glycemic control in older adults with type 2 diabetes is beneficial. Among non-older adults, except for long-term reductions in myocardial infarction and mortality with metformin, using medications to achieve glycated hemoglobin levels less than 7% is associated with harms, including higher mortality rates. Tight control has been consistently shown to produce higher rates of hypoglycemia in older adults. Given the long timeframe to achieve theorized microvascular benefits of tight control, glycemic targets should reflect patient goals, health status, and life expectancy. Reasonable glycemic targets would be 7.0 – 7.5% in healthy older adults with long life expectancy, 7.5 – 8.0% in those with moderate comorbidity and a life expectancy < 10 years, and 8.0 – 9.0% in those with multiple morbidities and shorter life expectancy.

Don't use benzodiazepines or other sedative-hypnotics in older adults as first choice for insomnia, agitation or delirium.

Large scale studies consistently show that the risk of motor vehicle accidents, falls and hip fractures leading to hospitalization and death can more than double in older adults taking benzodiazepines and other sedative-hypnotics. Older patients, their caregivers and their providers should recognize these potential harms when considering treatment strategies for insomnia, agitation or delirium. Use of benzodiazepines should be reserved for alcohol withdrawal symptoms/delirium tremens or severe generalized anxiety disorder unresponsive to other therapies.

Don't use antimicrobials to treat bacteriuria in older adults unless specific urinary tract symptoms are present.

Cohort studies have found no adverse outcomes for older men or women associated with asymptomatic bacteriuria. Antimicrobial treatment studies for asymptomatic bacteriuria in older adults demonstrate no benefits and show increased adverse antimicrobial effects. Consensus criteria has been developed to characterize the specific clinical symptoms that, when associated with bacteriuria, define urinary tract infection. Screening for and treatment of asymptomatic bacteriuria is recommended before urologic procedures for which mucosal bleeding is anticipated.

American Academy of Hospice and Palliative Medicine

Don't recommend percutaneous feeding tubes in patients with advanced dementia; instead, offer oral assisted feeding.

In advanced dementia, studies have found feeding tubes do not result in improved survival, prevention of aspiration pneumonia, or improved healing of pressure ulcers. Feeding tube use in such patients has actually been associated with pressure ulcer development, use of physical and pharmacological restraints, and patient distress about the tube itself. Assistance with oral feeding

is an evidence-based approach to provide nutrition for patients with advanced dementia and feeding problems; in the final phase of this disease, assisted feeding may focus on comfort and human interaction more than nutritional goals.

Don't delay palliative care for a patient with serious illness who has physical, psychological, social or spiritual distress because they are pursuing disease-directed treatment.

Numerous studies—including randomized trials—provide evidence that palliative care improves pain and symptom control, improves family satisfaction with care and reduces costs. Palliative care does not accelerate death, and may prolong life in selected populations.

Don't leave an implantable cardioverter-defibrillator (ICD) activated when it is inconsistent with the patient/family goals of care.

In about a quarter of patients with ICDs, the defibrillator fires within weeks preceding death. For patients with advanced irreversible diseases, defibrillator shocks rarely prevent death, may be painful to patients and are distressing to caregivers/family members. Currently there are no formal practice protocols to address deactivation; fewer than 10% of hospices have official policies. Advance care planning discussions should include the option of deactivating the ICD when it no longer supports the patient's goals.

Don't recommend more than a single fraction of palliative radiation for an uncomplicated painful bone metastasis.

As stated in the American Society for Radiation Oncology (ASTRO) 2011 guideline, single-fraction radiation to a previously un-irradiated peripheral bone or vertebral metastasis provides comparable pain relief and morbidity compared to multiple-fraction regimens while optimizing patient and caregiver convenience. Although it results in a higher incidence of later need for re-

treatment (20% vs. 8% for multi-fraction regimens), the decreased patient burden usually outweighs any considerations of long-term effectiveness for those with a limited life expectancy.

Don't use topical lorazepam (Ativan), diphenhydramine (Benadryl), haloperidol (Haldol) ("ABH") gel for nausea.

Topical drugs can be safe and effective, such as topical non-steroidal anti-inflammatory drugs for local arthritis symptoms. However, while topical gels are commonly prescribed in hospice practice, anti-nausea gels have not been proven effective in any large, well-designed or placebo-controlled trials. The active ingredients in ABH are not absorbed to systemic levels that could be effective. Only diphenhydramine (Benadryl) is absorbed via the skin, and then only after several hours and erratically at subtherapeutic levels. It is therefore not appropriate for "as needed" use. The use of agents given via inappropriate routes may delay or prevent the use of more effective interventions.

American Society of Clinical Oncology

Don't use cancer-directed therapy for solid tumor patients with the following characteristics: low performance status (3 or 4), no benefit from prior evidence-based interventions, not eligible for a clinical trial, and no strong evidence supporting the clinical value of further anti-cancer treatment.

Studies show that cancer directed treatments are likely to be ineffective for solid tumor patients who meet the above stated criteria. Exceptions include patients with functional limitations due to other conditions resulting in a low performance status or those with disease characteristics (e.g., mutations) that suggest a high likelihood of response to therapy. Implementation of this approach should be accompanied with appropriate palliative and supportive care.

IN ABOUT A QUARTER OF PATIENTS WITH ICDs, THE DEFIBRILLATOR FIRES WITHIN WEEKS PRECEDING DEATH. FOR PATIENTS WITH ADVANCED IRREVERSIBLE DISEASES, DEFIBRILLATOR SHOCKS RARELY PREVENT DEATH, MAY BE PAINFUL TO PATIENTS AND ARE DISTRESSING TO CAREGIVERS/FAMILY MEMBERS.

Don't perform positron emission tomography (PET), CT, and radionuclide bone scans in the staging of early prostate cancer at low risk for metastasis.

Imaging with PET, CT, or radionuclide bone scans can be useful in the staging of specific cancer types. However, these tests are often used in the staging evaluation of low-risk cancers, despite a lack of evidence suggesting they improve detection of metastatic disease or survival. Evidence does not support the use of these scans for staging of newly diagnosed low grade carcinoma of the prostate (Stage T1c/T2a, prostate-specific antigen (PSA)).

Don't perform PET, CT, and radionuclide bone scans in the staging of early breast cancer at low risk for metastasis.

Imaging with PET, CT, or radionuclide bone scans can be useful in the staging of specific cancer types. However, these tests are often used in the staging evaluation of low-risk cancers, despite a lack of evidence suggesting they improve detection of metastatic disease or survival. In breast cancer, for example, there is a lack of evidence demonstrating a benefit for the use of PET, CT, or radionuclide bone scans in asymptomatic individuals with newly identified ductal carcinoma in situ (DCIS), or clinical stage I or II disease. Unnecessary imaging can lead to harm through unnecessary invasive procedures, over-treatment, unnecessary radiation exposure, and misdiagnosis.

Don't perform surveillance testing (biomarkers) or imaging (PET, CT, and radionuclide bone scans) for asymptomatic individuals who have been treated for breast cancer with curative intent.

Surveillance testing with serum tumor markers or imaging has been shown to have clinical value for certain cancers (e.g., colorectal). However for breast cancer that has been treated with curative intent, several studies have shown there is no benefit from routine imaging or serial measure-

ment of serum tumor markers in asymptomatic patients. False-positive tests can lead to harm through unnecessary invasive procedures, over-treatment, unnecessary radiation exposure, and misdiagnosis.

American College of Rheumatology

Don't perform MRI of the peripheral joints to routinely monitor inflammatory arthritis.

Data evaluating MRI for the diagnosis and prognosis of rheumatoid arthritis are currently inadequate to justify widespread use of this technology for these purposes in clinical practice. Although bone edema assessed by MRI on a single occasion may be predictive of progression in certain RA populations, using MRI routinely is not cost-effective compared with the current standard of care, which includes clinical disease activity assessments and plain film radiography.

Don't prescribe biologics for rheumatoid arthritis before a trial of methotrexate (or other conventional non-biologic DMARDs).

High quality evidence suggests that methotrexate and other conventional non-biologic disease modifying antirheumatic drugs (DMARD) are effective in many patients with rheumatoid arthritis (RA). Initial therapy for RA should be a conventional non-biologic DMARDs unless these are contraindicated. If a patient has had an inadequate response to methotrexate with or without other non-biologic DMARDs during an initial 3-month trial, then biologic therapy can be considered. Exceptions include patients with high disease activity and poor prognostic features (functional limitations, disease outside the joints, seropositivity or bony damage), where biologic therapy may be appropriate first-line treatment.

Don't routinely repeat DXA scans more often than once every two years.

Initial screening for osteoporosis should be performed according to National Osteo-

porosis Foundation recommendations. The optimal interval for repeating Dual-energy X-ray Absorptiometry (DXA) scans is uncertain, but because changes in bone density over short intervals are often smaller than the measurement error of most DXA scanners, frequent testing (e.g. <2 years) is unnecessary in most patients. Even in high-risk patients receiving drug therapy for osteoporosis, DXA changes do not always correlate with probability of fracture. Therefore, DXAs should only be repeated if the result will influence clinical management or if rapid changes in bone density are expected. Recent evidence also suggests that healthy women age 67 and older with normal bone mass may not need additional DXA testing for up to ten years provided osteoporosis risk factors do not significantly change.

American Gastroenterological Association

For pharmacological treatment of patients with gastroesophageal reflux disease (GERD), long-term acid suppression therapy (proton pump inhibitors or histamine2 receptor antagonists) should be titrated to the lowest effective dose needed to achieve therapeutic goals.

The main identifiable risk associated with reducing or discontinuing acid suppression therapy is an increased symptom burden. It follows that the decision regarding the need for (and dosage of) maintenance therapy is driven by the impact of those residual symptoms on the patient's quality of life rather than as a disease control measure.

Do not repeat colorectal cancer screening (by any method) for 10 years after a high-quality colonoscopy is negative in average-risk individuals.

A screening colonoscopy every 10 years is the recommended interval for adults without increased risk for colorectal cancer, beginning at age 50 years. Published studies indicate the risk of cancer is low for 10 years after a high-quality colonoscopy fails to detect neoplasia in this population. Therefore,

following a high-quality colonoscopy with normal results the next interval for any colorectal screening should be 10 years following that normal colonoscopy.

Do not repeat colonoscopy for at least five years for patients who have one or two small (< 1 cm) adenomatous polyps, without high-grade dysplasia, completely removed via a high-quality colonoscopy.

The timing of a follow-up surveillance colonoscopy should be determined based on the results of a previous high-quality colonoscopy. Evidence-based (published) guidelines provide recommendations that patients with one or two small tubular adenomas with low grade dysplasia have surveillance colonoscopy five to 10 years after initial polypectomy. "The precise timing within this interval should be based on other clinical factors (such as prior colonoscopy findings, family history, and the preferences of the patient and judgment of the physician)."

For a patient with functional abdominal pain syndrome (as per ROME III criteria) CT scans should not be repeated unless there is a major change in clinical findings or symptoms.

There is a small, but measurable increase in one's cancer risk from x-ray exposure. An abdominal CT scan is one of the higher radiation exposure x-rays — equivalent to three years of natural background radiation. Due to this risk and the high costs of this procedure, CT scans should be performed only when they are likely to provide useful information that changes patient management.

American Urological Association

A routine bone scan is unnecessary in men with low-risk prostate cancer.

Low-risk patients(defined by using commonly accepted categories such as American Urological Association and National

Comprehensive Cancer Network guidelines) are unlikely to have disease identified by bone scan. Accordingly, bone scans are generally unnecessary in patients with newly diagnosed prostate cancer who have a PSA <20.0 ng/mL and a Gleason score 6 or less unless the patient's history or clinical examination suggests bony involvement. Progression to the bone is much more common in advanced local disease or in high-grade disease that is characterized by fast and aggressive growth into surrounding areas such as bones or lymph nodes.

Don't prescribe testosterone to men with erectile dysfunction who have normal testosterone levels.

While testosterone treatment is shown to increase sexual interest, there appears to be no significant influence on erectile function, at least not in men with normal testosterone levels. The information available in studies to date is insufficient to fully evaluate testosterone's efficacy in the treatment of men with erectile dysfunction who have normal testosterone levels.

Don't treat an elevated PSA with antibiotics for patients not experiencing other symptoms.

It had previously been suggested that a course of antibiotics might lead to a decrease in an initially raised PSA and reduce the need for prostate biopsy; however, there is a lack of clinical studies to show that antibiotics actually decrease PSA levels. It should also be noted that a decrease in PSA does not indicate an absence of prostate cancer. There is no information available on the implications of deferring a biopsy following a decrease in PSA.

American Society of Nephrology

Don't perform routine cancer screening for dialysis patients with limited life expectancies without signs or symptoms.

Due to high mortality among end-stage renal disease (ESRD) patients, routine can-

cer screening—including mammography, colonoscopy, PSA and Pap smears—in dialysis patients with limited life expectancy, such as those who are not transplant candidates, is not cost effective and does not improve survival. False-positive tests can cause harm: unnecessary procedures, overtreatment, misdiagnosis and increased stress. An individualized approach to cancer screening incorporating patients' cancer risk factors, expected survival and transplant status is required.

Avoid nonsteroidal anti-inflammatory drugs (NSAIDs) in individuals with hypertension or heart failure or chronic kidney disease (CKD) of all causes, including diabetes.

The use of NSAIDs, including cyclo-oxygenase type 2 (COX-2) inhibitors, for the pharmacological treatment of musculoskeletal pain can elevate blood pressure, make antihypertensive drugs less effective, cause fluid retention and worsen kidney function in these individuals. Other agents such as acetaminophen, tramadol or short-term use of narcotic analgesics may be safer than and as effective as NSAIDs.

Don't place peripherally inserted central catheters (PICC) in stage III–V CKD patients without consulting nephrology.

Venous preservation is critical for stage III–V CKD patients. Arteriovenous fistulas (AVF) are the best hemodialysis access, with fewer complications and lower patient mortality, versus grafts or catheters. Excessive venous puncture damages veins, destroying potential AVF sites. PICC lines and subclavian vein puncture can cause venous thrombosis and central vein stenosis. Early nephrology consultation increases AVF use at hemodialysis initiation and may avoid unnecessary PICC lines or central/peripheral vein puncture.

Don't initiate chronic dialysis without ensuring a shared decision-making process between patients, their families, and their physicians.



The decision to initiate chronic dialysis should be part of an individualized, shared decision-making process between patients, their families, and their physicians. This process includes eliciting individual patient goals and preferences and providing information on prognosis and expected benefits and harms of dialysis within the context of these goals and preferences. Limited observational data suggest that survival may not differ substantially for older adults with a high burden of co morbidity who initiate chronic dialysis versus those managed conservatively.

American Academy of Otolaryngology — Head and Neck Surgery Foundation

Don't order CT scans of the head/brain for sudden hearing loss.

CT scanning is expensive, exposes the patient to radiation and offers no useful information that would improve initial management. CT scanning may be appropriate in patients with focal neurologic findings, a history of trauma or chronic ear disease.

Don't prescribe oral antibiotics for uncomplicated acute tympanostomy tube otorrhea.

Oral antibiotics have significant adverse effects and do not provide adequate coverage of the bacteria that cause most episodes; in contrast, topically administered products do provide coverage for these organisms. Avoidance of oral antibiotics can reduce the spread of antibiotic resistance and the risk of opportunistic infections.

Don't prescribe oral antibiotics for uncomplicated acute external otitis.

Oral antibiotics have significant adverse effects and do not provide adequate coverage of the bacteria that cause most episodes; in contrast, topically administered products do provide coverage for these organisms. Avoidance of oral antibiotics can reduce the spread of antibiotic resistance and the risk of opportunistic infections.

Don't routinely obtain radiographic imaging for patients who meet diagnostic criteria for uncomplicated acute rhinosinusitis.

Imaging of the paranasal sinuses, including plain film radiography, CT and magnetic resonance imaging (MRI) is unnecessary in patients who meet the clinical diagnostic criteria for uncomplicated acute rhinosinusitis.

Don't obtain CT or magnetic resonance imaging (MRI) in patients with a primary complaint of hoarseness prior to examining the larynx.

Examination of the larynx with mirror or fiberoptic scope is the primary method for evaluating patients with hoarseness. Imaging is unnecessary in most patients and is both costly and has potential for radiation exposure. After laryngoscopy, evidence supports the use of imaging to further evaluate 1) vocal fold paralysis, or 2) a mass or lesion of the larynx.

American Society of Echocardiography

Don't order follow up or serial echocardiograms for surveillance after a finding of trace valvular regurgitation on an initial echocardiogram.

Trace mitral, tricuspid and pulmonic regurgitation can be detected in 70% to 90% of normal individuals and has no adverse clinical implications. The clinical significance of a small amount of aortic regurgitation with an otherwise normal echocardiographic study is unknown.

Don't repeat echocardiograms in stable, asymptomatic patients with a murmur/click, where a previous exam revealed no significant pathology.

Repeat imaging to address the same question, when no pathology has been previously found and there has been no clinical change in the patient's condition, is not indicated.

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Avoid echocardiograms for preoperative/perioperative assessment of patients with no history or symptoms of heart disease.

Perioperative echocardiography is used to clarify signs or symptoms of cardiovascular disease, or to investigate abnormal heart tests. Resting left ventricular (LV) function is not a consistent predictor of perioperative ischemic events; even reduced LV systolic function has poor predictive value for perioperative cardiac events.

Avoid using stress echocardiograms on asymptomatic patients who meet "low risk" scoring criteria for coronary disease.

Stress echocardiography is mostly used in symptomatic patients to assist in the diagnosis of obstructive coronary artery disease. There is very little information on using stress echocardiography in asymptomatic individuals for the purposes of cardiovascular risk assessment, as a stand-alone test or in addition to conventional risk factors.

Avoid transesophageal echocardiography (TEE) to detect cardiac sources of embolization if a source has been identified and patient management will not change.

Tests whose results will not alter management should not be ordered. Protocol-driven testing can be useful if it serves as a reminder not to omit a test or procedure, but should always be individualized to the particular patient. While TEE is safe, even the small degree of risk associated with a procedure is not justified if there is no expected clinical benefit.

Society of Cardiovascular CT

Don't use coronary CT angiography (CTA) in high risk emergency department patients presenting with acute chest pain.*

To date, randomized controlled trials evaluating use of coronary CTA angiography for individuals presenting with acute chest pain in the emergency department have been

limited to low or low-intermediate risk individuals.

Society of Nuclear Medicine and Molecular Imaging

Don't use PET/CT for cancer screening in healthy individuals.

The likelihood of finding cancer in healthy adults is extremely low (around 1%), based on studies using PET/CT for screening. Imaging without clear clinical indication is likely to identify harmless findings that lead to more tests, biopsy or unnecessary surgery.

Don't perform routine annual stress testing after coronary artery revascularization.

Routine annual stress testing in patients without symptoms does not usually change management. This practice may lead to unnecessary testing without any proven impact on patient management.

Don't use nuclear medicine thyroid scans to evaluate thyroid nodules in patients with normal thyroid gland function.

Nuclear medicine thyroid scanning does not conclusively determine whether thyroid nodules are benign or malignant. Cold nodules on thyroid scans will still require biopsy. Nuclear medicine thyroid scans are useful to evaluate the functional status of thyroid nodules in patients who are hyperthyroid.

Avoid using a CT angiogram to diagnose pulmonary embolism in young women with a normal chest radiograph; consider a radio-nuclide lung study ("V/Q study") instead.

When the clinical question is whether or not pulmonary emboli are present, a V/Q study can provide the answer with lower overall radiation dose to the breast than can CTA, even when performed with a breast shield.

Don't use PET imaging in the evaluation of patients with dementia unless the patient has been assessed by a specialist in this field.

Without objective evidence of dementia, the potential benefit of PET is unlikely to justify the cost or radiation risk. Dementia subtypes have overlapping patterns in PET imaging. Clinical evaluation and imaging often provide additive information and should be assessed together to make a reliable diagnosis and to plan care. For β -amyloid PET imaging, it is not currently known what a positive PET result in a cognitively normal person means; this method is not established for an individual prediction.

The Society of Thoracic Surgeons

Don't initiate routine evaluation of carotid artery disease prior to cardiac surgery in the absence of symptoms or other high-risk criteria.

Carotid stenosis with symptoms (stroke or transient ischemic attacks [TIA]) is a known risk for cardiovascular accident and appropriate for preoperative testing. The presence of a carotid bruit does not equate to an increased risk of stroke after cardiac surgery. Patients with carotid stenosis have a higher rate of cerebrovascular complications after cardiac surgery, but there is no evidence that prophylactic or concomitant carotid surgery decreases this rate of complications in asymptomatic patients. ACC/American Heart Association (P) 2011 guidelines for coronary artery bypass graft surgery indicate carotid artery duplex scanning is reasonable in selected patients who are considered to have high-risk features. However, this was based on a consensus and a low level of evidence. In addition, a recent consensus report from the United Kingdom questioned whether neurologic sequelae developing in cardiac surgery patients with asymptomatic carotid disease are due to the carotid artery disease or rather act as a surrogate for an increased stroke risk from atherosclerotic issues with the aorta. The Northern Manhattan Stroke Study concluded that carotid auscultation had poor sensitivity and positive predictive

value for carotid stenosis and so decisions on obtaining carotid duplex studies should be considered based on symptoms or risk factors rather than findings on auscultation.

Don't perform a routine pre-discharge echocardiogram after cardiac valve replacement surgery.

Pre-discharge cardiac echocardiography is useful after cardiac valve repair. It provides information regarding the integrity of the repair and allows the opportunity for early identification of problems that may need to be addressed surgically during the index hospitalization. Unlike valve repair, there is a lack of evidence that supports the routine use of cardiac echocardiography pre-discharge after cardiac valve replacement. Scenarios that would justify the use of pre-discharge cardiac echocardiography include: inability to perform intraoperative transesophageal echocardiography, clinical signs and symptoms worrisome for valvular malfunction or infection, or a large pericardial effusion.

Prior to cardiac surgery, there is no need for pulmonary function testing in the absence of respiratory symptoms.

PFTs can be helpful in determining risk in cardiac surgery, but patients with no pulmonary disease are unlikely to benefit and do not justify testing. Symptoms attributed to cardiac disease that are respiratory in nature should be better characterized with PFTs. Risk models for cardiac surgery developed from review of The Society of Thoracic Surgeons Adult Cardiac Surgery Database incorporate a variable for chronic lung disease. Only recently have actual forced expiratory volume (FEV1) and carbon monoxide diffusing capacity (DLCO) data been collected in the database. In the absence of respiratory symptoms or suggestive medical history, pulmonary function testing is quite unlikely to change patient management or assist in risk assessment. Although some data are beginning to emerge about preoperative pulmonary rehabili-

tation prior to cardiac surgery for patients with even mild to moderate obstructive disease, this does not directly extrapolate to asymptomatic patients.

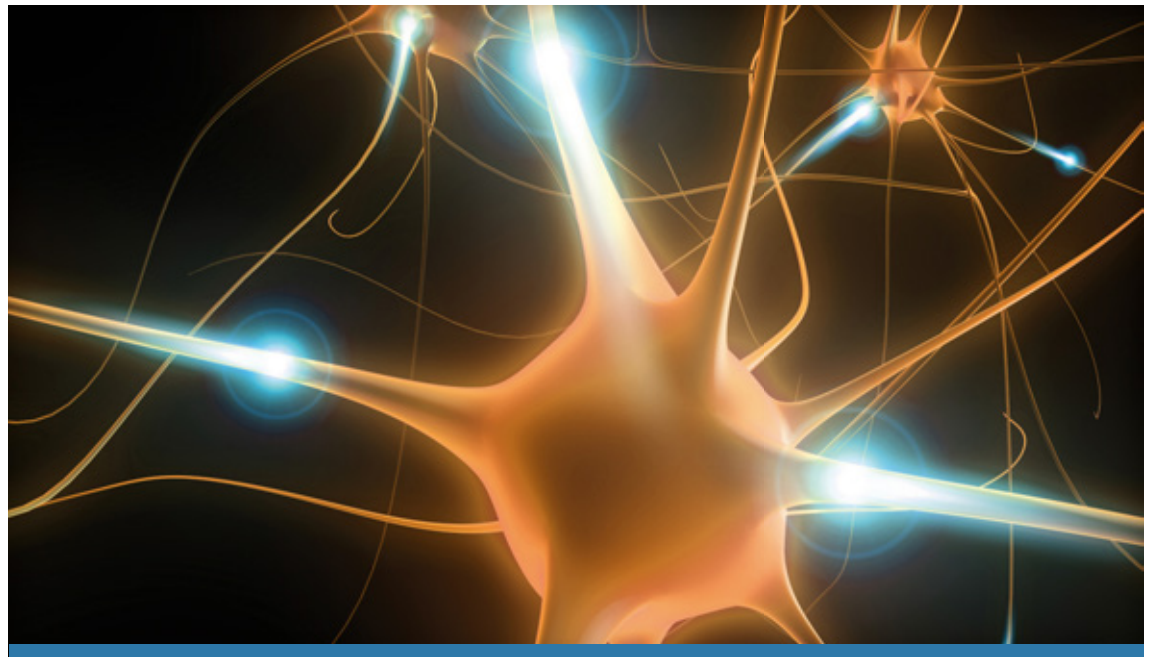
Society for Vascular Medicine

Refrain from percutaneous or surgical revascularization of peripheral artery stenosis in patients without claudication or critical limb ischemia.

Patients without symptoms will not benefit from attempts to improve circulation. No evidence exists to support improving circulation to prevent progression of disease. There is no proven preventive benefit, only symptomatic benefit.

Don't screen for renal artery stenosis in patients without resistant hypertension and with normal renal function, even if known atherosclerosis is present.

Performing surgery or angioplasty to improve circulation to the kidneys has



no proven preventive benefit, and shouldn't be considered unless there is evidence of symptoms, such as elevated blood pressure or decreased renal function.

American Academy of Neurology

Don't perform electroencephalography (EEG) for headaches.

EEG has no advantage over clinical evaluation in diagnosing headache, does not improve outcomes and increases cost. Recurrent headache is the most common pain problem, affecting 15% to 20% of people.

Don't use opioid or butalbital treatment for migraine except as a last resort.

Opioid and butalbital treatment for migraine should be avoided because more effective, migraine-specific treatments are available. Frequent use of opioid and butalbital treatment can worsen headaches. Opioids should be reserved for those with medical conditions precluding the use of migraine-specific treatments or for those who fail these treatments.

American Society for Clinical Pathology

Don't perform population based screening for 25-OH-Vitamin D deficiency.

Vitamin D deficiency is common in many populations, particularly in patients at higher latitudes, during winter months and in those with limited sun exposure. Over the counter Vitamin D supplements and increased summer sun exposure are sufficient for most otherwise healthy patients. Laboratory testing is appropriate in higher risk patients when results will be used to institute more aggressive therapy (e.g., osteoporosis, CKD, malabsorption, some infections, obese individuals).

Avoid routine preoperative testing for low risk surgeries without a clinical indication.

Most preoperative tests (typically a CBC, Prothrombin Time and Partial Prothromboplastin Time, basic metabolic panel and urinalysis) performed on elective surgical patients are normal. Findings influence management in under 3% of patients tested. In almost all cases, no adverse outcomes are observed when clinically stable patients undergo elective surgery, irrespective of whether an abnormal test is identified. Preoperative testing is appropriate in symptomatic patients and those with risks factors for which diagnostic testing can provide clarification of patient surgical risk.

American Academy of Allergy, Asthma & Immunology

Don't order sinus CT or indiscriminately prescribe antibiotics for uncomplicated acute rhinosinusitis.

Viral infections cause the majority of acute rhinosinusitis and only 0.5 percent to 2 percent progress to bacterial infections. Most acute rhinosinusitis resolves without treatment in two weeks. Uncomplicated acute rhinosinusitis is generally diagnosed clinically and does not require a sinus CT scan or other imaging. Antibiotics are not recommended for patients with uncomplicated acute rhinosinusitis who have mild illness and assurance of follow-up. If a decision is made to treat, amoxicillin should be first-

line antibiotic treatment for most acute rhinosinusitis.

Don't diagnose or manage asthma without spirometry.

Clinicians often rely solely upon symptoms when diagnosing and managing asthma, but these symptoms may be misleading and be from alternate causes. Therefore spirometry is essential to confirm the diagnosis in those patients who can perform this procedure. Recent guidelines highlight spirometry's value in stratifying disease severity and monitoring control. History and physical exam alone may over- or underestimate asthma control. Beyond the increased costs of care, repercussions of misdiagnosing asthma include delaying a correct diagnosis and treatment.

American Academy of Ophthalmology

Don't perform preoperative medical tests for eye surgery unless there are specific medical indications.

For many, preoperative tests are not necessary because eye surgeries are not lengthy and don't pose serious risks. An EKG should be ordered if patients have heart disease. A blood glucose test should be ordered if patients have diabetes. A potassium test should be ordered if patients are on diuretics. In general, patients scheduled for surgery do not need medical tests unless the history or physical examination indicates the need for a test, e.g., the existence of conditions noted above. Institutional policies should consider these issues.

Don't routinely order imaging tests for patients without symptoms or signs of significant eye disease.

If patients do not have symptoms or signs of significant disease pathology, then clinical imaging tests are not generally needed because a comprehensive history and physical examination will usually reveal if

CLINICIANS OFTEN RELY SOLELY UPON SYMPTOMS WHEN DIAGNOSING AND MANAGING ASTHMA, BUT THESE SYMPTOMS MAY BE MISLEADING AND BE FROM ALTERNATE CAUSES. THEREFORE SPIROMETRY IS ESSENTIAL TO CONFIRM THE DIAGNOSIS IN THOSE PATIENTS WHO CAN PERFORM THIS PROCEDURE.

eye disease is present or is getting worse. Examples of routine imaging include: visual-field testing; optical coherence tomography (OCT) testing; retinal imaging of patients with diabetes; and neuro imaging or fundus photography. If symptoms or signs of disease are present, then imaging tests may be needed to evaluate further and to help in treatment planning.

Don't order antibiotics for adenoviral conjunctivitis (pink eye).

Adenoviral conjunctivitis and bacterial conjunctivitis are different forms of infection that can be diagnosed by the ophthalmologist by clinical signs and symptoms, and if needed, by cultures. Antibiotics are useful for patients with bacterial conjunctivitis, particularly those with moderate to severe bacterial conjunctivitis. However, they are not useful for adenoviral conjunctivitis, and the overuse of antibiotics can lead to the emergence of bacteria that don't respond readily to available treatments. In cases of diagnostic uncertainty, patients may be followed closely to see if their condition resolves on its own, or if further treatment is required.

REENGINEERING HEALTH CARE: TOWARDS APPROPRIATE LEVEL OF CARE

Impact of clinical guidelines and financial incentives

Clinical practice guidelines usually advise physicians to screen earlier to detect occult disease. Many physicians believe that early diagnosis and subsequent intervention might improve health⁹. However, in order to prove that early diagnosis and intervention do improve health, physicians use surrogate end points, such as an improvement in the same test that diagnosed the disease in the first place. Detecting subclinical disease in some cases might do harm by leading to false labeling, causing inappropriate treatment, and making people who are otherwise well, feel sick⁹. Perhaps more importantly, the clinical practice guidelines rarely

take into account the long-term potential harms of decisions to broaden screening guidelines, and long-term cost considerations. Not only screenings are performed with widespread testing at younger ages, but the definition of disease is also shifting. In a recent US study, expanding the diagnosis of high cholesterol from 6.2 mmol/L to 5.2 mmol/L results in an 82% increase in individuals with a diagnosis of dyslipidemia, which represents more than 4.3 million people in the United States⁹.

Furthermore, through primary care reform initiatives, physicians in many jurisdictions are now paid pay-for-performance for many chronic diseases, which entails ordering more tests. These arrangements encourage more testing and more diagnosing, and treating more people. Financial incentives can foster or inhibit the appropriate use of health resources. Skeptics of pay-for-performance arrangements warn that particular care must be taken to ensure that any incentive-based system places a premium on making the most appropriate clinical decisions, instead of the least expensive ones⁷. Physicians' resistance or cooperation that is cognitively, rather than economically-based, raises a completely different set of incentives.

Patient-physician partnership

Many physicians often comply with patient requests for tests whether these are appropriate or not. Patients who come in requesting tests commonly want to be reassured. However, anyone rarely considers the cost consequences of such reassurance. Moreover, there is some evidence that higher levels of patient satisfaction are associated with ordering more tests and procedures or prescribing more medications¹².

Some researchers suggest that misunderstanding and miscommunication between physicians and patients explain a significant part of why unnecessary and even harmful tests and treatments are ordered⁸⁻¹⁴.

For example, many primary care physicians state that pressure from patients leads them to prescribe antibiotics when these are not indicated. Yet studies have shown that patients do not expect antibiotics nearly as often as doctors believe they do¹⁵⁻¹⁷. Patient satisfaction and understanding are closely related, and physicians can improve patient satisfaction by focusing on understanding. This can be achieved by acknowledging and validating patient concerns while providing factual information in an easy-to-understand manner¹⁸. Learning the communication skills necessary to enlist patient partnership in collaborative work is important. Clarifying that the risks may outweigh the benefits, and explaining the link between overutilization and cost increases, might prove essential in reengineering patient-physician relationship. Patient-centered approaches that discuss expectations and share information with patients have been shown to reduce antibiotic prescriptions in primary care¹⁹⁻²⁰.

Earlier diagnoses and more aggressive treatments appeal to most physicians to help patients dealing with uncertainty and to avoid any future lawsuits. In patients with chronic pain, or with enigmatic symptoms, tests and procedures buy time while waiting for the patient's body to heal on its own or to declare a serious illness. Because tests and procedures are available, physicians and patients use them. These tests might not contribute to diagnosis or treatment, but they make a patient believe that a physician is "doing something". One of the greatest challenges for physicians is to know when not to test. Perhaps physicians should "go back to the basics" of making a clinical diagnosis based on history and physical examination¹³. This would require reengineering of health care on part of both doctors and patients. Discussions about variation in patterns of care, appropriateness of care, and cost-effective ways of managing finite health care resources, should be carried out more often.

CONCLUSIONS

Central to the best practice of medicine becomes comparative-effectiveness research, including long term studies of clinical benefits and costs. Physicians must change practice patterns, through standard-of-practice guidelines, to practice in the most knowledge-based, least invasive, and less costly way. Physicians need to take a leadership role in teaching patients that more medicine is not better medicine, that costly efforts do not equal better health care. We need to explain to patients that new medical technology must be used with care and wisdom. ■

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Polish Pharmacoeconomic Society activities review



M. Szkultecka-Dębek, Polish Pharmacoeconomic Society

The Polish Pharmacoeconomic Society was actively involved in the organization of the ISPOR Chapters Forums during 15th ISPOR Annual European Congress. On 6th November the discussion was held with the involvement of the representatives of the Polish and Russian ISPOR chapters. The main topic was "HTA and reimbursement systems in Russia and Poland: common problems and solutions".

Due to differences in the healthcare systems between Russia and Poland and the new law on reimbursement having been recently implemented in Poland, the forum allowed for discussion about experience and challenges in both countries in reference to HTA and the reimbursement. The session was moderated by Professor Karina Jahnz-Rozyk the President of ISPOR Poland Regional Chapter and Professor Pavel Vorobiev the President of ISPOR Russia Regional Chapter.

The moderators and the speakers presented and discussed the use of HTA in Poland and Russia. They shared their experience in relation to risk-sharing agreements. Pricing of medicines and types of negotiations in their reimbursement systems were in the scope of the presentations as well. Special attention was paid to non-pharmaceutical technologies which criteria are needed to obtain reimbursement for a non-pharmaceutical technology, guidelines detailing the requirements and the use of HTA in the decision making process.

In December 2012 the Polish Pharmacoeconomic Society organized the 10th International Anniversary Conference of the Polish Pharmacoeconomic Society in Warsaw.

The main subject of the conference was "Pharmacoeconomics in Poland - summing up the decade". It was a unique opportunity to exchange experience with specialists from different countries participating in the event. Among others, the following plenary sessions took place: Ethical problems of financing orphan diseases presented by Professor Tomasz Pasierski, Vaccination against influenza in Poland - a public health problem by Professor Lidia Brydak, Pharmacy as an element of the health care system in Poland by Doctor Wojciech Giermaziak and The need of phase IV studies in obstructive pulmonary disease as a source for real life data discussed by Professor Karina Jahnz-Różyk. One of the plenary sessions involved invited guests from France, Ukraine, Romania, Latvia, Lithuania allowing for experience exchange in reference to reimbursement systems, the use of HTA and the need for real world data. There were three educational workshops dedicated to a network analysis as a tool for the synthesis of existing clinical data, to Real Life Information based MCDA and to the registries of medical data in terms of planning, implementation and analysis.

Keywords:
Polish Pharmacoeconomic Society

JHPOR, 2013, 1, 152-153

THE HEALTH RELATED QUALITY OF LIFE SECTION INDEPENDENTLY OF WORKING ON THE DICTIONARY OF QOL TERMINOLOGY, ORGANIZED IN MARCH THE FIRST EDUCATIONAL SESSION ABOUT QUALITY OF LIFE, CALLED "WIOSENNE SPOTKANIE EDUKACYJNE SEKCJI JAKOŚCI ŻYCIA POLSKIEGO TOWARZYSTWA FARMAKOEKONOMICZNEGO" (SPRING EDUCATIONAL MEETING OF THE QUALITY OF LIFE SECTION OF POLISH PHARMACOECONOMIC SOCIETY).

During the Conference, all the Pharmacoeconomics Society Sections presented their detailed annual reports and main activities in 2012:

Epidemiology and Cost of Disease Section organized a debate on technical capabilities, limitations and procedures for accessing cost data collected by public authorities.

Health Technology Assessment Section presented their report from the HTA guidelines revision and Professor Jacek Sptawiński discussed the problem of an off-label use of the drugs in Poland.

The Health Related Quality of Life Section (HRQoL) presented the report of activities. Work on a dictionary of quality of life and utility related terms will be continued in 2013. The implemented methodology for the dictionary preparation was presented by Doctor Monika Szkultecka-Dębek. Doctor Dominik Golicki presented new trends in quality of life and health states utilities' studies.

The Therapeutic Programs and Pharmaceutical Care Section (TPPC) changed the name due to broadened scope of areas of interest. The new name of the Section is Therapeutic Programs, Pharmaceutical Care and Pharmaceutical Law Section (TPPCPL).

The annual report was presented by Doctor Mariola Drozd. Doctor Magdalena Rdzanek presented the approach to financing of pharmaceutical care across the world.

After the Conference, the elections of the new Board were held at the General Meeting of the Polish Pharmacoeconomic Society.

The new Board will be in place for the period December 2012 - December 2016 and consists of:

*Doctor Joanna Lis - President
Professor Karina Jahnz-Różyk – Subsiding President
Doctor Maciej Niewada – President elect
Anna Zawada - Secretary
Professor Witold Owczarek- Treasurer
Professor Marcin Czech – Board Member*

2013 started very actively at the Society.

The Therapeutic Programs and Pharmaceutical Care section (TPPCPL) finalized the work on biosimilar products reimbursement regulations review in different countries and started working on costs assessment of the adverse events which could potentially be observed during treatment with products used in the Drug Programs. The methodology and best approach were agreed and the first phase of the project has already been finished. The project will continue throughout the whole 2013 and is focused on adverse events identified within the Programs grouped by disease areas.

The Health Related Quality of Life Section independently of working on the dictionary of QoL terminology, organized in March the first Educational Session about quality of life, called "Wiosenne Spotkanie Edukacyjne Sekcji Jakości Życia Polskiego Towarzystwa Farmakoeconomicznego" (Spring educational meeting of the Quality of Life Section of Polish Pharmacoeconomic Society).

An expert on quality of life from Poland, Doctor Joanna Mazur familiarized the meeting participants with the DISABKIDS questionnaire sharing the knowledge and experience from translation of the questionnaire into Polish. The discussion was around methodology of translation process, difficulties and availability of the questionnaire. Doctor Monika Szkultecka-Dębek explained and clarified the differences between quality of life and utilities and she also presented the methods to calculate utilities and their possible practical use. Doctor Patrycja Grabowska presented the questionnaires used in pulmonary diseases and Doctor Dominik Golicki brought the practical aspects of using different EQ5D questionnaires closer to the participants. Also the results of the Master's thesis of Jan Sieluk related to the use of QoL questionnaires in cardiology were presented.

Due to the very warm welcome of the session the HRQoL section will consider the organization of the next educational session in autumn 2013. ■

Early medical technology assessments of medical devices and tests



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Keywords:
diagnostic tests, medical devices, medical technology assessment, modelling

DOI: 10.7365/JHPOR.2013.3.2
JHPOR, 2013, 1, 26-37

ABSTRACT

Background: Classic medical technology assessment (MTA) is typically conducted at the end of the development process to assess the overall value of a drug, medical device or diagnostic test. Recently, researchers and manufacturers have recognized that MTA in the early phases could help to make better decisions about further development, the regulatory and reimbursement strategy, and allocating public support for new technologies. The aim of this study is to introduce the most commonly used methods in early MTAs of emerging technologies and examine which methods have been used in the early MTAs of medical devices and tests.

Methods: An explorative literature review.

Results: Classic MTA supports particularly regulators and payers in market and reimbursement decisions, while early MTA primarily supports decisions of manufacturers about investments and strategies regarding further devel-

opment as well as decisions by policy-makers about public support. Important methods that can be used in early MTAs of medical devices include early health economic modelling, the headroom method, the Bayesian analytical framework, clinical trial simulation, multi-criteria decision analysis and value of information analysis. Only a few articles have been described early HTAs of devices and tests and most of these have used economic modelling, sometimes in combination with other methods.

Conclusions: Various methods can be applied in performing early MTA. While early MTA follows the same steps as classic MTA, repeated assessments and sensitivity analysis play a more significant role.

INTRODUCTION

Classical medical technology assessment (MTA) is focused on the analysis of the costs and benefits of a technology from various perspectives, such as economic, clinical or policy perspective ¹. The definition of MTA

is the analysis of the implications of a medical technology in terms of its safety, efficiency, effectiveness, accessibility and equity, with the aim of supporting appropriate use of medical technologies by improving input to decision-making in policy and practice². These analyses are usually conducted at the end of the development process of a medical technology, typically after large clinical trials, when clinical and cost-effectiveness data are available¹. The rationale is that a full and proper assessment can be made only when enough data are available. The main goal of classical MTA is to support health policymaking about market approval or reimbursement of a technology³. However, the methods employed in MTA can be used in other ways. Some researchers have shown that similar methods can be conducted earlier in the development of a technology. The relevance of early MTA is that it could help to allocate public support effectively. Perhaps more importantly, from the industry perspective it can also inform research and development decisions to increase the chance of later market approval and reimbursement⁴. Relevant information acquired in an early stage can lead to changes that will improve the device during the development process in order to produce the most beneficial medical technology for society¹. The main difference between classical and early MTA is that classical MTA is conducted to support decision-making by regulators, payers and patients about the overall value of a technology, while early MTA helps manufacturers and investors to decide about the management of the development, as well as their regulatory and reimbursement strategy¹.

Different tools are available to perform early MTA studies, including early health economic modelling, clinical trial simulation and multi-criteria decision analysis⁴. However, the number of published articles on this topic is very limited. The aim of this study is to describe the most commonly used methods in early MTAs of emerging technologies and examine which methods

have been used in early MTAs of medical devices and tests.

MATERIALS AND METHODS

Since the research question of the difference between early MTA studies of medical tests and other technologies was too specific and focused to employ one specific searching keyword, an explorative literature research was conducted. The following databases were used: PubMed, The Cochrane Library, Embase, and Google Scholar by various keywords and MESH terms (health technology assessment, early technology assessment, early health technology assessment, medical technology assessment, economic evaluation, early stage, emerging technology, drugs, medical devices, and medical tests). In addition, the reference lists of relevant publications were examined. Since the literature base on this topic is very limited we did not make any restrictions about the year of the publication, but search only for articles published in English.

RESULTS

Differences between classical and early medical technology assessments

Classical MTA is usually conducted at the end of the development, when data is available about efficacy and safety, which are usually derived from clinical trials. At that stage the technology is ready to be introduced to the market and the main investments have already been made. If the technology does not obtain market approval or reimbursement, the manufacturer or the pharmaceutical firm can face serious financial consequences¹. In the last decade, many parties have recognized that economic analyses can be conducted earlier in the development process to obtain optimal future results. This would help the industry to produce technologies which are going to get market approval and reimbursement from the national health insurers. However the basic steps of classical and early technology assessment are the



same, such as decisions about the design of the study, measuring and valuing costs, measuring and valuing benefits, discounting, sensitivity analysis, which plays a more important role in early MTA, and finally, applying a decision rule, e.g. calculating an incremental cost-effectiveness ratio (ICER)⁵. It is difficult to define the cut-off point between classical and early MTA, which is before the technology is introduced to the market (Figure 1).

biggest impact on cost-effectiveness estimates and reduce uncertainty with clinical evidence. In the late stage, all data from clinical studies is available and much less uncertainty plays role. These studies are already considered as classical MTA and designed to inform market approval and reimbursement decisions.

