

Márk Péter Molnár MD, Msc

**Rationale, Effectiveness and Economy
of Therapy Management Programmes**

Corvinus University of Budapest, Institute of Management

Supervisor: Viktória Bodnár, PhD

© Márk Péter Molnár MD, MSc 2015.

Corvinus University of Budapest
Ph.D. Programme in Business Administration

**Rationale, Effectiveness and Economy
of Therapy Management Programmes**

Ph.D. dissertation

Márk Péter Molnár MD, MSc

Budapest, 2015

Table of Contents

1. Introduction	11
1.1. The purpose of the dissertation	11
1.2. Justification of the choice of subject	11
1.3. Previous research	16
1.4. A subject on the boundary between scientific disciplines	18
Medical aspects	20
Pharmacological aspects	20
Aspects related to economics	21
1.5. The theoretical background and the structure of the dissertation	22
2. Review of the theoretical background of patient adherence	25
2.1. The issue of patient adherence in modern medicine	25
2.2. Direct and indirect clinical impacts	27
2.3. Direct and indirect economic impacts at the level of patients, payers and pharmaceutical manufacturers	29
2.4. The fundamental concepts of patient adherence	35
Compliance	37
Adherence	38
Concordance	39
Persistence	39
2.5. The factors influencing patient adherence	40
Social/economic factors	40
Therapy-related factors	42
Patient-related factors	42
Factors related to the healthcare system and the healthcare team	43
Factors related to the medical status of the patient	44
2.6. Factors determining patient adherence as reflected by patient perception research in Hungary	45
Patient attitudes in statin therapy based on the research published by Csóka et al. in 2012	45

Patient attitudes in therapy for benign prostate conditions, based on the research published by Dankó and Molnár in 2011.....	48
2.7. The possibilities of measuring patient adherence	48
Prospective measurement options.....	50
Retrospective measurement techniques	50
3. Levels of adherence for major chronic diseases around the world and in Hungary	53
3.1. Hypertension	53
Background, epidemiology	53
International overview	54
Hungarian data	58
3.2. Lipid disorders	61
Background, epidemiology	61
International overview	62
Hungarian data	64
3.3. Diabetes.....	68
Background, epidemiology	68
International overview	69
Hungarian data	71
3.4. Benign prostatic hyperplasia (BPH)	72
Background, epidemiology	72
International overview	73
Hungarian data	74
3.5. Atrial fibrillation	75
Background, epidemiology	75
International overview	76
Hungarian data	77
3.6. Osteoporosis.....	78
Background, epidemiology	78
International overview	78
Hungarian data	81
4. The possible ways of improving patient adherence.....	83

4.1.	The possible points of intervention.....	83
	Influencing social and economic factors	84
	Influencing therapy-related factors.....	86
	Influencing patient-related factors.....	87
	Influencing factors related to the healthcare system and the healthcare team	88
	Influencing factors related to the medical status of the patient	89
4.2.	Therapy management programmes and patient education.....	90
4.3.	Measuring the effectiveness of therapy management programmes	92
4.4.	International results concerning the effectiveness of programmes aimed at improving adherence	93
5.	The empirical study.....	100
5.1.	Gaps in international and Hungarian literature	100
5.2.	Research objective, hypotheses.....	101
5.3.	Research methodology and therapeutic area.....	102
	The therapeutic area selected	102
	The structure of the therapy management programme.....	103
	Measuring the effectiveness of the therapy management programme.....	107
	Determining economy from the perspective of the pharmaceutical manufacturer	108
	Economy from the perspective of the social insurance fund.....	108
	Data Privacy Aspects.....	109
	Schedule.....	110
5.4.	Presentation and interpretation of research findings	111
	The effectiveness of the therapy management programme	111
	Effectiveness from the pharmaceutical manufacturer's perspective	115
	Effectiveness from the payer's perspective	116
5.5.	Validity, reliability and generalizability of the results.....	118
5.6.	Conclusions, areas for further research	120
6.	References	122