Economic evaluations, or cost-effectiveness analyses, represent a frequently

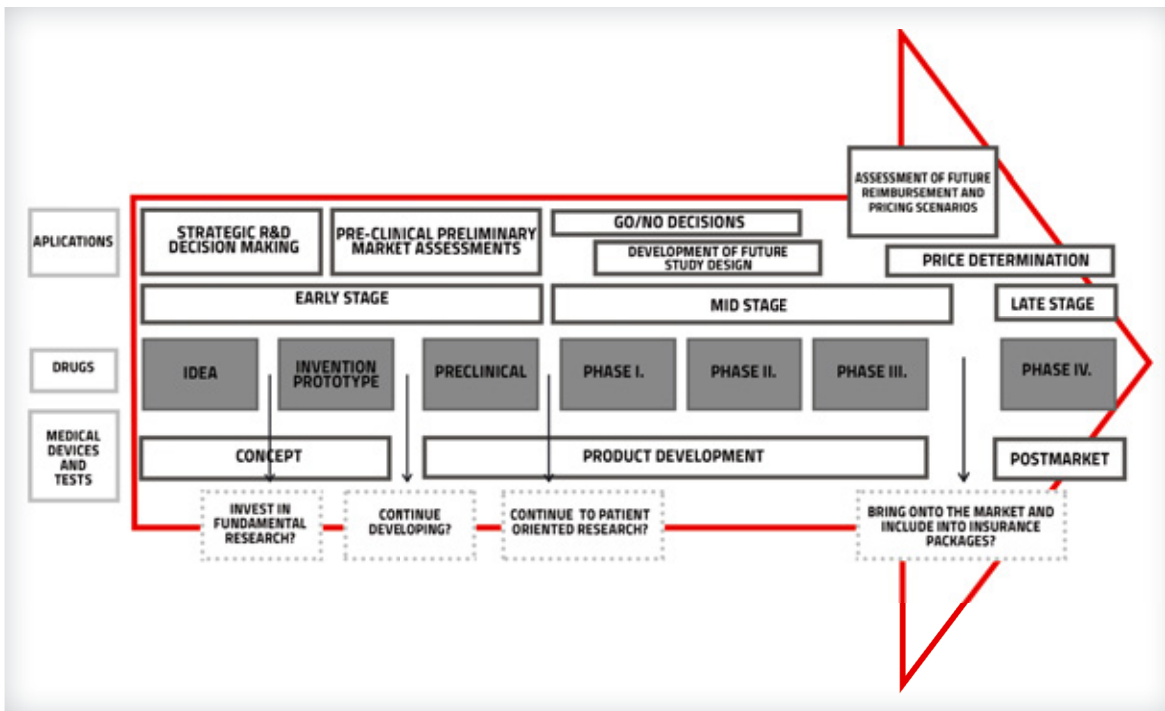


Figure 1. Medical technology development

Figure 1 shows how technology can develop over time, starting first as an idea or concept, which is converted into a prototype that it later studied using steadily more rigorous methods. According to Vallejo-Torres et al. the development process of a medical device can be divided into three stages: early, mid and late stage⁸. Since clinical and economic data are not yet available in the early stage, MTA has to rely on assumptions about these parameters⁸. In the mid stage, uncertainty about the effects and costs still plays a role, but some evidence from pre-clinical studies is available. The goal is to identify the parameters which have the

used component in classical HTAs but can, of course, be used in early HTAs. According to Hartz and John there are six different applications of an early economic evaluation. These are shown in the first row of Figure 1 and are listed below⁴.

- In the case of strategic R&D decision making, economic evaluation helps the manufacturer to avoid investing in potentially unsuccessful products.
- In pre-clinical preliminary market assessments, a prototype of the product is already available and the manufac-

turer or the investor would like to know what the potential target population, epidemiological factors, costs and effects are. For this purpose, they need data about the cost-effectiveness of the current therapies, because the less effective the available technologies, the more likely the new technology will be cost-effective.

- Go/no go decisions need to be made at various points in time. Obviously the data available needs to be used optimally and the amount of data will change over time. For example, data from market assessments must be used properly (and perhaps together with an economic model) to decide whether to continue developing the technology.
- Early economic evaluations can also help to design future trials. Usually, this means the design of a phase III trial, which is performed to determine the clinical effectiveness of the medical technology. The identification of the input parameters that have the most impact on cost-effectiveness is a crucial issue. It could contribute to a better resource allocation and to decide what kind of methods and studies are needed during the trial.
- For assessment of future reimbursement and pricing scenarios, economic evaluation under different scenarios is carried out. These data could be useful for policy makers about the emerging technology for future planning.
- For price determination many types of information besides the results of an economic evaluation are needed, such as consumer willingness-to-pay (WTP) and market characteristics. However early economic evaluation or MTA is crucial for deciding if the new technology will be profitable in a given country or market. It could also help to identify the level of efficacy or effectiveness that needs to be obtained by the new technology for a given price⁴.

ent questions raised by the manufacturer and investor in the different stages of the development process. These questions can be answered using early MTA studies⁹.

In sum, early MTA (including economic evaluations) can be applied in different ways to plan the future development of a technology. It therefore has the potential to help the manufacture to produce a product that is profitable for them, beneficial for the patient and affordable and cost-effective for payers.

METHODS USED IN EARLY MEDICAL TECHNOLOGY ASSESSMENT

This section contains a non-exhaustive list of methods that can be used in early MTA studies of medical devices and diagnostic tests. This list is based on what was found in the literature regarding early MTA in general.

EARLY HEALTH ECONOMIC MODELLING

Modelling is a frequently used technique in health economic evaluations, since they are simplified representations of real-life and therefore easy to use¹². They can be used in many ways, such as converting efficacy to effectiveness or short-term results to long-term results¹³. Just as modelling is commonly used to perform economic evaluations, so can modelling be used to facilitate an early economic evaluation. Moreover, early modelling requires the same inputs as late models⁴ and both rely on the same methods¹³. According to Annemans et al., it can function as an input into go/no go and priority setting decisions of the manufacturer, since it is able to predict the future economic value of the emerging technology. Early modelling can help to focus on potentially more cost-effective technologies and it can also serve with information for design further development. One special problem of early models is that a lot of uncertainty plays a role, due to a very limited data about the new technology and the inputs of the model¹³. Therefore, many scenarios have to be modelled during an early MTA.

THE HEADROOM METHOD IS A RELATIVELY SIMPLE THRESHOLD APPROACH DEVELOPED AT THE UNIVERSITY OF BIRMINGHAM THAT ESTIMATES THE MAXIMUM AMOUNT THAT A TECHNOLOGY COULD COST AND YET STILL BE CONSIDERED COST-EFFECTIVE

The last row of Figure 1 shows the differ-

HEADROOM METHOD

The headroom method is a relatively simple threshold approach developed at the University of Birmingham that estimates the maximum amount that a technology could cost and yet still be considered cost-effective⁶. According to the developers, “the headroom method is an approach to help avoid misguidedly investing in those technologies that will never be cost-effective”⁶. The main question to be answered is “Would it be cost-effective if it works as well as one would hope?” and the user can determine the range of prices at which the new technology would be cost-effective versus the comparator (e.g., current care).

THE HEADROOM METHOD HAS THREE STAGES:

1. Strategic considerations, or structuring and defining the business problem situation.
2. Defining the clinical problem, or defining all conditions of the current treatment, strengths and weaknesses, as specifically as possible. This information will enable calculation of the effectiveness gap (maximum health gain in quality-adjusted life-years, QALYs) (maxΔQALY) assuming different scenarios (optimistic, realistic, pessimistic, etc.).
3. Headroom analysis, where headroom is defined by calculating the maximum incremental cost of the new technology versus the comparator by multiplying the maximum health gain by the willingness-to-pay to gain one QAL (max ΔCost = WTP threshold*maxΔQALY).

The headroom method can help to make investment decisions without building a complex model with a lot of uncertainty. It is a useful tool for investors and manufacturers, because it provides information about the possible price in the future and the possible profit⁶. This tool could be used throughout the entire development process, since updating the inputs and recalculating the headroom will lead to better predictions

about the potential cost-effectiveness.

There are also limitations of the headroom method. One important one is that it only works when a payer uses an explicit WTP threshold, such as the GBP 20 000 and GBP 30 000 thresholds in the UK. However, most countries do not have such an explicit threshold. Secondly, it only focuses on cost-effectiveness, when in fact reimbursement decisions may be based on other factors.

THE BAYESIAN ANALYTICAL FRAMEWORK

Bayesian statistics have been increasingly used in health economic evaluations over the past years. It is certainly a useful tool for early MTAs since it allows evaluations to be performed repeatedly as the knowledge base evolves⁴. Spiegelhalter et al. define the approach as “the explicit quantitative use of external evidence in the design, monitoring, analysis, interpretation and reporting of a health technology assessment.”¹⁶. It is a mathematical-statistical mechanism where a prior assumption about a parameter, usually a probability distribution, is modified by the new information. The two main questions that can be answered by the Bayesian approach are “how might new evidence change what we currently believe?” and “if we continue the study, what is the chance we will get a significant result?”¹⁶. Spiegelhalter and his colleagues have listed several advantages and disadvantages of this approach in a thorough review about the Bayesian methods. The main advantages are that all evidence regarding a specific problem can be taken into account, that potential biases can be explicitly modelled, and the outputs can be used as inputs in a later health economic model. However, the most important disadvantage may be that specification of expected utilities is difficult and may require many assumptions about the use of the new technology¹⁷.

Since both diagnostic tests and medical devices are fast changing technologies, this approach could be a very useful tool for assess-

ing their likely cost-effectiveness. According to Vallejo-Torres et al. the Bayesian Analytical Framework could help the development of new technologies in three ways:

- Enhancing the estimation of likely cost-effectiveness in the investment decision process, and avoiding investments in a technology that could never be cost-effective,
- Helping companies to prioritize and make the choice between competing possibly cost-effective ideas or prototypes,
- Identifying in the early stages of development those parameters that have the largest impact on the likely cost-effectiveness of the product.

The suggestion by Vallejo-Torres et al. is to start the development process with a simple health economic analysis and de-

CLINICAL TRIAL SIMULATION

Clinical trial simulation (CTS) is a technique which synthesises available knowledge about the technology under development using mathematical relationships and models¹⁸. It can estimate different efficiency and tolerability profiles before clinical data are available¹⁸. It makes it possible to explore key assumptions before actual studies using human subjects and perform virtual studies to identify any weaknesses or limitations of the proposed study design^{19,20}. Its use can therefore help manufacturers to minimize the duration and costs of technology development²¹. The aims of CTS are to maximise the use of information from previous phases of the development and thereby improve trial protocols, maximize the probability of meeting the targets of the trial and maximise the results that a trial can yield.



ACCORDING TO VALLEJO-TORRES ET AL. THE BAYESIAN ANALYTICAL FRAMEWORK COULD HELP THE DEVELOPMENT OF NEW TECHNOLOGIES IN THREE WAYS:

- Enhancing the estimation of likely cost-effectiveness in the investment decision process, and avoiding investments in a technology that could never be cost-effective,
- Helping companies to prioritize and make the choice between competing possibly cost-effective ideas or prototypes,
- Identifying in the early stages of development those parameters that have the largest impact on the likely cost-effectiveness of the product.

velop it further every time, when more data becomes available. They state that the Bayesian approach would be more feasible in the mid-stage of medical device development and it combines the new, but limited, data with the prevailing beliefs at that moment⁸.

It can help to improve efficiency and also supply information that would otherwise not be available by other means⁴.

Clinical trial simulation is typically done by computer simulation, where the re-

al-world situation is mapped and then the simulation is used to predict and describe the situation and investigate the assumptions. The simulation should capture all crucial aspects of the real world to help manufacturers draw some conclusions about further development design²².

Most of the literature on CTS is about drug development, since clinical trials are much more important in the regulation and reimbursement policies for drugs than they are for medical device¹⁸. In drug development, CTS can help with dosage optimization, adaptation of a trial design and decisions about the optimal sample size and planning of the Phase III trial⁴. One interesting type of CTS is longitudinal stochastic modelling, which is a simulation technique that can describe individual behaviours. This could be important in assessments of medical devices and tests, due to learning effects and uncertainties about the usage of the device²⁰.

MULTI-CRITERIA DECISION ANALYSIS (MCDA)

Multi-criteria decision analysis (MCDA) is a method to support decisions between two or more discrete alternatives. It helps decision-makers in data organization and transparent decision making⁹. It has many validated methods, including analytic hierarchy process (AHP), conjoint analysis and contingent valuation. However, AHP is the only one that has been applied in early MTAs of medical devices. Further research about the usability of other MCDA methods in early MTAs would be valuable.

The analytic hierarchy process is a descriptive measurement theory which derives dominance priorities from a series of pairwise comparisons of homogeneous or similar elements on the basis of a common criterion or attribute, and then scales them using a hierarchy structure²³. This process make it possible to include patient preferences beyond clinical effectiveness as well as other criteria not included in other approaches like economic evaluations.

Therefore, its relevance for medical devices and diagnostic tests is noteworthy, since these other factors may play an important role in the uptake and cost-effectiveness of the technology²⁴. Since its results can be used as inputs for health economic modelling and since it includes patient preferences and additional effects of the medical technology, this method could be used by both manufacturers, to make go/no go decisions about further development, and payers about market approval or reimbursement.

Hummel et al. has used AHP to elicit expected relative diagnostic effectiveness, patient comfort and safety data, and then converted these relative priorities to absolute estimations to compare a new diagnostic method for breast cancer (photo-acoustic mammography, PAM) with the current practice (magnetic resonance imaging, MRI)²⁴. They then used these data as input in a health economic model (Markov model). They concluded that AHP can support the assessment of an emerging technology when clinical evidence is not available. However, they also added that the method has various methodological challenges, such as the best way to convert the relative AHP-derived priorities to absolute estimations and add weights to the additional criteria.

VALUE OF INFORMATION (VOI) ANALYSIS

The underlying principle of value of information (VOI) analysis is to compare the costs and benefits of obtaining additional information, or in other words, to assess the value of investing in further research⁴. It can answer different questions, such as "Should additional information be collected to better inform that decision?"²⁵. The aim of the analysis is to calculate the expected value of perfect information (EVPI), which reflects the maximum possible payoff from additional research, since making wrong decisions has an opportunity cost and extra information is valuable if it reduces the chance of a wrong decision^{18,26}. If the EVPI

Table 1. Summary of early MTA studies

Article	Diagnostic Test (DT) /Medical Device (MD)	Disease speciality	Aims	Results	Potential Results		
					Incremental costs	Incremental effects	Incremental C/E
Dong & Buxton(29)	(MD) Computer-assisted total knee replacement	Orthopaedy	Compare the cost-effectiveness of computer-assisted total knee replacement with the conventional manual method, using Markov modeling and Cohort Simulation methods.	Nine Markov health states were identified and a 30-year Cohort simulation was carried out. Compared to the conventional total knee replacement using computer-assisted surgery is a cost-saving technology, with small increase in effects. The model suggests that investing in CAS systems may reduce costs for health care.	-	+	favourable in the first 2 years, then dominant
Gaultney et al. (34)	(DT) Companion Diagnostics	Oncology	Conduct a cost-effectiveness analysis to assess the potential value of companion diagnostics in Chronic myeloid leukaemia (CML).	Companion diagnostics strategy in CML, compared to the current care (no testing) is both potential cost saving and health gaining strategy in a 2 years time horizon.	-	+	dominant in the base-case scenario
Hummel et al. (24)	(DT) Photo acoustic mammography (PAM)	Oncology	Using the Analytic Hierarchy Process with Health Economic Modeling for early MTA to elicit inputs for a Markov model and data about the patient preferences beyond clinical effectiveness.	PAM could be more effective than MRI, the currently used breast cancer imaging technique and this could lead to better cost-effectiveness and positive decisions about market approval or reimbursement. Especially, if criteria like patient comfort and risks are relatively more important than currently.	+	+	favourable
McAteer et al. (30)	(MD) Tissue Engineered Bladder tissue	Urology	Calculate the cost-effectiveness headroom for engineered bladder and demonstrate the usefulness of the Headroom Method.	The Headroom Method could help to make investment decisions without building a complex model with a lot of uncertainty. The headroom (maxCost) = €34 000, but even if it seems to be desirable the profit would be volume dependent.	+	+	favourable, but profit would be volume dependent
	(MD) Tissue Engineered Urethral tissue	Urology	Calculate the cost-effectiveness headroom for urethral tissue and demonstrate the usefulness of the Headroom Method.	The headroom for engineered urethral tissue is €605, which is too low, there is no prospect for producing this medical device profitably.	+	+	non-favourable, not profitable at this price
O'Prinsen et al. (15)	(MD) Home Rehabilitation System	Neurology	Calculate the (likely) cost-effectiveness ratio of a Home Rehabilitation System for stroke patients in China, and compare it with 3 other scenarios.	Compared to hospitalisation with rehabilitation, the technology is less cost-effective, but this type of care is not available for most people in China, due to several reasons. The technology offers a cost-effective alternative for stroke patients compared to no rehabilitation or hospitalization without rehabilitation scenarios.	-/+	-/+	less favourable/favourable/favourable
	(DT) Prostate-specific antigen (PSA) blood test	Oncology	Estimate the potential value of a prognostic test for prostate cancer.	A prognostic test, which could distinguish between high risk and low risk groups for disease progression would offer more cost-effective treatment.	N.S.	N.S.	favourable
Postmus et al. (31)	(DT) novel biomarker	Endocrinology	Perform an initial assessment of the conditions under which using the new biomarker technology is likely to become cost-effective.	If the costs of measuring the novel biomarker are expected to be low, there still seems to be room for improvement in the predictive performance of the existing model.	+	+	favourable

Table 2. Methodology of early MTA studies

Article	Medical Device (MD) /Diagnostic Test (DT)	Financed by	intended for/used by	Methodology													
				Early Health Economic Modeling	Headroom Method	Bayesian Analytical Framework	Clinical Trial Emulation	Multi-Criteria Decision Analysis	Value of Information Analysis	Strategic R&D Decision Making	Pre-clinical/primary market assessment	Go/no go decisions	Development of future study design and pricing scenarios	Assessment of future reimbursement	Price Determination		
Dong & Buxton(29)	(MD) Computer-assisted total knee replacement	Part of the MATCH Project, funded by the EPSRC and other sponsors	Industry, third party payers	x		x					x	x					
Gaultney et al. (34)	(DT) Companion Diagnostics	Unrestricted grant from PamGene	Manufacturer (various stakeholders)	x							x	x	x				
Hummel et al. (24)	(DT) Photo acoustic mammography (PAM)	Not stated	Manufacturer and Policy maker	x			x				x	x					
McAteer et al. (30)	(MD) Tissue Engineered Bladder tissue	EU's Systems Approach to TE Processes and Products (STEPS), EPSRC's Multidisciplinary Assessment of Technology Centre for Healthcare (MATCH), Regenerative Medicine	Manufacturer	x							x	x	x				x
	(MD) Tissue Engineered Urethral tissue			x							x	x	x				
O'Prinsen et al. (15)	(MD) Home Rehabilitation System	Philips	Industry	x								x		x			
	(DT) Prostate-specific antigen (PSA) blood test	Not stated	Industry	x								x	x				
Postmus et al. (31)	(DT) novel biomarker	Center for Translational Molecular Medicine (CTMM), TRIUMPH, Predict, PCCM, Netherlands Heart Foundation, Dutch Diabetes Research Foundation, Dutch Kidney Foundation	investors and analysts	x		x						x	x				

is higher than the cost of additional research, reducing uncertainty surrounding cost-effectiveness by performing research is beneficial^{18,27}. EVPI reaches its maximum when the uncertainty is the highest about

whether to continue or terminate the research and development of the new technology²⁸.

Originally, the expected cost of making

decisions under uncertainty is equal to the EVPI, which is the maximum a decision-maker would be willing to pay to eliminate uncertainty. This can be derived from the probability that the decision will be wrong and the possible consequences of this wrong decision²⁶. Additionally, partial EVPI can be calculated to focus the further research only on those parameters which have the most influence on the results²⁸. By estimating the partial EVPI we can see which parameters contribute to the uncertainty the most²⁶.

Miller has described VOI analysis for drug development, but we can also apply his findings to other medical technologies¹⁸. He concluded that VOI analysis is relevant in early MTAs for drugs, since the major cost of drug development is spent on obtaining additional information about the drug.

EARLY HTA STUDIES OF MEDICAL DEVICES AND TESTS

Six publications describing early medical technology assessments were found in the literature. The six articles describe the assessment of eight technologies, four of which were diagnostic tests and four of which were other types of medical devices. *Table 1* summarizes the aims and results of these studies. The studies focused on technologies in different medical specialties, the most frequent of which was oncology (n=3). In most cases, the primary aim of the study was to estimate the potential cost-effectiveness of the new technology. Interestingly, only one of the eight studies (tissue engineered urethral tissue) concluded that the technology was not likely to be cost-effective.

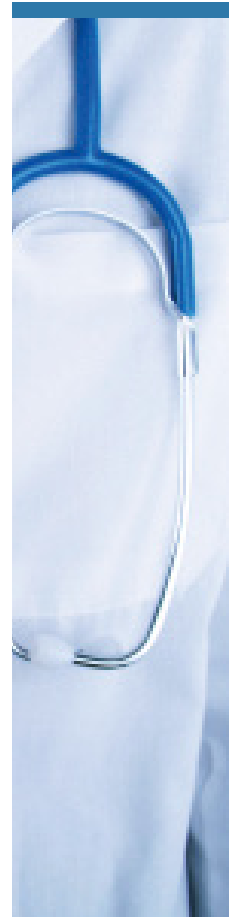
Table 2 provides more details about the studies and also shows the methodologies that were used. All studies were conducted to yield information for use by manufacturers, although some mentioned other users as well such as policymakers and investors. Most studies used modelling techniques, sometimes along with other methods such as MCDA or CTS. This combination meant

that a model served as the core of the study and that the other methods provided input data for that model. Regarding the application (or general purpose) of the study, most studies were performed as part of a pre-clinical preliminary market assessment or were performed to support a go/no go decision. For price determination only the headroom method was used, but we can see, that most of them were intended to support different decisions^{14,15,24,29-31}.

DIFFERENCES BETWEEN MEDICAL TECHNOLOGIES

The aim of this study was to examine the methodology of early MTAs of medical devices and tests that could be used and have been used in the past. We can distinguish between three kinds of medical technologies: drugs, medical devices and diagnostic tests.

A possible definition of diagnostic tests is technologies which do not interfere in the treatment, but only provide information to the clinician about the patient and disease progression³². Their value can be measured by their sensitivity and specificity, but as Fineberg perfectly summarized: "The ultimate value of the diagnostic test is that difference in health outcome resulting from the test: In what ways, to what extent, with what frequency, in which patients is health outcome improved because of this test?"³⁴. Most of their impact is indirect and the link between the performance of the test and health benefits of the patient is complex, although one should not forget that the testing of patients can also have its risks or side-effects^{12,33}. For example, in the case of a diagnostic test used to establish a diagnosis, several parameters have to be considered, including disease prevalence (prior probability), diagnostic accuracy (sensitivity, specificity), any direct effects of testing, and the benefits and risks of subsequent treatment on the diseased and non-diseased groups (both correctly and incorrectly diagnosed patients). The direct effects of a medical test are the testing-induced emotional,



cognitive and behavioural changes and the complications of a dangerous test¹².

In that sense, it could be argued that both early and classical HTAs of tests are harder to perform than other HTAs. Moreover, tests can be used in various ways, for a variety of disease and purposes. Many so-called diagnostic tests are not actually used for diagnosis per se, but for disease susceptibility testing, prognosis, selecting therapies, treatment response monitoring, monitoring for disease recurrence, etc. This diversity can make it hard to define the target condition of the test and the comparator in the economic evaluation³³.

The methodology of assessing the value of drugs is quite well defined. In stark contrast, it is not always clear how much evidence of effectiveness is needed in the case of medical devices and tests³⁶. Double-blind randomized controlled trials are part of the development process of pharmaceuticals and the data obtained from those studies serve as an input for MTAs. In the case of diagnostic tests, and also some medical devices, it can be more difficult to design such a study, and MTAs of these technologies are not always supported by RCT data³². Some RCTs of tests may require larger sample sizes and well-defined protocols that link testing, results and treatment decisions, since we need to evaluate all the effects and future consequences³³.

Taken together, there are essentially no overall differences in the methodology of early MTA of different technologies. However, upon closer inspection, one could imagine that there are nevertheless some factors that could lead to differences in the ways to perform early MTA. For example, since there are differences in the requirements for approval and reimbursement, one could expect differences in the choice of methodology and the way in which a methodology is applied. In that way, rational goal-directed approaches can well lead to different choices.

DISCUSSION

The aim of this study was to introduce the most commonly used methods in early MTAs of medical devices and tests. Various methods have been described in the literature for use in early MTA of drug and devices. We described six methods: early health economic modelling, headroom method, Bayesian analytical framework, clinical trial simulation, multi-criteria decision analysis and value of information analysis. The methods examined here can all help to make better decisions about whether and how to further develop medical technologies. They are not only relevant to drugs but also to medical devices and tests. Of these methods, one could argue that the methods are complementary since their purposes are not identical. For example, early health economic modelling can be viewed as an engine which can use the results from other methods (e.g., the analytic hierarchy process) to perform various calculations beyond just cost-effectiveness analyses. In fact, a model would be able to support clinical trial simulations or value of information analyses. Viewed in that way, it is not necessary to see the different methods as isolated options but rather as a set of tools that can be used together to perform early HTA. Each of the methods has its strengths and weaknesses. For example, the headroom method is a quick and easy model, which helps to make investment decisions without building a complex model. However it only works when explicit WTP thresholds are used by the payer.

A literature search only identified six publications describing early MTA studies of medical devices and tests. They described the assessments of eight technologies (four diagnostic tests and four other types of medical devices). Published studies have so far not utilised all of the available methodologies. While early MTA follows the same steps as classical MTA, repeated assessments and sensitivity analysis play a more significant role.

The limited number of studies can be explained by the fact that early MTAs are rarely published because they primarily support internal decisions by a company¹³. This means that a literature review will always have its limitations and that additional research will have to involve interviews with the different stakeholders to explore what methods they use in the early stages of technology development. Only then will it be possible to see what is done now and to explore what improvements can be made. In the case of medical devices and diagnostic tests there are special features which may determine the methodology of early MTA, such as the learning curve phenomenon or their sometimes indirect impact on patient recovery. While more research on the differences between medical devices and tests would also be valuable, one could argue that the diversity amongst both devices and tests is so great that a comparison between the early MTA of devices versus that of tests is only a partial solution. Instead, it may be possible that the most appropriate early MTA approach might vary from technology to technology, amongst both devices and tests.

In conclusion, the concept of early MTA represents a new way to evaluate technologies that should receive more attention in the future. Early MTA can help to reduce the time and investments required in developing new technology but also help to develop more effective and cost-effectiveness medical technologies. ■

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Availability of pneumococcal vaccination programmes in Europe.

An overview of funding mechanisms



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Keywords:
national vaccination programmes, access to vaccines, pneumococci, Europe, financing

DOI: 10.7365/JHPOR.2013.3.1
JHPOR, 2013, 1, 38-49

ABSTRACT

Increasing antibiotic resistance is a global problem. Vaccinations is one of the best solution to reduce the burden of infectious diseases. Despite universal access to antibiotics, pneumococci still are one of the major causes of morbidity and mortality in both developing and developed countries.

Criteria for making the decision on financing immunisation are similar in many countries and include identifying the target groups based on epidemiological risk, the clinical efficacy and safety of a vaccine, and the economic aspects of the implementation of vaccination. To reduce the risk of diseases caused by *Diplococcus pneumoniae* pneumococcal conjugate vaccine (PCV) is included in national immunisation programmes in most countries.

The paper describes international differences of organisations and funding mechanisms for pneumococcal vaccination. The analysis covered 34 countries in Europe. The study analyzed availabili-

ty and type of vaccines used in vaccination programmes, children in the target age group to vaccination, vaccination financing, level of co-payment to vaccination for children and mechanism of purchasing vaccines.

In most European countries, PCV is included in national immunisation programmes. The differences regard the availability of two types of conjugate pneumococcal vaccines (10-valent and 13-valent). The method of recommending vaccines, mechanism of purchasing and funding in different countries varies.

INTRODUCTION

The observed rapid technological progress in medicine is a continuous source of novel products, launched onto the market with newer and newer vaccines including combination vaccines. The availability of prophylactic vaccination programmes varies among European countries, being sometimes limited, while their selection depends on health-care policy decisions in particular countries. Also the funding systems of vaccines are differentiated. Under certain universal vaccina-

IN 2010, THERE WERE 21,565 CASES OF PNEUMOCOCCI-INDUCED DISEASES, RECORDED IN COUNTRIES OF THE EUROPEAN UNION AND OF THE EUROPEAN ECONOMIC AREA, AND THE AVERAGE MORBIDITY RATE WAS 5.22 CASES PER 100 THOUSAND POPULATION FOR A TOTAL OF 26 ANALYSED COUNTRIES. THE HIGHEST PERCENT OF REPORTED CASES WAS NOTED IN THE NORDIC COUNTRIES (DENMARK, FINLAND, SWEDEN, NORWAY) AND BELGIUM.

tion programmes, patients may receive vaccines free of charge, while in other cases the costs of vaccines may be shared or fully incurred by patients. Following some literature reports, if vaccines are not funded from state budget or if some cost proportion is incurred by patients, as it happens in certain countries, it may directly compromise the availability of vaccines and vaccination programmes. Decision criteria, regarding the source of funding prophylactic vaccinations, are fairly similar in various countries and encompass the identification of target groups, based on epidemiological evidence of risks, the clinical efficacy and safety of available vaccines and the cost-effectiveness and pharmaco-economic aspects of assumed vaccination.

Despite universal access to antibiotics, pneumococci are still among major causes of morbidity and mortality, both in developing and developed countries. Due to the increasing resistance of pneumococcal strains to antibiotics, immunoprophylaxis becomes a more and more favoured option¹.

There are two types of antipneumococcal vaccines. The first one is the immunogenic pneumococcal polysaccharide vaccine (PPV23), approved to trading in 1980. It contains purified capsular polysaccharides of 23 pneumococcal serotypes and is administered

in risk-group children above the second year of life, as well as in subjects above 65 years of life. In the year 2000, the other, conjugate vaccine, was launched onto the market and has been used ever since. Conjugate vaccines are new generation products, currently available in three forms: 7-valent pneumococcal conjugate vaccine (PCV7), 10-valent pneumococcal conjugate vaccine (PCV10) and 13-valent pneumococcal conjugate vaccine (PCV13,) consisting of antigens of specific pneumococcal, important from the epidemiological point of view. PCV7 vaccine has in most countries been replaced by newer generation products: PCV10 or PCV13 (available since 2009)¹.

Following registered indications, PCV10 can be administered to infants and children from 6 weeks to 5 years of age, while PCV13 is indicated for infants, children, and adolescents of 6 weeks till 17 years of age and for adults over 50 years of age².

It has been shown that conjugate pneumococcal vaccines not only reduce the risk of diseases, caused by *Diplococcus pneumoniae* in vaccinated subjects, but they also offer a certain protection level to unvaccinated population, unless vaccination programmes are maintained at high enough strength and for satisfactory time period (herd immunity).

AN ANALYSIS OF PROPHYLACTIC, ANTI-PNEUMOCOCCAL VACCINATION SOLUTIONS WAS BASED ON THE FOLLOWING CRITERIA:

- **the availability and type of vaccines in vaccination programmes,**
- **vaccination obligatoriness,**
- **vaccination funding sources,**
- **vaccine purchase mechanisms,**
- **location of patient access to vaccine**



EPIDEMIOLOGY

In 2010, there were 21,565 cases of pneumococci-induced diseases, recorded in countries of the European Union and of the European Economic Area², and the average morbidity rate was 5.22 cases per 100 thousand population for a total of 26 analysed countries. The highest percent of reported cases was noted in the Nordic countries (Denmark, Finland, Sweden, Norway) and Belgium. However, the presented data should be approached with caution, due the variability of monitoring systems and different scales of data completeness in particular countries. The highest prevalence of diseases of pneumococcal aetiology was recorded in the group of children at the age of 5 years (9.6/100,000) and in adults after 65 (14.4/100 000)³.

METHODOLOGY

The assessment of solutions, accepted with regards to prophylactic vaccinations against pneumococci has been limited to the use of PCV10 and PCV13 vaccines in the population of children. Legal regulations, logistic organisation and the mechanisms of funding pneumococcal vaccination have been evaluated in 34³ European countries. An analysis of prophylactic, anti-pneumococcal vaccination solutions was based on the following criteria:

- the availability and type of vaccines in vaccination programmes,
- vaccination obligatoriness,
- vaccination funding sources,
- vaccine purchase mechanisms,
- location of patient access to vaccine

The national vaccination schedules, available at the ECDC (European Centre for Disease Prevention and Control) website, have been verified by interview, carried out in particular countries. Eurostat and ECDC databases were also searched to collect epidemiological data and healthcare costs in the analysed countries. Recommendations for vaccinations came from the website of the Centre

for Disease Control and Prevention (CDC) or the ECDC and from the World Health Organization (WHO).

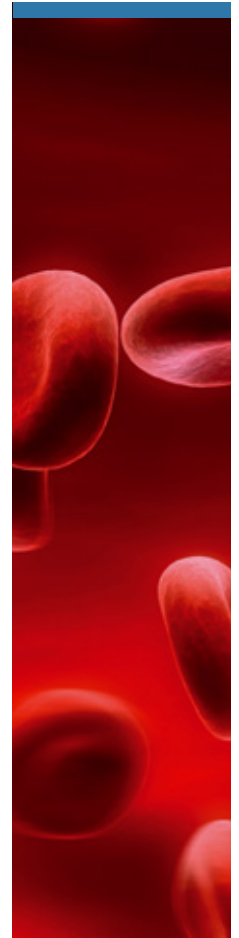
RECOMMENDATIONS

Following the recommendations of the American Advisory Committee on Immunization Practices (ACIP), regarding pneumococcal vaccination schedules for populations, aged from 0 to 18 years, a routine vaccination with PCV13 should be started in children at 2, 4, and 6 months of age (a three-dose protocol) with a booster dose to be administered between 12 and 15 months of age. Children between 14 and 59 months of age after a PCV7 vaccination series should receive one dose of PCV13, while in the catch up population⁴, one dose of PCV13 is recommended for all children between the 24th and the 59th month of life, which have not been covered by complete vaccination programme⁴.

Regarding the prophylactics against infections with pneumococci, the WHO recommends PCV10 and PCV13 vaccines to be administered in children from the 6th week till the 5th year of life. Additionally, the 13-valent vaccine is recommended in adults at the age ≥ 50 years. The WHO recommends to include PCV vaccinations in national vaccination programmes, especially in these countries, in which the mortality rate of newborns is higher than 50/1000 live births⁵ however, each country, when designing a vaccination schedule, should take into account the actual morbidity rates and the age, at which the highest morbidity is recorded⁵.

PCV IN NATIONAL VACCINATION PROGRAMMES

At present, i.e., at the beginning of 2013, anti-pneumococcal conjugate vaccines of new generation are commonly available in all the 34 analysed countries of Europe. In 29 countries of the European market, both PCV10 and PCV13 are registered. Until



the end of 2012, Synflorix (PCV10) had been available in 96 countries all over the world, including 22 countries of the European Union.

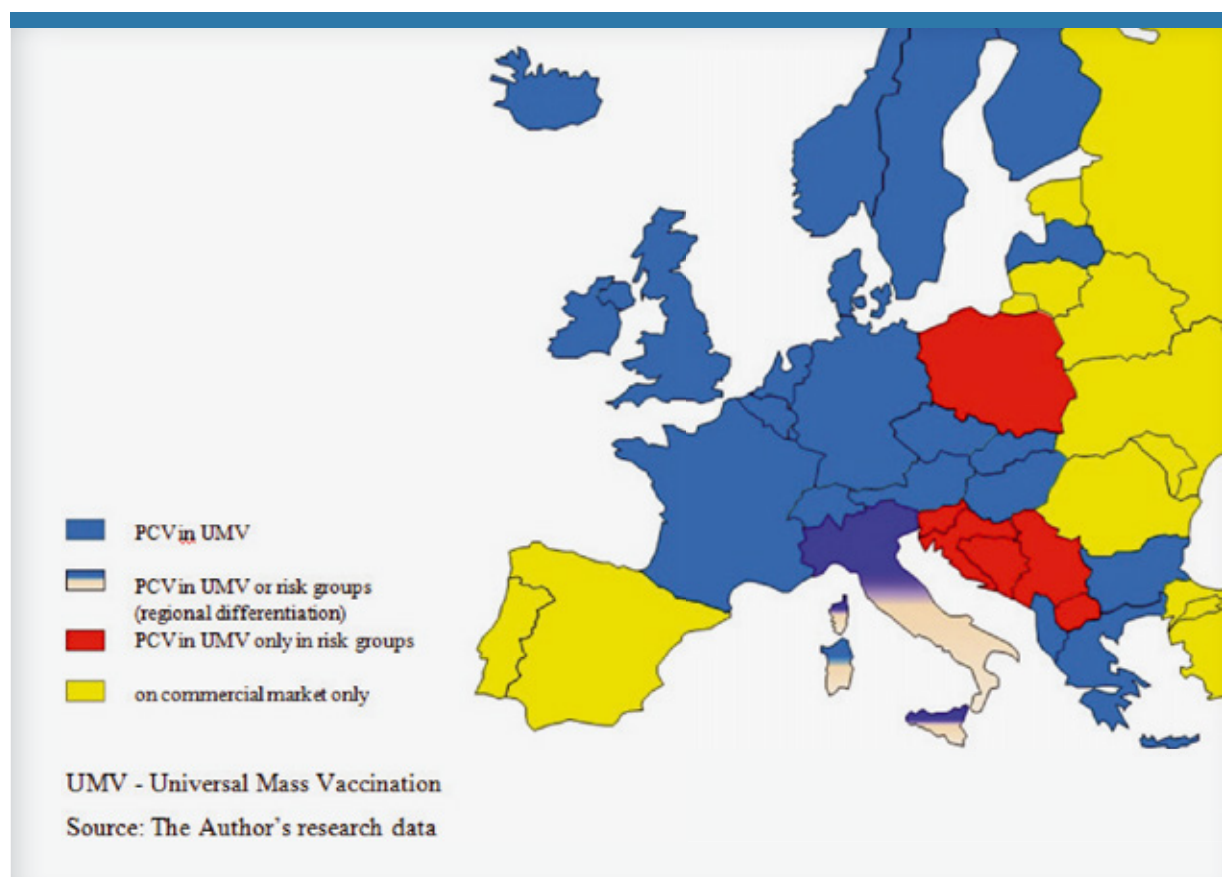
The proportion of vaccinations against pneumococci in national prophylactic programmes in Europe is differentiated and biased by many factors, including epidemiological and demographic structures, the socio-economic level and the weight of prophylactics in health care system adopted in a given country⁶. As a rule, PCV vaccinations are part of national vaccination programmes, what can be observed in the prevailing majority of countries. If there are differences, they are mainly related to vaccine agents and vaccination target groups. In 6 countries: Spain, Portugal, Romania, Estonia, Lithuania and Malta, anti-pneumococcal vaccinations are available exclusively at the commercial market⁷. In Serbia, conjugate, 10-and 13-valent vaccines were included in the national vaccination programme in March 2013 and, until that time, they had been available at the commercial market, however, with a possibility to get

full reimbursement from the Health Insurance Fund.

It appears from the available data for 2013 that in 19 countries, Synflorix⁵ is applied via vaccination calendars or programmes, dedicated to risk groups. In 20 countries, Prevenar⁶ is the available vaccine, while in 10 other countries, (Croatia, Czech Republic, Greece, Germany, Macedonia, Slovenia, Slovakia, Sweden, Serbia⁷ and Poland), both vaccines are used.

An analysis of public healthcare expenditure, expressed as a percentage of the gross domestic product (GDP), and of the implementation of PCV vaccination programmes by particular countries, taking into account vaccine types, did not show any relationship between the selection of more expensive (PCV13) or cheaper (PCV10) vaccine and the size of spending on healthcare. The Netherlands may be a good example, where healthcare expenditure in 2011 was the highest among the analysed countries, oscillating around 8.5% of the GDP, while the national vaccination programme included only

FIGURE 1.
AVAILABILITY
OF ANTIPNEUMOCOCCAL
VACCINES VIA
NATIONAL VACCINATION
PROGRAMMES IN EUROPE.



PCV10, reimbursed from March 2010 and replacing PCV7 vaccine⁸. In turn, Slovakia, where the public spending for healthcare in 2010 was 5.9% of the GDP, both vaccines are in the national vaccination programme, with prevalence of the 10-valent vaccine. In Poland, where the public spending on healthcare is one of the lowest (4.7% of the GDP), there is a free access of the risk group to the 10-valent vaccine and the 13-valent vaccine. In turn, both vaccines are recommended to and fully paid by other target groups, according to product characteristics. In Switzerland, where the public spending on healthcare is merely 2.1% of the GDP, vaccinations are funded under an immunisation programme for the entire cohort of children with a small, 10%, patient's share in the costs. An analysis of public spending on healthcare, expressed in a proportion of GDP, and the general availability of immunising agents indicate that these are not the only factors which determine product funding by the public payer⁸. See Figure 1 for PCV availability in Europe.

Due to the economic reasons full funding of innovative vaccines is not always possible. One of the mechanisms to solve the problem of inability to provide immunoprophylaxis to entire cohort is to differentiate the availability of vaccines, offering free-of-charge or partially paid vaccines for particular, defined risk groups. In 23 countries, PCV has been included in national vaccination programmes for the entire cohort of patients, while in other, like Poland⁹, Belgium, Croatia, Austria, Finland, the Netherlands, Germany, Iceland, Switzerland, Sweden, Bosnia and Herzegovina, and Serbia, vaccination is administered only to children in risk groups⁷. In Portugal, vaccinations are free of charge only in hospitals and only with PCV13, while on the commercial market, both vaccines are available at full price for other target groups, either at pharmacies or Health Centres. On the other hand, both in Poland and Croatia, both vaccines are available and recommended in vaccination calendars, as well as on commercial market

(in Croatia, Synflorix for children under two years of age, Prevenar13 over two years of age for the catch up population). In Italy, according to region, vaccinations are recommended for the entire population or only for patients at risk.

Vaccination schedules and target groups

In countries, where pneumococcal vaccination is carried out under national programmes, the adopted vaccination schedules, which specify the number and timing of vaccine administrations, are varied. This situation may result from a diversity in epidemiological exposures, different in particular countries. In general, the following three vaccination schedules are applied 2+1, 3+1 and 3+0⁷. Albania is the only country, where the booster dose is not provided and children are vaccinated at the 2nd, the 4th and the 6th month of life¹⁰.

In most European countries, the first vaccine in the 2+1 schedule is administered at the age of three months and the final dose at 5 months, while the booster dose is administered at 12 months of age (in Austria, Finland, Iceland, Italy, Sweden, Norway, Denmark and Slovakia the booster dose is recommended at 11 months). In the other countries on the 2+1 schedule, vaccinations are started at two months of life. The differences relate to time intervals between the priming doses (2 or 4 months) and the age of primary vaccination completion (11th – 15th month). In Romania, when the Ministry of health approves the new vaccination calendar, including anti-PCV agents, the vaccinations will be administered - similarly as in Belgium and the Great Britain – acc. to the 2+1 schedule .

Primary vaccination in the 3+1 schedule is carried out in two variants in European countries: three doses, beginning in the 2nd month of life and continued with two-month (Greece, Spain) or one-month intervals (Bulgaria, the Netherlands, Germany), and only in the Czech Republic, vaccination starts

at 3 months of life. Large discrepancies regard the time of booster dose administration, ranging from 11 to 18 months of life, depending on analysed country.

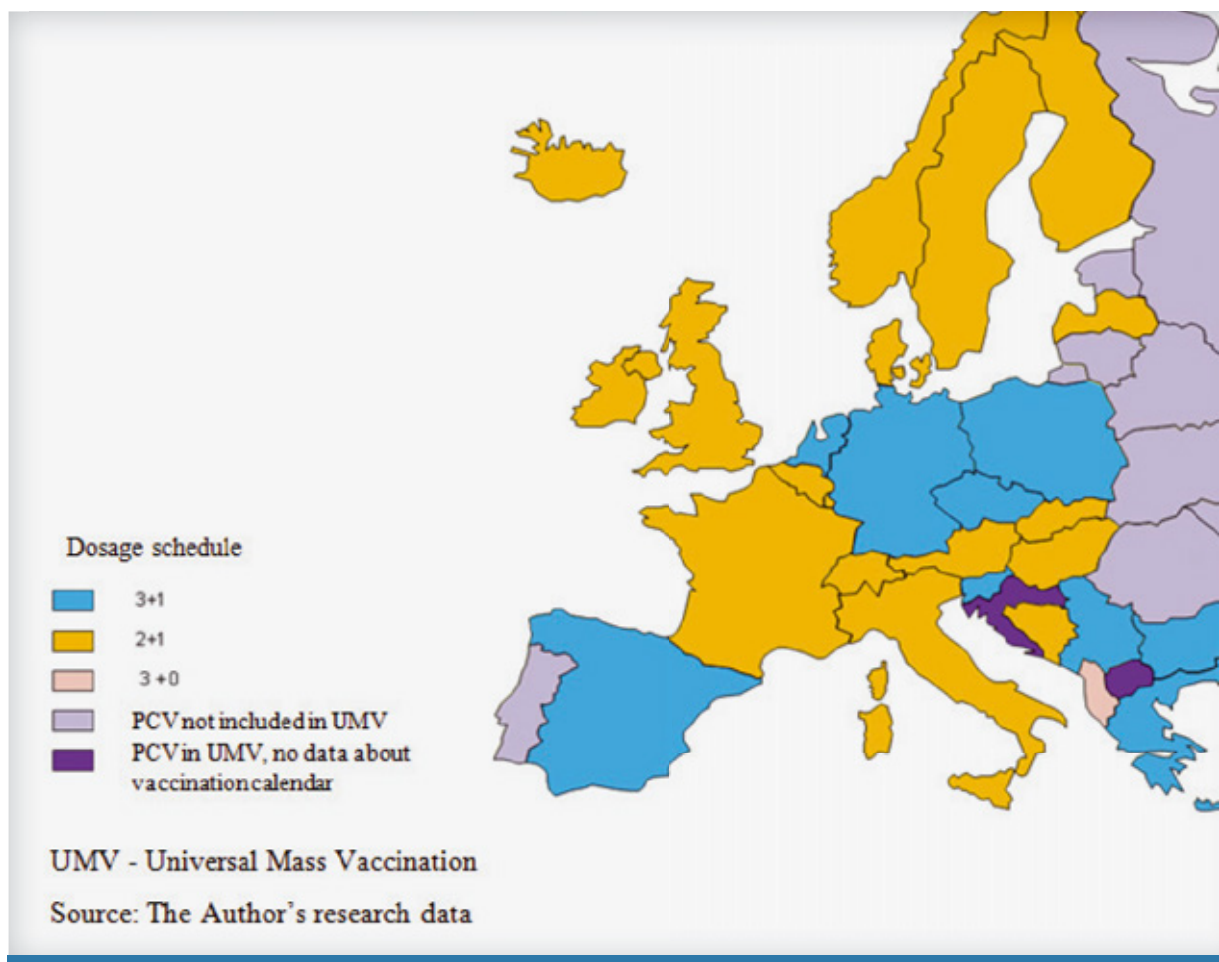
In Poland, basic vaccinations are also administered along the 3+1 schedule to high risk groups. The first dose is provided at 2 months of age with subsequent doses administered in one- or two-month intervals (3-4 and 5-6 months of life), while the booster dose is administered at 13-14

VACCINATION FUNDING

Compulsory vaccination programmes

In the prevailing majority of European countries, pneumococcal vaccination is not mandatory but recommended. Pneumococcal vaccination is compulsory for the entire population of children only in Greece, Bulgaria, and Slovakia. A specific situation is observed in Spain, where a conjugate vac-

FIGURE 2.
PCV VACCINE DOSING SCHEDULES – ACCORDING TO VACCINATION CALENDARS IN EUROPEAN COUNTRIES.



months of life. Various regimens of PCV administration do not delay the first dose of pneumococcal vaccine, which is administered between the 2nd and the 3rd month of life and, at the end of vaccination – up to the 6th month of life.

cine is not included in the national vaccination program but in Galicia, PCV vaccination is obligatory for the entire cohort of children, while in other regions, there is a diversity regarding recommended target groups ⁽¹⁾. In the regions, where vaccination is compulsory, it is completely free-of-charge for patients. In Slovakia, the more expensive

vaccine (PCV 13) is available at 69% charge.

Recommended vaccination

In countries, where PCV immunisation is optional, there are several alternative forms of access to vaccines. Funding mechanisms and the rules of patient participation in the costs are controlled by the healthcare model, as adopted in a given country. Pneumococcal vaccination can be either free-of-charge for the entire population or for predefined risk groups only, but vaccination reimbursement programmes are also common, e.g. at pharmacies, vaccination centres or at GP’s / paediatrician’s offices.

In case of recommended vaccinations, high price is often a limitation for broad and effective PCV vaccination programmes. This is why countries exercise different ways to compensate restricted access, for example, by sharing costs between the patient and the public payer. Large differences are observed among particular countries in reimbursement levels for the patient. It should be emphasised that one of the key factors, which determine vaccination programme efficacy is its universal, free-of-charge and compulsory availability.

In the following six countries: Germany, Albania, The Netherlands, Slovakia, Serbia and Greece, anti-PCV vaccinations, being part of national vaccination calendars, are fully financed from the public funds. Serbia employs an unusual solution, where, until the time, when the recommended PCV10 and PCV13 vaccinations were included in the vaccination schedule, they had been available on the commercial market but with a possibility of full reimbursement for patients in risk groups. In Albania, PCV10 vaccines are 100% reimbursed for all the children, born after 2010, while for those, born before 2010, as well as for persons choosing PCV13 vaccine, there is no reimbursement. In Germany, the reimbursement level for the two vaccines is 100% for the child population, while Greece provides a full reimbursement of PCV13 vaccine for the entire cohort

and of PCV10 vaccine for the subpopulation of children under 5 years only.

Partial reimbursement is provided in 6 countries. The lowest co-payment proportion is in Switzerland, amounting to 10% for PCV13 vaccine, which is the only one used in that country. In Spain, vaccinations are free-of-charge in some regions, while in others, both conjugate vaccines are 40% payable. In France, the social security cov-

Table 1. Reimbursement levels in selected European countries for PCV 10 and PCV 13 vaccines

COUNTRY	VACCINE TYPE	REIMBURSEMENT LEVEL	TARGET GROUP
SWITZERLAND	PCV13	90%	ENTIRE COHORT
SLOVAKIA	PCV13	100%	ENTIRE COHORT
	PCV13	69%	NO DATA
HUNGARY	PCV10	0%	ENTIRE COHORT TILL THE 2ND YEAR OF LIFE
	PCV13	100%	ENTIRE COHORT TILL THE 2ND YEAR OF LIFE
		70%	CHILDREN TILL THE 5TH YEAR OF LIFE
		0%	CHILDREN AFTER THE 5TH YEAR OF LIFE AND ADULTS
FRANCE	PCV13	65%	ENTIRE COHORT TILL THE 2ND YEAR OF LIFE AND CATCH UP CHILDREN AFTER THE 2ND YEAR OF LIFE
SPAIN*	PCV10	40%	RISK GROUP
	PCV13	40%	RISK GROUP
CZECH REPUBLIC	PCV10	FREE-OF-CHARGE	RISK GROUP
	PCV13	LACK OF DATA	RISK GROUP
SERBIA**	PCV10	100%	RISK GROUP
	PCV13	100%	RISK GROUP

* regional differentiation; at certain autonomous regions vaccines are free-of-charge

** before March 2013, the vaccines had been available on the commercial market (beside the national vaccination programme)

ers 65% of PCV13 cost, and PCV10 vaccine is not available on the market at all. A complex solution has been applied in Hungary, where the accepted schedule includes PCV13 vaccine with 70% reimbursement for children between 2 and 5 years of life and full payment for children over 5 and for adults. PCV10 vaccine is registered on the Hungarian market but is simply not available. See Table 1 for pooled data from countries with co-payment model. *Table 1 Reimbursement levels in selected European countries for PCV 10 and PCV 13 vaccines.*

ADDITIONAL FUNDING MECHANISMS

An additional mechanism to give patient a choice is to offer one vaccine free-of-charge, while other with partial or full payment. This solution was used in Slovakia and the Czech Republic: free immunoprophylaxis with PCV10 vaccine is recommended to the whole population, while the more expensive PCV13 vaccine is available with partial payment.

Alternatively, there are also local government prevention programmes that increase access of the local population to immunization, if vaccines are only available on the commercial market or are not covered by any compulsory programme. Such programmes are, among others, employed in Spain, Poland and Italy^⑩. Moreover, local government programmes allow to cover with vaccination catch up populations, as it is, among others, in Italy.

VACCINES ON COMMERCIAL MARKETS

The availability of vaccines, offered to the patient on the private market at full price, is found in some countries, together with vaccination in national programmes, e.g., in Bulgaria, Croatia, Poland, Lithuania, Romania, Bosnia and Herzegovina and, additionally, PCV7 vaccine is present on the market. In Hungary and Italy, PCV13 vaccine can be purchased at pharmacy (100% price) for children over 5 years old or for adults and in Hungary, also at vaccination centres. The

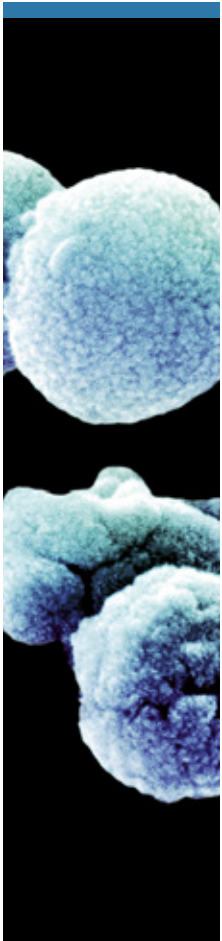
situation is similar in Albania, with one difference that only PCV10 vaccine is available. In most cases, the option of product availability on commercial market correlates with the economic status of country, especially with the amount of spending on health care. Following an analysis of European countries, if spending on health care is below 6% of GDP, vaccines are available on the commercial market at full price^⑧.

VACCINE PURCHASING MECHANISM

In most European countries, the purchase and distribution of conjugate pneumococcal vaccines, used in national immunisation programmes or in local government programmes, are controlled by the law of public procurement, both in countries with high and low expenditures on health care.

Vaccines may also be available via reimbursement lists. In Germany, Slovakia, Greece, and Serbia, 13- and 10-valent vaccines are on the list of reimbursed drugs and in Switzerland, the list includes PCV13 vaccine only. In France, Hungary, Italy and Spain, PCV13 vaccine is on the list of reimbursed medicines and can also be purchased via public procurement. The only possible way to purchase PCV10 vaccine in Spain is by invitation to tender. Sweden is the only one among the analysed countries, where both vaccines are on the list of reimbursed drugs and can be purchased by public procurement. A similar situation will take place in Serbia, including an implementation of the new vaccination programme, planned for August 2013. Differences in the vaccine purchasing mechanism in one country are associated with local vaccination policies adopted in particular regions of the country.

In most countries, vaccines are acquired via public procurement at the central level. The availability of the 10-valent vaccine for the public health care system results from tender procedures in Latvia, Bulgaria, Finland, Albania, Iceland, The Netherlands and Cyprus, while the 13-valent is purchased by public procurement in Denmark, Portu-



gal, Norway, the United Kingdom, Ireland and Hungary. In Macedonia, Slovenia, Croatia, and Poland, vaccines are purchased via central tender procedure, involving both types of vaccines. In Romania and Serbia, the updated vaccination programme is to include PCV vaccination and thus the purchase of those vaccines will be carried out via central tender procedures. In Croatia, an invitation to tender is announced every three years. Tenders for vaccines at regional level are announced in the following four countries only: Spain, Bosnia and Herzegovina (two tenders during a year), Sweden (in 10 regions) and in Italy (in 20 regions)⁸.

In Poland, vaccines are purchased in compliance with the Act of January 29, 2004 on the Public Procurement Law. A central invitation to tender is announced by the Department of Public Procurement – a unit, acting on behalf of the Ministry of Health¹⁴. See Table 2 below for detailed data of vaccine purchasing via public procurement in particular countries.

ANALYSIS OF VACCINATION COVERAGE IN THE EUROPEAN POPULATION

Data on the level of vaccination coverage at the European level are limited and the lack of information from 22 analysed countries prevented the analysis from being complete and precluding key conclusions on the analysed topic. However, in data, published by the WHO¹², a case of Germany is noteworthy as, despite widely available PCV13 and PCV10 vaccines for the entire population plus a 100% reimbursement of both vaccines and high spending on health care – the actual percentage of vaccinated subjects is relatively low. Moreover, the level of vaccination coverage varies much among the “Lender”, ranging from 23.3% (Hamburg) to 70% (Saxony-Anhalt)¹³. A relatively low percentage of people are vaccinated in Latvia and Hungary, what may be due to low expenditures on health care vs. other, analysed countries (4.1 and 5.1% of GDP, respectively)⁸.

Table 2. Availability of vaccines via public procurement at central or regional level during the years 2009-2013.

	PCV10	PCV13
2009	-	ITALY, BELGIUM
2010	BULGARIA, FINLAND, ALBANIA, CZECH REPUBLIC, CYPRUS, SWEDEN	DENMARK, HUNGARY, CZECH REPUBLIC, ITALY, BELGIUM, IRELAND, SWEDEN
2011	BULGARIA, FINLAND, ALBANIA, ISLAND, CZECH REPUBLIC, BOSNIA AND HERZEGOVINA, CYPRUS AUSTRIA, POLAND, SWEDEN, CROATIA	NORWAY, IRELAND, THE NETHERLANDS, HUNGARY, CZECH REPUBLIC, ITALY, BELGIUM, DENMARK, POLAND, SWEDEN, CROATIA
2012	AUSTRIA, BULGARIA, FINLAND, ALBANIA, ISLAND, CZECH REPUBLIC, BOSNIA AND HERZEGOVINA, CYPRUS, POLAND, SWEDEN	MACEDONIA, NORWAY, IRELAND, HUNGARY CZECH REPUBLIC, ITALY, BELGIUM, GREAT BRITAIN, THE NETHERLANDS, DENMARK, POLAND, SWEDEN
2013	LATVIA, SPAIN, BULGARIA, FINLAND, ALBANIA, ISLAND, CZECH REPUBLIC, SWEDEN, CYPRUS, AUSTRIA, POLAND	MACEDONIA*; SPAIN, BULGARIA, NORWAY, THE NETHERLANDS, IRELAND, CZECH REPUBLIC, ITALY, SWEDEN, BOSNIA AND HERZEGOVINA, BELGIUM, GREAT BRITAIN, DENMARK, POLAND

* Tender not yet announced

Table 3. The percentage of subjects vaccinated during the years 2009 - 2011, 3 doses of PCV

COUNTRY	2011 %	2010 %	2009 %
BULGARIA	94	69	BD
BELGIUM	NO DATA	84	84
DENMARK	90	88	86
FRANCE	89	89	NO DATA
THE NETHERLANDS	96	96	96
GERMANY ⁹	NO DATA	NO DATA	72
HUNGARY	84	NO DATA	NO DATA
IRELAND	90	43	NO DATA
LATVIA	78	NO DATA	NO DATA
NORWAY	92	91	91
SLOVAKIA	99	99	99
SWEDEN	60	60	60
GREAT BRITAIN AND NORTHERN IRELAND	90	89	NO DATA

Source: WHO Vaccine Preventable Diseases Monitoring System, http://apps.who.int/immunization_monitoring/en/globalsummary/countryprofileselect.cfm,

Rieck T. Impfquoten bei der Schuleingangsuntersuchung in Deutschland 2011. Epidemiologisches Bulletin 22. April 2013 / Nr. 16

An analysis of the available data leads to a conclusion that the compulsory vaccination against pneumococcus in Slovakia results in the highest percentage of vaccinations (as much as 99%) which, in the future, will result in a high degree of resistance in the rest of the population. In other countries, where immunisation is not compulsory, vaccination coverage is lower than in Slovakia, but close to 90%. Table 3 below presents pneumococcal vaccination status during the years 2009–2011.

COMMON AVAILABILITY OF VACCINATION AGENTS ON DOMESTIC MARKETS

Due to continuous changes, brought about by new technologies in the pharmaceutical sector, market shares of the analysed vaccines are very different in particular European countries. In 11 countries, the 13-valent vaccine has got a majority share, close to 100%. In Poland, since 2011, both vaccines have been available in national immunisation programmes and an analysis of the recent years shows an increased market share for PCV10 vaccine. Only in Finland, is the 10-valent vaccine recommended and free-of-charge for all children, having full market share and being funded since 2010. In Slovakia, Synflorix, introduced in 2011 to the national immunisation programme for children, has also got a predominant market share, while in Malta, pneumococcal vaccination is only available on the commercial market with recorded higher sales for the 10-valent vaccine. In Slovenia, Sweden, Serbia, and the Czech Republic, market shares of available vaccines (free of charge or with partial charge) are very close. The situation is similar in Estonia and Romania, although vaccines in these countries are only available at full price on the commercial market¹⁰.

CONCLUSIONS

An analysis of pneumococcal vaccination systems in Europe shows significant differences among countries and in many respects, mainly in recommended vaccination

schedules and target groups. Despite varying vaccination schemes, the age, when the first vaccine dose and the booster dose are administered is similar in most European countries. The differences are related to the availability of two conjugate pneumococcal vaccines (10-valent and 13-valent), included in vaccination schedules. Vaccine recommendation apparatus is different in particular countries. Vaccination is compulsory in a few countries and, in some other countries, there are regional differences in vaccination scope and target group definition. Advisory committees, which define national vaccination schedules, do not always recommend the type of vaccine to be administered to patients, in some countries, for example, the decision belongs to a general practitioner/paediatrician or the patient himself/herself. The choice of vaccine is often associated with patient's participation in the cost of more expensive vaccines.

In countries with decentralised administrative structure, such as Germany, Spain, Italy, or Sweden, the scope of recommended vaccinations may differ in autonomous regions. The registration and approval of vaccines on the market are controlled by the central government, while the purchase of vaccines is usually arranged by public procurement at regional levels. Despite that, the vast majority of European countries demonstrate a centralised policy of preventive immunization, based on the public payer system. In a few countries, PCV vaccinations are on the list of reimbursed drugs, but the central procurement by the Ministry of Health is definitely a more widespread mechanism. The inclusion of PCV vaccination in the national schedule – or its lack - does not depend directly on the socio-economic status of a country and may result from habitual and system tradition. Despite that, in 90% of cases, PCV13 vaccine is funded by the public payer. The cost-effectiveness of immunisation is one of the criteria for decisions, although not the only one. The type of available and funded vaccine is not fully dependent on the level of expenditure on health care in the analysed European

countries, as supported by analyses of health expenditures, expressed in percentage of GDP. The patient co-payment model is – in case of vaccines – more common in countries with lower spending on health care, except France (8.3% of GDP), where there is surcharge for PCV13 vaccine. The evaluation of the efficacy of the studied vaccines is not presented in this study, as the vaccines have been used only recently on different national markets, while benefits from immunoprophylaxis may be assessed after several years only^⑤.

In conclusion, a trend is observed in European countries towards updating and expanding national immunisation programmes by innovative immunising agents and via public health care systems, although the funding mechanisms for PCV vaccination are diversified, being in most countries controlled by decisions of the central government. ■

DISCLOSURES

The study was sponsored by GlaxoSmithKline Pharmaceuticals SA

FOOTNOTES:

- ① Synflorix vaccine was approved to trading at the EU on 30 March 2009 and Prevenar 13 vaccine – on 9 December 2009
- ② Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, Island, Ireland, Italy, Latvia, Lichtenstein, Lithuania, Malta, Holland, Norway, Poland, Rumania, Slovakia, Slovenia, Spain, Sweden, Great Britain
- ③ Albania, Austria, Bulgaria, Bosnia and Herzegovina, Belgium, Croatia, Czech Republic, Cyprus, Denmark, Estonia, France, Finland, Germany, Greece, Hungary, Italy, Ireland, Island, Latvia, Lithuania, Malta, Macedonia, Norway, Poland, Portugal, Romania, Switzerland, Sweden, Slovenia, Serbia, Spain, Slovakia, Holland, Great Britain.
- ④ Catch up is an additional vaccination of several year groups, older from the target group at the time of vaccination programme introduction.
- ⑤ Austria, Bulgaria, Croatia, Czech Republic, Finland, Greece, the Netherlands, Germany, Iceland, Macedonia, Slovenia, Slovakia, Sweden, Albania, Serbia, Bosnia and Herzegovina, Latvia, Poland.
- ⑥ Belgium, Croatia, Czech Republic, Greece, Germany, Ireland, Hungary, Italy, Macedonia, Slovenia, Slovakia, Switzerland, Sweden, the United Kingdom, Serbia, Norway, France, Bosnia and Herzegovina, Denmark, Poland.
- ⑦ In Serbia, in the national vaccination programme since March 2013.
- ⑧ The Author's research data
- ⑨ Data refer to 4 doses of PCV. Rieck T. Impfquoten bei der Schuleingangsuntersuchung in Deutschland 2011. Epidemiologisches Bulletin 22. April 2013 / No. 10. The Author's research data
- ⑩ The Author's research data

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14. Act of 29 January 2004 Public Procurement Law Dz. U. of 2004 No. 19 item. 177 as amended.



Development of education on Pharmacoeconomics in Ukraine



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ABSTRACT

The education on pharmacoeconomics for postgraduate pharmacists has been introduced in Ukraine since 2000. The objects, the pharmacoeconomic methods and evidence-based pharmacy, specific terms are being systematized and adapted in Ukraine.

The discipline of "Pharmacoeconomics" has been entered into curricula, programs for graduate and postgraduate students specializing in pharmacy and clinical pharmacy. We published textbook, tutorials for study on pharmacoeconomics and the Ministry of Health of Ukraine approved of the the pharmacoeconomics curricula, the first author's textbook for students - „Principles of pharmacoeconomics" (2002), for postgraduate pharmacists "Pharmacoeconomics" (2007) used in 12 medical (pharmaceutical) universities in Ukraine.

The active conduct of scientific pharmacoeconomic research in Ukraine, their results are used in the Central Formulary Committee Health of Ukraine while reviewing the State formulary and formu-

lary committees for local formularies. In Ukraine 3 doctoral dissertations and 21 PhD theses were defended during 2004-2012. The results of pharmacoeconomic research in budget purchase and for creation of State Formulary of medicine of Ukraine and local formularies in medical hospitals were used.

Since 2000 the World Health Organization (WHO) and the Pharmaceutical International Federation (FIP) have developed a strategic plan for the globalization of pharmaceutical education, creation of appropriate training modules pharmacist as an expert in modern health care, which provides physicians and health care managers with proven information about the cost effectiveness of medical technology and increases quality pharmaceutical care 1,3. The analysis of the curriculum of pharmaceutical faculties in Europe showed that the pharmacoeconomics discipline was included in the curriculum of the Bachelor, Master of Pharmacy and Doctor of Philosophy 1,2. In 2000 Pharmacoeconomics as a discipline was introduced into the curriculum and training program of postgraduate education for pharmacists in Ukraine.

Keywords:

education, education pharmacoeconomics, pharmacists, pharmacoeconomics, scientific pharmacoeconomic research

DOI: 10.7365/JHPOR.2013.3.1
JHPOR, 2013, 1, 50-57

THE LEADING INSTITUTION WHICH PERFORMS CERTAIN FUNCTIONS I.E. HTA - HEALTH TECHNOLOGY ASSESSMENT ARE AND A SPECIAL DEPARTMENT IN THE STATE EXPERT CENTER OF MOH UKRAINE CENTRAL FORMULARY COMMITTEE. THIS IS THE DEPARTMENT OF THE RATIONAL PHARMACOTHERAPY AND THE PROVISION OF THE STATE FORMULARY SYSTEM.

THE ORGANIZATION OF THE HEALTH CARE SYSTEM IN UKRAINE

According to the Constitution of Ukraine every citizen has the right to receive free medical care. Financing of the health care is offered at the expense of the state budget and local budgets. Mandatory health insurance is still unavailable. Also financing health care is subject to voluntary private insurance.

In 2002, the Ministry of Health of Ukraine approved of the „Using pharmaeconomics evaluation of medicine“ guidelines which contain methods of pharmaco-economic analyses applied in practice in the provincial departments of health of 25 regions in Ukraine. These guidelines are used in planning costs for state programs providing drugs for population and these programs are aimed at oncology, diabetes patients and at victims of Chernobyl.

The registration system of side effects of drugs was introduced in Ukraine in 2006. Systematized data on identified serious side effects are submitted annually to the Ministry of Health and published in medical journals.

The Cabinet of Ministers of Ukraine adopted a resolution in 2010 which was introduced to conduct mandatory verification of medicinal products registered in Ukraine according to the requirements of good manufacturing practice (GMP).

In January 2011 Ukraine, which is represented by the State Service of Ukraine on drugs, became a member of the International System of Pharmaceutical Inspection Cooperation (PIC/S).

The Ukrainian pharmaceutical market has a register of almost 14 000 medicines of which only 10% are the original drugs. In Ukraine State Program on Population drugs was approved during 2004-2010 with the assistance of the fundamentals of the

formulary system of medicine. In 2009 the state Ministry of Health approved of the first state formulary for medical hospitals. In 2012 the 4th edition of the state formulary of medicines used in medical hospitals was approved.

The leading institution which performs certain functions i.e. HTA - Health Technology Assessment are and a special department in the State Expert Center of MoH Ukraine Central Formulary Committee. This is the department of the rational pharmacotherapy and the provision of the state formulary system. The following HTA elements are used to enter a drug into the state formulary of Ukraine:

A pharmaceutical manufacturer submits documentation, which provides registration data, and shows whether the drug is entered in international clinical protocols and guidelines, WHO formulary, other formularies built on the principle of evidence, guidelines from HTA (as NICE, SIGN), systematic reviews, results of randomized clinical trials, cohort studies, case control and economic research.

In the absence of any information the formulary is not created. All materials are submitted in two copies of the cover letter and all enclosed printed materials serving as proof of international studies and published results of national pharmaco-economic studies. The experts of the Formulary Committee conduct a preliminary review and issue an opinion on registration of the drug in the State formulary of Ukraine.

At the second stage the Committee assembles once per month. The Expert Commission consists only of clinical experts. The list of experts from the pharmaceutical manufacturer is not open to the public. It is usual that main specialists MOH are in the Commission. The same documentation is considered as in the first stage. With the positive outcome of the previous stage, they can adopt or reject or postpone a State Formulary decision until the following assembly.

The ordinance of the Ministry of Health of Ukraine No 769 of 13.09.2010 was approved under the name of "Concept of the pharmaceutical sector of Health for 2011-2020", according to which the system of formulary drugs for the Ukrainian population will be actively implemented.

There is a necessity to create an independent HTA Agency for further implementation of the formulary system. The Agency will create a database of already conducted PE research in Ukraine and inform about their results and the adequacy of the budget for medicines, in particular innovative drugs.

The creation of the HTA Agency is particularly important due to the resolution of Cabinet of Ministers of 5th September 2012 No 907 On approval of the partial reimbursement of medicines for the treatment of patients with hypertension.

THE EDUCATIONAL PROCESS ON PHARMACOECONOMICS IN UKRAINE

In general methodological aspects of evidence-based pharmacy and pharmacoeconomics processed by Western scientists i.e. M.Drummond, JS.McCombs, JF.Mauskopf, K.Bonk and others^{2,4}. What has been done to support the learning process of pharmacoeconomics in Ukraine? Since 1999 authors have systematized and adapted in Ukrainian the objects of pharmacoeconomics research and evidence-based pharmacy, specific terms according to the ISPOR terms.

In 2000 the collaboration with International Society for Pharmacoeconomics and Outcomes Research – ISPOR began, which is the lead agency for the coordination and development scientific and practical pharmacoeconomic research globally. As the initiative of the Department of Management and Economy and Medicine Technology, Faculty of Postgraduate Education the discipline "Pharmacoeconomics" for postgraduate education of pharmacists was introduced in 2000. As the first informational support

of practical pharmacists in the periodicals pharmaceutical publications „Halician Pharmacy" (Lviv), „Weekly Pharmacy" (Kyiv) the educational materials on pharmacoeconomics were published⁷.

In 2001 we created and published the first standard curriculum "Pharmacoeconomics" for students of pharmaceutical faculties, approved by the Ministry of Health of Ukraine. In 2002, the Ministry of Health of Ukraine approved the first author's textbook for students „Principles of pharmacoeconomics" in Ukrainian, used in 10 medical (pharmaceutical) universities.

In 2003, the "Pharmacoeconomics" discipline was included into the curriculum of postgraduate training of pharmacists on the following specialties - „organization and management of pharmacy" and "general pharmacy". There was a need for a new adaptation for practical continuation of education for pharmacists. We prepared a textbook for postgraduate training of pharmacists - "Pharmacoeconomics" approved by MoH in 2007. This tutorial contains the requirements already enforced Presidential Decrees, Resolutions of the Cabinet of Ministers, orders of MoH regulating the use of pharmacoeconomic analysis in the development of formulary for medical hospitals as well as the creation of the State Formulary of medicine in Ukraine.

In methodological developments of practical training of pharmacoeconomic analysis materials for problem-based learning on specific local data were prepared control tests about pharmacoeconomic evaluation of hypolipidemic drugs based on evidence-based data concern therapeutic efficacy, effectiveness, hypoglycemic agents in patients with diabetes mellitus were included. These control tests include the availability of the domestic product, its dosage, packaging, wholesale cost of the producer.

Subsequent tutorials on pharmacoeco-

Table 1. Medical universities which offer training on pharmacoeconomics in Ukraine

EDUCATIONAL INSTITUTION	PHARMACY/ CLINICAL PHARMACY	EDUCATIONAL LEVEL	
		GRADUATE	POSTGRADUATE
M. PIROGOV VINNITSA NATIONAL MEDICAL UNIVERSITY	+/+	+	
BUKOVYNA STATE MEDICAL UNIVERSITY (CHERNIVTSI)	+/+	+	
DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY	+/+	+	+
DNIPROPETROVSK MEDICAL ACADEMY	/+	+	
DONETS STATE MEDICAL UNIVERSITY	+/	+	
IVANO-FRANKIVSK NATIONAL MEDICAL UNIVERSITY	+/		
LUGANSK STATE MEDICAL UNIVERSITY	+/+	+	
O. BOHOMOLETS NATIONAL MEDICAL UNIVERSITY (KIYV)	+/	+	
P. SHUPYKA NATIONAL ACADEMY OF POSTGRADUATE EDUCATION (KIYV)	+/		+
NATIONAL PHARMACEUTICAL UNIVERSITY (KHARKIV)	+/+	+	-
I. HORBACHEVSKY TERNOPIL STATE MEDICAL UNIVERSITY	+/+	+	
KHARKIV MEDICAL ACADEMY OF POSTGRADUATE EDUCATION	+		+
ZAPORIZHYA STATE MEDICAL UNIVERSITY	+/+	+	+

nomics in Ukrainian scientists distributed to other educational institutions. It should be noted that there is a significant differentiation of teaching pharmacoeconomics material for pharmacists studying „organization and management of pharmacy“. They pay more attention to issues of formulary supply of patients determining the need for medications. Pharmacist stuing „general pharmacy“ obtain more information on pharmacoeconomic aspects of pharmacotherapy of common diseases to apply knowledge related to patient-based recommendations for effective, safe and cost-effective pharmacotherapy. At practical course and seminars postgraduate students acquire skills of pharmacoeconomic evaluation of drugs using information from a database of evidence-based medicine, computed cost-effectiveness ratio of drugs to treat common diseases. We have conducted educational courses for 6000 practical pharmacists in the Western regions of Ukraine.

In 2007, according to the requirements of Bologna educational process, in collaboration with scientists from the National Pharmaceutical University (Kharkiv) we developed the curriculum of „Pharmacoeconomics“ for credit-modular system approved by the Ministry of Health of Ukraine. We published in Ukraine the first textbook „Pharmacoeconomics“ (author O.Zaliska, ed.B.L.Parnovsky. - 2007. - 376 p.), which is approved by the Ministry of Health of Ukraine for training students of faculties such as “Pharmacy” and “Clinical Pharmacy”^{8,9}. The curriculum and the textbook are used to educate pharmacists and clinical pharmacists in 10 medical universities (Table 1).

In 2004 Olha Zaliska successfully defended the first doctoral dissertation “The theoretical basis of “Pharmacoeconomics” and its practical use in Ukraine”, which gave a strong impetus for the development of scientific and pharmacoeconomic studies, the results of which were implemented in practice of medical and pharmaceutical⁵. Now are conducted research pharmacoeconomic

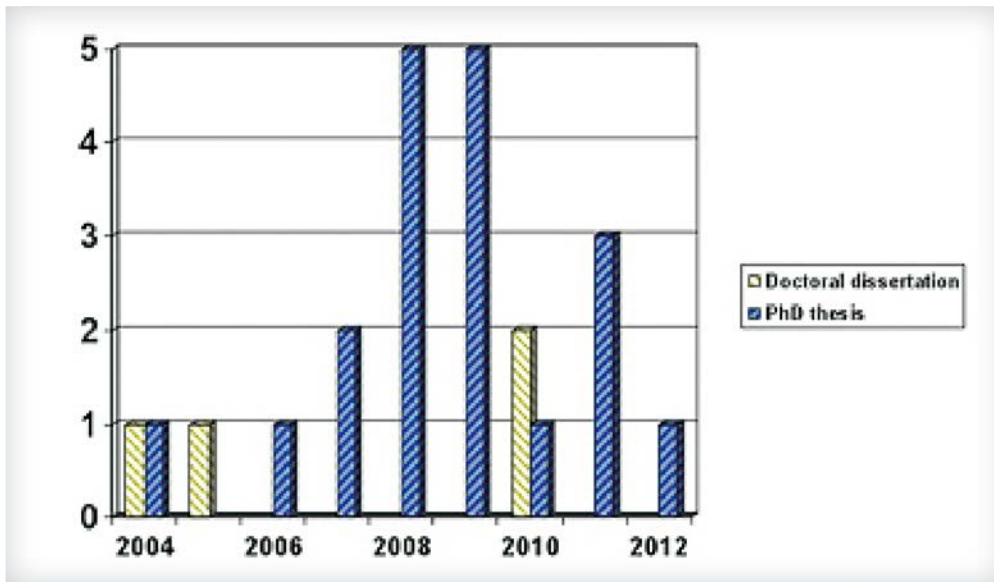


Figure 1. The scientific pharmaco-economic research for 2004-2012 in Ukraine

conomic studies, these results are presented and defended 3 doctoral and 21 PhD theses in Ukraine. The dynamics of pharmaco-economics is research presented in Figure 1.

In 2001, at the ISPOR invitation Olha Zaliszka made an podium presentation at the 4th ISPOR European Congress in Cannes (France), which showed the first steps of study as a discipline of „pharmaco-economics“ in the education process and health care in Ukraine, contributed to the development of educational technologies in Ukraine.

In January 2008 based on results of training of pharmaco-economics in Ukraine, ISPOR Board approved of the Ukrainian chapter - USPOR at the Danylo Halytsky Lviv National Medical University and ammended the English page on website with www.ispor.org/local_chapter/Ukraine.

Key activities of Ukrainian USPOR include processing techniques of pharmaco-economic studies according to international requirements and recommendations relevant to national health care, use of their results at the legislative level, particularly when viewing the National List of essential medi-

cines and medical devices which is the basis for public procurement. Priority directions of the Ukrainian Department USPOR are to train health professionals with the knowledge of pharmaco-economic methodology and its terms.

To implement educational and practical directions on pharmaco-economics on 17April, 2008 at the Department of Organization and Economy of Pharmacy and Medicine Technology Faculty of Continuing Education of Danylo Halytsky Lviv National Medical University a „Pharmaco-economics in Ukraine“ conference was held: status and prospects of pharmaco-economic studies“ conducted by scientists of the department and with the participation of the heads of pharmacy, specialists in organizing and managing pharmacy in Lviv and Lviv regional pharmaceutical corporations⁶.

For a more extensive review of the activities of Ukrainian pharmaco-economic studies (USPOR) we have created the first Ukrainian website online www.uspor.org, which contains information materials from international meetings and congresses on pharmaco-economics, bibliographic

sources of pharmacoeconomic studies published in national and international journals. We also consider the possibility of a web page teaching materials on the pharmacoeconomic analysis for e-learning practice and future pharmacists and their quality of methods in pharmacoeconomics.

The leading aim of pharmacoeconomics Ukrainian website is to spread knowledge of the science, pharmacoeconomics methods among professionals of medicine and pharmacy, on current trends in pharmacoeconomic studies according to the International Society of pharmacoeconomic studies - ISPOR and presentation of results at national conference and ISPOR European Congresses.

During the training courses pharmacists learn the history of pharmacoeconomics, its objects, object studies, relationships with other pharmaceutical, medical sciences, have a detailed study time in accordance with the requirements of the International Society of pharmacoeconomic research (ISPOR) from the official publication „ ISPOR Book of Terms“. Students get acquainted with the methods of pharmacoeconomic analysis of drugs „cost-effectiveness“, „minimizing cost“, „cost-benefit“, „cost-benefit“, „cost of illness“ and use their results to optimize pharmacotherapy. Much attention is devoted to the principles of drug formulary system software. It is in accordance with the requirements of “Concept development of pharmacy sector for 2011-2020” which involves the use of pharmacoeconomics and the formulary system in Ukraine.

It should be noted that the differentiation is made in teaching materials in pharmacoeconomics: in the faculty of „organization and management of pharmacy“ greater attention is paid to the organization of the formulary of patients determining the need for medications. Pharmacist faculty of „general pharmacy“ focus more information on pharmacoeconomic aspects of pharmacotherapy of common diseases for further application

of knowledge to provide patient-based recommendations for effective and cost-effective drug.

In practical seminars the focus is the evaluation of cost-effectiveness ratio calculated for drugs to treat common diseases.

By the decision of the International Society for Pharmacoeconomic Research (ISPOR) (2008) Ukrainian Chapter of the ISPOR (USPOR) was established. The Ukrainian website www.uspor.org was created. It presents information materials on the activities of international organizations and educational materials, research papers on theoretical directions and results of pharmacoeconomic studies in Ukraine.

Since 2008 the Department of Management and Economy of Pharmacy and Medicine Technology Postgraduate Faculty has been systematically conducting scientific and practical conferences for pharmacists on „Pharmacoeconomics globally and Ukraine“, which deals with topical messages of pharmacoeconomic studies in European countries, their use and results in the reimbursement of medicines according to the ISPOR European Congress, and also directions of implementation and pharmacoeconomics of formulary system in Ukraine.

We implemented the system of “lifelong education on pharmacoeconomics” for pharmacists during postgraduate courses. After passing the certification of pharmacists continue to use educational materials from the theory of pharmacoeconomics with a website www.uspor.org¹¹.

If they do not have access to the Internet, pharmacists may read publications in scientific journals i.e. „Pharmaceutical Journal“, „Clinical Pharmacy“, „Pharmacist-Practitioner“, „Pharmacist“ and study terminology, current activities of ISPOR. Thus pharmacists themselves explore their knowledge of the terminology of the ISPOR Book of Terms presented on the website. In June 2012, the 7th

Scientific Conference „Pharmacoeconomics in Ukraine” was held, which was attended by over 100 practical pharmacists.

It should be noted that the lectures and seminars of pharmacoeconomics for 2000-2011 academic years were held for more than 11 000 postgraduate pharmacists in Lutsk, Lviv, Ivano-Frankivsk, Uzhhorod, Rivne, Ternopil, Khmelnytsky and Chernivtsi regions.

SUMMARY

Reforming higher pharmaceutical education requirements under the Bologna Declaration should help prepare pharmacists to use modern disciplines, master new technologies and new knowledge by using the credit-module system. The introduction of lifelong education of pharmacists on “Pharmacoeconomics” using distance learning demonstrates the relevance and appropriateness of skills acquisition pharmacoeconomic analysis of the system of postgraduate training for pharmacists.

The modern pharmacist is free to navigate the scientific information, to be able to distinguish between materials of questionable value against reliable and useful data that serve as the basis to make management decisions in health care and with the help of an individual patient. ■

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Experience of the Latvian medicines reimbursement system



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In Latvia, the drug reimbursement system for outpatient treatment develops under limited resources. The reimbursement is performed against the degree of severity of certain diseases.

The largest part of the health care budget recourses for the reimbursement system is allocated for groups of diagnoses 'Diseases of the circulatory system' (21.48% of total expenditures in 2012), 'Endocrine, nutritional und metabolic diseases' (20.44% of total expenditures in 2012) and 'Neoplasms' (14.60% of total expenditures in 2012). Taking into account the rapid growth of the reimbursement expenditures in 2011 as well as the patients' co-payment for non-reference medicinal products certain measures have been implemented such as refund, depending on the exceeded market share, which was implemented for the period of 2011-2012 and amounted to LVL 3.7million in 2011 and LVL 2million in 2012. The two-level tender system has been implemented since September 2011 for interchangeable medicinal products and for newly diagnosed patients only reference medicine is reimbursed by the NHS at the time of the first treatment. As the result of these activities with the increased number of pa-

tients an average price per prescription was reduced from LVL 15.30 in 2011 to LVL 14.43 in 2012 the expenditures per patient were reduced from LVL 157.38 in 2011 to LVL 145.63 in 2012. With the strictly limited state budget, a necessity to use additional possibilities to optimise the resource allocation for the health care program and prevention activities remain topical.

The current Latvian drug reimbursement system for outpatient treatment has been developed since the 1990s. The procedures for the reimbursement are a set of measures which provides a patient with an opportunity to acquire medicinal products and medical devices the expenditures for the acquisition of which are completely or partially covered by the state budget funds in accordance with the Regulation No 899 of the Cabinet of Ministers of the Republic of Latvia "Procedures for the Reimbursement of Expenditures for the Acquisition of Medicinal Products and Medicinal Devices Intended for Out-patient Medical Treatment" (hereinafter – Regulation No 899). Expenditures for the acquisition of medicinal products and medical devices for nineteen groups of diagnoses (classified by the ICD-10) are reimbursed applying the following reimbursement categories ¹:

Keywords:
Latvia, medicinal product,
reimbursement system

DOI: 10.7365/JHPOR.2013.3.1
JHPOR, 2013, 1, 58-63

- Category I – reimbursement in the amount of 100% provided it has been determined that a patient has a chronic, life-threatening disease or a disease, which causes serious irreversible disability and the medical treatment of which requires the use of the respective medicinal products in order to maintain the patient’s vital functions;
 - Category II – reimbursement in the amount of 75% provided it has been determined that a patient has a chronic disease in the medical treatment of which the maintenance of the patient’s vital functions is made difficult or which causes serious disability without the use of the respective medicinal products;
- and
- Category III – reimbursement in the amount of 50% provided it has been determined that a patient has a chronic or acute disease in the medical treatment of which the use of the respective medicinal products is necessary in order to maintain or improve the patient’s state of health or in case where vaccines are paid for from the funds granted for reimbursement. Approximately 60% of the total state budget funds allocated for the reimbursement system are spent for Category I, 32% – for Category II and 8% – for the reimbursement Category III². The largest portion of the health care budget recurses for the reimbursement system is allocated for group of diagnoses ‘Diseases of the circulatory system’ (21.48% of total expenditures in 2012),

Table 1. State budget expenditures for reimbursement of outpatient treatment at the seven largest diagnoses groups (by amount of expenditures) in Latvia, 2010-2012 (prepared by the author, the source of the data of^{2,3})

EDUCATIONAL INSTITUTION	2010		2011		2012	
	ACTUAL EXPENDITURES		ACTUAL EXPENDITURES		ACTUAL EXPENDITURES	
	MILLION LVL	% OF TOTAL	MILLION LVL	% OF TOTAL	MILLION LVL	% OF TOTAL
ENDOCRINE, NUTRITIONAL AND METABOLIC DISEASES	16,04	21,57%	16,72	20,27%	16,67	20,44%
DISEASES OF THE CIRCULATORY SYSTEM	14,39	19,35%	18,12	21,96%	17,52	21,48%
NEOPLASMS	10,17	13,68%	11,84	14,35%	11,91	14,60%
DISEASES OF THE NERVOUS SYSTEM	5,85	7,87%	5,89	7,14%	6,02	7,38%
DISEASES OF THE RESPIRATORY SYSTEM	4,28	5,76%	4,54	5,50%	4,62	5,67%
MENTAL AND BEHAVIOURAL DISORDERS	4,24	5,70%	4,23	5,13%	3,56	4,37%
INFECTIONS AND PARASITIC DISEASES	3,85	5,18%	5,32	6,45%	4,90	6,01%

'Endocrine, nutritional und metabolic diseases' (20.44% of total expenditures in 2012) and 'Neoplasms' (14.60% of total expenditures in 2012) (Table 1)³.

The list of reimbursable medicinal products consists of three parts – List A, List B and List C. The list of reimbursable medicinal products is drawn up according to the following basic principles ¹:

- List A includes medicinal products of equal therapeutic efficiency within the scope of the common name of the medicinal products or the pharmacotherapeutic group of the medicinal products and medical devices of the same type of the use (reference price system);
 - List B includes such medicinal products and medical devices, which are not interchangeable;
- and
- List C includes such medicinal products and medical devices, costs of which for medical treatment of one patient exceed 3 000 LVL per year and pharmaceutical companies have to provide patients with medicinal products for at least 10% of the amount payable from state funds.

In order to include medicinal products and medical devices into the list of reimbursable medicinal products, the marketing authorisation holder (MAH) submits a written application to the National Health Service (NHS) containing clinical information (a summary of clinical trials, indications, target groups of patients etc.) pharmacoeconomic information (pharmacoeconomic calculations in accordance with the Baltic guidelines for the economic evaluation of the medicinal products (Estonia, Latvia, Lithuania) which came into force in 2002, information regarding the sales prices, calculation of the anticipated consumption of funds granted for reimbursement, including the comparative therapy and the number of patients as well as the calculation regarding the probable quantity and the estimated turnover of the medicinal products to be sold in Latvia in ac-

cordance with the procedures of reimbursement).