List of Figures

Figure 1: The system of objectives of the research effort (my own figure, used at a meeting of the Hungarian Health Communication Society on 26 January 2011)	17
Figure 2: Relationship between adherence and mortality with cardioprotective drugs (Ho [2006])	29
Figure 3: The “victims” of patient nonadherence (own illustration)	30
Figure 4: Health care costs due to nonadherence – USA, 2008 (Capgemini Consulting [2011] p. 9)	32
Figure 5: The system of interest relationships between the three key stakeholders if patient nonadherence takes the form of getting but not taking the drugs (own illustration)	33
Figure 6: Conflicts of interest associated with patients’ failure to have prescriptions filled (own illustration)	34
Figure 7: Definitions of adherence-related sciences in the relevant literature (ABC Project Team [2012] p. 19)	36
Figure 8: The five sets of factors influencing patient adherence according to the WHO (WHO [2003] p. 27)	40
Figure 9: Frequency / regularity of taking statins (Csóka et al [2012] p. 1)	46
Figure 10: Relationship between adherence and patients’ own perceptions of their lipid levels (Csóka et al. [2012] p. 3)	47
Figure 11: Relationship between significance ascribed to potential complications and patient adherence in statin therapy (Csóka et al. [2012] p. 3)	47
Figure 12: Persistence of antihypertensive therapies (Wogen [2003] p. 427)	56
Figure 13: Persistence of antihypertensive therapies I (my figure based on Lachaine et al [2006])	57
Figure 14: Persistence of antihypertensive therapies II (my figure based on Gogovor et al [2007])	58
Figure 15: The one-year fosinopril persistence of Hungarian patients (Molnár-Dankó [2011])	59

Figure 16: Four-year fosinopril persistence of Hungarian patients (Molnár-Dankó [2011])	60
Figure 17: Proportion of non-adherent patients in European countries (ABC Project Team [2012] p. 91)	61
Figure 18: Statin persistence measurement results (my figure based on Simonyi [2013b]) p. 8).....	63
Figure 19: 12-month fibrate persistence (Simonyi-Molnár-Pálosi [2014] p. 95).....	65
Figure 20: 6 and 12-month persistence of lipid-lowering drugs (Molnár-Dankó [2010] p. 16)	66
Figure 21: Statin persistence in primary and secondary prevention (Márk et al [2013] p. 172)	68
Figure 22: Monotherapies of diabetes: adherence values for each active substance (Colombo et al [2012] p. 658)	70
Figure 23: Fixed dose combination therapies for diabetes: adherence values for individual combinations (Colombo et al [2012] p. 658).....	70
Figure 24: Metformin, sulfonylurea monotherapies and metformin + sulfonylurea combination, 1 and 2-year persistence values (Dailey et al [2001] p. 1317).....	71
Figure 25: Adherence of diabetics between 1999 and 2003, % (Doró [2005] p. 895) ...	71
Figure 26: 12-month OAD persistence (Jermendy et al [2012] p. CR75).....	72
Figure 27: One-year persistence in the pharmaceutical treatment of BPH (Dankó-Molnár-Piróth [2011])	75
Figure 28: Persistence curve of VKA therapies (Simonyi-Molnár [2014])	77
Figure 29: Adherence and persistence values for osteoporosis medicines (Hilgsmann et al [2012] p. 608)	79
Figure 30: Adherence values for osteoporosis medications I. (Curtis et al [2013] p. 4).80	
Figure 31: Adherence values for osteoporosis medications II. (Curtis et al [2013] p. 4)81	
Figure 32: Persistence of antiporotic drugs (Cheng et al [2013] p. 1010.)	81
Figure 33: Full therapeutic persistence of medications used for the treatment of osteoporosis (60-day grace period) – 1 April 2007 - 2009 (my figure from a meeting of the Hungarian Health Communication Association on 26 January 2011)	82
Figure 34: Points of intervention for payers in order to improve patient adherence (own illustration).....	85

Figure 35: An ideal therapy management programme for the treatment of hypertension, which targets all five groups of factors (own illustration)	91
Figure 36: 12-month persistency of the total population treated with dutasteride and tamsulosin fixed dose combination (own illustration)	112
Figure 37: 12-month persistency of the population treated with dutasteride and tamsulosin fixed dose combination but certainly left out of the programme (own illustration)	113
Figure 38: 12-month persistency of the population treated with dutasteride and tamsulosin fixed dose combination and certainly took part in the programme (own illustration)	113
Figure 39: Comparison of persiscent curves from the control and the examination groups (own illustration)	114
Figure 40: Estimated cost of an invasive urological treatment	117

1. Introduction

1.1. The purpose of the dissertation

My dissertation is a scientific investigation of the justification, effectiveness and economy of activities aimed at supporting patients in order to ensure that they want to and are able to perform the steps required for regaining their health in a maximally active and medically appropriate fashion. The thesis shows why there is – or at least, why there may be – a need for such activities in modern healthcare systems, details the possible types, participants and forms of those activities, and attempts to furnish an answer to the question of which stakeholders may derive a benefit from those activities in an economic sense. Theoretically speaking, it is certainly clear that all the stakeholders of healthcare systems – or more narrowly, the supply chain of pharmaceuticals – may derive a profit from improvements in the cooperation of patients; my dissertation seeks to answer the question whether that is a sufficient basis for the stronger claim that therapy management programmes themselves are of actual benefit for all the stakeholders in the supply chain of pharmaceuticals.