While examining an application regarding the inclusion of medicinal products or medical devices into the list of reimbursable medicinal products, the NHS performs a medical assessment and economic assessment. The economic assessment includes the following evaluation¹:

1. treatment expenses, in using the relevant medicinal products or medical devices, and their effects upon the funds granted for the health care including reimbursement (including the effects of possible adverse reactions caused by the use of the medicinal products or medical devices during the course of treatment and the treatment costs);
 2. therapeutic efficiency and costs of the new common medicinal product names in comparison with another type of available treatment in accordance with the Baltic guidelines for economic evaluation of the medicinal products
- and
3. prices of medicinal products and medical devices in comparison with prices of the respective medicinal products and medical devices in certain European Union Member States.

Prices of reimbursed medicines are negotiated between the NHS and the MAHs. A general principle in accordance with the Regulation No 899 is that prices should not exceed the prices in Estonia and Lithuania and the third lower price in the Czech Republic, Denmark, Hungary, Rumania and Slovak Republic. The limited mark-ups for wholesalers and pharmacies are applied. The number of patients treated through the reimbursement system rises every year. The biggest number of patients is treated through the reimbursement system in the group of diagnoses for 'Diseases of the cir-

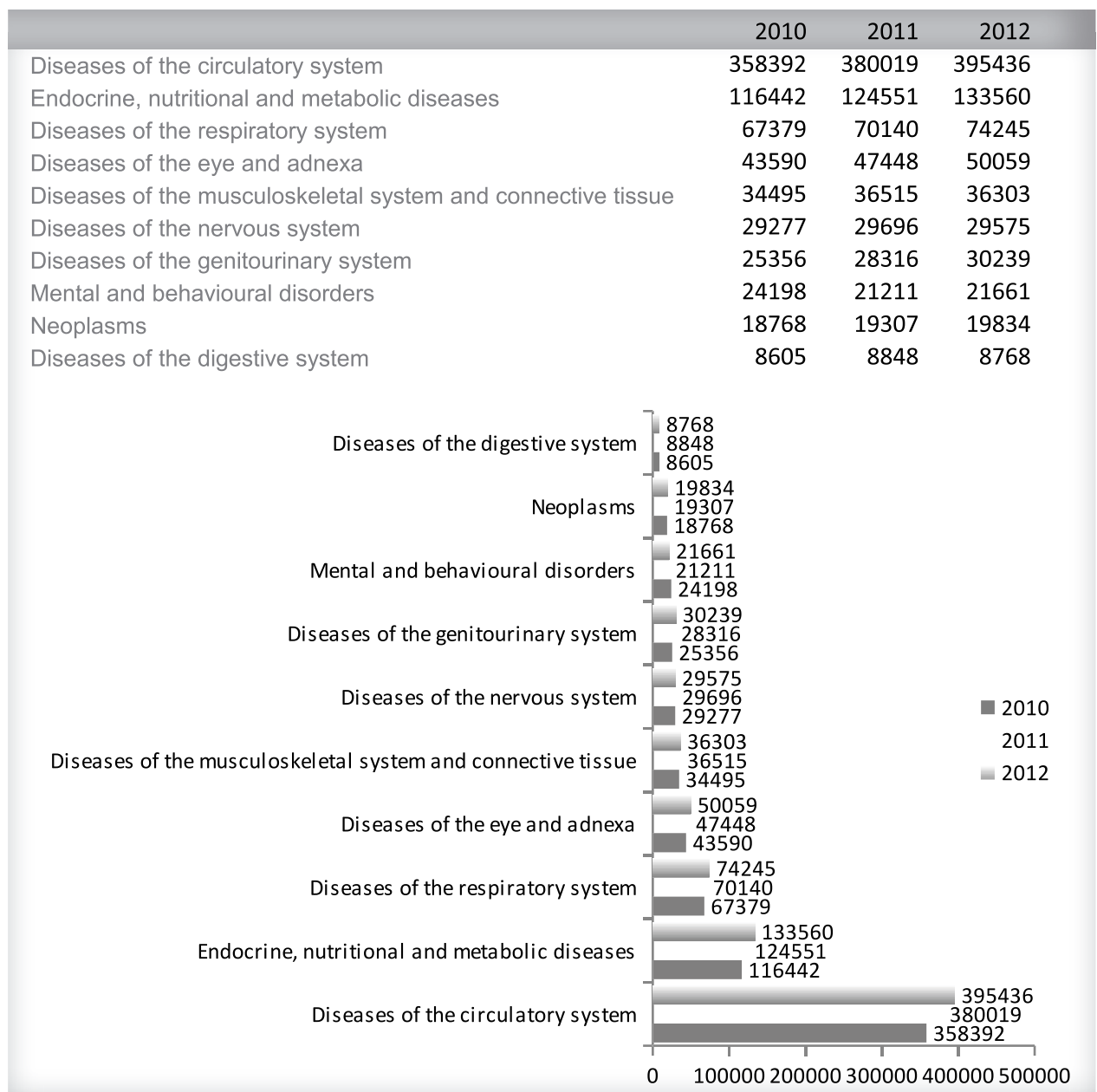


Figure 1. Number of patients treated in reimbursement system for outpatient treatment at ten largest diagnoses groups (by number of patients) in Latvia, 2010-2012 (prepared by author, using the data of^{2,3})

Table 2. Total state budget expenditures for reimbursement of outpatient treatment and number of patients treated in Latvia, 2010-2012 (prepared by author, using the data of^{2,3})

YEAR	NUMBER OF PATIENTS TREATED	STATE BUDGET EXPENDITURES, LVL	EXPENDITURES PER PATIENT, LVL	EXPENDITURES PER PRESCRIPTION, LVL
2010	505773	74358648	147,02	14,39
2011	524282	82513870	157,38	15,30
2012	559978	81551251	145,63	14,43

culatory system', 'Endocrine, nutritional and metabolic diseases' and 'Diseases of the respiratory system' (Figure 1).

Taking into account the rapid growth of the reimbursement expenditures in 2011 (Table 2), as well as the increased patients' co-payment for non-reference medicinal products (Figure 2) the certain measures have been implemented^{1,3}:

- Pay-back system has been implemented for the period of 2011-2012, in accordance with that the MAHs, depending on their market share, had to compensate to the NHS a certain degree if the annual medicines budget is exceeded. This pay-back system amounted to LVL 3.7 million in 2011 and LVL 2 million in 2012.

- The two-level tender system has been implemented for medicinal products of List A, as well as for newly diagnosed patients only a reference medicine is reimbursed by the NHS at the first time of treatment since September 2011. As the result of these activities in circumstances of the increased number of patients (Table 2), the average price per prescription was reduced from LVL 15.30 in 2011 to LVL 14.43 in 2012, as well as the expenditures per patient were reduced from LVL 157.38 in 2011 to LVL 145.63 in 2012.

The National Health Service, on the basis of the decision of the doctors' council of the relevant treatment field, is entitled to take a decision regarding the reimbursement of expenditures for the acquisition

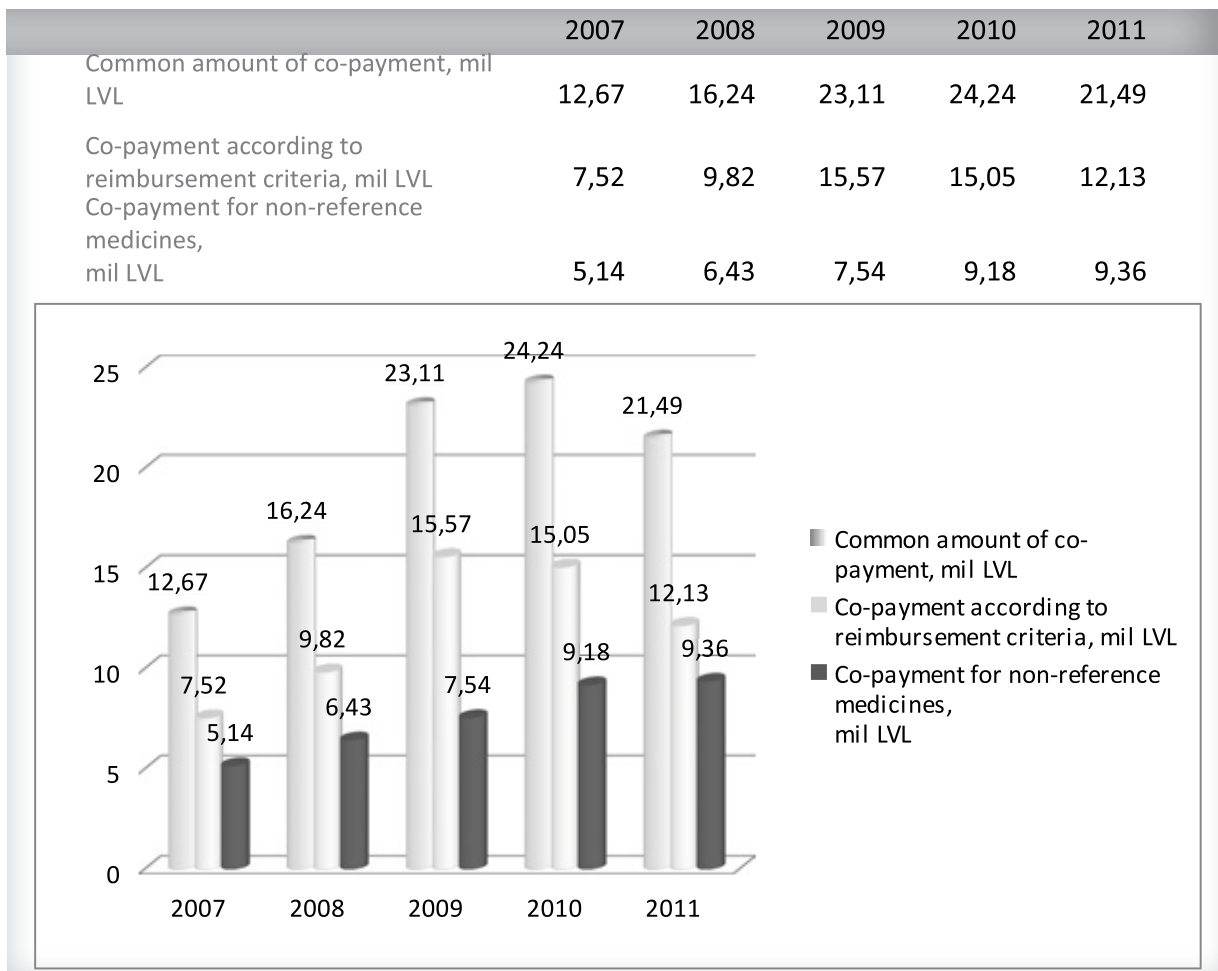


Figure 2. Patients' co-payment tendencies in reimbursement system for outpatient treatment in Latvia, 2007-2011³

of medicinal products and medical devices for individual patients. In 2012 the NHS provided the individual compensation for 554 patients including patients of the rare diseases which are not entered into the common list of the reimbursed diagnoses. The individual agreements between the NHS and MAHs, such as price-volume agreements as well as possibilities to cover the co-payment of the patients those receive reimbursement through individual compensation have been introduced since October 2011. Additionally since 1st September 2012 the expenditures of all prescription medicines have been reimbursed in the amount of 50% for treatment of children under 2 years of age and in the amount of 25% for the treatment of pregnant women.

The implemented measures have insured the significant improvement and optimisation of resources management but in the circumstances of the strictly limited state budget a necessity to use additional possibilities to optimise the resources allocation to the health care programs and prevention activities remain topical. ■

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The German AMNOG and its current potential implications on the Spanish and Belgian pricing and reimbursement decisions



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Keywords:
AMNOG, health
technology assessment,
pharmaceutical policy

DOI: 10.7365/JHPOR.2013.3.1
JHPOR, 2013, 1, 64-71

ABSTRACT

Background: EU policymakers have implemented mechanisms to slow down the rate of increase in health care costs. The most recent reform that came into effect in Germany was the Act to Reorganise the Pharmaceutical Market (AMNOG - Das Arzneimittelmarktneuordnungsgesetz).

Methods: Exemplarily for countries, which used Germany as a price reference country, Spain and Belgium were chosen for pilot evaluation if AMNOG might have any further impact on reimbursement and pricing decisions in these countries. The general market access and potential impacts on clinical development programs will be discussed and evaluated.

Results: In Spain, GBA assessments may influence the central decisions in pricing and reimbursement in the sense that lower prices will be expected for new drugs in the benchmarking process. In Belgium, AMNOG will also have an impact: the Price Commission will possibly observe lower prices than before, what may lead to other decisions for approved Belgian prices. More importantly, the

decisions in Germany, related to added benefits of new drugs, might influence the Commission members.

Finally, clinical developments of new compounds may also be influenced by AMNOG, regarding the requests of reimbursement decision makers for special clinical trial designs.

Conclusions: The potential impact on additional clinical benefits and price decisions with the Spitzenverband der Krankenkassen may be observed in some other countries as well. Furthermore, the impact on future clinical development programs of new compounds might as well be significant. Further research and experience in Germany and other countries is needed and awaited.

INTRODUCTION: HEALTH CARE REFORMS AND AMNOG

In recent years, the introduction of new innovative medicinal products has become increasingly challenging in result of budget pressures, the introduction of more complicated listing procedures and higher demands on the added value of medicinal products and other therapies. For the most part, policy measures have relied on budgeting or price controls, including negotiated

prospective budgets for hospitals, centralized negotiated budgets for outpatient physicians, including drug prescriptions, and limitations on payments for particular medications. The autonomous behaviors of prescribers have been restricted and controlled by national clinical guidelines, local formularies and/or local agreements between prescribers and health insurers, who sanction for deviant prescription behaviors or reward “proper” adherence to the rules. Although each country in Europe has its own specific cost containment measures and restrictions for market access, the above-mentioned changes have a similar impact on each new medicinal product, introduced in Europe: summarised as an increasing number of refusals and restricted access to new therapies, following negative reimbursement decisions. Because those traditional central cost containment measures were only partially successful, due to a potential lack of incentives, the health authorities in Europe started developing and implementing incentives for efficient health care delivery. Despite considerable differences among various European countries, there are two related and commonly observed trends: implementation of market-mimicking mechanisms and decentralisation of health care decision-making process. The key aim of these reforms is to control increasing health care costs, which has become an important part in the overall expenditure for social care.

Governments and policymakers of EU member states have, over the last decade, implemented a series of mechanisms and reforms to slow down the rate of increase in health care costs. The most recent reform, that has come into effect in Germany, is the Act to Reorganise the Pharmaceutical Market (AMNOG), which has changed Germany’s traditional status of their market, known as a “fast-entry and premium-priced” trading environment. With the new reform in place, the pharmaceutical manufacturers are now required to show not only the benefits from their new drug vs. placebo, but also

to unveil any additional benefits from their new medicinal products over and above appropriate therapeutic alternatives. According to the Federal Ministry of Health (MoH), the extent of additional benefits from a new drug will be classified in one of the following categories:

1. Remarkable additional benefit;
2. Considerable additional benefit;
3. Minor additional benefit;
4. Additional benefit not quantifiable;
5. No evidence for additional benefit;
6. Less benefit than from a comparable product.

At the time of market access, a manufacturer has to submit a ‘benefit dossier’ to the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) for assessment. The dossier must specify the conducted studies, information on tested medical indications, therapeutic benefits, additional benefits in comparison to alternative treatments, the cost of therapy and the expected expenses of the therapy for the SHI, the estimated number of patients or patient groups expected to benefit from the new drug and special requirements in place to assure compliance and adherence of patients, prescribed the drug to be used. The G-BA, the Institute for Quality and Efficiency in Healthcare (IQWiG; Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen) or third parties commissioned by the G-BA should assess and publish the dossier within three months. Over the following three months, the manufacturer will have an opportunity to comment during an organised hearing. During this time, the G-BA will reach a final decision on additional benefits, based on the results of the assessment (additional benefit/no additional benefit). If no additional benefit for a drug can be demonstrated, it will be classified

IN RECENT YEARS, THE INTRODUCTION OF NEW INNOVATIVE MEDICINAL PRODUCTS HAS BECOME INCREASINGLY CHALLENGING IN RESULT OF BUDGET PRESSURES, THE INTRODUCTION OF MORE COMPLICATED LISTING PROCEDURES AND HIGHER DEMANDS ON THE ADDED VALUE OF MEDICINAL PRODUCTS AND OTHER THERAPIES

directly into a reference-price group. If no reference price group exists, this new drug will be discounted to set the reimbursement price no higher than that of a relevant comparable product. If the new drug is considered to show an additional benefit, then its price will be negotiated in centralised contracts between the Head Association of the SHI funds (GKV-SV) and the manufacturer, according to § 130b SGB V 1. The negotiated price should be as high as that of the comparable product, plus a mark-up reflecting the additional benefit; and it will be binding for all German SHI as well as for private health funds. This new price will be effective after thirteen months from market launch of the new drug. Should an agreement fail to be reached within one year, an arbitration body will decide on a rebate, based on an international reference price. If this negotiated price is not accepted (by either party), both the manufacturer and the SHI can ask for a cost-effectiveness analysis (CEA) to be undertaken by IQWiG with perspective of determination of a CEA-based price (which would then become applicable retrospectively from the start of month 13). If price negotiations bring a lower reimbursement price for the SHI, the official list prices will not change. Therefore, other European countries cannot take advantage of lower list prices for their negotiations.

HISTORICAL DEVELOPMENT: GERMANY AS A PRICE-REFERENCE COUNTRY FOR OTHER COUNTRIES

It has been speculated that the implications of AMNOG on the pharmaceutical market will be significant. AMNOG may not only have significant impacts on drug prices in Germany, but may also be reflected in international drug prices. German drug prices influence – directly or indirectly, formally or informally – the international drug reference prices in 19 countries, including: Austria, Belgium, Cyprus, Czech Republic, Estonia, Finland, France, Greece, Hungary, Ireland, Italy, Latvia, The Netherlands, Norway, Romania, Slovakia, Slovenia, Spain and Switzerland. The countries, which do not

refer to German prices, include: Bulgaria, Croatia, Denmark, Lithuania, Poland, Portugal, Sweden, and the UK. Out of all European (here: EU-27) countries, only UK, Sweden, Germany, and Denmark do not currently have an external price referencing policy. In Denmark, this policy has been discontinued since 2005. In Sweden, external referencing was ceased in 2002. The factor of external reference pricing is already affecting the path of product launches in Europe. For example, Boehringer-Ingelheim and Lilly ceased launching their type II diabetes drug, linagliptin (Trajenta®), for fear of negative pricing prospects for the product.

SUMMARY OF FIRST ASSESSMENTS AND PRICING NEGOTIATIONS WITHIN AMNOG

Within the first 28 months, up to April 2013, dossiers for more than 50 pharmaceutical specialties have been submitted to the G-BA. The results of benefit assessments so far: 35 assessments completed, six close to be finished, and seven have just started. Three pharmaceuticals were exempted from the early benefit assessment for an insignificant budget impact for the statutory health insurance in Germany and one has no status.

Comparing the manufacturer's dossiers, the benefit assessment of the IQWiG and the final resolutions, published by the G-BA, striking is the difference, regarding the estimation of potential innovations and additional benefits in comparison to standard therapy. Only for some drugs was the manufacturer's positive estimation fully approved by the IQWiG or the G-BA. For some pharmaceuticals, assessed for several indications, the evaluation has provided different results for different indications, ranging, e.g., from „significant additional benefit“ in one indication to „no additional benefit“ in another (e.g. Ticagrelor).

For the 35 pharmaceuticals, so far finally assessed, the results are as follows: 13 have no proven additional benefit, which means the G-BA has to check whether they could

be allocated to the existing reference price group or whether a new reference price group could be formed. If a drug with no additional benefit cannot be allocated to any reference price group, the GKV-Spitzenverband (National Association of Statutory Health Insurance Funds) and the pharmaceutical company have to negotiate a rebate, resulting in annual treatment costs not higher

these pharmaceuticals, the rebate on the list price has already been or still has to be negotiated between the manufacturer and the GKV-Spitzenverband. Two drugs have directly been allocated to a reference price group.

Some pharmaceuticals have already re-entered the assessment process for a second time. The very short period for the re-entry



than those for appropriate comparable product. Three products do not have any quantifiable benefit, 13 reveal marginal and six fairly significant additional benefit. Five products have been regarded to be pharmaceuticals for the treatment of a rare disease in accordance with EC regulation (No. 141/2000 / orphan drugs) and, therefore, the additional medical benefit is said to have been proven through market authorization. For

is due to the fact that the assessment procedure is new to all parties involved. In case the additional benefit could not be proven because of missing evidence pursuant to article 35a paragraph 1 sentence 5 SGB V (Sozialgesetzbuch V / Fifth Book of the German Social Code), the pharmaceutical company was free to submit a new dossier at any time until 31st December 2012. From 1st January 2013, submitting a new dossier for a second

benefit assessment is only possible after one year.

The G-BA has decided to perform a benefit assessment for the three DPP-4-inhibitors (sitagliptin, vildagliptin and saxagliptin). This is for the first time that pharmaceuticals from the established market have to prove their additional benefit in comparison to standard therapy. On April 18th 2013, the G-BA published criteria for the benefit assessment for drugs of the established market and defined the drugs to be assessed. So far, six pharmaceuticals or groups of pharmaceuticals – namely for severe pain, osteoporosis, the prevention of stroke for patients with atrial fibrillation, diabetes, depression and rheumatoid arthritis – will be called upon until the end of 2013.

Beside the differences in the estimation of the potential innovation and the additional benefit in comparison to the standard therapy, the major topic of the discussion between the pharmaceutical company on one hand and the G-BA and IQWiG on the other is the definition of the, so-called, „appropriate comparator“. In accordance to AMNOG regulations, the manufacturer may suggest a comparator in the dossier, but the final decision is up to the G-BA. As an example, the manufacturer of linagliptin suggested the DPP-4-inhibitor sitagliptin as an appropriate comparator, whereas the G-BA decided to compare with the combination of sulfonyleurea and metformin. The fear of the manufacturer was evidently such that if a branded drug is compared with generics, the final price will be much lower than if it were compared with another branded drug. Therefore, the pharmaceutical company withdrew linagliptin from the German market after the publication of the G-BA resolution.

The pricing negotiations between several manufacturers and the GKV-Spitzenverband started this year in January with a “noisy” campaign in press media. The major topic of discussion was the group of countries with the reference price. As the negotiating

parties could not agree on this question, the arbitration body had to decide about the basket of reference countries. The 15 countries named are Belgium, Denmark, Finland, France, Greece, UK, Ireland, Italy, the Netherlands, Austria, Portugal, Sweden, Slovakia, Czech Republic and Spain. These 15 countries represent the majority of the EU commercial power and about 80% of the EU population. Due to the fact that they differ in many economical parameters, the discussion is still continued if only countries of comparable GNP should be chosen for comparison.

Despite the on-going discussions, there are first results of the pricing negotiations. Until April 2013, the GKV-Spitzenverband and the manufacturers had negotiated a rebate for 17 pharmaceuticals. For another three pharmaceuticals, the rebate had to be fixed by the arbitration board. Only a few results have been published in detail as press releases on the website of the GKV-Spitzenverband. A list of all the 20 pharmaceuticals, though without any details, has also been published by the GKV-Spitzenverband. A.T.I Arzneimittelinformation Berlin GmbH has published the detailed results for the first 14 drugs at the end of January 2013. With price (P) being only one variable of the total turnover expression (P*Q), there is still a number of volume restrictions, stating that these drugs may only be used within their assessed indications and if “economically appropriate”. The GKV-Spitzenverband has published an information on its website, when a prescription for ticagrelor, pifenedon or abirateron may be justified on the grounds of being a “special feature” of the doctor’s office (“Praxisbesonderheit”) and may, therefore, be perceived as economically appropriate.

DISCUSSION: A POTENTIAL IMPACT OF AMNOG ON THE EUROPEAN PRICING & REIMBURSEMENT LANDSCAPE

For a globally operating pharmaceutical company, the clinical development program of a (new) compound is essential for that

THE PRICING NEGOTIATIONS BETWEEN SEVERAL MANUFACTURERS AND THE GKV-SPITZENVERBAND STARTED THIS YEAR IN JANUARY WITH A “NOISY” CAMPAIGN IN PRESS MEDIA. THE MAJOR TOPIC OF DISCUSSION WAS THE GROUP OF COUNTRIES WITH THE REFERENCE PRICE.

compound's lifecycle and commercial success. Hence, the study phases and, especially the countries having a significant impact on the study design and implementation, are crucial at every stage of the process. Normally, larger countries with higher business potentials have a larger impact in terms of clinical design decisions (currently especially the US). As the German market is still an important market in terms of business, price-setting, and even potential impact on other (smaller) markets, this could now also change the development side of a (new) compound. For example, the clinical endpoints and comparators of choice could be chosen to satisfy the German standard, and this might then also have an impact on other countries. Or, in the outcomes space, a patient-relevant endpoint (e.g. overall survival in oncology) might be chosen over a surrogate endpoint (e.g. progression-free survival in oncology), as this might increase the chances of success and hence a better price in Germany. Potentially, there might now also be more than a few studies being executed for marketing authorization and market access, dependent on different regions in the world: Europe, with a special focus on Germany and the UK, might have other requirements than the US or Asia.

During the last decade, the common practice of the pharmaceutical companies was targeted to first market new agents in those "free price" countries with high income level, such as Germany, where high prices could be easily fixed without reducing the expected sales and, later on, to apply for similar prices in the remaining countries. If regulators did not agree with requested prices, some companies challenged to withdraw the new agent from that market, claiming that a parallel trading at lower level would reduce their profit margins, which would, in turn, lead to cuts in research and development activities. Hence, negotiations usually ended in a minus 10-15% from the benchmarked original price abroad.

At present (in 2013), in Spain, the new Royal Decree Law (16/2012) consolidates

the idea of aligning new products' prices to the lowest existing prices and it also opens a possibility to review prices after a certain period, if, e.g., a new information becomes available. There is still no feedback from these latter activities. Re-evaluation of products in terms of efficacy and price has been possible in Spain during the last 3 decades, since the introduction of the General Act of Health (year 1986), the former Law of Drugs (year 1992) and the newer Act of Drugs (year 2006). However, this re-evaluation has adopted several forms. For instance, during the 1990s and the following decade, there were several price cuts and delistings of drugs from public reimbursement, based on efficacy grounds (at least, it was claimed to be based on those grounds) as well as on the low level of severity of the diseases targeted by those drugs. However, it was believed that a higher budget control promoted those decisions. Other examples of this practice come from the fact that, since new drugs are more effective than the former ones, a review of the prices of those older ones is possible because, in relative terms, they have lost efficacy. Frequently, this review takes place at the hospital level where higher discounts are requested by hospital pharmacies and accepted by manufacturers, without modifying the official price of the agents (that perhaps is also used as benchmark by other countries). Regional directions of pharmacy and regional health technology assessment agencies also review many drugs on terms of effectiveness and safety and produce reports and recommendations regarding their prescription. Based on these reports, regional health authorities may also request discounts, guide the decisions of physicians by writing protocols, and program procurement and/or dispensing software in an effort to constrain electronic prescriptions.

The impact of NICE has been important in this field, given that its reports are public and visible on the web site. Many Spanish health authorities read those reports to better understand the value of new agents and to know the features and concerns around them. This knowledge is integrated in the

decision-making process of both central and regional health authorities. However, GBA assessments are not so influential yet on the decision processes as those coming from NICE, perhaps due to the way they are reported or to its more recent arrival to the arena of the evaluation. However, the new policy to fix prices in Germany will also certainly have some influence on the Spanish central decisions, regarding price and reimbursement in the sense that lower prices will be expected for new drugs in the benchmarking process.

In Belgium, pricing and reimbursement decisions for new drugs are based on several criteria, and the current system is already in place since 2002. If a manufacturer of a new drug claims that this drug has an added therapeutical benefit and requests a price premium, compared to current care, then this new drug is evaluated based on 4 criteria:

- 1°. the size of the therapeutical added value;*
- 2°. The therapeutical and social need;*
- 3°. The cost-effectiveness and*
- 4°. The impact on the health care budget.*

Although these criteria are supposed to be investigated at the same time, in practice, the first question that is systematically asked by the Commission for the Reimbursement of Medicines, is the question about the therapeutical added value.

Only if this added therapeutical benefit is clear and agreed upon by the commission members with 2/3rd majority, the other criteria become relevant.

In the meantime, and initially separate from this reimbursement process, the pricing commission compares the proposed price by the manufacturer with prices in other countries, such as Germany (see above). After 3 months, the pricing commission advises the CRM about the acceptability or not of the proposed price level. But it is then the CRM that, based on the above-mentioned 4 criteria, may still decide that the price proposed by the manufacturer (and hence the proposed reimbursement level) is too high given the therapeutical need, the cost-effectiveness and the impact on the budget. The CRM will then force down the price and reimbursement level of the new drug.



Hence, the Belgian system does include, for already more than 10 years, a value-based pricing component.

The new principles and procedures, as set forth in AMNOG, will definitely have an impact on Belgian decisions as well, and it will be in 2 ways. First, the price commission will possibly observe lower prices than before in Germany which may lead to other decisions on approved Belgian prices. Second, and more importantly, the CRM will look carefully at the decisions in Germany related to added benefit of new drugs, and this will certainly influence the commission members. The issue of the right selection of comparator has not been sorted yet in Belgium, since, in contrast to, for instance, Australia, Canada, Sweden, and the UK, the practice of mixed treatment comparisons via network meta-analyses has not yet been well-adopted in Belgium.

CONCLUSIONS

The Act to Reorganise the Pharmaceutical Market (AMNOG) in Germany has obviously had a significant impact on the market ac-

cess and pricing of new pharmaceuticals in Germany. The potential impact of AMNOG outcomes, especially GBA decisions, on the additional clinical benefit and the price decisions with the Spitzenverband der Krankenkassen, might have an impact in some other countries as well, as described in this article. Furthermore, the impact on future clinical development programs of new compounds may be significant as well. Further research and experience in Germany and other countries are needed and awaited. ■



The influence of the reimbursement act on the Polish pharmaceutical market



W.Giermaziak, Home Medical Library, Poland

ABSTRACT

On 12th May 2011, the Act on Reimbursement of Medicines, Foodstuffs Intended for Particular Nutritional Purposes and Medical Devices was introduced to the Polish healthcare system.

After one year of the Act being operational, the government concluded that the bill was bringing certain benefits to the taxpayer by, sometimes, drastic cuts in the immediate profits of producers, importers and retail and wholesale businesses, both in private and public healthcare. Simultaneously with government actions, various analyses are underway from the private sector initiative (including, among other, IMS Health Poland, Pharma Expert, Kamssoft, WHO, and some European law firms).

The implemented changes in the pricing process of medicinal and medical products (a flexible system of price setting); an array of medications with identical/near identical profile into, so-called, limit groups and narrowing the scope of reimbursement to drugs, administered in compliance with their intended use, as well as the integration of the new

legal provisions with the already existing regulations have brought substantial financial benefits to the taxpayer. Rationalisation of expenses, incurred by NFZ (the Healthcare Fund), was the primary goal of the Reimbursement Act, while extending the scope for the use of medication particles, as well as of the latest medical technologies, e.g., in new or modified medication programmes. The aim of this study was an analysis of the overall functioning and results of the Reimbursement Act after one year from its implementation.

THE PHARMACEUTICAL MARKET IN POLAND (2011)

IMS Health Poland's analysis, made on the basis of the elementary indicators characterising pharmaceutical markets in Europe, shows that Poland places far behind in the ranking. The applied parameters included: the total of the pharmaceutical market, average medication prices, reimbursement levels or medication consumption per capita, see Table 1 for a detailed presentation¹. It should be emphasised that the values encompass the year 2011, hence before the implementation of the Reimbursement Act in January 2012.

Keywords:

healthcare system, medications prices, medications refund/reimbursement, pharmaceutical legislation, the reimbursement bill

DOI: 10.7365/JHPOR.2013.3.1
JHPOR, 2013, 1, 72-81

THE REIMBURSEMENT ACT: PREMISES, INTERESTED PARTIES AND PROPOSALS TO CHANGE THE LEGISLATION

The Act of May 12, 2011, on Reimbursement of Medicines, Foodstuffs Intended for Particular Nutritional Purposes and Medical Devices was amended by the Act of January 13, 2012 on Reimbursement of Medicines, Foodstuffs Intended for Particular Nutritional Purposes and Medical Devices (Journal of Laws of 2012, No 0 item 95), its main goal being to rationalize public expenses, while keeping capital dues, which should generate substantial savings for the state budget and a reduction of medication prices for patients. However, the chief goal of the new Act was to bring order to the market of reimbursed medications by enhanced availability of relatively new medications (the Polish market of reimbursed medications encompasses mainly generic products from domestic production and import) and an extending range of innovative Products. Following the Transparency Directive of the

EU, the Act guarantees transparency and contributes to Poland's image of trustworthy, transparent European and world partner in business. The interested parties include all subjects of the pharmaceutical market in Poland (Figure 1, Pharma Expert, 2011).

The major changes, brought by the Act to the pharmaceutical market, include:

- a certain stabilisation and more effective control of public expenses for the reimbursement of medications and medical products, which amount to 17 % of total funds allocated for guaranteed medical services;
- pay-backs when supply limits are exceeded;
- fixed prices (set by the Minister of Health after negotiations with involved parties or their proxies) and fixed wholesale margins for reimbursed medications;
- limit groups under a common financing limit. The limits are set as the highest price out of the lowest wholesale prices

Table 1. Comparison indicators ¹

Comparison of main parameters in 2011 year

Parameter	Poland's position among the other analyzed European markets	Value for Poland	Average value for markets being analyzed	Average value deviation (for Poland)
Total pharmaceutical market	6 of 26	4,9 mld €	---	---
Total pharmacy market per capita	6 of 26	110 €	225 €	- 51 %
Health maintenance expenditures per capita	22 of 23	1 389 \$	3 434 \$	- 60 %
Innovation medications average prices	21 of 22	7,1 €	17,3 €	- 59 %
Generic medications average prices	26 of 27	2,8 €	4,9 €	- 43 %
Patient co-paying medication level	1 of 13	67,0 %	34,4 %	+ 32 pp
Percent of the generic medications of on sale value	1 of 23	66,3 %	39,5 %	+ 27 pp
Medication consumption per capita (in CU unites)	12 of 22	1 400 CU	1 515 CU	- 7,5 %

for a daily dose of a medication (Defined Daily Dose - DDD), which complements 15% of the monthly turnover of a given limit group;

- modified criteria to include medications on reimbursement lists, with a close association with medical product characteristics (supported by verified scientific evidence);
- the decision is made by the Secretary of State for Health after a recommendation from the Transparency Board, an opinion of President of The Agency for Health Technology Assessment (AOTM), the position of the Economic Commission and the clinical and practical importance of assessed product;
- announced publication of the list with reimbursed medications every two months, dynamically illustrating the reimbursement process in Poland;
- elimination of the, so-called, „faulty reimbursement“; So far, a non-reimbursed medication, equivalent to the substance on the reimbursement list and its price being lower than the limit price of the reimbursed medication, could be sold by pharmacy as a reimbursed product. Now, only the products, which are on the list of reimbursed medications, apply for refund;
- banned advertising. The Act, as the first among legal acts, dedicated to healthcare and the only one in the legislation today, has introduced a ban on discounts for medications, foods for special purposes and other medical products at all their distribution levels.

PHARMACY MARKET

Throughout 2011, the pharmacy market was tightly consolidated – about 68 % of all the pharmacies were included in commercial chains or sales groups. The initial capital of chain pharmacies unequivocally reveals their financial associations and business relationships with the biggest wholesalers in Poland. The other pharmacies are in private hands, mostly of family businesses,



Figure 1. Stakeholders

demonstrating various purchasing structures. At the time of the Act implementation, there were 13,985 pharmacies on the Polish market (source: Central Statistical Office 2011). The value of the medications on sale at pharmacies reached the amount of PLN 22.3 billion.

The onset of negotiations on procedures, carried out by the Ministry of Health with involved parties, brought about a considerable panic on the market in December 2011, artificially heated up by the media and demonstrated by unrest at pharmacies and excessive buying. Doctors prescribed more drugs, especially for long-term medical conditions, as well as for popular medical products, e.g., sugar level assessment strips or dressing packages for long-term care. That enhanced trading at pharmacies considerably diminished their stock levels of medical products, sold against prescription, e.g., an average stock volume in October 2011 was sufficient

for 33 selling days, in November 2011, it was enough for 31 days, while in December 2011, the average stock volume was traded within 20 days only. This lower stock potentials in December 2011 and the observed small decreasing tendency in November 2011, could also have been dictated by conscious decisions of pharmacy owners to reduce stocks against the applicable tax policy.

The December rise of pharmacy retail sales caused a soaring increase in the value of reimbursed medications, more distinctive in analyses as the sales rates in January and February 2012 were much lower, probably also for the necessity to refill stocks and gradually return to turnover stability and serving the needs of patients. See Table 2 for a comparison of the pharmacy market values between the years 2010 and 2011.

On the basis of the presented comparison it is difficult to draw unequivocal conclusion as to the vital influence of the results of the act treated as a beacon of drastic changes in the system on the Polish pharmacy market.

A particularly important change is the total ban on advertising of the reimbursed medications, practically, at every trading level. This particular regulation has raised much controversy, stirring emotions among many

products, perceive the Act as unconstitutional and damaging for their profits. The fragment in the Act on banning the advertising is not specific as the Act does not forbid advertising materials to be displayed / exposed at the pharmacy. Moreover, shop-window and outdoor advertising is allowed, as long as it encourages the use of a given product but without any references to the price aspect. As far as the prices of medications are concerned, the Act obligates pharmacists to inform the public about the cheapest equivalents of reimbursed products available at other pharmacies.

The Act obligates the Minister to publish the lists of reimbursed medications every two months and support the Economic Commission to attain desired economic outcomes in negotiations with involved parties. The end effect is the influence of the publication of the reimbursed medications lists on the pharmacy market.

The dynamics of the Polish pharmacy market, observed during the first half-year from the Act implementation is shown in Figure 2, Table 3. A decrease of reimbursement by approximately 1.6%, recorded during that half-year, was a noticeable observation, indicating the efficacy of the Act for the price normalisation trend, while shedding light on the scale of overestimating its benefits, especially as the major costs were still incurred by the taxpayer.

THROUGHOUT 2011, THE PHARMACY MARKET WAS TIGHTLY CONSOLIDATED – ABOUT 68 % OF ALL THE PHARMACIES WERE INCLUDED IN COMMERCIAL CHAINS OR SALES GROUPS. THE INITIAL CAPITAL OF CHAIN PHARMACIES UNEQUIVOCALLY REVEALS THEIR FINANCIAL ASSOCIATIONS AND BUSINESS RELATIONSHIPS WITH THE BIGGEST WHOLESALERS IN POLAND.

Table 2. Comparison of the pharmacy market values between the years 2010 and 2011

BEFORE 1ST JANUARY 2012	AFTER 1ST JANUARY 2012
<p>BANNED ADVERTISING / PROMOTION AT PHARMACIES OF REIMBURSED PRODUCTS AND OF PRODUCTS WITH THE NAME IDENTICAL WITH REIMBURSED PRODUCTS</p>	<ul style="list-style-type: none"> • TOTAL BAN ON ADVERTISING/PROMOTION OF PRESCRIBED DRUGS - EXCEPT OTC PRODUCTS • NEITHER PHARMACY LOCATION NOR WORKING HOURS CAN BE USED FOR ANY PROMOTION • NO ADHERENCE TO THESE RULES MAY SUBJECT OF FINANCIAL PENALTY (UP TO PLN 50.00 THOUSAND)

groups of interest. A group of pharmacist trade unions, who used to lobby this solution, have been supporting its implementation as equalizing the positions of market players. On the other hand, manufacturing and trading businesses, which were before used to unconstrained advertising of medical

tion trend, while shedding light on the scale of overestimating its benefits, especially as the major costs were still incurred by the taxpayer.

The Polish Pharmaceutical Chamber rep-

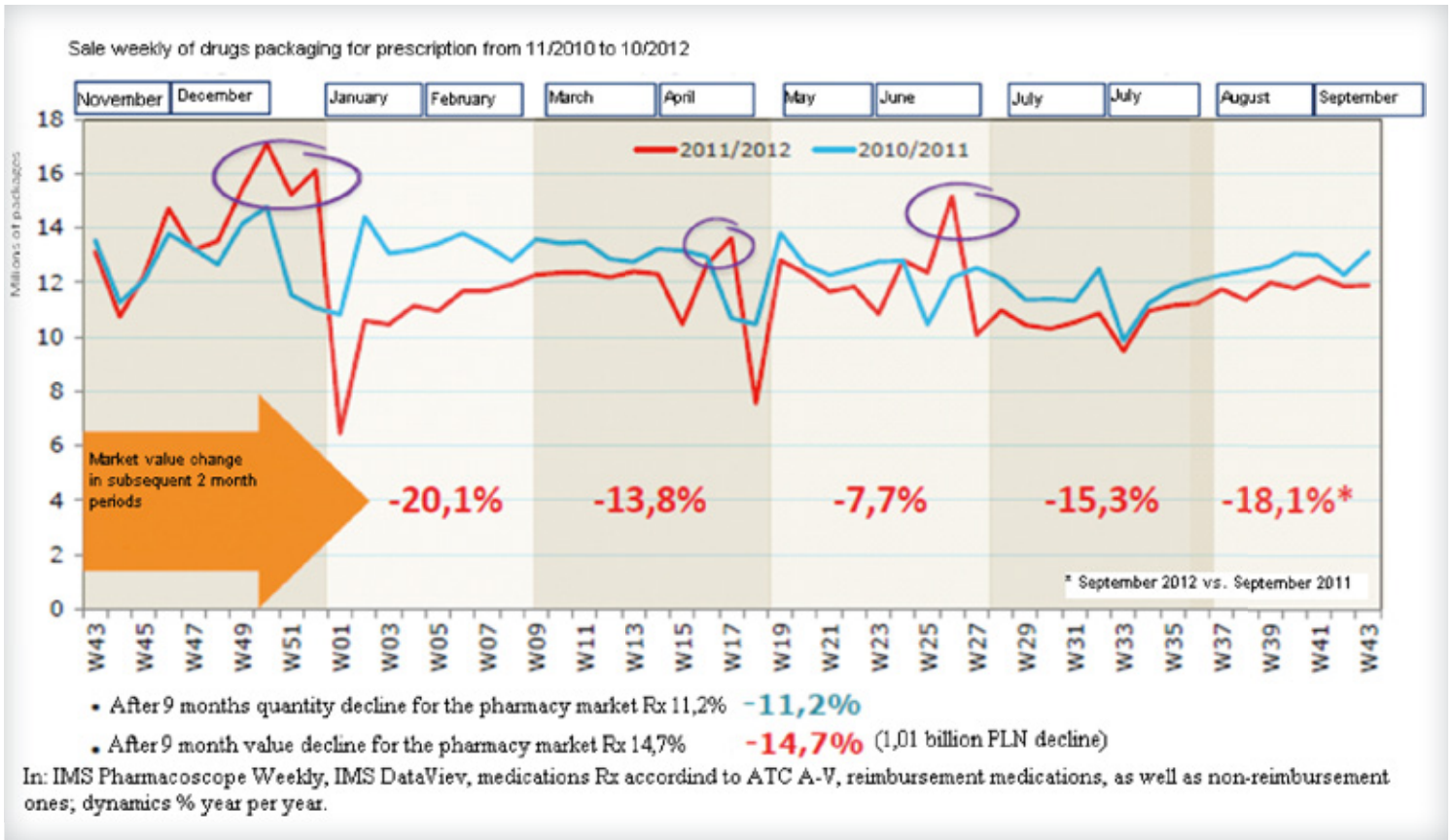


Figure 2. Weekly sale rates of prescribed medications from November 2010 to October 2012

Table 3. Global pharmacy market January-July 2012²

GLOBAL PHARMACY MARKET	JANUARY – JULY 2012	CHANGE %
TOTAL TURNOVER (IN THOUSAND PLN)	15 000 123	-3.7%
REIMBURSED PRESCRIBED DRUGS (IN THOUSAND PLN)	5 558 362	-19.9%
PRESCRIBED DRUGS FOR FULL PRICE (IN THOUSAND PLN)	3 332 489	14.7 %
OTC (IN THOUSAND PLN)	5 998 218	6.4 %
REIMBURSEMENT AMOUNT (IN THOUSAND PLN)	3 932 210	-15.8 %

resents pharmacists in Poland and, as it has been mentioned above, it supported the legislation works on the Act, as well as assisten in its implementation. The crown argument raised by the pharmacists was the government’s proposal to introduce fixed prices and margin on reimbursed medications. *Figure 3 demonstrates that approximately 50 % of pharmacists negatively evaluate the impact of the Act on the condition of pharmacies.*

Before going to the question of patients and their situation after the implementation of the Act, I will present the health condition of the Polish society, based on a sample research by Prof. Johannes Siegrist from the Medical Faculty at the University of Dusseldorf, President of the WHO EURO Work and Employment Task Group. *Life expectancy in the WHO’s European Region in 2010 is shown in Figure 4.*

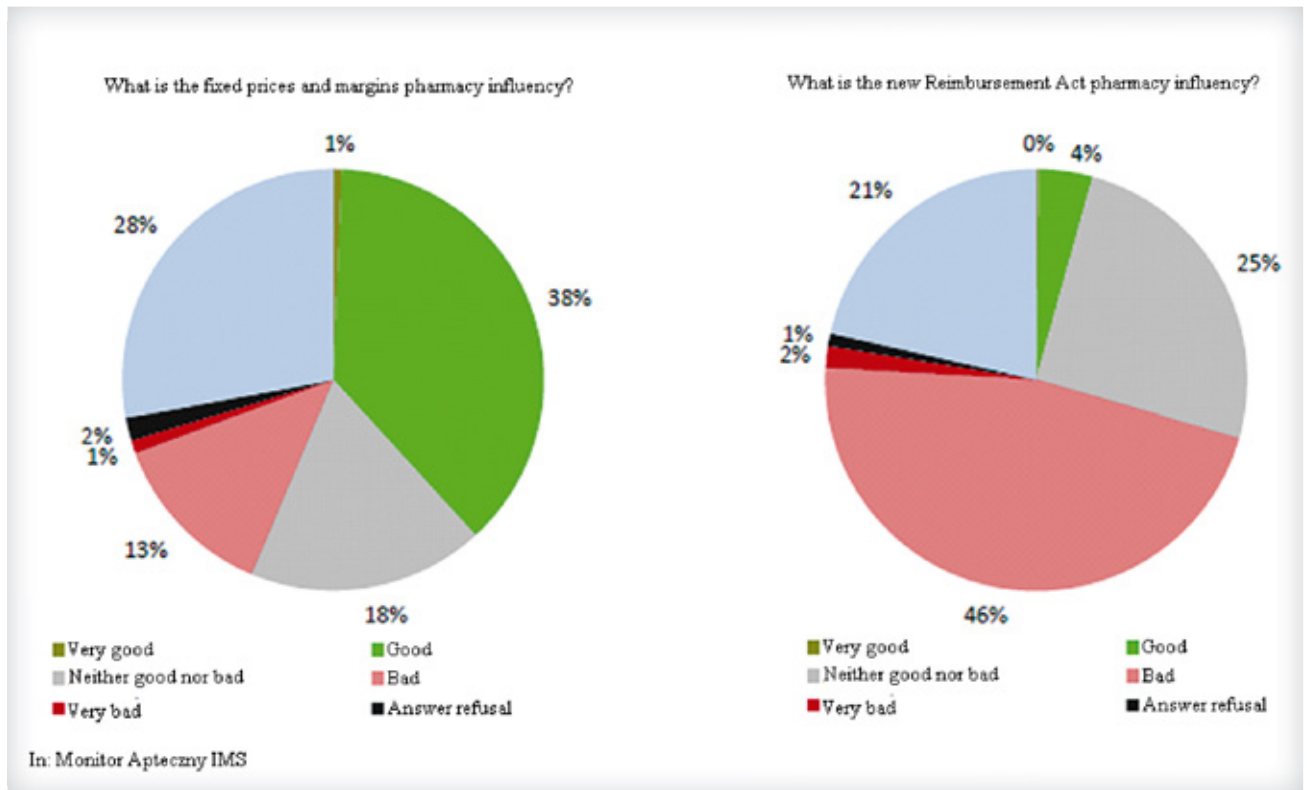


Figure 3. Pharmacists’ perception of the new Reimbursement Act

These results generate a question about the real ownership structure of the pharmacies, while bringing up a real dilemma: vocation or commercialization!?

According to the data, published by the Pharma Expert in the middle of 2012, the estimated predictions of the Polish pharmacy market assume the year 2012 to close with PLN 25.6 billion, i.e., with a decrease of approximately 4 to 6 % vs. the outcome of 2011 and, analogically, the reimbursement would fall by approximately 17 to 19 % vs. 2011 down to PLN 7.1 billion.

In this comparison, Poland ranks the third. Compared with other European countries, it is an average position. However, it may be a bit thought-provoking when social health determinants were analyse on the following three levels:

- the macrolevel: international determining factors, both economic and political: the results of economic growth and economic crisis, threats to the environment, and, most important, the observance of human rights in the context of health-care inequalities;

- the domestic level: the influence of healthcare systems and social policies especially health inequalities and ineffective management systems – governments – e.g., performance of healthcare services;
- the level of life circumstances: a detailed analysis of scientific proof and commissions, regarding the early life stages and childhood, puberty, health-detrimental impacts in the middle age in the context of working life and older age, including age-related medical conditions, demanding treatment and care.

ical unfitnes of various aetiologies (approximately 10 %), overall self-admitted weak health condition (approx. 15 %).

The quoted research and evaluation figures constitute an observation of an average working-age group of the Polish society and should be the point of reference to patients’ data vs. the results of the implementation of the Reimbursement Act.

A reduced patient’s share in the cost of reimbursed medications was one of the objectives of the implemented Act. Data, as provided by research, performed by all

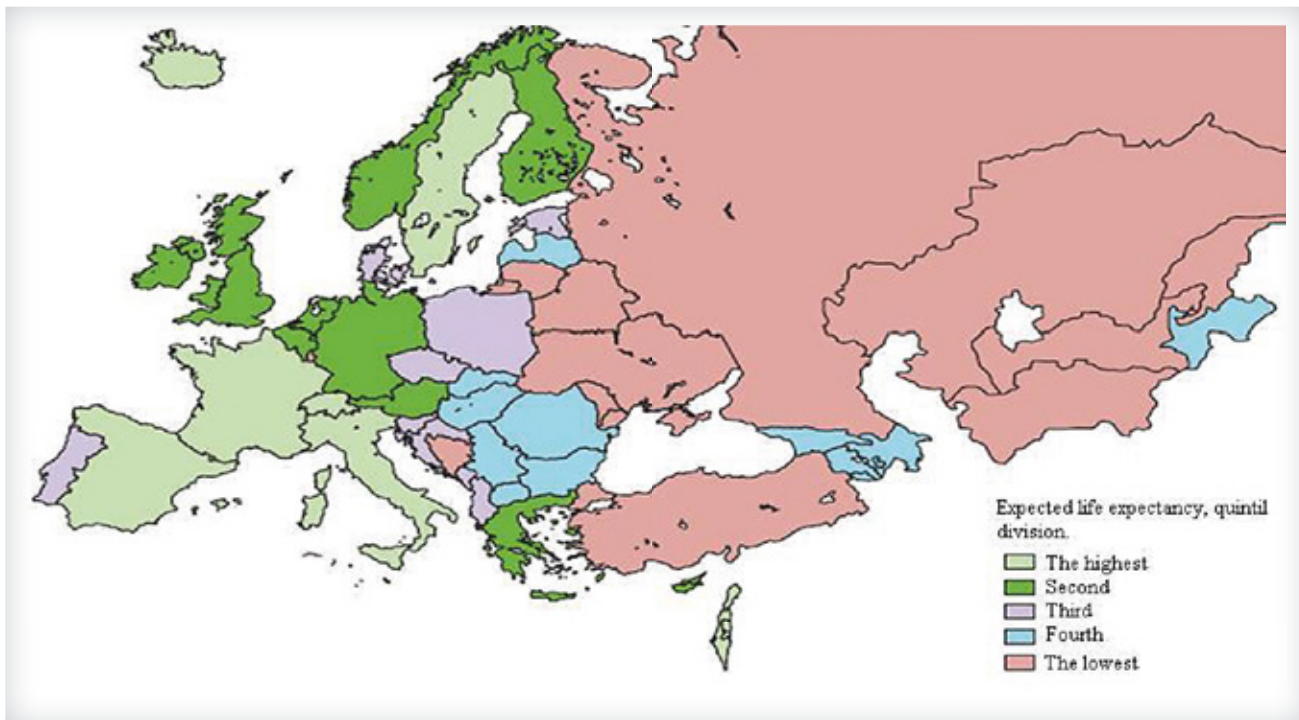


Figure 3. Pharmacists’ perception of the new Reim

The first two periods, childhood and middle age, similarly to all the above-mentioned levels of health determinants, are in correlation with the use of medications, therapeutical systems, thus becoming a target of healthcare policy of the government.

Health, in its quality sense, according to the research the WHO EURO’s Task Group, carried out in middle-aged population shows that this age group is most prone to coronary disease (8 to 15 %), depression (20-25 %), phys-

market participants, constantly monitoring the Polish medications market, indicate a small increase of patient’s share in the initial stage of the Act implementation, which was 34% in 2011, when „faulty reimbursement” was acceptable and patients had an unconstrained access to approximately 4400 reimbursed substances. In 2012, the reimbursed medication lists include 3061 substances and the level of co-payment was 34.9 % (out of that group, 2800 medications were already reimbursed in 2011), while

1600 medications, reimbursed in 2011, are now full-paid. The way of estimating patient's share in the payment for drugs, based on simple adding of the prices of fully-paid medication, which used to be reimbursed before, greatly increases the level of patient's co-payment, which, by this estimation system, reaches 37.9 %, hence an increase by 4 %. This method of estimating the patient's share is detrimental to the Act's objectives, since the medications that did not find their way to reimbursed medications list should not be subject of arithmetic summation of the amount of patient's share, reached in negotiations, due to the fact that there still may be green light for their comeback to reimbursed medication lists, of course by meeting the requirements, specified in the Act and finding a positive approach of responsible subjects. Market arrangements and the time period of the Act being operative have brought about a systematic decrease in reimbursed medication prices, followed by continuous dynamic, qualitative and quantitative changes in published lists. Keeping that in mind and taking into account the growing tendency in the patient's share in the costs of generic (39.6 %) and innovative medications (35.3 %), based on a wrong, in my opinion, premise, leads to a false conclusion that Poland demonstrates the highest level of patient's share in the costs of reimbursed medications.

A much more dangerous phenomenon, which could be observed in the first year of the Act, was a continuous increase in the sales of reimbursed medications at full price. This phenomenon can be explained by the quality changes in the Regulation on prescriptions, whose implementation almost simultaneous with the reimbursement Act, brought much confusion in the doctors' prescription practices, a wave of protest from doctor groups against the Regulation's provision to follow the guidelines of the Medicinal Product Characteristic. The outspoken worry of the doctor groups about possible consequences of wrongly drafted prescrip-

tions supported the ongoing trend to prescribe fully-reimbursed medications.

The system of estimating the limit and recurring changes in the reimbursed medication lists, published every two months, brings a sense of destabilization, particularly in long-term patients. As the time goes by, this phenomenon is gradually disappearing because the prices of the medications are more and more stable, which also points to an overall stabilization on the reimbursed medications market. Another question is the problem of availability of the cheapest equivalents, which should constitute the basis for wholesale and retail trading. However, it is rather difficult to buy the cheapest equivalents in the retail system. The explanation of this phenomenon can be found in the financial policy of wholesalers and the financial relations between them and manufacturers, which can imply the availability of the cheapest reimbursed medications at pharmacies.

DISTRIBUTION AND WHOLESALERS

In result of the Act implementation, a simplified scheme of medication distribution can be presented as follows: the producer/the responsible subject – pre-wholesale – wholesale – pharmacy – the patient. The Act has also introduced vital regulations, lowering wholesale margins and stabilising prices at retail level.

The reduced margins in the distribution chain have brought about urgent cost-cutting, including employment reduction, limited frequency of deliveries and reducing stocks, thus overall substantial changes in the distribution chain. The wholesale market is still a dynamically developing economic sphere, integrally associated with generated national economic outcome. After one year from the Act implementation, it is too early to draw conclusions about this particular sector of the pharmaceutical market. A full reduction of wholesale margin, what is in compliance with the provisions

of the Reimbursement Act, and proposals of the Economic Commission may support a development of pharmaco-economic indicators to assist in a preliminary evaluation of the effects, which the new legislation has brought.

DOCTORS

Based on a phone survey, conducted by the Medycyna Praktyczna Journal between the 6th and the 7th September 2012, out of 200 doctors, participating in the survey by random selection, it is difficult to resist an impression of poor quality in prescribing of reimbursed medications (Table 4, Table 5). The only thing is to hope that this state of affairs will gradually normalize.

CONCLUSIONS

The Reimbursement Act has been the first Act to introduce such vital changes to the healthcare system. Discussing particular issues of the reimbursement system point by point, I have tried to show current effects of the Act. Analysing the economic results of the NFZ and the market pharmaceutical configuration in terms of pharmacological quality, availability and patient's shares in medication costs, it seems that certain amendments to the Act would be necessary, to correct its faults, perceived from the practical perspective of its implementation in the field of actual healthcare arrangements, with stabilisation and normalisation of the medication market in Poland to be its primary targets. ■

Table 4. Reimbursement drugs prescriptions behaviors of polish doctors

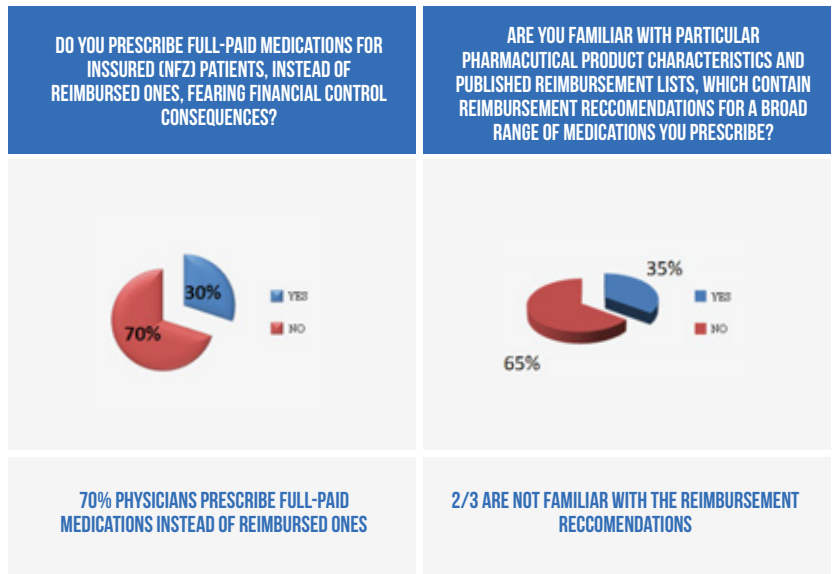
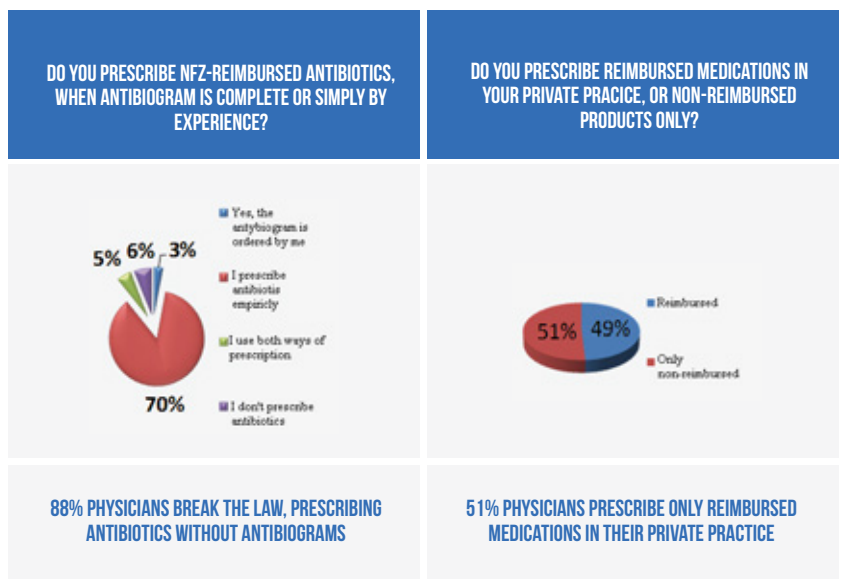


Table 5. Reimbursement drugs prescriptions behioeres of polish doctors



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Limit's groups – reimbursement reflections



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The idea of limit's groups utilized by the Act of 12 May 2011 on the reimbursement of medicinal products, special purpose dietary supplements and medical devices is not an unique concept related only to the field of reimbursed products used for medical purposes.

It results from the natural human need of reality rearrangement. This need manifests in grouping different things and ideas having common properties, usefulness and characteristics. Through the common criteria we can replace each subject belonging to the same group. The grouping is a very frequently observed form of human activity. It begins in childhood (e.g. grouping toys according to their colors, shapes, etc.) and is still present in adulthood (e.g. grouping food/meals according to their main constituent: proteins, carbohydrates, fats). Both childhood and adulthood experiences with grouping help identify things with a similar application. The same concerns medicinal products in the reimbursement system.

The need for seeking methods to avoid an excessive payment for pharmacotherapy available at a lower cost is justified by the fact the prices of so called "original drugs"

are greatly overpriced even after the patent expiry. This is a worldwide phenomena and some available comparisons of Active Pharmaceutical Ingredients (API's) and ready to use product prices are very impressive. According to some examples given by the United States Department of Commerce, the price of one "original" tablet containing 10 mg of amlodipine can be even 134,000% more than the price of 10 mg of the API and the price of one "original" capsule containing 20 mg of omeprazole can be 69,000% more expensive than the same amount of API. Hopefully, there are available generic pharmaceutical products (generics) which offer the same efficacy and safety at a price much lower than branded products. The reimbursed costs/prices of generics decrease along with the increase of the number of available products on the market as a result of commonly known trade rule. This loads to the multiplication of reimbursed units of generics for the same amount of money comparing to the number of soled and reimbursed branded products. It is clearly seen in the number of published reports inclusive of the IMS Health report by Sheppard et al.

Additionally to the price pressure put by generics onto originators who make the costs of medicines more realistic, it is also

Keywords:

December 2012, summary of the lecture given during the 10th International Anniversary Conference of the Polish Pharmacoeconomics Society

DOI: 10.7365/JHPOR.2013.3.1
JHPOR, 2013, 1, 82-83

another way for positive (from the payer's point of view) price regulation of reimbursed drugs. The fact remains that not all drugs containing different (considering the chemical aspect) active substances differ in terms of their mechanism of effect, and consequently indications, safety and clinical efficacy/usefulness. There is a number of very homogeneous groups of drugs in terms of pharmacological properties and the place of therapy despite the fact that they contain different active substances (so called "congeners" or "me-too" drugs). These "new" drugs in contrast to genuinely innovative compounds having new mechanisms of effect or affecting previously unknown points of activity, carry no significant progress into the therapy but benefit from patent protection. They do not undergo competition of generics unless their patent protection expires, and finally generate excessive (unnecessary) reimbursement costs. But we should know (and remember) that the therapeutic effects of the previously mentioned excessively priced drugs, can be obtained by significantly cheaper generics of originators whose patent protection expired.

Thus, the need for establishing limit groups appears obvious - it is dictated by rationalization and economy reasons.

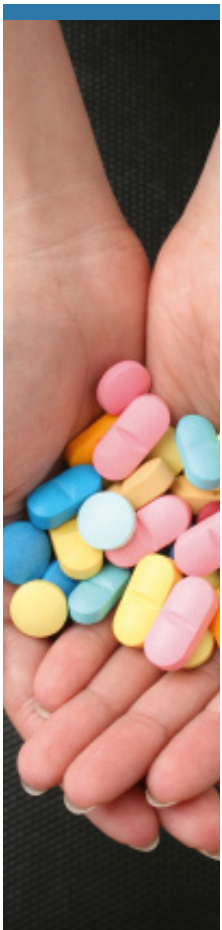
The criteria allowing the qualification of different drugs into the same limit group are defined by the Act of 12 May 2011 on the reimbursement of medicinal products, special purpose dietary supplements and medical devices. They cover the same or different INN but the same therapeutic effect and a similar mechanism of effect. In the process of grouping and establishing limit groups different sources of data and opinions are used including the opinions created by Agency for Health Technology Assessment (AHTA/OTM), members of Economic Commission, ATC classification system, foreign reimbursement decisions/regulations, other sources. The ATC classification deserves special attention - it is a clear,

logical, constantly updated survey of active substances grouped according to criteria which can support majority of decisions on replacement of many drugs with other ones.

The limit lists established under the Reimbursement Act clearly illustrate similarities and possible interchangeability of drugs grouped under the same heading. The best examples are highly homogeneous groups named "Drugs affecting lipid metabolism – reductase HMG-CoA inhibitors", "Anticancer and immunomodulatory drugs – enzyme inhibitors – oral aromatase inhibitors", "ACE inhibitors – single and fixed dose products", "Corticosteroids for inhalation", etc.

The results of establishing limit groups as a barrier for uncontrolled reimbursement and excessive outflow of public money have a positive outcome. This tool of reimbursement regulation guarantees the access to all important drugs for the majority of patients furthermore protects the national economy against wasteful loss of funds. We observe that this opinion is shared by a number of independent bodies not associated or related to the Ministry of Health and the National Health Fund (NHF). This summarizes our opinion that the work of the Economic Committee under on the Act of 12 May 2011 on the reimbursement of medicinal products, special purpose dietary supplements and medical devices has significant share in the process of the improvement of the Polish reimbursement system.

To recapitulate, the idea of the limit groups and their implementation is a very useful and relatively simple tool for creation of positive changes on the market of the reimbursed drugs. It serves the purpose of the optimization of public expenditures for drugs, protects patients against excessive co-payment, and finally, stimulates prescribers to make choices of more cost-effective therapies offering the same clinical efficacy as more expensive therapies. ■



Biosimilar drugs-reimbursement regulations.

Polish ISPOR chapter's Therapeutic Programs and Pharmaceutical Care (TPPC) task force report



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Keywords:
biosimilar, health technology assessment, reimbursement

DOI: 10.7365/JHPOR.2013.3.1
JHPOR, 2013, 1, 84-91

ABSTRACT

Objectives: Due to the increased number in biosimilar drugs getting marketing authorization, there is a question to be answered which reimbursement procedure should be followed

Methods: The TPPC task force has checked the approach to biosimilar drugs by WHO, at the EMA level and in a few countries worldwide. Among other aspects discussed, we concentrated on the production process of the reference (original) drugs and biosimilars and looked for differences. An internet search was performed checking the definitions as well as regulatory and reimbursement processes worldwide, with focus on the countries having HTA procedure in place.

Findings: It was found that due to specifics of biosimilars, detailed and comprehensive regulatory processes have been established centrally for EU states. No reimbursement guidelines have been identified. Due to lack of specific reimbursement guidelines TPPC agreed on a need to define a biosimilar drugs reimbursement process in Poland.

TPPC task force also agreed that due to central European registration pro-

cess the definitions for biosimilar drug in Poland should be in line with the EMA guidelines.

The reimbursement process is different in each EU member state and it should be defined for these products on a country level. Probably, it also requires specific guidelines to be developed, especially in countries such as Poland with "HTA dependent reimbursement process".

Conclusions: TPPC task force has only identified regulatory guidelines and its opinion is that in Poland, a detailed reimbursement process should be developed in the way it also includes the biosimilar drugs.

BACKGROUND AND OBJECTIVES

Since the European Union (EU) introduced the Directive 2004/27/EC biosimilar drugs started to be registered by European Medicines Agency (EMA)¹. These drugs are similar to reference (original) biological drugs, which contain an active substance such as protein or protein complex and can be produced only by living cells. This group of drugs and the regulations related to registration/marketing authorisation create many discussions around the world. Especially the

immunogenicity is an issue which cannot be ignored. We do not always observe clinical effect with the antibodies formation. However, sometimes the clinical effects are significant and could be the cause of severe disease. Immunogenicity may impact efficacy, biodistribution and pharmacokinetics of the drug, which can cause toxicity and interfere with other therapeutic products. Hypersensitivity reactions, cross-neutralization of endogenous substances, or changes in physiological functions can also be a result of immunogenicity.

There are many drug-related factors which can have influence on the immunologic system, like manufacturing process, formulation, dosage, packaging process and storage conditions.

As the patients' safety is unquestionably of the biggest importance, the regulations implemented in the countries for registration/marketing authorisation and reimbursement should take it into consideration. 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 would be reasonable if biosimilar drugs were subject to the same formalities as reference (original) drugs. Within the EU the drug registration/marketing authorisation process is unified with the central procedure, which is not the case in other countries across the world where the registration/marketing authorisation process is linked or followed by reimbursement process, which finally has an impact on drugs availability for patients. Due to more biosimilar drugs registrations expected in the future, there is a question to be answered regarding the reimbursement procedure to be followed.

Neither the provisions of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human nor the Polish Act of September 6, 2001 Pharmaceutical Law does not provide a legal definition of bio-

logical or biosimilar product. Both legal regimes recognize, however, that the biological products which are similar to biological reference product (ie. biosimilar products) cannot be identified with generic products and, therefore, provide specific rules for the marketing authorization of biosimilar products. The TPPC task force searched for solutions in other countries, which could be implemented in Poland.

METHODOLOGY

The TPPC task force started discussions about the biosimilar drugs reimbursement pathways in 2011. The approach to biosimilar drugs worldwide with special focus on EU and at the EMA level was checked.

A review of current legal regulations concerning biosimilar drugs has been performed with special attention to definitions of biosimilar drug, regulatory processes implemented and reimbursement guidelines in place in different countries. There was no limitation towards the countries in scope.

Different databases have been reviewed to identify published regulations concerning biosimilar drugs across the whole world. Special search focus was on reimbursement regulations and on guidelines issued by worldwide known and experienced Health Technology Assessment (HTA) Agencies. The Polish HTA, when preparing the verification analysis related to the assessed product, checks the reimbursement guidelines issued by National Institute for Health and Clinical Excellence in UK (NICE), in Scotland by the Scottish Medicines Consortium (SMC), by Haute Autorite de la Sante in France (HAS), in Australia by Pharmaceutical Benefits Advisory Committee (PBAC), and in Canada by the Canadian Agency for Drugs and Technologies in Health (CADTH)².

The search done by TPPC focused on the following words: "biosimilars", "biosimilar drug definition", "guidelines", "HTA", "reimbursement", "reimbursement guidelines" and it was conducted using Internet.

THE TPPC TASK FORCE STARTED DISCUSSIONS ABOUT THE BIOSIMILAR DRUGS REIMBURSEMENT PATHWAYS IN 2011. THE APPROACH TO BIOSIMILAR DRUGS WORLDWIDE WITH SPECIAL FOCUS ON EU AND AT THE EMA LEVEL WAS CHECKED.

The identified definitions and regulations have been presented at the TPPC task force meetings and discussed by team members in terms of suitability for adaptation to the Polish health care system.

FINDINGS

Among other aspects discussed by the task force, we concentrated on the production process of the reference (original) biologic drugs and a biosimilar drug looking for differences. Finally an agreement was reached that following EMA regulations there is a need to define what a biosimilar drug is in the Polish legal system. The TPPC task force agreed on the following definition:

Biosimilar drug is a drug produced using biotechnological methodology and it is similar in terms of medicinal product design, pharmacological and pharmacokinetic properties, safety and efficacy, but not identical to the original registered and authorized reference biological medicinal product.

This definition was presented to the Board at the Polish ISPOR Chapter meeting in December 2011 as the one proposed to be included in the future legal acts regarding reimbursement and HTA.

Regarding legal regulations on biologic drugs legislation including biosimilar drugs search, it was found that the regulations started to be prepared and implemented in those countries where the biosimilar drugs are already in the market or are expected in a short term.

In 2012 EMA issued a draft revised 'overarching' guideline on similar biological (biosimilar) medicinal products for consultation. In addition, EMA have issued and continue to update product specific biosimilar guidelines which are available on the EMA website³.

Among other information available on EMA website the following definition on biosimilars can be found: "a similar biological or ,bi-

osimilar' medicine is a biological medicine that is similar to another biological medicine that has already been authorised for use", "Biological medicines are medicines that are made by or derived from a biological source, such as a bacterium or yeast. They can consist of relatively small molecules such as human insulin or erythropoietin, or complex molecules such as monoclonal antibodies⁴.

So far, EMA have assessed 15 applications on biosimilars submitted by different com-



panies, 12 out of 15 have been authorized by EMA for use in the EU (including one with patient safety warning), for 1 biosimilar EMA has recommended the refusal of marketing authorization and for 2 biosimilar drugs the marketing authorisations have been withdrawn at the request of the marketing-authorisation holders (companies)⁵.

Apart from the detailed guidelines taking into account transparency issues for the public, EMA publishes general information on biosimilars, including requirements for authorization of biosimilar medicines, indicating that the company needs to carry out studies to show that the medicine is similar to the reference medicine, does not have any meaningful differences from the reference medicine in terms of quality, safety or efficacy⁴. EMA, in the last Directive regarding pharmacovigilance and amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, considers safety monitoring of biosimilar drugs as a priority. It states that some medicinal products are authorised subject to additional monitoring. This includes all medicinal products with a new active substance and biological medicinal products, including biosimilars, which are priorities for pharmacovigilance⁶.

For transparency reasons, in September 2012, EMA published a brief document titled "Questions and answers on biosimilar medicines (similar biological medicinal products)"⁷. EMA published first adopted guidelines on similar biological medicinal products in September 2005 (effective since October 2005) as the result of Committee for Medicinal Products for Human Use (CHMP) discussion which took place in June-November 2004⁸.

The approach by the World Health Organization (WHO) is that biosimilar medicines are biotherapeutic products that are similar in terms of quality, safety and efficacy to the reference product already licensed. WHO provides globally accepted norms and standards for the evaluation of biosim-

ilar products. Written standards established through the Expert Committee on Biological Standardization (ECBS) serve as a basis for setting national requirements for production, quality control and overall regulation of biological medicines. In addition, International Standards for measurement are essential tools for the establishment of potential for biological medicines worldwide. Therefore, WHO has developed guidelines for the assessment of biosimilar products (SBPs)⁹. The intention of this document is to provide globally acceptable principles for licensing biotherapeutic products that are claimed to be similar to biotherapeutic products of assured quality, safety, and efficacy that have been licensed based on a full licensing dossier. On the basis of proven similarity, the licensing of SBPs will rely, in part, on non-clinical and clinical data generated with an already licensed reference biotherapeutic product (RBP). This guideline can be adopted as a whole, or partially, by national registration authorities worldwide or used as a basis for establishing national regulatory frameworks for licensure of these products.

WHO guidelines specify the key principles of licensing SBPs that indicate the need to demonstrate comparability to the reference product in both preclinical studies and clinical trials. Full documentation on the quality of both the drug substance and the drug product is always required to meet the standards required by the national regulatory authorities in relation to innovative products⁹.

In the United States (US) the Food and Drug Administration Agency (FDA) defines that a biosimilar is a biological product that is highly similar to a U.S.-licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product¹⁰.

The Association of British Pharmaceutical Industry (ABPI) working on the biosimilar topic recommended that biosimilar medicines should be subject to full Health Technology Assessment processes in the UK as for other medicines in order that they can be appropriately assessed for clinical and cost effectiveness using the appropriate evidence base. It should be stated clearly in the main section of the HTA guidance that is issued that the medicine appraised is a biosimilar¹¹.

ABPI also recommends that biosimilar products should be recorded on UK PharmaScan by companies as soon as they enter Phase III clinical trials or within three years of their expected launch date so they can be reported upon by the NHS horizon scanning agencies for HTA topic selection purposes¹¹.

The Scottish Medicines Consortium (SMC) and All Wales Medicine Strategy Group (AWMSG) (where appropriate) should routinely appraise biosimilar medicines and the NICE topic selection process should be used to identify those biosimilars which should be subject to NICE appraisal¹¹.

In Australia Pharmaceutical Benefit Advisory Committee (PBAC) an independent statutory advisory body to Minister of Health in its current guidelines for HTA (2008 version of the PBAC Guidelines) plan as next step to consider further guidance in relation to other technical policy issues and, among others, the biosimilars are in scope¹².

Japan's Ministry of Health, Labour and Welfare (MHLW) has issued guidance on biosimilars, which sets out the policies regarding requests on development and regulatory approval application for biosimilars in Japan, according to a report by Pharma Japan¹³. The definition is as follows: „Biosimilars are drugs which are equivalent and homogeneous to original biopharmaceuticals in terms of quality, efficacy and safety and which are developed by manufacturers different from

those of the original biopharmaceuticals“.

WHO guidelines were used as a reference and basis to create local guidelines in many countries. The organization makes the information about the adapted and implemented guidelines available on their website.

According to the published information the biosimilar drug is defined and regulatory guidelines are available in the following Latin American countries¹⁴.

The President of Mexican United States in 2011 issued a Decree that amends and adds various provisions to the regulation of health supplies, defining SBP as non-innovative biotechnological drug that proves to be bio-comparable in terms of safety, quality, and effectiveness, based on the specific tests established for this purpose by the law.

In Cuba in 2011 the Ministry of Health published the Resolution number 56/2011 specifying the requisites for registration of known biological products, and according to that resolution the SBP is a biological product produced by multiple manufacturers, in which the active substance is comparable in terms of quality, safety, and efficacy profiles to the active substance of an already licensed RBP in Cuba or in other countries. The dosage form, the potency, and indications should be the same as those of the RBP.

In Guatemala, biosimilar drug is defined as biologic/biotechnological medication that has demonstrated, by an exercise of biosimilarity and biocomparability, that is similar or comparable in terms of quality, safety, efficacy, and immunogenicity to the reference medication (Technical standard 67-2010: Sanitary reference registry of biological and biotechnological products/Ministry of public health and social assistance, 2010).

Costa Rica defines SBP as biological

medication that has been demonstrated by the exercise of biosimilarity to be similar in terms of quality, safety, and efficacy to the reference biological medication (RTCR 440: 2010 Regulation on the inscription and control of biological medications/ Presidency of the Republic – Ministry of Health).

Regulatory guidelines related to biosimilar drugs were also identified in India, Saudi Arabia, Turkey, Iran, Pakistan and Korea.

In India in 2012 the "Guidelines on Similar Biologics" have been published. They were prepared by Central Drugs Standard Control Organization (CDSCO) and the Department of Biotechnology (DBT) lay down the regulatory pathway for a similar biologic claiming to be similar to an already authorized reference biologic¹⁵.

The guidelines address the regulatory pathway regarding manufacturing process and quality aspects for similar biologics. These guidelines also address the pre-market regulatory requirements including comparability exercise for quality, preclinical and clinical studies and post market regulatory requirements for similar biologics¹⁵.

The Drug Sector of the Saudi Food and Drug Authority (SFDA) as an organization that is concerned about availability of medicines and safety of patients, in December 2010 issued the guidelines related to biosimilar drugs registration process in Saudi Arabia¹⁶. The content of this document was assembled through extensive search and research of the European Medicines Agency (EMA) Guidelines, the International Conference on Harmonization (ICH) Guidelines and other resources including published, peer reviewed articles. The guidelines should be revisited biannually for evaluation, improvement, revision, and amendment. Just as for conventional chemical products, the prerequisites for marketing authorization of a biosimilar are proof of quality, safety, and efficacy. These three issues must be clearly addressed when assessing com-

parability between a biosimilar and the reference medicinal product.

In Turkey the first guidelines for registration of biosimilar drugs were published in 2008, since that time some changes have been introduced¹⁷. The document introduced the concept of biosimilar medicinal products and guidelines for application. Reference documents for similarity statements and definitions were EMEA/CHMP guidelines.

The parliament in Pakistan approved mandate of the Drug Regulatory Authority of Pakistan (DRAP), but also defined a separate registration pathway for Biologics and guidelines for Biosimilars (in line with WHO Guidelines)¹⁸.

In Korea biosimilar product is regulated under the same regulation as biological products. The difference from new biological product is that biosimilar product requires full comparability data with reference product. Korean guideline for biosimilar products was developed in line with the WHO's guidelines and most of the recommendations were based on similar principle. The difference is in relation to the clinical evaluation required to demonstrate similarity¹⁹.

DISCUSSION

Poland being part of EU follows the EMA regulations in relation to the regulatory process. EMA is working on the best approach to biosimilar drugs implementation in Europe but the focus is on the regulatory process taking into consideration the differences towards the reference (original) biological drugs and safety issues. However, drug registration/marketing authorisation is not equal to access to treatment. Many European countries have specific reimbursement procedures or guidelines in place and some of them take into account the economic arguments in the decision-making process. In those countries there are special agencies or dedicated governmental bodies estab-

JAPAN'S MINISTRY OF HEALTH, LABOUR AND WELFARE (MHLW) HAS ISSUED GUIDANCE ON BIOSIMILARS, WHICH SETS OUT THE POLICIES REGARDING REQUESTS ON DEVELOPMENT AND REGULATORY APPROVAL APPLICATION FOR BIOSIMILARS IN JAPAN, ACCORDING TO A REPORT BY PHARMA JAPAN

lished to assess the new health technology impact on the healthcare system, clinical and economic value of the new technology and its safety. As an example we can consider the impact of NICE on the final decisions to finance a new product in UK or the Polish HTA agency (AHTAPOL) influence in Poland.

The TPPC task force, as part of the Polish Pharmacoeconomical Society, is interested in the current reimbursement regulations and is looking for the future trends within the Drug dedicated Programs in Poland which have identified biosimilars entry into the Programs as a potential field for further development and discussion. Firstly the biosimilar drug definition was discussed as the starting point for further discussion. There is no doubt that Poland being a member of EU should follow EMA regulations and the definition proposed by Polish TPPC task force was in line with the one proposed by EMA.

Concentrating the efforts on reimbursement guidelines it was expected that during the search a reimbursement specific guidelines or HTA guidelines which would include an approach to biosimilar drugs would be identified. This has not happened. In our opinion it does not mean that there is no need for such guidelines. The example of PBAC in Australia, planning inclusion of biosimilar drugs in the next HTA guidelines edition confirmed the TPPC task forces opinion that a similar process is needed in Poland. Members of TPPC task force discussed it and agreed on the need to include, the definition of biosimilar drugs in the existing guidelines for Poland and also to define the requirements to be fulfilled for reimbursement.

CONCLUSIONS

Having EMA, WHO and FDA guidelines in place is not enough. Local regulations and legal acts should address multiple areas, going beyond the regulatory approval process. Due to only regulatory guidelines being identified, the TPPC task force's opinion is that in Poland, a country which has HTA regulations

in place, a detailed reimbursement process should be developed including the biosimilar drugs' presence. It should not be solely limited to the cost – effectiveness of the new technologies and the impact on payer's budget but also the evaluation of the efficacy and safety in comparison to the standard therapy used should be considered. ■

ACKNOWLEDGEMENTS

We would like to express our gratitude to Iga Lipska for her assistance regarding EMA position



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The evaluation of the effectiveness of funding treatment programs in rheumatology



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Keywords:
biological drugs
in rheumatology,
pharmacoeconomics,
therapy cost

DOI: 10.7365/JHPOR.2013.3.1
JHPOR, 2013, 1, 92-109

BACKGROUND

Abstract: The public payer in Poland has been financing biological drugs in rheumatology since 2004. Until now, there have been no analyses of the influence of this type of funding on the cost level for the public payer. Financing over an 8 year period allows an objective approach towards the results.

Materials and methods: Data extracted with the use of data tools reported to the National Health Fund (NFZ) by health service providers, including drugs used in a patient's therapy. For data analysis, statistic tools were used: Statistica 9 and 10 and Excel spreadsheet.

Results: The number of people treated in Poland with biological drugs is approx. 5% of the potential population with rheumatoid joint inflammation diagnosis and juvenile idiopathic joint inflammation. In the analyses, the results of the Kobelt-Kasteng report have been confirmed, referring to the differences existing in Europe when it comes to therapy cost disparity. The cost of therapy in Poland increases depending on the

type of therapy: infliximab (for patients up to 70kg), then rituximab and etanercept, adalimumab and infliximab (for patients over 70kg). The calculated price index and therapy cost indicates that the costs of such therapies are lower in Poland in comparison with other countries. The r-Pearson correlation factor of 0.61 to 0.73 indicates that there is an accurate balance between the number of clinics conducting the therapy and the number of patients. In the analyzed period, the budget for the rheumatology biological drug therapy increased.

INTRODUCTION

The development of medical technologies, both in the area of medical and drug technologies, allows better patient care and a more effective treatment of various diseases which have not had enough therapeutic options so far. At the same time, the public payer in Poland has been asked to cover additional expenses. In the organization of the health care system in Poland, which is financed entirely by the public payer, so-called therapeutic programmes have been introduced, which allow strict spending control, and they are considered to be a temporary stage before adding the



drug to the reimbursement drug list. Financing new and expensive technologies in the form of a separate budget, meant for therapies of particular diseases, began in Poland in 2004. The first of such programmes was the rheumatoid joint inflammation program financed in the Silesian Province. In spite of the fact that the programme lasted for 8 years there are no publications which would allow an effective assessment of this form of payment for health care services, which makes one think, that an attempt to make such an assessment is a necessity. In rheumatology, financial settlement of health services in the form of therapeutic programmes was used in rheumatoid joint inflammation treatment with leflunomid and biological drugs (adalimumab, etanercept, infliximab, rituksimab). The goal of this study was to analyze the health programme used in 2004 in various forms in rheumatology to assess:

1. if the form of the therapeutic programme allows limiting therapy costs in the observed period of time;
2. if the form of the therapeutic programme does not have any negative influence on the availability of the therapy and the drug distribution in particular regions of Poland;
3. the level of the therapeutic programme budget use and regional differences.

MATERIAL AND METHODS

Health services are financed by the Na-

tional Health Fund in Poland (NFZ) on the basis of the Act and Health Ministry Ordinance^{1,2,3}. Treating patients within the scope of rheumatological diseases on the therapeutic/drug programme is based on the health services contract on the conditions of hospital health service (so-called hospital contract). The organization, financing, and financial settlement of health services are specified for service contractors in the NFZ CEO flats^{4,5}. The financial settlement is based on an xml announcement specified by the Ministry of Health ordinance, which includes unique patient identification number (PESEL number) and the medical procedure code which was used with the particular patient^{6,7}. The reporting has a hierarchical character, which means the code of the signed contract and the code of the medical procedure which was used are reported. The NFZ data has been analysed in terms of: contracts and reporting when it comes to contract realization for therapeutic/drug programmes in rheumatology. Analysis of the data related to the period 2004-2012, in which biological treatment in therapeutic programmes was funded. Different drugs are incorporated into the programme at different times and this is reflected in the description of tables and figures. In the search, SQL query has been used and computer application Business Object in 6.5 version and XI using a filter which is in accordance with the scope code (different for different years), for which contracts have been signed and the code of the medical procedure used (different in reference to various active substances). The data concerning the drug gross costs in particular countries was taken from

THE DEVELOPMENT OF MEDICAL TECHNOLOGIES, BOTH IN THE AREA OF MEDICAL AND DRUG TECHNOLOGIES, ALLOWS BETTER PATIENT CARE AND A MORE EFFECTIVE TREATMENT OF VARIOUS DISEASES WHICH HAVE NOT HAD ENOUGH THERAPEUTIC OPTIONS SO FAR.

IMS Health company (1st quarter of 2010). For the correlation analysis r-Pearson correlation factor has been used for the data set "Region population" vs. "Drug costs" and "Region population" vs. "The number of patients" included in the Excel spreadsheet and Statistica 9.0 program. In order to standardize the results concerning patient therapy costs in various European countries the index weights have been calculated according to the formula:

RESULTS

The potential population of patients, with the assumption that the epidemiology will be similar to other countries, could account for approx. 60,000 people^{8,9}. According to the information reported by the service providers, this is the number of patients who were diagnosed with M05, M06 or M08 (Table 1):

The number of all the patients in 2012 exceeded 80,000 people, but among this number there are people who were diagnosed with the disease and the therapy was not conducted (the diagnosis was then changed in the process). The conducted analyses of drug prices and costs revealed considerable differences, the biggest differences exist in Austria for biological drugs, the lowest in Great Britain (Etanercept), Hungary (Adalimumab, Rituximab) and France (Infliximab). The range of drug costs (the price of 1mg in Euro) between the countries chosen for the analysis is (with the minimal price basis): for Leflunomid approx. 650%; for Etanercept 224%; for Adalimumab 248%; for Rituximab 291%; for Infliximab 268%.

$$Inx_{cen} = \sum_{LEFLUNOMID}^{cena\ 1\ mg} + \sum_{ETANERCEPT}^{cena\ 1\ mg} + \sum_{INFLIXIMAB}^{cena\ 1\ mg} + \sum_{ADALIMUMAB}^{cena\ 1\ mg} + \sum_{RITUXIMAB}^{cena\ 1\ mg}$$

for prices – the total price for 1mg of particular drugs (where cena=price)

$$Inx_{kosztu}^{roczny} = \sum_{LEFLUNOMID}^{wart\ terapii} + \sum_{ETANERCEPT}^{wart\ terapii} + \sum_{INFLIXIMAB}^{wart\ terapii} + \sum_{ADALIMUMAB}^{wart\ terapii} + \sum_{RITUXIMA}^{wart\ terapii}$$

for the cost of annual therapy – the total price of the therapy with particular drugs (where roczny koszt=annual cost and wart terapii=the cost of the therapy)

The assumption which was made during the research is that a higher index value corresponds with higher patient therapy cost in the country regardless of the drug with which the therapy was conducted. In calculating the cost of the treatment, the treatment regimen defined in the Product Characteristics was used.

Table 1. Number of patients with diagnoses M05; M06; M08 between 2004-2012

ICD-10	2004	2005	2006	2007	2008	2009	2010	2011	2012
M05	66 554	67 589	69 578	70 540	76 661	79 808	80 529	82 794	80 374
M06	27 174	26 991	28 056	28 442	31 552	33 564	34 024	35 620	33 871
M08	3 031	3 258	3 266	3 199	3 284	3 422	3 467	3 638	3 411

The data analysis has confirmed the results of the Kobelt-Kasteng report¹⁰. The difference in the average cost of treatment of a patient has been observed between Western Europe (12,900 € which is 52,995 PLN) and Central-Eastern Europe (3,750 € which is 15,405 PLN). The total cost of the Rheumatoid Joint Inflammation treatment (RZS) in Europe reaches € 25.1 billion (103.1 billion PLN).

The calculated price index showed absolutely the highest value of drug prices in Austria, Switzerland and Germany ranked second, while the lowest price index occurs in England, Hungary and Poland. A comparison of therapy costs is possible with the use of the calculated price weight index. One can also use weights specified by the cost of one-shot and annual therapy. In the case of one-shot therapy per patient, the weight

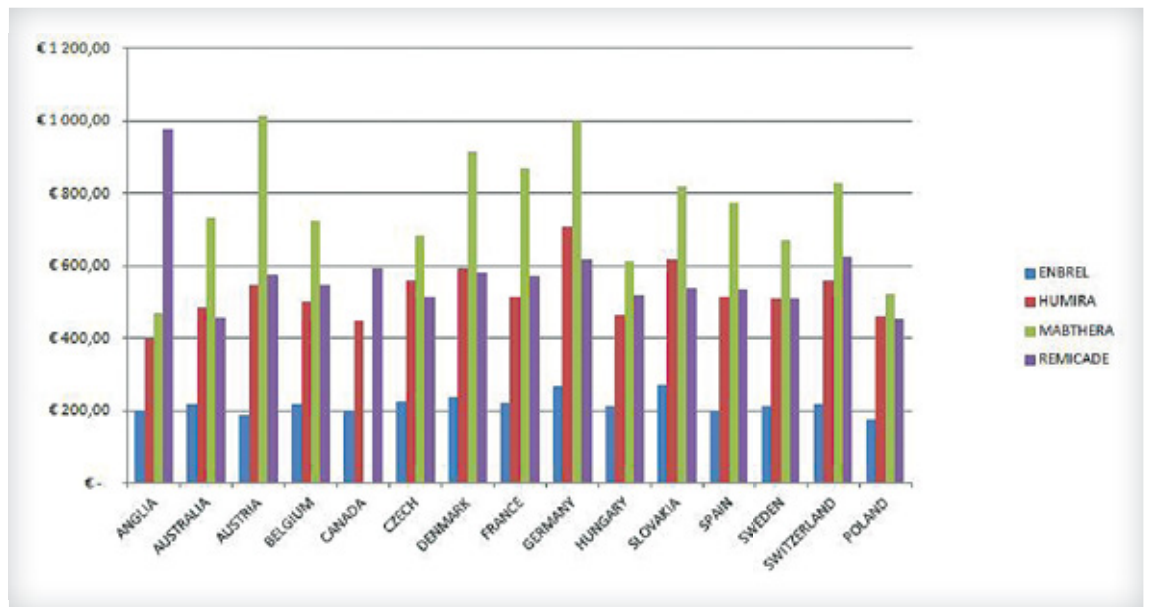


Figure 1. Comparison of 1 ampoule of biological drug in various countries (producer net price in 2009)

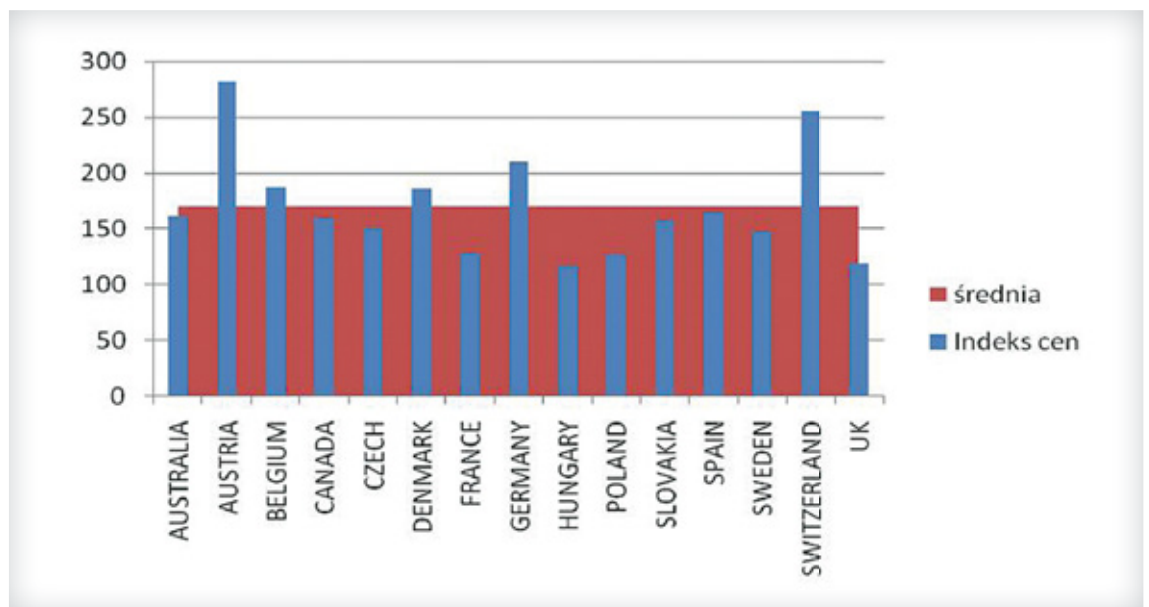


Figure 2. The ranking of particular countries according to the drug cost index (1mg, gross, in PLN)

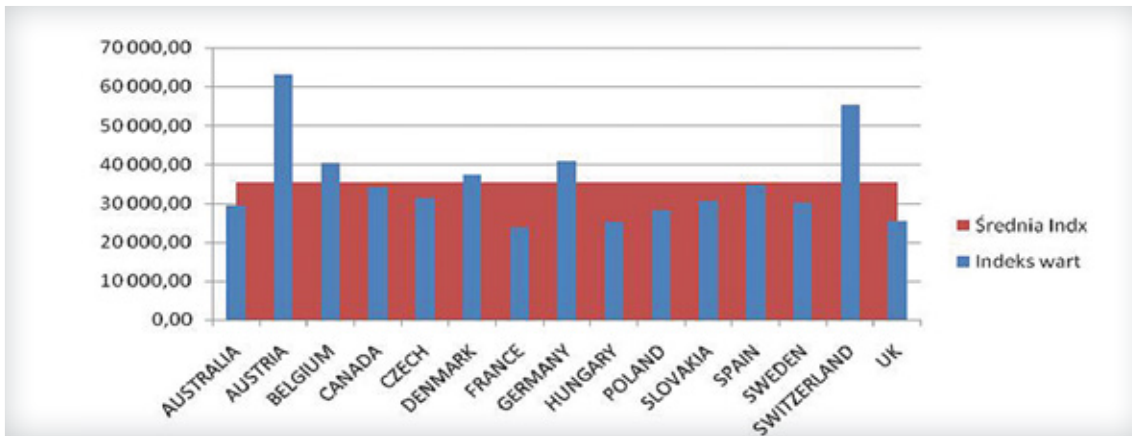


Figure 3. The ranking of particular countries according to the one-shot therapy value

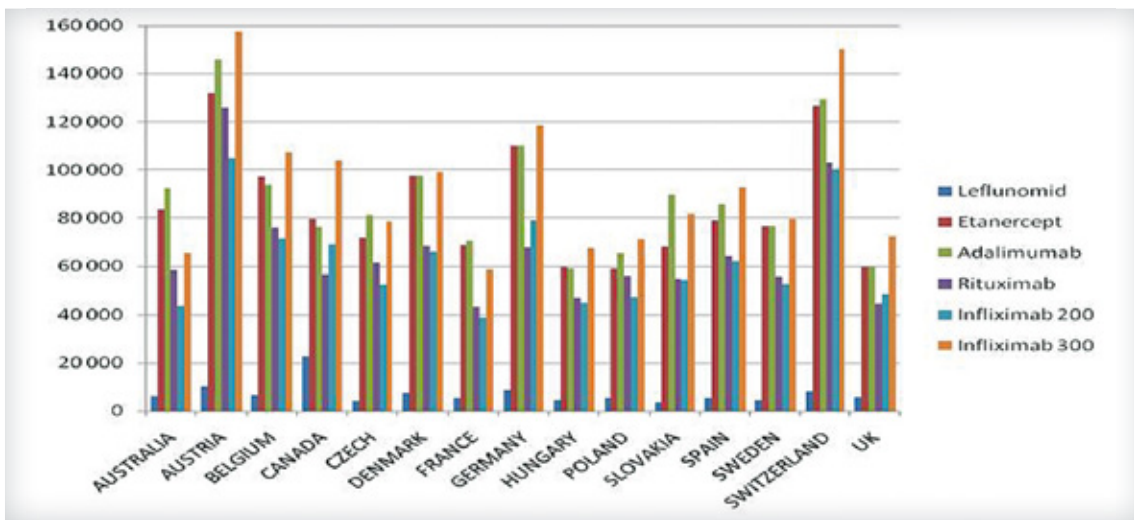


Figure 4. The value of the annual therapy of one patient (in PLN) with a particular drug molecule in particular countries

Table 2. The number of patients, together with the kind of drug used, treated in rheumatology therapeutic programmes in 2004-2010

	2004	2005	2006	2007	2008	2009	2010
ADALIMUMAB				1	106	242	937
ETANERCEPTUM			621	1089	1350	1397	1730
INFLIXIMAB ETANERCEPT	140	529					
INFLIXIMABUM			274	396	642	739	484
LEFLUNOMID		2328	2656	2686	2804	2764	2701
RITUXIMABUM				13	178	337	401
TOTAL	140	2857	3551	4185	5080	5479	6253

index of one-shot therapy has been calculated.

The highest cost of one-shot drug therapy is in Austria and Switzerland, the lowest one is in Great Britain and France. Costs of annual therapy with particular drugs depend on the price of the drug, the dosing method

and, in the case of Infliximab, the patient's weight.

The highest costs of biological treatment per patient are in:

- Austria – adalimumab treatment is the most expensive one among the ana-

Table 3. The value of money spent on leflunomid therapy in particular provinces in 2004-2009

NHF (NATIONAL HEALTH FUND)	2005	2006	2007	2008	2009	2010	TOTAL
DOLNOŚLĄSKI	191 140,00	409 021,20	346 720,40	509 924,78	592 737,60	693 705,12	2 743 249,10
KUJAWSKO-POMORSKI	180 880,00	313 740,00	406 800,00	413 580,00	475 680,60	505 549,20	2 296 229,80
LUBELSKI	183 350,00	329 023,80	464 612,05	560 077,80	477 511,80	430 117,48	2 444 692,93
LUBUSKI	54 340,00	73 962,00	37 494,60	67 370,68	47 493,16	44 826,08	325 486,52
ŁÓDZKI	612 560,00	1 001 019,60	999 329,76	1 051 606,92	980 087,32	849 844,12	5 494 447,72
MAŁOPOLSKI	422 940,00	976 778,40	916 781,84	867 567,04	843 840,20	832 936,26	4 860 843,74
MAZOWIECKI	884 260,00	981 348,00	819 550,20	834 393,00	936 924,00	1 115 581,56	5 572 056,76
OPOLSKI	168 720,00	242 906,40	305 683,06	362 208,60	348 036,00	352 521,00	1 780 075,06
PODKARPACKI	226 100,00	600 846,00	588 115,06	637 946,40	654 020,64	657 084,20	3 364 112,30
PODLASKI	168 340,00	182 498,40	132 264,00	109 848,00	112 320,00	96 876,00	802 146,40
POMORSKI	273 600,00	423 738,00	557 575,20	729 440,40	773 572,80	762 091,20	3 520 017,60
ŚLĄSKI		774 673,20	671 595,86	857 784,36	688 967,76	655 204,68	3 648 225,86
ŚWIĘTOKRZYSKI	286 335,62	405 652,80	359 568,60	316 033,80	290 508,00	253 636,92	1 911 735,74
WARMIŃSKO-MAZURSKI	156 940,00	171 612,00	193 201,20	201 631,20	249 240,00	236 808,00	1 209 432,40
WIELKOPOLSKI	263 201,20	595 111,20	533 882,44	458 364,00	450 552,00	403 865,28	2 704 976,12
ZACHODNIOPOMORSKI	375 060,00	447 048,00	445 710,00	549 660,00	359 352,00	296 728,20	2 473 558,20

Table 4. The number of patients who were treated with leflunomid in a particular year and province in 2005-2010

NHF (NATIONAL HEALTH FUND)	2005	2006	2007	2008	2009	2010
DOLNOŚLĄSKI	126	126	122	178	218	219
KUJAWSKO-POMORSKI	81	106	134	160	155	154
LUBELSKI	97	105	167	191	188	166
LUBUSKI	29	27	19	22	20	16
ŁÓDZKI	320	328	316	310	292	268
MAŁOPOLSKI	289	313	304	296	274	259
MAZOWIECKI	428	374	293	305	358	422
OPOLSKI	73	93	108	114	114	111
PODKARPACKI	147	174	190	205	208	215
PODLASKI	70	54	34	29	35	28
POMORSKI	186	133	213	223	247	259
ŚLĄSKI		324	287	279	258	215
ŚWIĘTOKRZYSKI	112	115	107	92	88	80
WARMIŃSKO-MAZURSKI	52	47	58	63	68	73
WIELKOPOLSKI	136	159	166	155	123	121
ZACHODNIOPOMORSKI	182	180	170	183	119	97
TOTAL	2328	2658	2688	2805	2765	270

lysed countries (over 145,000 PLN for annual therapy);

- Switzerland – adalimumab treatment is over 129,000 PLN for annual treatment;
- Germany – adalimumab treatment is over 12,000 PLN for annual treatment
- The following, most costly medical procedures concern the use of etanercept in Austria (over 107,000 PLN), Switzerland (over 106,000 PLN) and Germany (over 96,000 PLN).

THERAPIES WITH INDIVIDUAL ACTIVE SUBSTANCES

The reports on the therapies using etanercept and infliximab in the years 2004-2005 was accounted for in the form of a monthly lump sum, so it is not possible to isolate the individual values. In the scope of the programmes, the population included in them continued to increase in 2010, reaching the number of about 6,000, which represents about 5% of the population in Poland.

An analysis, that takes into account the performance of services with the division into individual active substances, rendered the following results:

Leflunomide - the value of the funds amounted to 14% of the share in the rheumatology-dedicated programmes, the greatest funds - approx. 5.5 million PLN (2005-2005) were paid by the Masovian and Łódź divisions.

In total, approx. 2,600 patients were treated, the largest number of patients, i.e. approx. 2,000, were treated in the Masovian, Łódź and Lesser Poland divisions and the number of patients was the lowest in the Lubuskie division.

The highest incidence of the disease occurs at the age of 55 and women account for 83% of the patients. The average cost of the treatment amounted to 2,500-3,000 PLN.

Infliximab - the value of the funds spent on the treatment of patients was 47 million

PLN (in the years 2006-2010). The highest amount of the funds (11 million PLN) was used in the Masovian Province and the Kuyavian-Pomeranian Province (9.3 million PLN) and it was the lowest in the Lubuskie Province (approx. 0.55 million PLN).

The highest number of patients (556 persons) was treated in the Masovian Province (approx. 80 patients per year) and the Kuyavian-Pomeranian Province (419 patients, 26 persons per year). The lowest number of patients was treated in the Opole Province (75 persons in total).

The distribution of the number of the patients according to their age indicates the dominance of patients aged 48-57. Women make up 79% of the patients. The average annual cost of the therapy amounted to 18,000-25,000 PLN per patient.

Etanercept - the value of the funds paid to service providers amounted to 166.7 million PLN in the years 2006-2010. The largest amount of the funds was used in the Silesian Province (22.2 million PLN) the Lesser Poland Province (18.9 million PLN) and the Masovian Province (1.1 million PLN) and the lowest was in the Lubuskie Province.

The highest number of patients was treated in the Silesian Province (approx. 200 patients per year, 864 in total) and the Masovian Province (170 patients per year, 815 patients in total).

Etanercept is the only biological drug approved for the treatment of children, so there are two predominating groups: children at approx. 15 years of age and adults at the age of 56 years. Female patients dominate both the population of children (70%) and adults (69%). The average annual cost of the therapy amounted to 24,000-32,000 PLN per patient.

Adalimumab - was funded by the therapeutic programme from the end of 2007. At that time, 23.53 million PLN was spent in total for the treatment with this molecule, the largest

Table 5. The province participation in infliximab treatment budget spending in 2004-2010

NHF (NATIONAL HEALTH FUND)	2004	2005	2006	2007	2008	2009	2010	TOTAL
DOLNOŚLĄSKI	35 000	775 000	711 650	787 213	999 411	1 331 070	500 019	5 139 364
KUJAWSKO-POMORSKI	23 125	2 201 500	902 225	1 153 294	1 856 836	2 012 084	1 238 433	9 387 497
LUBELSKI		928 990	436 596	524 874	727 047	632 467	297 496	3 547 469
LUBUSKI	120 000	215 000	32 500	18 478	8 455	111 926	51 978	558 337
ŁÓDZKI	5 000	592 970	117 125	132 189	163 460	738 900	593 766	2 343 411
MAŁOPOLSKI	530 000	1 370 000	435 000	587 133	859 894	928 846	952 721	5 663 594
MAZOWIECKI	1 056 235	3 168 500	1 455 755	1 295 916	1 236 186	1 638 335	1 422 778	11 273 705
OPOLSKI	315 000	315 000	240 000	265 265	240 973	190 242	118 373	1 684 853
PODKARPACKI	700 000	1 035 000	252 500	233 834	273 948	525 351	174 198	3 194 832
PODLASKI	335 000	566 820	220 000	344 375	600 376	741 063	464 275	3 271 909
POMORSKI		112 500	70 458	177 770	209 087	501 594	361 724	1 433 133
ŚLĄSKI			265 000	277 440	684 987	1 511 475	1 045 800	3 784 703
ŚWIĘTOKRZYSKI		625 700	285 860	422 120	687 401	761 224	347 063	3 129 368
WARMIŃSKO-MAZURSKI		510 150	136 848	184 807	355 296	247 127	141 646	1 575 873
WIELKOPOLSKI		491 719	421 425	763 505	1 560 999	1 394 344	923 219	5 555 210
ZACHODNIOPOMORSKI		467 900		447 348	759 393	583 697	392 427	2 650 764

amount of the funds was used in the Silesian Province (3.6 million PLN, 15.33%), the Masovian Province (3 million PLN, 12.9%) and in the Lesser Poland Province (3 million PLN, 11.65%) and the lowest amount (0.14 million PLN) was spent in the Lubuskie Province.

The average annual cost of the therapy

amounted to approx. 16,000-23,000 PLN per patient.

The largest number of patients was treated in the Silesian Province (227 persons), the Masovian Province (162 person) and the number of patients was the lowest in the Lubuskie Province⁵. Women predominate



Table 6. The number of patients treated with infliximab in 2004-2010

NHF (NATIONAL HEALTH FUND)	2004	2005	2006	2007	2008	2009	2010
DOLNOŚLĄSKI	3	41	37	40	64	73	30
KUJAWSKO-POMORSKI	10	68	46	55	83	92	65
LUBELSKI		36	18	28	42	40	21
LUBUSKI	5	7	1	1	1	6	5
ŁÓDZKI	1	26	5	6	15	48	38
MAŁOPOLSKI	32	60	21	34	49	52	46
MAZOWIECKI	44	147	60	62	82	94	67
OPOLSKI	12	11	9	14	13	10	6
PODKARPACKI	23	32	9	12	17	26	13
PODLASKI	10	26	10	18	31	33	24
POMORSKI		9	3	14	14	23	18
ŚLĄSKI			19	16	42	77	56
ŚWIĘTOKRZYSKI		19	10	17	38	36	19
WARMIŃSKO-MAZURSKI		14	8	10	25	11	8
WIELKOPOLSKI		22	18	42	83	80	49
ZACHODNIOPOMORSKI		14		27	43	38	20
TOTAL	140	532	274	396	642	739	485

among the patients and the predominating age of the patients was 55.

Rituximab - this molecule was the second-line treatment after using previous

therapeutic options. Since 2007, 24 million PLN was spent on it, the highest amount of the funds, i.e. 4.3 million PLN was used in the Masovian Province and not much less was used in the Lesser Poland Province

Table 7. The distribution of money spent on etanercept in 2006-2009

NHF (NATIONAL HEALTH FUND)	2006	2007	2008	2009	2010	TOTAL
DOLNOŚLĄSKI	572 541	933 693	2 390 220	2 664 739	3 057 202	9 618 395
KUJAWSKO-POMORSKI	2 209 250	3 398 717	3 627 110	4 624 276	4 654 351	18 513 704
LUBELSKI	1 072 550	1 530 267	2 286 273	2 163 544	1 920 355	8 972 989
LUBUSKI	181 250	162 778	329 543	307 504	174 871	1 155 945
ŁÓDZKI	1 183 225	1 395 574	1 846 805	1 333 022	2 409 907	8 168 533
MAŁOPOLSKI	2 128 068	2 556 450	5 221 515	4 369 856	4 578 536	18 854 424
MAZOWIECKI	2 703 527	3 474 085	4 626 721	3 916 251	4 802 628	19 523 213
OPOLSKI	147 500	323 903	743 046	906 768	747 630	2 868 847
PODKARPACKI	1 105 155	1 434 205	1 854 487	1 385 340	1 492 133	7 271 320
PODLASKI	710 625	1 093 920	2 787 787	2 617 663	1 529 103	8 739 098
POMORSKI	323 589	761 116	1 359 052	1 426 795	1 380 922	5 251 475
ŚLĄSKI	2 134 100	3 152 328	6 396 265	4 728 711	5 778 752	22 190 157
ŚWIĘTOKRZYSKI	501 994	646 515	1 225 308	1 456 782	2 055 207	5 885 806
WARMIŃSKO-MAZURSKI	497 250	487 130	784 103	772 957	678 409	3 219 849
WIELKOPOLSKI	1 403 800	2 421 444	4 397 694	4 936 527	4 531 193	17 690 658
ZACHODNIOPOMORSKI	943 891	1 480 004	2 221 023	2 424 110	1 745 805	8 814 834
TOTAL	17 820 321	25 254 136	42 098 960	40 036 854	41 539 014	166 739 247

Table 8. The number of patients treated with etanercept in 2006-2010 in particular provinces

NHF (NATIONAL HEALTH FUND)	2006	2007	2008	2009	2010
DOLNOŚLĄSKI	26	57	96	109	136
KUJAWSKO-POMORSKI	76	103	123	128	187
LUBELSKI	38	61	75	81	93
LUBUSKI	6	9	12	10	7
ŁÓDZKI	32	52	48	62	101
MAŁOPOLSKI	72	134	161	162	182
MAZOWIECKI	94	168	179	168	206
OPOLSKI	5	16	25	23	25
PODKARPACKI	30	41	58	61	70
PODLASKI	29	57	77	83	77
POMORSKI	13	38	44	48	62
ŚLĄSKI	101	165	187	176	235
ŚWIĘTOKRZYSKI	12	20	36	51	65
WARMIŃSKO-MAZURSKI	16	17	23	24	29
WIELKOPOLSKI	40	101	137	139	179
ZACHODNIOPOMORSKI	34	52	70	74	77

Table 9. The value of the money reported as a cost of the adalimumab therapy in particular provinces

NHF (NATIONAL HEALTH FUND)	2007	2008	2009	2010	TOTAL
DOLNOŚLĄSKI		175 402,50	443 152,50	1 117 200,00	1 735 755,00
KUJAWSKO-POMORSKI		241 552,50	321 300,00	1 600 200,00	2 163 052,50
LUBELSKI	2 100,00	153 300,00	396 900,00	705 600,00	1 257 900,00
LUBUSKI		35 700,00	31 500,00	69 300,00	136 500,00
ŁÓDZKI			149 100,00	914 130,00	1 063 230,00
MAŁOPOLSKI		174 300,00	678 300,00	1 892 100,00	2 744 700,00
MAZOWIECKI		281 400,00	726 705,00	2 030 805,00	3 038 910,00
OPOLSKI		16 800,00	117 600,00	273 000,00	407 400,00
PODKARPACKI		12 600,00	159 600,00	745 500,00	917 700,00
PODLASKI		119 700,00	214 200,00	497 700,00	831 600,00
POMORSKI		155 400,00	541 800,00	848 400,00	1 545 600,00
ŚLĄSKI		199 500,00	544 425,00	2 868 652,50	3 612 577,50
ŚWIĘTOKRZYSKI		8 400,00	168 000,00	535 500,00	711 900,00
WARMIŃSKO-MAZURSKI				168 000,00	168 000,00
WIELKOPOLSKI		191 100,00	827 400,00	1 507 800,00	2 526 300,00
ZACHODNIOPOMORSKI		21 000,00	256 200,00	422 205,00	699 405,00

Table 10. The number of patients treated with adalimumab in 2007-2010

NHF (NATIONAL HEALTH FUND)	2007	2008	2009	2010
DOLNOŚLĄSKI		11	30	77
KUJAWSKO-POMORSKI		11	11	104
LUBELSKI	1	5	20	38
LUBUSKI		1	1	3
ŁÓDZKI			7	54
MAŁOPOLSKI		10	24	93
MAZOWIECKI		20	31	111
OPOLSKI		2	5	10
PODKARPACKI		2	8	41
PODLASKI		5	7	30
POMORSKI		8	17	34
ŚLĄSKI		10	39	178
ŚWIĘTOKRZYSKI		1	11	31
WARMIŃSKO-MAZURSKI				12
WIELKOPOLSKI		16	24	94
ZACHODNIOPOMORSKI		4	7	27
TOTAL	1	106	242	937



Table 11. The value of money spent on the rituximab therapy on the therapeutic programmes with the division into provinces

NHF (NATIONAL HEALTH FUND)	2007	2008	2009	2010	TOTAL
DOLNOŚLĄSKI	24 450,00	255 092,24	500 955,00	897 315,00	1 677 812,24
KUJAWSKO-POMORSKI		481 880,00	825 750,00	760 791,00	2 068 421,00
LUBELSKI		124 755,00	550 500,00	584 631,00	1 259 886,00
LUBUSKI		22 020,00	66 060,00	187 170,00	275 250,00
ŁÓDZKI		256 725,00	220 200,00	451 410,00	928 335,00
MAŁOPOLSKI	85 575,00	584 445,00	902 930,10	1 381 755,00	2 954 705,10
MAZOWIECKI	122 300,00	894 073,00	1 398 270,00	1 915 740,00	4 330 383,00
OPOLSKI		95 370,00	154 140,00	264 240,00	513 750,00
PODKARPACKI	12 225,00	156 495,00	363 330,00	550 500,00	1 082 550,00
PODLASKI		238 500,00	121 110,00	214 695,00	574 305,00
POMORSKI	24 450,00	73 350,00	110 100,00	99 090,00	306 990,00
ŚLĄSKI	24 450,00	649 290,00	781 710,00	1 376 250,00	2 831 700,00
ŚWIĘTOKRZYSKI		239 720,00	239 720,00	456 915,00	1 026 935,00
WARMIŃSKO-MAZURSKI		81 950,00	154 140,00	220 200,00	456 290,00
WIELKOPOLSKI		495 360,00	836 760,00	1 255 140,00	2 587 260,00
ZACHODNIOPOMORSKI		92 960,00	484 440,00	330 300,00	907 700,00

The evaluation of the effectiveness of funding treatment programs in rheumatology

Table 12. The number of patients treated with rituximab on rheumatology therapeutic programmes in 2007-2010

NHF (NATIONAL HEALTH FUND)	2007	2008	2009	2010
DOLNOŚLĄSKI	1	10	28	39
KUJAWSKO-POMORSKI		13	34	26
LUBELSKI		6	23	35
LUBUSKI		1	3	6
ŁÓDZKI		11	10	19
MAŁOPOLSKI	4	23	43	48
MAZOWIECKI	5	31	52	62
OPOLSKI		4	7	11
PODKARPACKI	1	6	17	20
PODLASKI		11	6	8
POMORSKI	1	4	5	6
ŚLĄSKI	1	26	37	47
ŚWIĘTOKRZYSKI		7	12	17
WARMIŃSKO-MAZURSKI		3	5	8
WIELKOPOLSKI		18	36	46
ZACHODNIOPOMORSKI		4	19	13

(2.9 million PLN) and the lowest share of the funds (0.28 million PLN) was used in the Lubuskie Province.

The highest number of patients was treated in the Masovian Province (approx. 50 patients per year), and the Lesser Poland Province ranked second (approx. 30 patients per year, followed by the Silesian Province (111 in total) and the Greater Poland Province (approx. 100 patients).

The average annual number of patients treated with rituximab was approx. 230. There are two peaks in the dominant numbers of patients: the first one at the age of approx. 26 and the other at the age of 58; there are more women among the patients - 83.5%. The average cost of the treatment for one patient is slightly higher than 25,000 PLN.

DISCUSSION

The prices of the drugs under analysis in Poland fall within the range of the lowest prices in Europe (3-4 rank in this respect), apart from rituximab, which is available at a price close to the average price in Europe. The cheapest is the annual infliximab therapy in patients weighing less than 70 kg. Lower prices of biological drugs in Poland are the results of the adoption of the negotiation system by the National Health Fund and the Ministry of Health that made it possible, during the analyzed period, to cut the prices of drugs, which led to a reduction in the annual cost of treatment per patient. Infliximab is followed by rituximab and etanercept and then adalimumab and the therapy with infliximab in patients weighing over 70 kg is the most expensive. The number of centres conducting the treatment within the therapeutic programme gradually increased in the period under analysis from 34 to 81. The number of centres was correlated with the population of the individual provinces at the correlation coefficient ranging from 0.61 to 0.73. The value of renegotiated therapeutic contracts (which were subsequently

performed) increased from 4,964,882 PLN in 2004 to 89,804,313 PLN in 2009, the value of the used budget was lower and amounted from 3.1 mln PLN in 2004 to 75.5 mln PLN in 2009. It amounted to, relatively, 62.5% in 2004 and 84% in 2009 of the budget. The highest expenses per inhabitant were incurred in the Kuyavian-Pomeranian Province and in the Podlasie Province, the expenses were the lowest in the Lubuskie Province and the Pearson correlation coefficient ranged from 0.46 to 0.88 for the individual provinces and substances, indicating similar expenses and physicians' preferences forced by the programme. The expenditure for therapeutic programmes ranged from 1.18% to 18.53% of the total rheumatology expenditure in various provinces and years. The number of patients treated within the programme increased from 140 in the year 2004 to 5864 in the year 2010. Women accounted for approx. 75-80% of the patients, usually at an age ranging from 50 to 60 (37%).

Leflunomide was the most frequently used drug (the largest number of patients in 2009 was 2804), etanercept was the most frequently used biological drug (the largest number of patients in 2010 was 1730), followed by adalimumab (937 patients in 2010), infliximab was used less frequently (739 patients in 2009) and rituximab (401 patients in 2010). Etanercept had the highest reimbursement value (166,739,247 PLN), and the reimbursement value was the lowest for adalimumab (23,560,530 PLN). The unit cost of the therapy incurred by the payer per patient treated since 2008 has remained practically stable and it amounts to 13,500 PLN, despite inflation observed in this period (less than 3,000 PLN for leflunomide, 20,000 PLN for infliximab, 27,000 PLN etanercept, 18,000 PLN for adalimumab and 25,000 PLN for rituximab).

SUMMARY

As a result of the analysis, it was shown that:

1. The therapeutic programme kept a stable cost of the therapy over the observed period of time. The organization of the health provision having a clearly defined framework allows the use of high-cost treatments for patients more efficiently and precise definition of the population allows all stakeholders to achieve their goals.
2. The form of the therapeutic programme did not have any negative influence on the distribution and use of the drugs in individual regions of Poland. In the analyzed period, the number of patient treatment in therapeutic programmes grew steadily.
3. It has been shown that 90% of the budget dedicated to the programme was used despite differences between regions. In order to achieve efficiency in the use of resources, the contract value must be correlated with the ability of health providers and the population size in the region. Healthcare providers (hospitals) are utilizing the granted resources in the optimal way. ■

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Is extending of a TTO experiment to 23 states per respondent justifiable?

An empirical answer from Polish EQ-5D valuation study



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ABSTRACT

Background: A population of respondents valued 13 EQ-5D health states, using the time trade-off (TTO) method. In further studies, a higher number of states per respondent (16 or 17) was used. Theoretically, with more states per respondent at hand means more available valuations, i.e. higher model estimation accuracy or a possibility to have fewer respondents in a study. A possible problem with extending TTO may be the physical fatigue of respondents who may simply be too tired to credibly answer subsequent questions.

The goal of the study was to evaluate results of TTO experiment expanded to 23 states per respondent in a Polish valuation study.

Methods: A total of 6,769 TTO valuations were available from 305 respondents after exclusions. Regression models were designed, explaining the impact of EQ-5D domains on health state and tested the stability of regression coefficients as more TTO experiments from a single respondent were used. We also performed a statistical and graphical com-

parison of value sets, made of a varying number of TTO experiments.

Results: Regression coefficients of two parsimonious models, built on 1st-17th (n=5,009) or 18th-23rd (n=1,760) v did not differ significantly in Chow test (p=0.5521). Similarly, regression coefficients of three parsimonious models built on 1st-5th (n=1,461), 6th-17th (n=3,548) or 18th-23rd (n=1,760) valuations, did not differ significantly in the Chow test (p=0.4334), either.

Conclusion: As no systematic changes were found in model parameters, due to TTO experiment extension, no risk of bias or efficiency decrease in model estimation may be assumed. The reported study supports a possibility of more health states per respondent in TTO valuations.

INTRODUCTION

Economic analysis is one of the three key components of health technology assessment (HTA) report and cost-utility analysis (CUA) is probably the most common type of economic analysis. In CUA, costs are measured in monetary units and benefits are expressed in quality adjusted life years

Keywords:

EQ-5D valuation, quality of life, quality-adjusted life years, social values, time trade-off

DOI: 10.7365/JHPOR.2013.3.1
 JHPOR, 2013, 1, 110-117

(QALYs). QALYs are calculated by multiplying the number of life years gained by a quality-of-life weight of a given health state. The methods, which determine quality-of-life weights, are divided into: direct, such as the time-trade off (TTO) method, standard gamble (SG) and visual analogue scale (VAS), or indirect, employing utility instruments, such as EQ-5D, Short Form 6D (SF-6D), Health Utilities Index Mark 2 or Mark 3 (HUI-2 and HUI-3). In order to use a questionnaire as a generic preference tool, somebody has to previously value health states, described by the questionnaire, using one of the above-mentioned direct methods, TTO being the most common in this context. See^{1,2} for a detailed description of TTO and the valuation procedure^{1,2}.

At first, in EQ-5D valuation studies, based on TTO method – in United Kingdom³, Spain⁴, Germany⁵ and United States² - respondents from the general population valued 13 health states. Some further studies used lower – 7 (Zimbabwe⁶) or extended number of states per respondent - 16 (Denmark⁷) or 17 (Japan⁸ and the Netherlands⁹). In a Polish TTO valuation study, 23 health states were presented to each respondent, and this has been the highest number used so far in a general population preference study¹⁰.

Theoretically, a higher number of health states per respondent means more available valuations, what may decrease estimation error and increase estimation model accuracy or allow for fewer respondents in the study; the latter advantage is favorable with regards to obvious budgetary limitations. However, a possible problem with TTO method extension may simply be physical fatigue of respondents to answer the last TTO questions with satisfactory credibility level.

There are different ways to verify if TTO exercise extension results in bias or not. The results of testing the stability of means and variances of consecutive TTO valuations were described in detail elsewhere¹⁰.

Simply, a comparison of health state values, regardless whether assigned in the middle or at the end of experiment, showed no statistically significant differences, neither in means or in variances.

The aim of the present study was to evaluate a possible bias, resulting from TTO experiment expansion to 23 states per respondent in a Polish valuation study. Stability of regression coefficients was assessed in models, based on health state valuations from different stages of TTO experiment.

MATERIALS AND METHODS

Polish valuation study

The data, employed in the reported study, originated from a Polish EQ-5D valuation study, performed in 2008 [10]. That study was based on the modified Measurement and Valuation of Health (MVH) protocol. Each respondent ranked 10 health states, valued four health states, using the VAS methodology and 23, using the TTO method. A total of 7,351 TTO valuations from 321 respondents were available before exclusions and 6,769 from 305 respondents after exclusions (see Table 1).

Stability of regression coefficients within TTO experiment

In order to verify the stability of regression coefficients, while using an increasing number of TTO experiments per respondent, the Chow test was employed¹¹. The Chow test was performed on the whole sample, divided into two or three subgroups. In the first case, the whole sample was divided into subgroups, with experiments 1-17 (n=5,009) and 18-23 (n=1,760). The second version was designed in such a way as to account for possible instability during the warm-up period in the first TTO experiments. Thus the whole sample was divided into three “periods”: 1-5 (n=1,461), 6-17 (n=3,548) and 18-23 (n=1,760) experiments. In both cases, the basic model with no interaction terms was

THE AIM OF THE PRESENT STUDY WAS TO EVALUATE A POSSIBLE BIAS, RESULTING FROM TTO EXPERIMENT EXPANSION TO 23 STATES PER RESPONDENT IN A POLISH VALUATION STUDY. STABILITY OF REGRESSION COEFFICIENTS WAS ASSESSED IN MODELS, BASED ON HEALTH STATE VALUATIONS FROM DIFFERENT STAGES OF TTO EXPERIMENT.

STATE	NUMBER OF VALUATIONS AS TTO EXPERIMENT				TOTAL
	1ST-5TH	6TH-13TH	14TH-17TH	18TH-23RD	
11112	66	39	18	33	156
11113	28	58	22	41	149
11121	61	26	18	32	137
11122	54	45	17	42	158
11131	33	49	25	33	140
11133	22	67	32	42	163
11211	54	46	19	35	154
11312	32	38	17	48	135
12111	66	33	17	17	133
12121	53	35	21	26	135
12221	46	44	15	25	130
12222	42	48	32	35	157
12223	14	58	26	33	131
13212	32	36	22	44	134
13311	25	56	20	31	132
13332	19	64	39	40	162
21111	55	54	20	27	156
21133	22	62	30	48	162
21222	37	45	22	33	137
21232	26	58	26	50	160
21312	31	57	17	46	151
21323	16	52	26	39	133
22112	52	43	32	29	156
22121	51	43	25	21	140
22122	50	46	15	44	155
22222	71	98	40	81	290
22233	11	58	28	45	142
22323	27	58	36	37	158
22331	18	63	41	40	162
23232	26	48	30	37	141
23313	20	45	36	40	141
23321	16	56	39	49	160
23333	33	61	32	35	161
32211	22	53	28	29	132
32223	21	47	27	46	141
32232	22	51	29	60	162
32313	23	77	25	38	163
32331	23	59	44	35	161
32333	27	59	22	43	151
33212	13	62	26	38	139
33232	17	56	27	42	142
33321	15	63	28	34	140
33323	27	46	26	43	142
33333	42	100	50	93	285
TOTAL	1461	2362	1187	1769	6789

Table 1. The number of available health state valuations from the Polish EQ-5D TTO-based valuation study after exclusions

applied. Accordingly, in the former case, the equality of 11 parameters was tested (constant term and 10 domain specific parameters) in two subperiods and, in the latter one, the equality between the second and the third subperiod was additionally verified (the equivalence of the first and the third subperiod is implied automatically, hence 11 and 22 restrictions, respectively). The null hypothesis was that the parameters are equal in two or three subgroups, as appropriate.

Value sets, based on above-mentioned two or three “period” models, were graphically compared, as well as contrasted with a Polish EQ-5D TTO value set, calculating the following values: (1) the mean absolute difference between health states values, (2) the number of health states (out of 243) with values different by more than 0.01, 0.02, 0.03, 0.05 or 0.10 from the Polish value set and (3) the correlation coefficient between value sets, using simple linear regression.

RESULTS

Regression coefficients of the two parsimonious models, built on valuations from 1-17 or 18-23 experiment, did not differ significantly ($p=0.5521$; see Table 2).

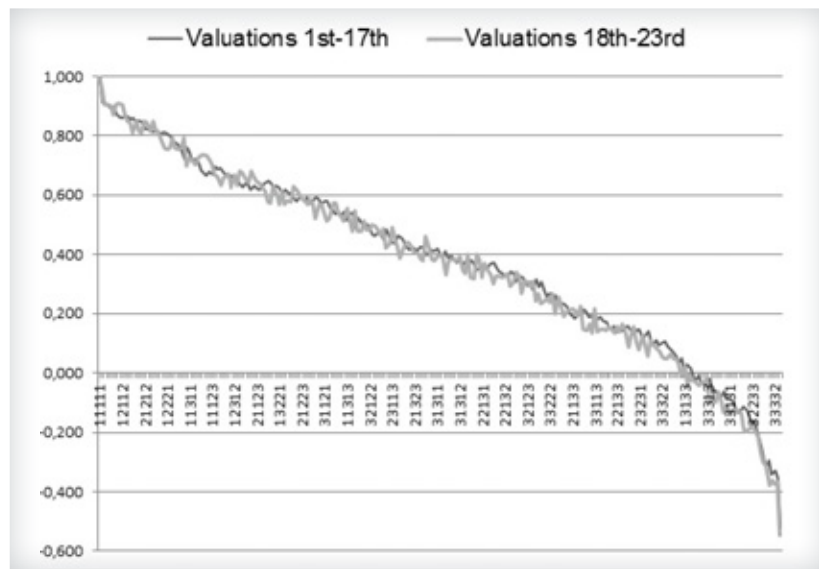


Figure 1. Graphical comparison of two value sets: (1) built on valuations from 1st to 17th experiment and (2) built on valuations from 18th to 23rd experiment.

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Table 2. Regression coefficients (SD) of two parsimonious models, built on valuations from 1st-17th or 18th-23rd experiment

	VALUATIONS 1ST-17TH	VALUATIONS 18TH-23RD
CONST.	0.052 (0.021)	0.039 (0.033)
M02	0.047 (0.013)	0.054 (0.024)
M03	0.321 (0.016)	0.332 (0.03)
SC2	0.054 (0.014)	0.059 (0.026)
SC3	0.233 (0.017)	0.245 (0.029)
UA2	0.038 (0.015)	0.058 (0.03)
UA3	0.205 (0.016)	0.237 (0.029)
PD2	0.049 (0.013)	0.091 (0.025)
PD3	0.483 (0.014)	0.524 (0.025)
AD2	0.036 (0.014)	-0.002 (0.026)
AD3	0.227 (0.014)	0.169 (0.026)
SUM OF SQUARED ERRORS	1013.82	417.829
THE NUMBER OF OBSERVATIONS	5009	1760
CHOW TEST		P=0.5521

Table 3. Regression coefficients (SD) of three parsimonious models, built on valuations from 1st-5th, 6th-17th 18th-23rd experiment

	VALUATIONS 1ST-5TH	VALUATIONS 6TH-17TH	VALUATIONS 18TH-23RD
CONST.	0.075 (0.024)	0.029 (0.025)	0.039 (0.033)
MO2	0.051 (0.021)	0.050 (0.016)	0.054 (0.024)
MO3	0.331 (0.031)	0.323 (0.019)	0.332 (0.03)
SC2	0.027 (0.021)	0.061 (0.018)	0.059 (0.026)
SC3	0.203 (0.03)	0.249 (0.021)	0.245 (0.029)
UA2	0.016 (0.023)	0.058 (0.02)	0.058 (0.03)
UA3	0.183 (0.028)	0.218 (0.02)	0.237 (0.029)
PD2	0.028 (0.021)	0.063 (0.017)	0.091 (0.025)
PD3	0.447 (0.025)	0.497 (0.016)	0.524 (0.025)
AD2	0.038 (0.022)	0.031 (0.018)	-0.002 (0.026)
AD3	0.250 (0.027)	0.222 (0.016)	0.169 (0.026)
SUM OF SQUARED ERRORS	210.448	800.68	417.829
NUMBER OF OBSERVATIONS	1461	3548	1760
CHOW TEST			P=0.4334

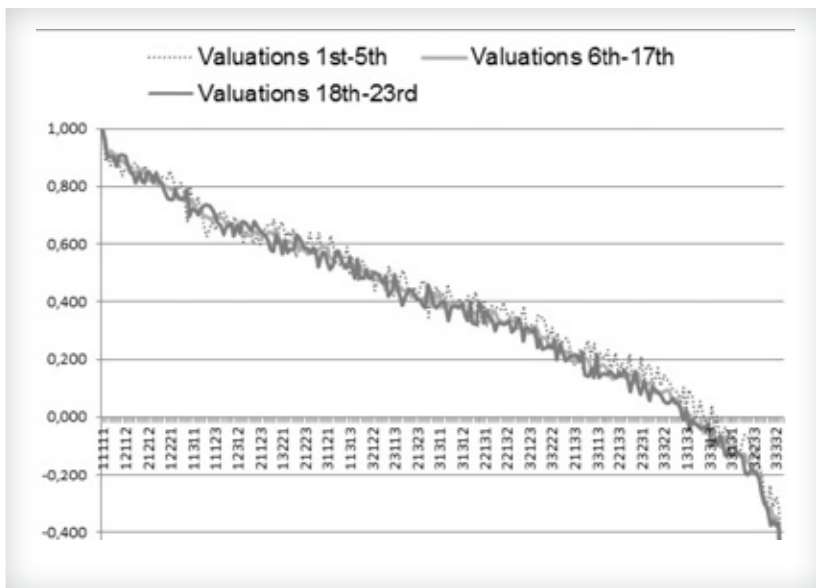


Figure 2. Graphical comparison of three value sets: (1) built on valuations from 1st to 5th experiment, (2) built on valuations from 6th to 17th experiment and (3) built on valuations from 18th to 23rd experiment.

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Table 4. Comparison of four different experimental value sets with the Polish EQ-5D TTO value set

	MODEL BUILT ON:			
	VALUATIONS FROM 1ST- 5TH EXPERIMENT (N=1,461)	VALUATIONS FROM 6TH - 17TH EXPERIMENT (N=3,548)	VALUATIONS FROM 1ST-17TH EXPERIMENT (N=5,009)	VALUATIONS FROM 18TH-23RD EXPERIMENT (N=1,760)
MEAN ABSOLUTE DIFFERENCE	0.031	0.009	0.009	0.022
NO. (OUT OF 243) >0.01 VS. POLISH	186	83	87	170
NO. (OUT OF 243) >0.02 VS. POLISH	153	26	13	118
NO. (OUT OF 243) >0.03 VS. POLISH	120	0	0	70
NO. (OUT OF 243) >0.05 VS. POLISH	45	0	0	15
NO. (OUT OF 243) >0.10 VS. POLISH	0	0	0	0
R ² VS. POLISH TTO VALUE SET	0.990	0.999	0.999	0.994

Similarly, regression coefficients of the three parsimonious models, built on valuations from 1-5, 6-17 or 18-23 experiments, did not differ significantly, either ($p=0.4334$; see Table 3).

A graphical comparison of the two value sets, based on 1-17 or 18-23 experiments, shows that although individual states differ, both sets are similar (see Figure 1).

A graphical comparison of three value sets shows that, in a set built on valuations from experiments 1-5, the health states closest to death are valued somewhat higher than in the two other sets (see Figure 2).

Table 4 presents a statistical summary of cross-model comparisons.

The mean absolute differences between health states values were relatively low (from 0.009 to 0.031) and health states values correlated significantly (R^2 from 0.990 to 0.999). The most outlying value set was built on valuations from experiments 1-5.

DISCUSSION

No systematic changes were identified

in model parameters after TTO experiment extension. The stability of regression coefficients within TTO experiment was verified using the Chow test and failed to show that parameters were not equal. Value sets, built on experiments 1-5, 6-17, 1-17 or 18-23, were similar, both in cross-comparisons and in a comparison to the Polish EQ-5D value set.

The most outlying value included the valuations from experiments 1-5, what seems fairly normal, as the first TTO valuations are sort of a warm-up task. In valuation of the first health states, respondents learn the rules of and get familiar with TTO exercise. Moreover, the first states differed from the states valued later on, as interviewers were asked not to reveal states worse than death at the beginning of the TTO exercise. The fact that respondents require this warm up period may prompt using more experiments per respondent, so as to outweigh the somewhat atypical initial valuations in subsequent analysis.

The obtained results should be approached together with the earlier presented analysis¹⁰. Regardless whether the comparison of health state values was assigned in the middle (position 6 to 17) or at the end (position

18 to 23) of the experiment, no statistically significant differences were observed, either in mean values or in variances, using the Holm-Bonferroni correction. We therefore inferred that additional states were valuable by increasing credibility (with identical means) and precision of the final estimation (did not inflate the total variance).

The combined results of both studies have strong practical implications. In a valuation study, an extension of TTO experiment means that more health state valuations will be obtained in the same population of respondents. It also means that credible valuations can be performed in population samples of moderate size. The results may support the estimation of national value sets in other countries, especially in situations of study budget constraints.

CONCLUSIONS

The present study supports the use of more health states per respondent in TTO experiments than it was previously assumed. No systematic changes were found in model parameters after TTO experiment extension. Therefore, there is no risk of bias or efficiency decrease in the estimation. This finding provides evidence for the need to improve the efficiency of valuation protocols and supports the estimation of national value sets in other countries. ■

ACKNOWLEDGEMENTS

This study was supported in part by unrestricted grants from GSK Commercial, Pfizer Poland, and Astra Zeneca Pharma Poland.

We are grateful to Anna Jabłońska, Anna Jawoszek, Aneta Dwojak, Ola Możeńska, Anna Gąsiewska, Malwina Hołownia, Krzysztof Orłowski, Szymon Zawodnik, Agnieszka Gączkowska, Adam Golicki, and Łukasz Kottowski from Student Pharmacoeconomics Chapter, Medical University of Warsaw for assistance in data collection.

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Home enteral nutrition (HEN) – a complex cost-saving solution to long-term artificial nutrition



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Keywords:

enteral nutrition, home artificial nutrition, home enteral nutrition, Home enteral tube feeding

DOI: 10.7365/JHPOR.2013.3.1
JHPOR, 2013, 1, 118-125

ABSTRACT

Background: Home enteral nutrition (HEN) was introduced in Poland several years ago. However, the benefits of such medical care have been questioned recently due to the growing costs in the health system. The purpose of this study was to examine the effect of a complex specialized home enteral nutrition on clinical outcome variables in HEN patients.

Methods: The observational study included 102 patients (51 women, 51 men, mean age 54.6 years) receiving HEN with homemade diets for at least 12 months before starting a specialized home nutrition program for another 12 months consisting of the provision of commercial enteral formulae and the guidance of a nutrition support team. Both study periods were compared in terms of the number of hospital admissions, length of hospital and intensive care unit stay, and costs of hospitalization.

Results: Implementation of the HEN program significantly reduced the number of hospital incidents and the length of hospital admissions and the duration

of ICU stay. The need for hospitalization and ICU admission was significantly reduced with odds ratios of 0.083 (95%CI 0.051 to 0.133, $P < 0.001$) and 0.259 (95%CI 0.124 to 0.539, $P < 0.001$) respectively. The specialized HEN was associated with a significant decrease in the prevalence of pneumonia (24.1% vs 14.2%), respiratory failure (7.3% vs 1.9%), urinary tract infection (11.3% vs 4.9%), and anemia (3.9% vs 0%) requiring hospitalization. The mean cost of hospital treatment decreased from 546.18 to 101.69 EURO/year/patient.

Conclusions: The specialized HEN care program reduces morbidity and costs related to long-term enteral feeding at home.

INTRODUCTION

The recent epoch of tube feeding started at the beginning of the 20th century when gastric access was used for the provision of nutrients^{1,2}. Consequently, enteral feeding became the preferred route of nutritional support due to its physiological advantages, low morbidity, and favorable costs compared to parenteral nutrition. One of the aspects of nutritional support, which was introduced in order to enable a patient's care

at home was home enteral nutrition (HEN) via either noninvasive (nasogastric or nasojejunal catheters) or invasive (gastro- or jejunostomy) accesses. Although home enteral nutrition, including HEN, has been used for many years, some recent reports have questioned the actual benefits of these interventions, mostly due to rapidly growing costs of HEN, which suggest that enteral nutrition may be susceptible to overuse, particularly in long-term care settings^{3,4,5,6,7,8}.

The incidence of home enteral nutrition in the United States is four to ten times higher than in other western countries, and doubled between 1989 and 1992^{6,7,8,9,10,11,12,13,14}. In the United States the annual prevalence of home enteral nutrition was approximately 175.0 per 100,000 population, while the incidence reported in a recent European survey was 16.3 patients per 100,000 inhabitants^{10,11,13}. The increasing popularity of HEN is associated with significant annual costs to the health system. In the United States, HEN costs were estimated between 9,000 and 25,000 USD per patient in 2000, while in some European countries varied between 9,048 and 10,140 USD a year^{7,8}. The widespread use of home enteral nutrition escalating the costs of home care has raised some concern about the cost-efficiency of the procedure for the National Health Systems^{6,7,8}. However, data validating the benefits of home nutritional support by the enteral route are rare and very heterogeneous, as it is not feasible nowadays to carry out a clinical trial recruiting patients deprived of specialized home feeding.

The reimbursement of home enteral nutrition by the Polish National Health Service started in 2007. As no other form of financial support was available earlier for these patients, they were forced to prepare blenderized homemade diets for tube feeding using household products. This unique situation provided an exceptional opportunity to evaluate changes in clinical outcomes following the implementation of a specialized nutritional support program. The pur-

pose of this study was to examine the influence of commercial enteral diets combined with the guidance of specialized nutritional support team on clinical outcome variables in patients receiving nutrition support at home via the enteral route by tube.

METHODS

An electronic database of 2114 patients treated between January 2008 and December 2010 at 12 centers of home enteral nutrition belonging to a home nutrition company and distributed in all regions of Poland was reviewed. All patients receiving HEN with homemade diets for 12 months before starting specialized nutritional support and continuing on HEN for the subsequent 12 months were selected as the study population. During the initial 12-month period, before home company could supervise the therapy, patients were fed at home with homemade diets consisting of regular meals prepared for the patient the same way as for other family members, but blenderized. The products were administered via feeding tubes (nasogastric or gastrostomy/jejunostomy) as a bolus of 50 to 100 milliliters 5 to 6 times daily. Patients were supervised by their general practitioner and no special nutritional care was provided. The assessment of this initial 12-month period was performed on a retrospective basis.

The second 12-month period was assessed prospectively; during this period patients received complex nutritional care by members of the home nutrition company's personnel: physicians (general surgeon, internal diseases specialist, anesthesiologist, gastroenterologist), qualified nurses, dietitian, physiotherapist, and psychologist. Initially, patients and their caregivers were visited at home by one or more of the team members and instructed regarding tube feeding regimes and care of the access. The nutritional status was assessed at the first home visit using clinical examination, NRS and SGA scales, laboratory tests, and anthropometry (triceps skinfold, midarm cir-

AN ELECTRONIC DATABASE OF 2114 PATIENTS TREATED BETWEEN JANUARY 2008 AND DECEMBER 2010 AT 12 CENTERS OF HOME ENTERAL NUTRITION BELONGING TO A HOME NUTRITION COMPANY AND DISTRIBUTED IN ALL REGIONS OF POLAND WAS REVIEWED.

cumference). Regular follow-up visits with laboratory tests were scheduled at the beginning of the treatment, in case of emergency and on the regular basis every 2 to 3 months. Laboratory test included: erythrocytes, leukocytes, hemoglobin, haematocrite, platelets, acid-base balance, serum sodium, potassium, calcium, magnesium, phosphate concentration, glucose, albumin, serum and urea amylase and lipase, blood urea, creatinine, cholesterol and triglycerides, bilirubin, aspartate aminotransferase (AST) alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), alkalinephosphatase (ALP), International normalized ratio (INR), and C-reactive protein (CRP). Those visits also included nutritional assessment, nutritional access' check and the evaluation of a general status.

Additional visits depended on individual patient requirements. Enteral feeding was based on enteral iso- or hypercaloric, standard or fibre rich, iso- or protein rich diets provided by Nutricia Ltd. and Fresenius Kabi Poland. Diets were administered as boluses (150 – 300 milliliters), microboluses (50 – 100 milliliters/ dose) or continuous infusion (20 ml/ hour at the beginning up to 150 ml/ hour during normal treatment) to meet the caloric goal, which was estimated at 30-35 kcal/kg. The intake of the enteral feedings were supervised by nurses and physicians during home visits. At the same time, members of family or caregivers or patients themselves were asked to keep records on the patient's intake and, most of all, follow our recommendations. Gravitational infusion systems as well as pumps were used depending on the gastrointestinal access and treatment compliance. The type of diet was based on the following factors: the type of primary disease determining energy and protein requirements (i.e. higher energy amount required in cystic fibrosis patients, lower in neurological patients), presence of complications (i.e. specialized formula diets in stress ulcer patients), fluid restrictions (i.e. hypercaloric formula in cystic fibrosis children with overnight feeding) and



type of enteral access (i.e. oligopeptic diets in jejunostomy patients). In cases where nutritional needs could not be met due to enteral formula intolerance or treatment complications, diets were changed (i.e. in case of constipation the formula was changed from standard into fiber-rich) and administration regimen was modified (i.e. from boluses into continuous infusion).

Patients were informed about advantages of commercial diets and prospects of our home care prior to enrollment. Then they were informed about the regimen by physicians and the introduction of HEN was conducted gradually. At the end of this process an informed consent was signed and

patients or their families or legal caregivers agreed to the therapy and gave permission to use their medical history.

To evaluate the efficacy of specialized HEN, both study periods were compared in terms of the number of hospital admissions, length of hospital and intensive care unit (ICU) stay, and costs of hospitalization. Costs of hospital treatment were evaluated based on the diagnosis-related group (DRG) system adopted in 2007 by the Polish National Health Service and calculating the payments for hospitals based primarily on the diagnosis of discharged patients.

Statistical analysis

The differences in proportions between groups were evaluated using the Chi-square test. The Wilcoxon signed ranks test was used to detect differences in quantitative parameters before and after implementation of HEN. Significance level (P) <0.05 was considered statistically significant. Statistical analysis was performed using the SPSS v.16 (SPSS Inc., Chicago, Illinois, USA) software package.

RESULTS

Detailed medical records were available for 102 patients (51 female, 51 male, mean age 54.6 years, range: 2 months – 89 years old). Enteral nutrition was initiated due to neuromuscular swallowing disorders ($n=75$), cancer-related dysphagia ($n=20$), cystic fibrosis ($n=5$), and other causes ($n=2$). The latter group included one case of chronic pancreatitis and one gastrointestinal motility disorder. Percutaneous endoscopic gastrostomy (PEG) was the most common gastrointestinal access (61%) followed by a nasogastric tube (21%). Surgical gastrostomy and jejunostomy were carried out in 15% and 3% patients, respectively. Iso-caloric and hypercaloric formulas were used in 87.7% and 12.3% of patients, respectively. 27.6% patients received fiber rich diets and hyperproteic formulae were used

in 4.9% patients. Enteral formulae covered 100% of daily protein and energy requirements (1.2 – 2.0 g/kg/day and 30 – 35 kcal/kg/day) and 85-100% of water requirement (30 – 40 ml/kg/day).

The implementation of a specialized HEN care program significantly reduced the number of hospital admissions, as well as the length of hospital and ICU stay (Table 1). The need for hospitalization and ICU admission was significantly reduced with odds ratios of 0.083 (95%CI 0.051 to 0.133, $P<0.001$) and 0.259 (95%CI 0.124 to 0.539, $P<0.001$), respectively. These changes significantly reduced mean annual costs of hospitalization from 546.18 EURO (95%CI 656.32 to 873.01) to 101.69 EURO (95%CI 85.02 to 199.72; 95%CI). An additional subgroup analysis by age groups (children, adults), type of enteral formula (isocaloric vs hypercaloric) and home nutrition centre failed to demonstrate any differences in outcome parameters.

Specialized HEN during the second 12-month period was associated with a significant decrease in the prevalence of pneumonia (24.1% vs 14.2%), respiratory failure (7.3% vs 1.9%), urinary tract infection (11.3% vs 4.9%), and anemia (3.9% vs 0%). Although nearly all other complications were more frequent during the first 12-month period, the differences compared to the specialized HEN were not statistically significant. The only complication more frequent in the HEN group was feeding tube occlusion, which was probably caused by the lack of experience of families, previously using home diets, during the initial period of HEN.

DISCUSSION

In most European countries, reimbursement of diets for home enteral nutrition is covered by the National Health Systems, while in the United States costs are generally covered by private insurance companies¹². In some cases this kind of reimbursement may increase the consumption

of health care resources and raises doubts about the cost-effectiveness of home enteral nutrition^{6,7,8}. Therefore, changes in the reimbursement policy implemented since 2007 by the Polish National Health Service provided an exceptional opportunity to evaluate the actual benefits of a modern system of nutritional support at home consisting of commercial enteral formulae and the oversight of dedicated Nutrition Support Team. Between 2007 and 2009, our home nutrition company provided a complex nutritional solution, including the shipment of enteral diets and equipment, regular visits of physicians and nurses, laboratory tests, and transportation of patients to and from hospitals for 680 patients receiving home enteral nutrition. This group of patients corresponded to over a half of about 1300 patients treated in Poland. The selection of a homogenous population of patients fed only by tubes obviates the potential bias of many previous studies, where home enteral nutrition was defined as the provision of diets by tube or oral feedings and included subjects with disorders having the chance to improve over time^{12,16,17}.

There are many potential advantages of using HEN and economic evaluations have demonstrated that home nutrition support is up to 75% more cost-effective than prolonged therapy in hospitals or nursing homes with savings of \$3100 to \$4200 per patient^{8,18,19,20}. However, despite the high numbers of patients receiving enteral tube feeding, there is still insufficient evidence to clearly support its beneficial effects in various populations^{3,4,5}. Some studies suggested that home enteral nutrition may even be associated with poorer survival rates or impaired quality of life of patients and their caregivers^{21,22,23,24,25,26,27}.

Current practice recommendations for enteral nutrition formulated by ASPEN state that selection of the enteral formulation must rely on several parameters, such as nutritional and physical assessment, metabolic abnormalities, gastrointestinal function,

overall medical condition, and expected outcomes¹⁷. However, not only the superiority of specialized over standard enteral formulae remains insufficiently substantiated, but also there are no firm data supporting clinical benefits of commercial diets over blenderized food^{8,20,28}. Nevertheless, it is generally believed that commercial enteral formulae are superior to homemade enteral diets^{2,9,10,29,30}. These assumptions are based on previous observations demonstrating that blenderized enteral tube diets, even prepared in a hospital setting, contain unpredictable levels nutrients and their physical properties may be unsuitable for infusion through feeding tubes^{32,32}. Moreover, marked bacterial contamination poses the risk of potentially serious complications in some patients^{33,34,35}. Despite all those facts, no randomized controlled trials have been published comparing clinical outcomes of HEN in patients with either homemade or commercial diets, and blenderized food is still used due to economic reasons in cases when the reimbursement policy is inadequate^{11,36,37,38}. The paucity of observational, retrospective studies, focused mainly on the nutritional and microbiological parameters of diets instead of clinical outcome criteria makes drawing of reliable conclusions even more difficult.

The concept of specialized nutritional support teams (NSTs) was initially developed for in-hospital patients and home parenteral nutrition, demonstrating significant reductions in metabolic and mechanical complications³⁹. Such a team approach was subsequently implemented for hospital enteral nutrition, suggesting that greater numbers of patients attained appropriate energy and nitrogen balance, as well as reduced complication rates⁴⁰. However, due to the paucity of adequate clinical trials evaluating the oversight of NSTs for home enteral nutrition, many physicians view this type of nutritional intervention as not routinely requiring monitoring or specialized interventions, compared to the parenteral route^{11,41,42,43}. Although the first randomized clinical tri-

CURRENT PRACTICE RECOMMENDATIONS FOR ENTERAL NUTRITION FORMULATED BY ASPEN STATE THAT SELECTION OF THE ENTERAL FORMULATION MUST RELY ON SEVERAL PARAMETERS, SUCH AS NUTRITIONAL AND PHYSICAL ASSESSMENT, METABOLIC ABNORMALITIES, GASTROINTESTINAL FUNCTION, OVERALL MEDICAL CONDITION, AND EXPECTED OUTCOMES

al on NSTs for HEN failed to provide data demonstrating a significant reduction of the health care costs, the authors demonstrated a saving of 21% per patient⁴⁴. Moreover, the supervised group had fewer and briefer episodes of readmissions and less demand for general practitioners and district nurse inputs.

Our study demonstrated that the change from poorly supervised HEN using homemade food to the specialized nutritional support with standard enteral formulae

of HEN, such as quality of life, could not be addressed. However, such a randomized study, involving a control group receiving only homemade food without appropriate medical supervision would hardly be justified ethically. In many cases withdrawal or limitations of reimbursement by the health care providers, such as the current recommendations implemented by the Polish National Health Service, forces some patients to use this old-fashioned type of feeding for economic reasons. Apparently, inappropriate restrictions not only increase the overall costs

Table 1. Number of hospital admissions, their length and cost

*Wilcoxon Signed Ranks Test

PARAMETER	BEFORE HETF	AFTER HETF	P*
NUMBER OF HOSPITAL ADMISSIONS MEAN (95%CI) MEDIAN (INTERQUARTILE RANGE)	1.09 (0.96-1.22) 1 (2)	0.21 (0.14-0.28) 0 (0)	<0.001
DURATION OF HOSPITALIZATION, DAYS MEAN (95% CI) MEDIAN (INTERQUARTILE RANGE)	20.84 (17.29-24.39) 13 (30)	3.83 (2.13-5.53) 0 (0)	<0.001
DURATION OF ICU STAY, DAYS MEAN (95% CI) MEDIAN (INTERQUARTILE RANGE)	2.35 (1.32-3.37) 0 (0)	0.50 (0.09-0.92) 0 (0)	<0.001
COSTS OF HOSPITALIZATION, EURO MEAN (95%CI) MEDIAN (INTERQUARTILE RANGE)	546.18 (468.8 – 623.58) 471.00 (943)	101.69 (60.73 – 142.66) 0 (0)	<0.001

produced substantial improvements in clinical end-points such as the need and length of hospital admissions, as well as rates of several complications. Therefore, to our knowledge, this is the first large-scale report substantiating clinically and economically the benefits of such a complex solution to the health system. Reasons for this are various. In our opinion the reasons for the significant decrease of hospital admissions, ICU stay and the length of hospital stay were as follows: the use of commercial diets, which were nutritionally complete as opposed to blenderized meals, tight control of diet intake, and the monitoring of treatment results thanks to physicians' and nurses' visits as well as routine laboratory tests. Due to the observational design of this study some other important aspects

of health care, but also increase morbidity rates and potentially impair patients' quality of life.

In conclusion, this study demonstrated that management of HEN by a nutrition support team reduces morbidity and may reduce costs to the health system. Due to the rising costs of home enteral nutrition, these patients should be adequately supervised and provided with appropriate enteral diets to maximize the benefits of such a therapy.

Conflict of interest

All authors cooperate as lecturers with Nutricia Ltd, Fresenius Kabi, Baxter, B Braun and Nestle. ■

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Clinical effectiveness analysis of LMWH in the prevention of deep vein thrombosis and pulmonary embolism



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ABSTRACT

Background: The aim of the study was to assess the clinical effectiveness of low molecular weight heparins in prevention of deep vein thrombosis and pulmonary embolism in comparison with physical methods, unfractionated heparin and placebo, by a systematic review of reports in medical literature.

Methods: The assessment of the clinical effectiveness of undertaken interventions was compliant with the principles of systematic review (EBM), based on the Cochrane Collaboration guidelines. Statistical analysis and meta-analysis were performed by means of the RevMan 4.2 software version.

Results: Regarding the risk of postoperative overall deep-vein thrombosis and proximal deep-vein thrombosis, a meta-analysis of obtained results revealed a trend towards low-molecular-weight heparin versus the results of physical methods. However, the difference between the analyzed groups did not reach statistical significance.

Compared to placebo, the results of deep vein thrombosis risk assessment by meta-analysis showed statistically significant differences in favor of low-molecular-weight heparins (RR = 0.50, 95% CI: 0.34, 0.74, P = 0.0004, NNT = 23).

In comparison to the group, receiving unfractionated heparin, the observed differences did not attain statistical significance, neither in thromboembolism prevention nor in deep vein thrombosis treatment.

Regarding the risk of any bleeding episodes, the meta-analysis showed a statistically significant difference in favor of low-molecular-weight heparins administered in the study group vs. placebo results in the control group (RR = 1.55, 95% CI: 1.07, 2.24, P = 0.02) with the NNH equal to 94.

Conclusions: Low molecular weight heparins are effective and safe treatment for venous thromboembolism versus placebo, however, no statistically significant advantages were observed vs. physical methods or unfractionated heparins.

Keywords:

UFH, Venous thromboembolic, Venous thromboembolism, deep vein thrombosis, DVT, intermittent pneumatic compression, IPC, LMWH, low-molecular-weight heparin, PE, pulmonary embolism

DOI: 10.7365/JHPOR.2013.3.1
JHPOR, 2013, 1, 126-139

INTRODUCTION

Low molecular weight heparins are used with increasing frequency in the primary prevention and treatment of venous thrombosis and acute myocardial infarction. Low molecular weight heparins (LMWH) are more expensive than unfractionated heparin but associated with additional benefits, such as shorter hospitalization and the possibility of treatment at home.

Due to the increasing popularity of LMWH and the relatively high public reimbursement, allocated for this group of drugs, there are more and more questions about the cost-effectiveness of such procedures. This analysis provides some basis for consideration of the advisability of using low molecular weight heparins. Based on meta-analyses of available clinical evidence, an assessment was conducted of the clinical effects of low molecular weight heparins versus placebo, unfractionated heparin or physical methods.

CLINICAL PICTURE AND EPIDEMIOLOGY OF VENOUS THROMBOEMBOLISM

The definition of venous thromboembolism includes two diseases: Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), which is often a complication of the former.

Deep vein thrombosis and related complications – pulmonary embolism and the post-thrombotic syndrome – form a very serious interdisciplinary problem of today's medicine, with various risks which may result from these complications. Pulmonary embolism is a severe, life-threatening disease, and the post-thrombotic syndrome, a chronic condition – is often the cause of permanent disability⁴⁷.

According to the Polish data, deep vein thrombosis affects about 50 thousand people per year and pulmonary embolism of varying severity is identified in about 20 thousand people, being the cause of about

10% of all hospital deaths and a leader among preventable causes of mortality. Frequently, deep vein thrombosis has an occult clinical course. It can occur in hospitalized patients, as well as in apparently healthy individuals at any time during their life. Pulmonary embolism is often the first and final sign of deep vein thrombosis. The majority of unrecognized cases of thrombosis lead to the thrombotic syndrome and incidents of pulmonary embolism, later followed by chronic pulmonary hypertension⁴⁸.

The treatment of venous thromboembolism complications is extremely expensive – the costs are comparable to expenditures in oncology, arising not only from the treatment of acute thrombosis or early complications, but also from treatment of the post-thrombotic syndrome and pulmonary hypertension. Indirect costs are associated with days on sick-leave and paid sickness benefits.

PREVENTION OF VENOUS THROMBOEMBOLISM

Physical methods (intermittent pneumatic compression): The aim of physical methods is to reduce venous stasis in the legs, a major contributor to thrombosis formation. These methods are easy, and require relatively cheap measures, while being proven as fairly effective for patients with a moderate risk of thrombotic events. However, in cases of high risk of thrombosis, the outcomes are not satisfactory.

Safety is a great advantage of the physical methods, especially where the risk of bleeding complications, associated with the use of anticoagulants, is unacceptable, for example, after neurosurgical procedures, multiple accidental trauma or surgery within the eyeball.

Pharmacological methods: Pharmacological methods rely on the drugs that inhibit blood clotting. Despite a long list of available products, the medicinal products, most readily used in the prophylaxis of venous thromboembolism, are heparin and oral an-

SAFETY IS A GREAT ADVANTAGE OF THE PHYSICAL METHODS, ESPECIALLY WHERE THE RISK OF BLEEDING COMPLICATIONS, ASSOCIATED WITH THE USE OF ANTICOAGULANTS, IS UNACCEPTABLE, FOR EXAMPLE, AFTER NEUROSURGICAL PROCEDURES, MULTIPLE ACCIDENTAL TRAUMA OR SURGERY WITHIN THE EYEBALL.

ticoagulants. Unfractionated heparin (UFH), administered subcutaneously and in small doses (5000 IU every 8-12 hrs.) is a standard method to prevent venous thromboembolism in patients with moderate and high risk of thrombosis. Low molecular weight heparins, administered by subcutaneous injection in small doses, demonstrate a significantly higher bioavailability (> 90%) vs. unfractionated heparin (20-30%). They also present a longer half-life and may be used

idence Based Medicine principles, with the following electronic databases:

- The Cochrane Controlled Trials Register (CENTRAL)
- Cochrane Database of Systematic Reviews (CDSR)
- Medline (PubMed)
- Embase
- BioMed Central
- and medical electronic portals:

Table 1. Issues vs key words in literature review

ISSUE	KEY WORDS
CLINICAL PROBLEM, POPULATION	(#1) VENOUS THROMBOEMBOLISM (#2) DEEP VEIN THROMBOSIS (#3) PULMONARY EMBOLISM
INTERVENTION	(#4) LOW MOLECULAR WEIGHT HEPARIN (#5) ENOXAPARIN (#6) NADROPARIN (FRAXIPARIN) (#7) DALTEPARIN
COMPARATORS	(#8) MECHANICAL DEVICES (#9) PLACEBO (#10) UNFRACTIONATED HEPARIN
OUTCOMES	(#11) THROMBOPROPHYLAXIS (#12) VTE, DVT PROPHYLAXIS (#13) VTE, DVT PREVENTION (#14) ADVERSE EVENT (#14) BLEEDING COMPLICATION, RISK OF HAEMORRHAGE
STUDY DESIGN	(#15) RANDOMIZED CONTROLLED TRIAL (#16) RANDOMIZED CLINICAL TRIAL (#16) RCT (#17) CLINICAL TRIAL

in single daily doses. They do not require laboratory monitoring of their anticoagulant activity, due to their improved pharmacokinetic properties.

Other pharmacological therapies include oral anticoagulants, dextran, heparinoids and specific inhibitors of enzymes.

METHODS

The search strategy was based on the Ev-

- BIOSIS Previews
- CINAHL Database
- PsycINFO
- European Public Assessment Report (EPAR)
- Health Canada
- Netherlands Pharmacovigilance Centre Lareb
- The Uppsala Monitoring Centre, and
- Thompson Micromedex

Additionally, to find more reliable data, a secondary search was carried out (systematic reviews and meta-analyses) in medical databases and existing independent HTA reports, available on the websites of institutions, cooperating with the Agency for Health Technology Assessment: International Network of Agencies for Health Technology Assessment (INAHTA), Health Technology Assessment International (HTAi) and the Centre for Reviews and Dissemination (CRD

obtained by manual search of selected journals, the use of search engines and by contacts with authors of clinical trials.

Date from the last search of medical databases: 10 September 2007

The decision issue was defined according to the PICOS pattern (population, intervention, comparator, outcomes, study design) (Table 1).

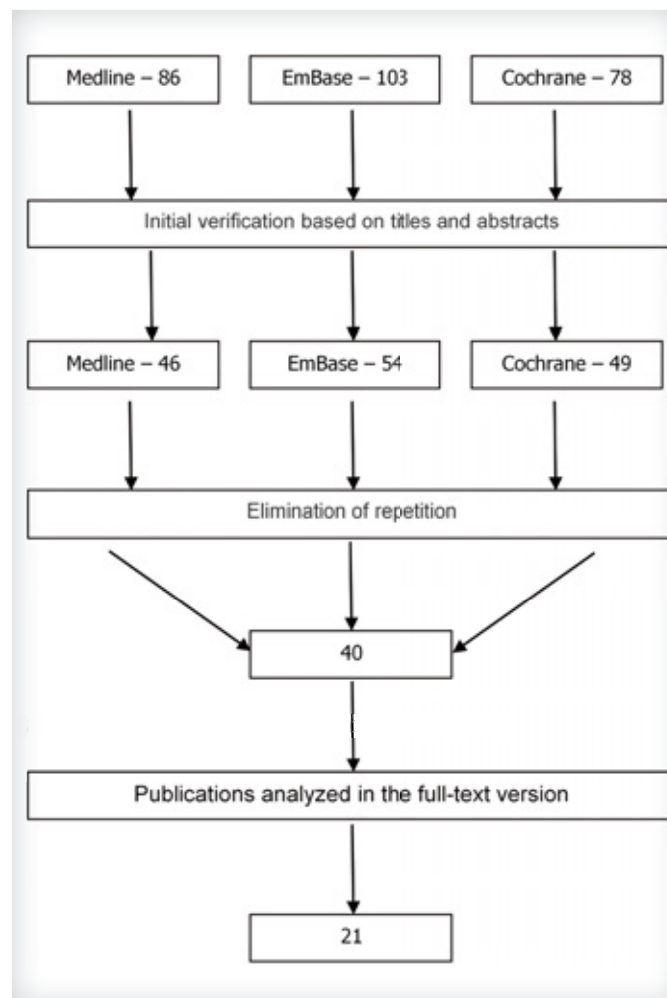


Figure 2. Overall episodes of deep vein thrombosis

Scientific papers were also sought in sources other than medical information databases: in bibliographies of published literature reviews and references, used in clinical research publications, reports and abstracts from scientific conferences and clinical trial registries. Clinical experts were also invited to consult. Additional information was

RESULTS

In result of searching medical databases, 267 publications were found on the use of low molecular weight heparins in prevention of venous thromboembolism (Figure 1).

Initially, 40 publications were selected with data meeting inclusion criteria. Full texts of scientific reports were analysed to assess their reliability, providing, 21 publications, out of the original set of randomized clinical trials, which met the criteria and were eligible for later analysis in compliance with predefined assumptions.

Additionally, four secondary studies were found, being meta-analyses of the clinical efficacy and safety of low molecular weight heparins in prevention and treatment of venous thromboembolism, as compared with the physical methods, placebo or unfractionated heparin.

At all stages, the selection was made independently by two analysts. In any case of disagreement in verification, based on full text analysis of scientific reports, a final position was attained by consensus.

META-ANALYSIS RESULTS

LMVH vs physical methods (Fig. 2, Fig. 3)

Treatment – LMWH

Control – physical methods (foot pump)

Outcome – overall episodes of deep vein thrombosis

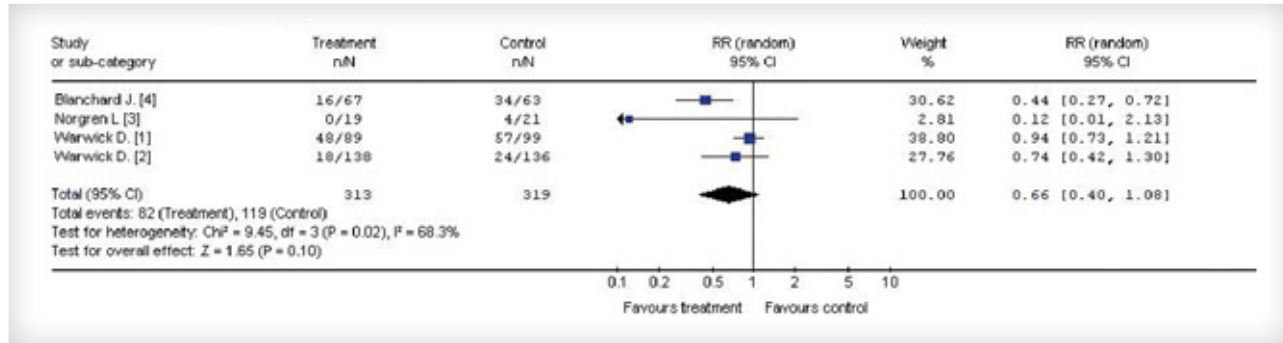


Figure 2. Overall episodes of proximal deep vein thrombosi

Treatment – LMWH

Control – physical methods (foot pump)

Outcome – episodes of proximal deep vein thrombosis

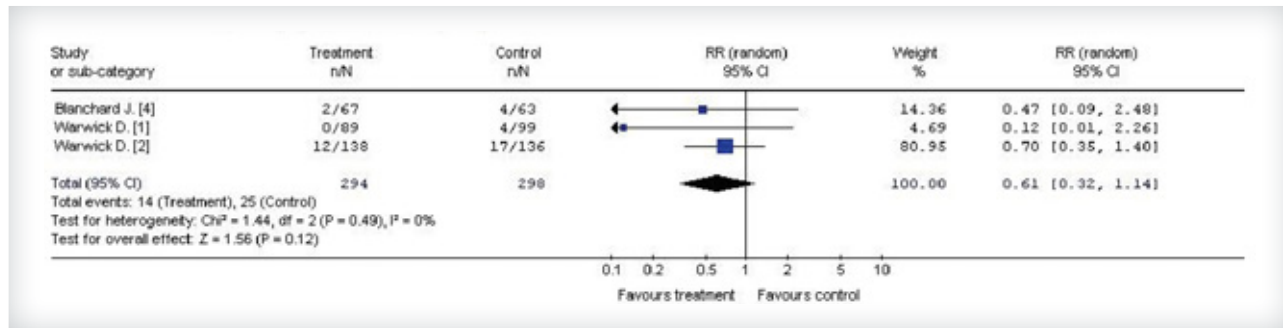


Figure 3. Overall episodes of proximal deep vein thrombosis

Table 2. Episodes of deep vein thrombosis vs. episodes of proximal deep vein thrombosis in metaanalysis studies

MEASURED ENDPOINT	NUMBER OF STUDIES	PATIENTS % (LMWH)	PATIENT % (FOOT PUMP)	RR [95% CI]	GRADE SCORE
EPISODES OF DEEP VEIN THROMBOSIS	4	26.2%	37.3%	0.66 [0.40; 1.08] NS	HIGH
EPISODES OF PROXIMAL DEEP VEIN THROMBOSIS	3	4.8%	8.4%	0.61 [0.32, 1.14] NS	HIGH

With regard to the risk of postoperative deep vein thrombosis in both the total number of cases and the number of cases with proximal deep vein thrombosis, meta-analysis studies^{1,2,3,4} showed a trend in favour of low molecular weight heparins versus the physical methods (intermittent pneumatic

compression). The difference between the analyzed groups, however, did not reach statistical significance (RR = 0.66, 95% CI: 0.40, 1.08, p = 0.10). (RR = 0.61, 95% CI: 0.32, 1.14, p = 0.12) (Table 2). **LMWH vs placebo (Fig. 4, Fig.5, Fig.6, Fig.7)**

Treatment – LMWH

Control - placebo

Outcome – episodes of deep vein thrombosis

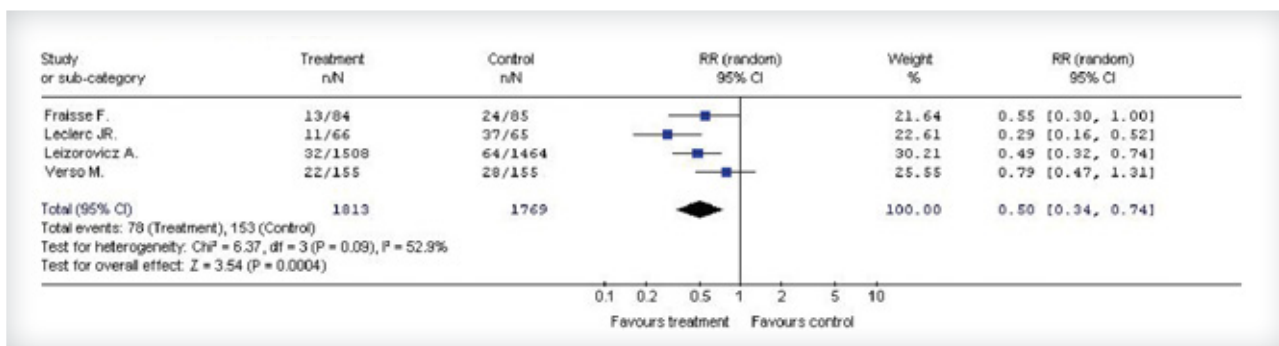


Figure 4. Episodes of deep vein thrombosis

With regard to the risk of deep vein thrombosis, meta-analysis results of four primary clinical trials showed a statistically significant difference between the benefits of low molecular weight heparins in the study group vs. the placebo-treated control group. (RR = 0.50, 95% CI: 0.34, 0.74, p = 0.0004).

The NNT (the Number Needed to Treat) was 23, which means that the administration of low molecular weight heparins instead of placebo to 23 patients, during the period of follow-up, was associated with avoiding deep vein thrombosis in one of them.

Treatment – LMWH

Control – placebo

Outcome – any bleeding episodes

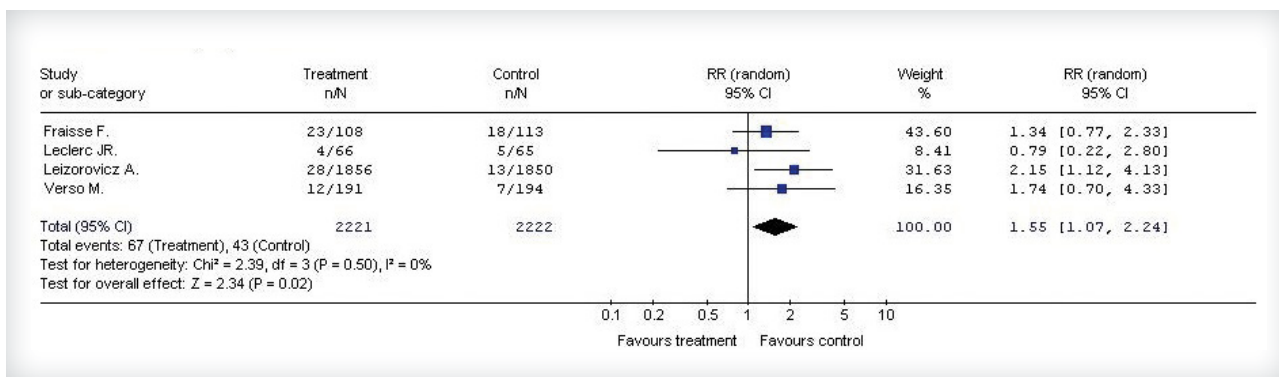


Figure 5. Any bleeding episodes

Treatment – LMWH
 Control – placebo
 Outcome – major bleeding episodes

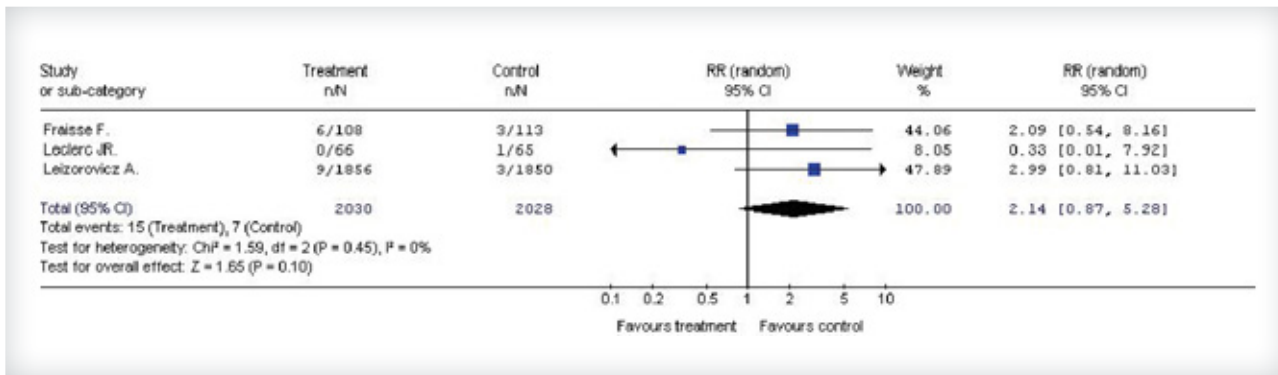


Figure 6. Major bleeding episodes

Treatment – LMWH
 Control – placebo
 Outcome – death

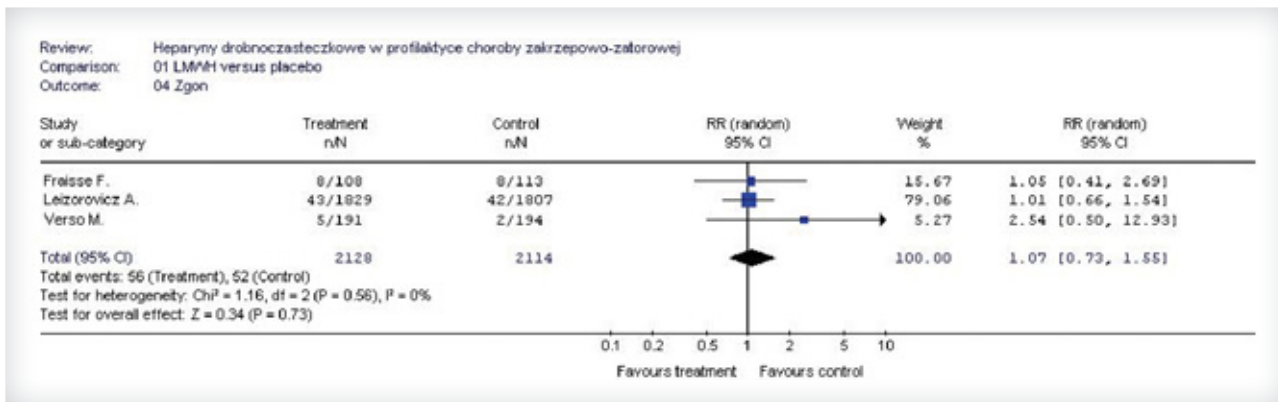


Figure 7. Mortality rates

Regarding the risk of any incidents of bleeding, the meta-analysis showed a statistically significant difference in favour of low molecular weight heparins, administered in the study group and compared to placebo in the control group (RR = 1.55, 95% CI: 1.07, 2.24, P = 0.02).

The NNH parameter (the Number Needed to Harm) was 94, which means that the administration of LMWH instead of placebo to 94 patients during the follow-up period was associated with bleeding events in one of them.

With regard to the risk of death from any cause, and clinically significant bleeding, the meta-analysis showed no statistically sig-

nificant differences between the compared groups (RR = 2.14, 95% CI: 0.87, 5.28, P = 0.10); (RR = 1.55, 95% CI: 0.73, 1.55, P = 0.73) (Table 3).

The meta-analysis showed a 50% decrease in the risk of deep venous thrombosis after low molecular weight heparins, compared to placebo, and NNT = 23. Only one study of pulmonary embolism did not confirm the statistically significant activity of LMWH versus placebo. There were no significant differences between the groups regarding the risk of clinically significant bleeding, which indicates an acceptable safety profile of low molecular weight heparins. Their high antithrombotic efficacy is much higher than any of the risks of bleeding events.

Table 3. Risk of any incidents of bleeding (LMWH vs. placebo)

MEASURED ENDPOINT	NUMBER OF STUDIES	PATIENTS % (LMWH)	PATIENT % (PLACEBO)	RR [95% CI] NNT/NNH*	GRADE SCORE
EPISODES OF DEEP VEIN THROMBOSIS	4	4,3%	8,6%	0,50 [0,34, 0,74] NNT = 23	HIGH
MINOR BLEEDING EPISODES	4	3%	1,9%	1,55 [1,07, 2,24] NNH = 94	HIGH
MAJOR BLEEDING EPISODES	4	0,7%	0,3%	2,14 [0,87, 5,28] NS	HIGH
DEATH	4	2,6%	2,5%	1,07 [0,73, 1,55] NS	HIGH

* NNT and NNH parameters were calculated for statistically significant differences between the compared groups

** not significant

LMWH vs. UFH (Fig. 8, Fig. 9, Fig.10, Fig.11)

Treatment – LMWH

Control - UFH

Outcome – episodes of deep vein thrombosis

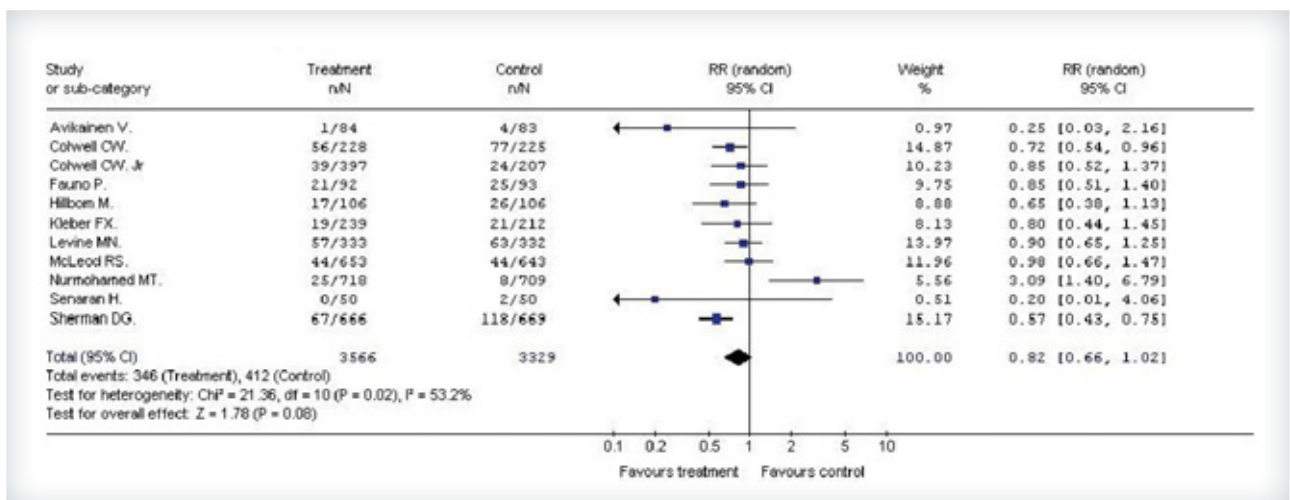


Figure 8. Episodes of deep vein thrombosis

Treatment – LMWH
 Control - UFH
 Outcome – episodes of pulmonary embolism

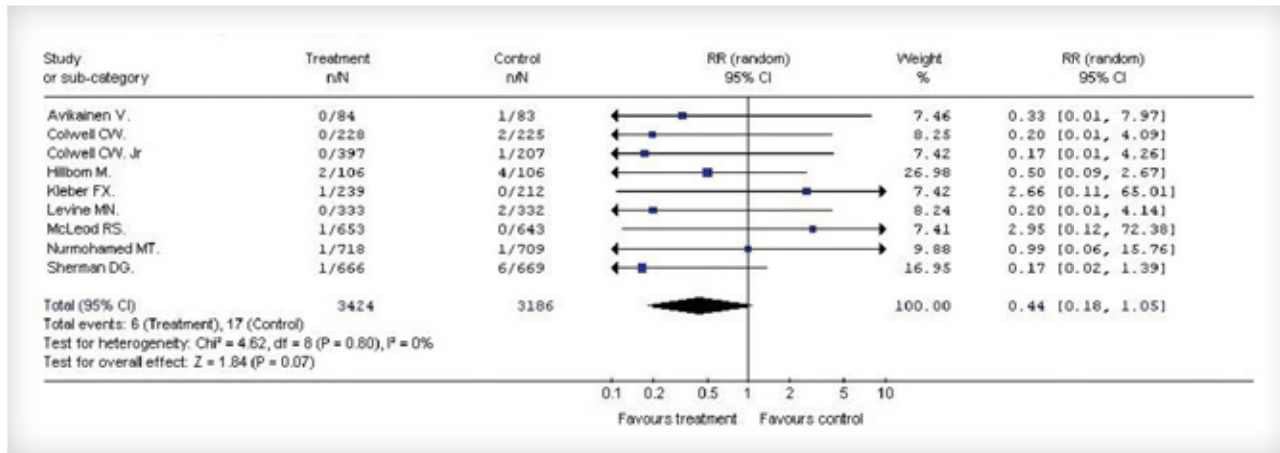


Figure 9. Episodes of pulmonary embolism

Treatment – LMWH
 Control – UFH
 Outcome – any bleeding episodes

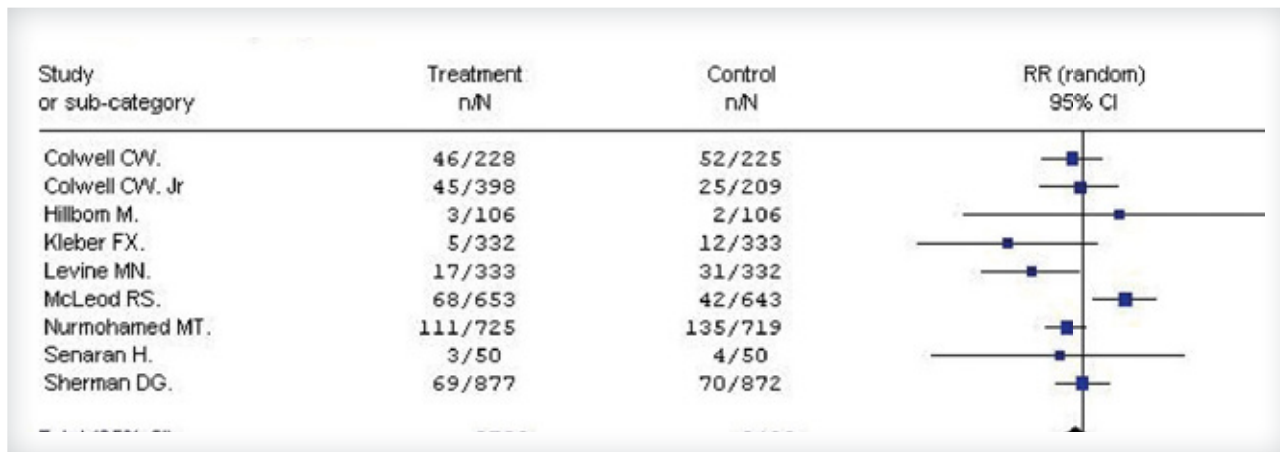


Figure 10. Any bleeding episodes

A meta-analysis of clinical efficacy showed a trend in favor of LMWHs vs UFH in the prevention of thromboembolism. However, differences in the incidence of deep vein thrombosis and pulmonary embolism,

did not achieve statistical significance (RR = 0.82, 95% CI: 0.66, 1.02, p = 0.08); (RR = 0.44, 95% CI: 0.18, 1.05, p = 0.07).

Clinical effectiveness analysis of LMWH in the prevention of deep vein thrombosis and pulmonary embolism

Treatment – LMWH

Control – UFH

Outcome – major bleeding episodes – clinically significant

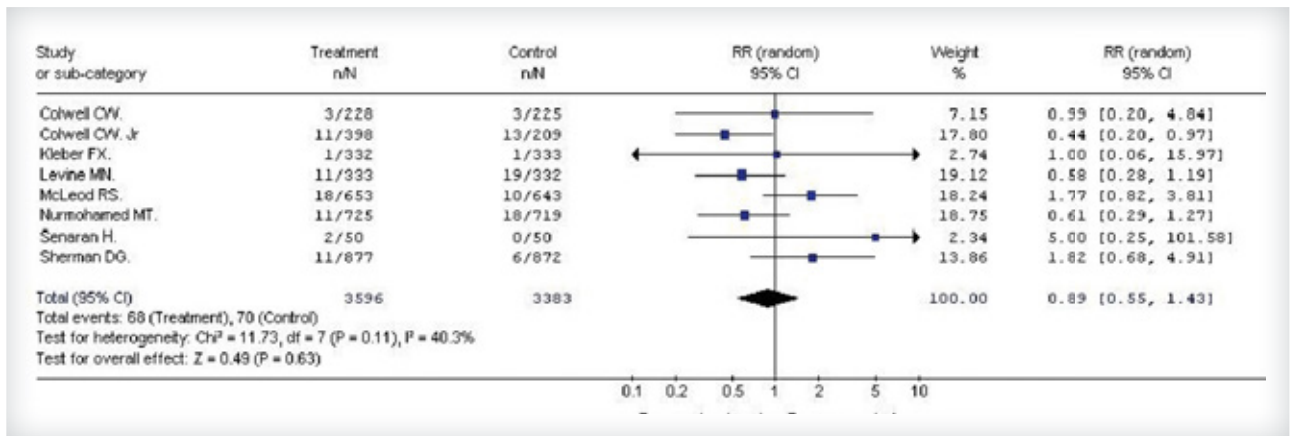


Figure 11. Major bleeding episodes

Treatment – LMWH

Control – UFH

Outcome – death

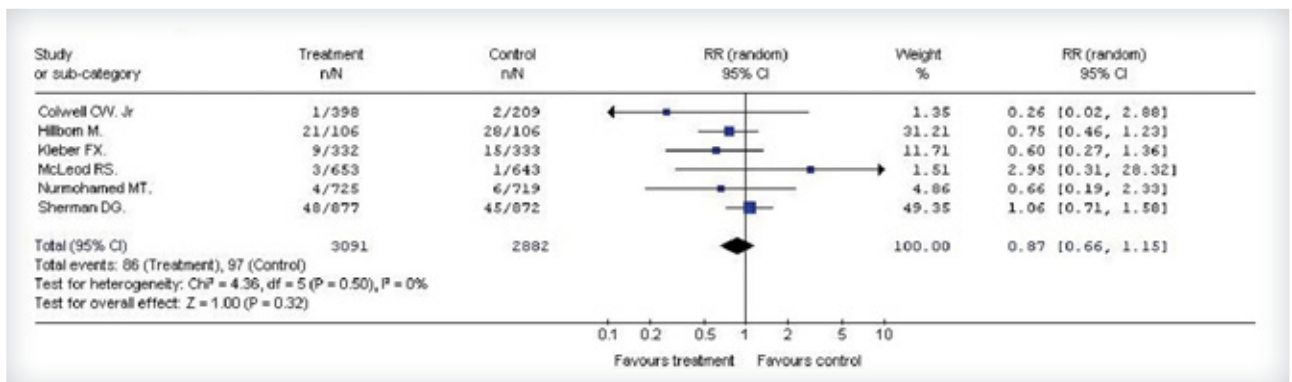


Figure 12. Mortality rates

In all the measured safety parameters after LMWH vs. UFH, the risk of minor and major bleeding and the mortality rates were slightly lower in the groups, receiving low molecular weight heparins, compared to the control group. However, the differences

between the analyzed therapeutic options were not statistically significant. (RR=0.91; 95% CI: 0.73, 1.13; p=0.39); (RR = 0.89; 95% CI: 0.55, 1.43; p = 0.63); (RR = 0.87; 95% CI: 0.66, 1.15; p = 0.32) (Table 4).

Table 4. Risk of minor and major bleeding and the mortality rates (LMWH vs. UFH)

MEASURED ENDPOINT	NUMBER OF STUDIES	PATIENTS % (LMWH)	PATIENT % (UFH)	RR [95% CI] NNT/NNH*	GRADE SCORE
EPISODES OF DEEP VEIN THROMBOSIS	11	9,7%	12,4%	0,82 [0,66, 1,02] NS	HIGH
EPISODES OF PULMONARY EMBOLISM	9	0,20%	0,53%	0,44 [0,18, 1,05] NS	HIGH
MINOR BLEEDING EPISODES	9	9,9%	10,7%	0,91 [0,73, 1,13] NS	HIGH
MAJOR BLEEDING EPISODES	8	1,9%	2,1%	0,89 [0,55, 1,43] NS	HIGH
DEATH	6	2,8%	3,4%	0,87 [0,66, 1,15] NS	HIGH

The Meta-analysis showed no statistically significant differences between LMWH and UFH in all the assessed endpoints. A trend was identified, suggesting a higher clinical efficacy of low molecular weight heparins.

DISCUSSION

The increasing prevalence of risk factors for venous thromboembolism, as well as the progress in diagnostic methods, leads to an increasing number of diagnosed cases. Along with an elevated risk of disease, the sales rates of low molecular weight heparins are steadily rising. In some countries, the costs of low molecular weight heparins is among the highest of all reimbursed drugs.

This analysis attempts to complement the studies, forming a base for consideration of the rationality of the use of low molecular weight heparins. The results of the meta-analyses enable a more accurate assess-

ment of the clinical effectiveness of low molecular weight heparins, in comparison to individual studies. The results confirm the effectiveness and safety of LMWH in prevention of venous thromboembolism, while drawing attention to the fact that most of the assessed endpoints did not achieve statistically significant difference, compared to cheaper treatments, such as the physical methods or unfractionated heparin. This fact should be taken into consideration in the conditions, where cheaper therapies (as the above-mentioned UFH and the physical methods) are readily available.

The use of LMWH in the prevention and treatment of venous thromboembolism, when compared with unfractionated heparin, is more convenient in practice. It does not require the activated partial thromboplastin time (APTT) to be determined nor the use of infusion pumps. The easy use of LMWH, combined with their pharmacoki-

netic properties, allows for administration of the drug in outpatient settings or even at home. There is also a financial aspect of hospitalization, which has been omitted in this analysis. The most advantageous feature of low molecular weight heparins, compared to heparin, is the predictable relationship between dose and effect of anticoagulant, which translates into a dosage based on the weight of the patient, without laboratory monitoring.

The most common and also the most feared complication of both unfractionated heparin and low molecular weight heparins is bleeding. The risk of bleeding is higher in case of unfractionated heparin, however, the difference in the reported study was not statistically significant.

The present analysis leads to a surprising conclusion that the physical methods are highly effective, when compared to LMWH. Trials assessing the end point of deep vein thrombosis risk, included studies with ambiguous results. On the other hand, the meta-analysis did not confirm statistically significant superiority of LMWH. In case of a high probability of complications, including bleeding, and of the coexistence of additional risk factors, the use of physical methods is recommended as an effective thromboprophylaxis. They can be an alternative when contraindications to anticoagulants exist.

In the analyzed studies, there were no other significant, treatment-associated, adverse effects, other than bleeding incidents. This demonstrates an acceptable safety profile of low molecular weight heparins, compared to placebo³⁻⁶, and a significantly better safety profile, compared to unfractionated heparin⁷⁻¹⁵. Significant clinical benefits, arising from their use, outweigh the potential risk of adverse effects, such as bleeding.

CONCLUSIONS

The results of this analysis demonstrate the effectiveness of low molecular weight heparins and safety of their use in prevention of deep vein thrombosis and pulmonary embolism. However, they also draw attention to the lack of statistical significance in a number of parameters versus other, less expensive methods, such as unfractionated heparin or physical methods (foot pump). Additionally, it should be noted that all the results of the meta-analyses take into account the realities of presented clinical trials and cannot be directly transferred into the reality of the Polish medical practice. ■



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The impact of the modification of the composition and the quantity of extemporaneous preparation on its price value



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Keywords:
community pharmacy,
extemporaneous
preparation, price value

DOI: 10.7365/JHPOR.2013.3.1
JHPOR, 2013, 1, 140-151

ABSTRACT

Background: The aim of this study is the analysis and estimation of the impact of the modification of the composition of extemporaneous preparation dispensed by the community pharmacy on their price value. The modification of ointment base, dosage form, active ingredient and excipient concentration, prescribing two separate preparations instead of double quantity of extemporaneous preparation, prices of the ingredients and packaging have been evaluated.

Material and method: 1407 prescriptions have been prescribed by 330 doctors providing their practice in 212 medical institutions. On the basis of these prescriptions five community pharmacies situated in Olsztyn, Elbląg, Pasiek and Ilawa in Warmian-Masurian Voivodeship made 1407 extemporaneous preparations in 2011. The information contained in prescriptions has become a foundation for creating a database using MS Excel tool. Statistical analysis and arithmetic mean have been applied.

Results: The average price value of the extemporaneous preparations in the

test material amounts to PLN 34.05. The price value of 90% of the extemporaneous preparations is within PLN 15.89 – PLN 50.00 . The price value of 10% is above PLN 50.00 including 1% over PLN 100.00. The modification of the ointment base has triggered, on average, a 38% increase of the price value, the modification of dosage form - 37%, prescribing two separate preparations instead of double quantity of the extemporaneous preparation - 32%, modification of active ingredient concentration - 23%, modification of excipient concentration - 14%. The purchase prices of ingredients and packaging have not been uniform.

INTRODUCTION

The extemporaneous preparation has been defined under the act of the law – Pharmaceutical law and defines a medicinal product compounded of pharmaceutical material or ready-made medicinal products within 48 hours of submitting the prescription by a patient or within 4 hours when the composition of the extemporaneous preparation contains narcotic drugs or carries an annotation „dispense immediately” a pharmacy upon a doctor’s prescription

or the one prescribed by a veterinarian¹. All aspects regarding the conditions of composition, quality assessment and the rules of the reimbursement are regulated by the law. Since 2002 newly formed community pharmacies are obliged to be adjusted to make extemporaneous preparations. An applicant who wishes to obtain a license to operate a community pharmacy is required to hold appropriate premises. The area of the premises consists of the basic and sub- areas. The basic area includes among others space to compound extemporaneous preparations; extemporaneous preparation area which may be equipped with a lock and washing space. Both types of space have an increased fold of ventilation against other areas of a pharmacy². A pharmacy consists among others of prescription area covered with easily washable material, resistant to chemical substances, weight-ranging scales, a device to receive purified water with a properly secured collecting vessel if the pharmacy makes purified water, a table covered with easily washable material resistant to chemical substances, glass to compound extemporaneous preparations, containers and prescription utensils properly labeled and prepared to compound extemporaneous preparations separated from containers and utensils for potent drugs. If a pharmacy compounds preparations in aseptic conditions then it is to be equipped with the area with the laminar flow to compound medications in aseptic conditions and a sterilizer³.

In the Warmian-Mazurian voivodeship, according to the NHF data in 2011, ca 200 thousand extemporaneous preparations compounded were reimbursed for over PLN 6 million⁴. The market value consists of the following factors: the purchase price of pharmaceutical materials, the purchase price of packaging, the cost of compounding an extemporaneous preparation – taxa laborum and the 25% pharmacy margin. The only fixed element is the taxa laborum which in 2011 amounted to PLN 12.33 among others for powders divided up to 20

pieces, non-divided powders (simple and compound) up to 80g, suppositories, globules and rods up to 12 pieces, solutions, concoctions, suspensions, emulsions up to 250 g, liquid medications for external use (if they contain alcohol, the quantity of alcohol based on 95% may not exceed 100g) up to 500 g, ointments, creams, liniments and pastes up to 100g, drops for internal and external use up to 40g and up to PLN 24.66 - for eye, ear and nose drops as well as eye ointments compounded in aseptic conditions up to 10g and the previously mentioned forms of medications compounded in aseptic conditions in accordance with the requirements of Polish Pharmacopoeia or with recommendations prescribed by a doctor or containing an antibiotic⁵.

AIM OF THE STUDY

The purpose of this paper was the analysis and assessment of the impact of the modification and composition of extemporaneous preparations compounded in the group of community pharmacies on their price value. The modifications of the ointment base, the form of the extemporaneous preparation, the prescribing of two separate preparations instead of the double quantity of the extemporaneous preparation, the modification of the active ingredient concentration in the extemporaneous preparation, the modification of the excipient ingredient concentration in the extemporaneous preparation as well as the modification of the ingredients and packaging were evaluated.

MATERIALS AND METHODS

1407 prescriptions issued in 2011 which constituted the basis to compound 1407 extemporaneous preparations in a selected group of pharmacies in the area of Olsztyn, Elblag, Paslek and Ilawa in the Warmian-Mazurian Voivodship were analyzed and assessed. Out of the analyzed prescriptions the following data were drawn: the composition of the extemporaneous preparation, the

1407 PRESCRIPTIONS ISSUED IN 2011 WHICH CONSTITUTED THE BASIS TO COMPOUND 1407 EXTEMPORANEOUS PREPARATIONS IN A SELECTED GROUP OF PHARMACIES IN THE AREA OF OLSZTYN, ELBLAG, PASLEK AND ILAWA IN THE WARMIAN-MASURIAN VOIVODSHIP WERE ANALYZED AND ASSESSED.

form of the preparation, the quantity of the preparation in grams and pieces as well as the value of the extemporaneous preparation compounded.

With the obtained data data bases were prepared with the MS EXCEL tool. The statistical analysis with the use of the measures of distribution was applied.

RESULTS

In the analyzed group of five pharmacies 1407 extemporaneous preparations were compounded within one year. The

compositions of the preparations were defined by 330 medical doctors working in 212 medical institutions. The average price value of the extemporaneous preparation amounted to PLN 34.05. The value of 90% of preparations was within the range of PLN 15.89 - PLN 50.00. The value of 10% of preparations was over PLN 50.00 including 1% of preparations worth over PLN 100.00. Figure 1 presents the quantity and price value of the extemporaneous preparations compounded on the basis of the analyzed group of prescriptions.

PLN 15.89 - PLN 20.00	145
PLN 20.01 - PLN 30.00	547
PLN 30.01 - PLN 40.00	385
PLN 40.01 - PLN 50.00	189
PLN 50.01 - PLN 60.00	53
PLN 60.01 - PLN 70.00	41
PLN 70.01 - PLN 80.00	28
PLN 80.01 - PLN 90.00	6
PLN 90.01 - PLN 100.00	5
over PLN 100.00	8
Total	1407

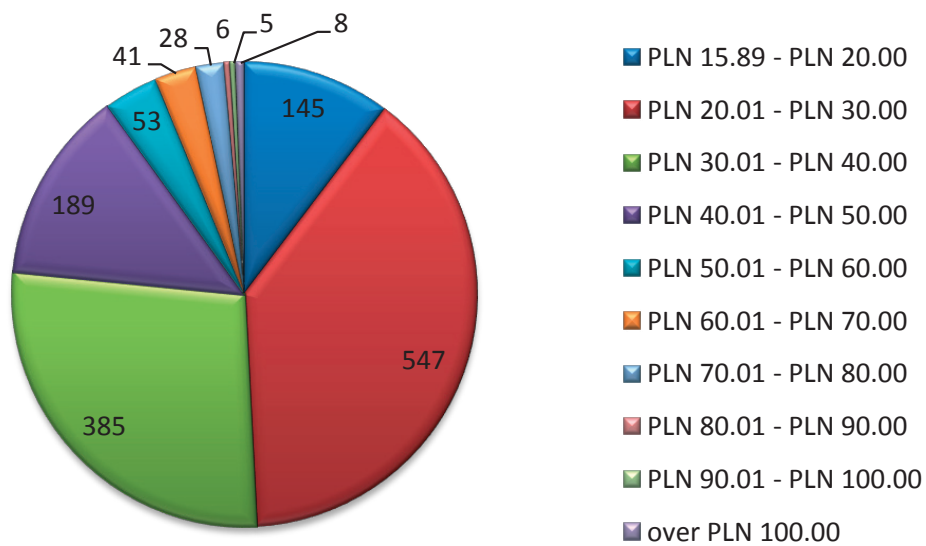


Figure 1 The quantity and the price value of the extemporaneous preparations made on the basis of the analyzed group of prescriptions

The impact of the modification of the composition and the quantity of extemporaneous preparation on its price value

Table 1. The examples of the increase of the price value of the extemporaneous preparation connected with change of the ointment base

ITEM	COMPOSITION OF EXTEMPORANEOUS PREPARATION	MODIFICATION OF OINTMENT BASE	PRICE VALUE INCREASE
1.	3% SOL. ACIDI BORICI; LANOLINI; VASELINI FLAVI AA AD 100,0	VASELINUM ALBUM, LANOLINUM W RÓWNYCH CZĘŚCIACH	+41%
		EUCERINUM, LANOLINUM IN EQUAL PARTS	+53%
2.	ACIDI SALICYLICI 10,0; HASCOBAZA AD 100,0	LEKOBAZA	+54%
3.	ACIDI SALICYLICI 20,0; VASELINI ALBI AD 200,0	LEKOBAZA	+161%
4.	ACIDI SALICYLICI 5,0; VASELINI ALBI AD 100,0	OLEUM RICINI 10,0; OLEUM RAPAE 85,0	+15%
		OLEUM RICINI, OLEUM RAPAE IN EQUAL PARTS	+29%
5.	HYDROCORTISONI 0,15; VASELINI ALBI AD 50,0	HASCOBAZA	+13%
6.	HYDROCORTISONI 0,25; VIT.A 50 000J.M.; VASELINI ALBI AD 50,0	HASCOBAZA	+19%
7.	HYDROCORTISONI 0,5; VASELINI ALBI AD 100,0	UNGUENTUM CHOLESTEROLI	+11%
		GLICEROLUM 10,0; LANOLINUM 89,5	+11%
		HASCOBAZA	+22%
		LEKOBAZA	+42%
		GLICEROLUM 10,0; LEKOBAZA 89,5	+49%
8.	UREA 10,0; EUCERINI; VASELINI ALBI AA AD 100,0	HASCOBAZA	+3%
9.	UREA 5,0; AQUA DESTILATAE, EUCERINI, VASELINI ALBI AA AD 100,0	AQUA DESTILATA Q.S.; EUCERINUM; VASELINUM ALBUM IN EQUAL PARTS	+25%
		HASCOBAZA	+37%
10.	VIT.A 10,0; VIT.E 10,0; HASCOBAZA AD 200,0	LEKOBAZA	+15%

Modification of the ointment base

Different ointment bases were used to prepare the ointment of the defined composition and the quantity of active substances. The type the applied base influences the price value of the extemporaneous preparations. The observed changes referred to the following modification:

- the modification of the lipophilic anhydrous hydrocarbon (petrolatum) base into the amphiphilic (Hascobaza and Lekobaza) base,

- the modification of the lipophilic anhydrous hydrocarbon (petrolatum) base into the absorbent (cholesterol ointment) base,

- the modification of the absorbent hydrated base (the combination of water, petrolatum and lanoline) into the amphiphilic (Hascobaza) base,

- the modification of the absorbent hydrated base (the combination of water and eucerin) into the absorbent (cholesterol ointment) base,

- the change of the lipophilic anhydrous hydrocarbon (petrolatum) base into a different lipophilic absorbent hydrated base (the combination of canola and castor oils – the simultaneous modification of the form of the extemporaneous preparation),

- the modification of the absorbent base (the

Table 2. The examples of the price value increase connected with the modification of the form of the extemporaneous preparation

ITEM	COMPOSITION OF EXTEMPORANEOUS PREPARATION	MODIFICATION OF COMPOSITION OF EXTEMPORANEOUS PREPARATION (CHANGE OF FORM)	PRICE VALUE INCREASE
1.	0,3% SOL. ZINCI SULFURICI 100,0	ZINCI SULFURICI 0,3; AQUA DESTILATAE 20,0; EUCERINI AD 100,0	+80%
2.	ACIDI SALICYLICI 10,0; OL. RICINI; OL.RAPAE AA AD 100,0	ACIDI SALICYLICI 10,0; VASELINI ALBI AD 100,0	+54%
3.	ACIDI SALICYLICI 5,0; VASELINI ALBI AD 100,0	ACIDI SALICYLICI 5,0; OL. RICINI 10,0; OL. RAPAE AD 100,0	+20%
4.	ACIDI SALICYLIICHTYOLI 3,0; ZINCI OXYDATI 20,0; OL. RAPAE AD 100,0 CI 5,0; VASELINI ALBI AD 100,0	ICHTYOLI 3,0; ZINCI OXYDATI; TALCI VENETI AA 25,0; AQUA DESTILATAE AD 100,0	+13%
5.	VIT.E 20,0; OL. MENTHAE PIPERIRTAE 0,4; GLICEROLI AD 200,0	VIT.E 20,0; UNG. CHOLESTEROLI AD 200,0	+57%
6.	ZINCI OXYDATI 50,0; OL. RAPAE 50,0	ZINCI OXYDATI 50,0; TALCI VENETI 50,0; 40% FORMALINI 20GTT.	+39%

cholesterol ointment) into the amphiphilic base (Hascobaza),

- the modifications in the proportions of the compound of the bases.

It has been proven that the modification of the base triggered the price value increase of the extemporaneous preparation by 38% on average, the biggest increase was noted with the modification of petrolatum into Lekobaza or Hascobaza. It is particularly evident in the case of ointment containing 10% of salicylic acid made in the double quantity (Table 1 item 3) where the modification of the base attributed to the increase of the price value of the extemporaneous preparation by 161%. In Table 1 the examples of the analyzed increases of the price value of the extemporaneous preparation.

MODIFICATION OF THE FORM OF THE EXTEMPORANEOUS PREPARATION

In the analyzed prescriptions it has been found that the performed modification of the extemporaneous preparation related to the modification of the applied base. The active ingredient and its quantity were not changed. The observed changes covered the following modifications of the extemporaneous preparation:

- the modification of the aqueous solution into the absorbent hydrated base,

- the modification of the oil solution into the ointment of anhydrous hydrocarbon lipophilic base,

- the modification of the anhydrous hydrocarbon lipophilic base into the oil solution,

- the modification of the oil solution into the aqueous suspension,

- the modification of the glycerol solution into the absorbent ointment base,

- the modification of the oil solution into the undivided powder for external use.

The examples of the compositions of extemporaneous preparations before and after the modification including the level of the increase of the price value are shown in Table 2. It was demonstrated that the modification of the form of the drug caused the increase of the price value of the extemporaneous preparations by 37% on average. The highest increase was observed in the case of the change of the aqueous solution into the absorbent ointment base, which caused the 80% increase of the price value of the extemporaneous preparation (Table 2 item 1).

MODIFICATION OF PRESCRIBING TWO SEPARATE PREPARATIONS INSTEAD OF THE DOUBLE QUANTITY OF THE EXTEMPORANEOUS PREPARATION

In 2011 in justified cases a medical doctor could prescribe the double quantity of the extemporaneous preparation if the drug stability was maintained over the period of the use of the drug⁷. A pharmacist compounding and calculating the price of the extemporaneous preparation charged one cost of the compounding of the extemporaneous preparation – taxa laborum (PLN 12.33) and the cost of packaging. In the case of a medical doctor prescribing the drug with two separate prescriptions, a pharmacist preparing and calculating the price of the extemporaneous preparation charged a double costs of the compounding of the extemporaneous preparation – 2 x taxa laborum (2 x PLN 12.33 = PLN 24.66) and the cost of two pieces of packaging. On the basis of the conducted analysis it has been found that prescribing two separate preparations instead of the double quantity of the extemporaneous preparation increased the price value by 32% on average. In Table 3 the examples of such prescriptions are shown.

Table 3. The examples of the price value increase connected with the prescribing of two separate preparations instead of the double quantity of the extemporaneous preparation

ITEM	COMPOSITION OF EXTEMPORANEOUS PREPARATION – ONE PRESCRIPTION	COMPOSITION OF EXTEMPORANEOUS PREPARATION – TWO PRESCRIPTIONS	PRICE VALUE INCREASE
1.	10% UNG. KALII IODATI 200,0	10% UNG. KALII IODATI 100,0	+32%
2.	2% UNG. DETREOMYCINI 200,0	2% UNG. DETREOMYCINI 100,0	+22%
3.	ACIDI SALICYLICI 20,0; VASELINI ALBI AD 200,0	ACIDI SALICYLICI 10,0; VASELINI ALBI AD 100,0	+35%
4.	ACIDI SALICYLICI 10,0; VASELINI ALBI AD 200,0	ACIDI SALICYLICI 20,0; VASELINI ALBI AD 100,0	+22%
5.	AQUA DESTILATAE; EUCERINI; VASELINI ALBI AA AD 200,0	AQUA DESTILATAE; EUCERINI; VASELINI ALBI AA AD 100,0	+25%
6.	HYDROCORTISONI 1,0; VASELINI AD 200,0	HYDROCORTISONI 0,5; VASELINI ALBI AD 100,0	+ 23%
7.	HYDROCORTISONI 2,0; HASCBAZA AD 200,0	HYDROCORTISONI 1,0; HASCBAZA AD 100	+24%
8.	HYDROCORTISONI 2,0; VASELINI ALBI AD 200,0	HYDROCORTISONI 1,0; VASELINI ALBI AD 100,0	+41%
9.	UREA 10,0; HASCBAZA AD 200,0	UREA 5,0; HASCBAZA AD 100,0	+27%
10.	3% SOL. ACIDI BORICI 30,0; UNG.CHOLESTEROLI AD 200,0	3% SOL. ACIDI BORICI 15,0; UNG.CHOLESTEROLI AD 100,0	+48%

The impact of the modification of the composition and the quantity of extemporaneous preparation on its price value

MODIFICATION OF THE ACTIVE INGREDIENT CONCENTRATION

The composition of many drugs of the same character differed solely with the active ingredient concentration. Consequently the increase of the active ingredient concentration attributed to the increase of the price value of the extemporaneous preparation by 23% on average. In the case of sulfur ointment compounded on the basis

of petrolatum the sulfur concentration increased from 10% to 30% (Table 4 item 11) and attributed to the decrease of the price value of the preparation. The applied active ingredient i.e. the precipitated sulfur was in this case cheaper than the ointment base i.e. petrolatum. The increase of the cheaper ingredient to replace the more expensive one caused the decrease of the price value of the extemporaneous preparation.

Table 4. The examples of the price change relating to the change of the active ingredient concentration in the extemporaneous preparation

ITEM	COMPOSITION OF EXTEMPORANEOUS PREPARATION	CHANGE OF ACTIVE INGREDIENT CONCENTRATION	PRICE VALUE INCREASE
1.	0,25% SOL. ZINCI SULFURICI 250,0	0,5% SOL. ZINCI SULFURICI 250,0	+19%
2.	0,3% SOL. ZINCI SULFURICI 500,0	0,5% SOL. ZINCI SULFURICI 500,0	+39%
3.	3% SOL. ICTHYOLI 500,0	10% SOL. ICTHYOLI 500,0	+32%
4.	2% SOL. KALII IODATI 500,0	10% SOL. KALII IODATI 500,0	+83%
5.	2% SOL. NOVOCAINI 500,0	3% SOL. NOVOCAINI 500,0	+6%
6.	HYDROCORTISONI 0,5; VASELINI ALBI AD 100,0	HYDROCORTISONI 1,0; VASELINI ALBI AD 100,0	+32%
7.	HYDROCORTISONI 0,12; HASCObAZA AD 50,0	HYDROCORTISONI 0,25; HASCObAZA AD 50,0	+5%
8.	NATRII THIOSULFURICI 1,5; GLICERINI 5,0; AQUA DESTILATA AD 100,0	NATRII THIOSULFURICI 2,0; GLICERINI 5,0; AQUA DESTILATA AD 100,0	+5%
9.	VIT.A 10 000J.M.; UNG.CHOLESTEROLI AD 100,0	VIT.A 50 000J.M.; UNG.CHOLESTEROLI AD 100,0	+19%
10.	HYDROCORTISONI 0,5; HASCObAZA AD 100,0	HYDROCORTISONI 1,0; HASCObAZA AD 100,0	+41%
11.	SULF. PPTI. 10,0; VASELINI ALBI AD 200,0	SULF. PPTI. 30,0; VASELINI ALBI AD 200,0	-6%

MODIFICATION OF EXCEPIENT CONCENTRATION

Excipients are the chemical substances or their compounds which may not in the applied quantities have any pharmacological effect of their own nor may they react adversely and influence the preparation stability⁸. Adding such substances is essential to make a proper form of the drug substance,

to increase its stability, to improve organoleptic parameters as well as to improve respective pharmacokinetic properties. It has been found that the increase of quantity of excipients in the drug form increased the price value of the extemporaneous preparation by 14% on average. Table 5 presents examples of such prescriptions.

Table 5. The examples of the increase of the price value related to the modification of the excipient concentration

ITEM	COMPOSITION OF EXTEMPORANEOUS PREPARATION	MODIFICATION OF EXCEPIENT CONCENTRATION	PRICE VALUE INCREASE
1.	ACIDI SALICYLICI 5,0; OL. RICINI 10,0; OL. RAPAE AD 100,0	ACIDI SALICYLICI 5,0; OL. RICINI 25,0; OL. RAPAE AD 100,0	+11%
2.	HYDROCORTISONI 0,375; 3% SOL. ACIDI BORICI 10,0; VASELINI ALBI; EUCERINI AA AD 100,0	HYDROCORTISONI 0,375; MENTHOLI 0,5; 3% SOL. ACIDI BORICI 10,0; VASELINI ALBI; EUCERINI AA AD 100,0	+5%
3.	UREA 5,0; AQUA DESTILATAE; EUCERINI; VASELINI ALBI AA AD 100,0	UREA 5,0; AQUA DESTILATAE Q.S.; EUCERINI; VASELINI ALBI AD 100,0	+25%
4.	VIT.A+D3 10,0; GLICEROLI 200,0; OL. MENTHAE PIPERITAE 0,05	VIT.A+D3 10,0; GLICEROLI 200,0; OL. MENTHAE PIPERITAE 0,1	+5%
5.	VIT.A+D3 10,0; GLICEROLI 400,0; OL. MENTHAE PIPERITAE 0,05	VIT.A+D3 10,0; GLICEROLI 400,0; OL. MENTHAE PIPERITAE 0,1	+6%
6.	ZINCI OXYDATI 0,2; LINOMAG 1,0; OL. LINI AD 100,0	ZINCI OXYDATI 0,2; LINOMAG 3,0; OL. LINI AD 100,0	+40%

MODIFICATION OF THE CHANGE OF PRICES OF INGREDIENTS AND PACKAGING

Different price values of extemporaneous preparations of the same composition made and priced at different pharmacies has been found. The purchase prices of pharmaceutical ingredients and packaging were not uniform. Despite the lack of modification in the

composition of the extemporaneous preparation price values differed within the range of a few up to more than ten percent. The following factors influenced the different price values: the purchase price of pharmaceutical ingredients dependent of the warehouse and the size of the bulk packaging (small packaging reflects a higher price per 1 g of the pharmaceutical ingredient), the pur-

The impact of the modification of the composition and the quantity of extemporaneous preparation on its price value

chase price of packaging of an extemporaneous preparation (the price of the ointment packaging of 100g ranged from PLN 0,60 to PLN 6) as well as the incorrect valuation of extemporaneous preparations. In Table 6 the examples of the price increase of the extemporaneous preparations of the same composition made in different pharmacies are presented.

Table 6. The examples of the price value increase of the extemporaneous preparations of the same composition compounded in different pharmacies

ITEM	COMPOSITION OF EXTEMPORANEOUS PREPARATION	PHARMACY WHERE THE PREPARATION WAS MADE	PRICE VALUE IN PLN (INCREASE)
1.	10% UNG. KALII IODATI 50,0	PHARMACY NO 3	29.57
		PHARMACY NO 4	32.19 (+9%)
		PHARMACY NO 5	32.58 (+10%)
2.	3% SOL. ACIDI BORICI; LANOLINI; EUCERINI AA AD 100,0	PHARMACY NO 5	28.86
		PHARMACY NO 3	32.06 (+11%)
3.	3% SOL. ACIDI BORICI; VASELINI ALBI; PARAFFINI LIQ.; LANOLINI AA 25,0	PHARMACY NO 1	23.56
		PHARMACY NO 5	24.53 (+4%)
4.	NATRII THIOSULFURICI 2,0; GLICERINI 5,0; AQUAE DESTILATAE AD 100,0	PHARMACY NO 3	17.84
		PHARMACY NO 5	19.09 (+7%)
		PHARMACY NO 4	19.56 (+10%)

DISCUSSION

The possibility to compound an extemporaneous preparation in a community pharmacy with a prescription from a medical doctor complements pharmacotherapy and is the response to the lack of ready-made drugs manufactured by the pharmaceutical industry as well as provides adjustment to customized patients' needs.

The composition of the extemporaneous preparation is determined by the doctor prescribing the drug. Each modification of the composition of the extemporaneous preparation is connected with the quality and quantity of ingredients to compound it. Con-

sequently this results in the change of the price value of the extemporaneous preparation made. The greatest impact on the increase of the price value of the extemporaneous preparation has been found with the modification of the ointment base from the traditional lipophilic to the novel amphiphilic base. The amphiphilic base is universal and its application allows for making multiphase

ointment types, or depending on the quantity and types of medical substance prescribed and water, the emulsion of the o/w or w/o types may be compounded. This universal characteristic is not provided by the cheaper lipophilic or absorbent bases. A similar impact on the price value is found with the modification of the form of the preparation connected with the modification of the applied base. This same active ingredient contained in the extemporaneous preparation i.e. aqueous solution, oil solution, glycerol solution, ointment, suspension, powder for external use determine a different price value of the extemporaneous preparation compounded.

Significant savings of public money has been observed when prescribing two separate preparations instead of double quantity of extemporaneous preparation. The saving amounted to the cost of compounding the extemporaneous preparation and the cost of one piece of packaging. Currently this solution is impossible due to the fact of the law forbidding to prescribe double quantity of an extemporaneous preparation⁶.

The modification of the concentration of the active ingredient triggered both the increase as well as the decrease of the price value of the extemporaneous preparation. If the purchase price of the active ingredient per 1 g was higher than the purchase price of the solvent or the ointment base then the price value increased. If the purchase price of the active ingredient per 1g was lower than the purchase price of the solvent or the ointment base, then the price value of the extemporaneous preparation decreased. The lowest increase was marked with the change of the excipient concentration.

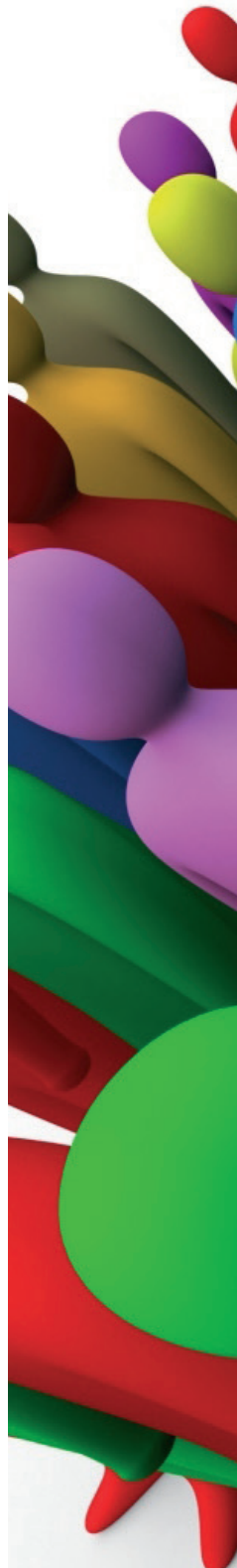
Despite the same composition extemporaneous preparations reached different price values in different pharmacies. The pharmacies which compound many extemporaneous preparations have been buying pharmaceutical ingredients in larger wholesale packaging with no risk of exceeding the expiration date and of incurring losses. However pharmacies which rarely compound extemporaneous preparations purchased pharmaceutical ingredients in smaller packaging what increased the price of 1 g. The prices of packaging were also different. Additionally a different price value is related to the incorrect pricing of the extemporaneous preparation.

CONCLUSIONS

1. It has been demonstrated that the modification of the change and number of ingredients used to compound the extemporaneous preparation has influenced the price value.

2. The increase of the price value also has resulted from the variable price of the purchase of pharmaceutical ingredients and packaging.

3. The different price values of the extemporaneous preparations of the same composition have been found in different pharmacies. ■



The impact of the modification of the composition and the quantity of extemporaneous preparation on its price value



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