1.2. Justification of the choice of subject

There are innumerable objective as well as personal, subjective arguments for my choice of subject. Among objective arguments, I would emphasise the fact that modern healthcare systems, which aim for maximum efficiency and operate in an evidence-based fashion, aided by scientific results are gradually losing the ability to *retain the human face of healing*, with the result that so-called conventional healthcare is becoming mechanistic, inhuman. Within that increasingly sterile framework, the patient's person, their personality get lost, and we are forced to admit with increasing frequency that while we provide ever more costly and innovative medical technologies and medications, their actual, real-life effect decreases and eventually vanishes because patients do not cooperate with the specialists that treat them and they do not get involved in the therapeutic process. They do not cooperate – that is to say, they do not comply with instructions, or they do not comply with them accurately, either on purpose or possibly despite their best intentions (WHO [2003] p.

3; ABC Project Team [2012] p. 5). There may be a number of factors that explain the phenomenon – as we will see later – including, to mention a few, lack of knowledge, simple forgetfulness, or conscious and wilful refusal to cooperate. In the pharmaceutical supply systems of developed countries, which consume significant financial resources, it has become an everyday occurrence that a course of medications costing five thousand dollars a month fails to bring the expected results because nobody has taught the patient that if they don't take the medicine during a meal, the acidity of the stomach will neutralise the active ingredient. In another, equally absurd and common scenario, the most modern pharmaceutical product ends up in the waste bin because the colour of the pill has bad connotations attached in the culture where it was prescribed, leading to the patient refusing to take it due to his superstitious beliefs.

As, in recent decades, healthcare systems have been consuming increasingly significant funds and modern medical technologies have become increasingly costly, considerations of economy have come increasingly to the forefront of attention. Also as a result of that, the cooperation – or non-cooperation – of patients has also become more important both for specialists in the field and theoreticians. In the medical literature of recent years, patient adherence has become an increasingly significant issue, and most recently, the economic aspects of that theme have also been the subject of an increasing number of research papers (ABC Project Team [2012] p. 5). So the subject sits well with the research trends of recent years.

In addition to the objective argument for selecting this subject that the issue of patient adherence has become a focal point of scientific research in the fields of medical science, pharmacology as well as economics, I must also mention a number of personal motivations. It was primarily on account of those personal motivations that I decided, as a researcher, to achieve as good an understanding as possible of the complex and almost inscrutable process that leads a patient to cooperate with healthcare professionals, or, as the case may be, to not cooperate with them. My personal motivations primarily spring from the fact that over the last 10 years, as a practising

specialist, I have worked in four different roles that all made the harmful impacts of the lack of patient adherence palpable to me. Firstly, as a practising physician prescribing courses of treatment, secondly, for an insurance company responsible for the financing of medical treatment, thirdly as a consultant to pharmaceutical companies for whom treatments generate sales revenue, and fourthly as an inventor and leader for a company developing therapy management solutions using telecommunications equipment. I shall present each of those roles briefly below.

Although not as a practising doctor for quite a while, but still thinking with a doctor's mindset, I am very interested in the contradiction between our selecting the best treatment for an individual patient based on the most reliable evidence, with the utmost thoroughness, while in reality, the distortion in the end result caused by lack of cooperation on the patient's part is at least a full order of magnitude greater than by an incorrect choice of drug. It is as if we spent hours measuring the direction and strength of the wind before shooting at a target, while paying no heed whatsoever to the actual distance we will shoot. In everyday life, doctors do their best to find the drug for their patient which, based on scientific evidence, the data of the literature and domestic as well as international guidelines, is going to have the most beneficial effect. Prescribing the "best" product selected in that fashion gives rise to the illusion that the patient is on the best course to recovery. However, knowing the results of the analyses of patient adherence, the situation is a great deal less favourable and more complicated. Choosing the medically optimal treatment does not imply that the advantageous effects expected on the basis of the sterile data in the literature will materialise in everyday life, with an everyday patient (Balikó [2007]). Prescribing the correct dose of the most effective statin preparation for a patient struggling with high lipid levels is not a guarantee of success in itself. If the correct medical decision is not followed by the appropriate organisational, educational and psychological process, i.e. the provision of appropriate support for the therapy, we would be more likely to be correct if we assumed that the patient was not going to comply with our instructions and will not take the medicine as prescribed. I am certain that all scientific and educational work – including this dissertation – that assists practising doctors with

improving the efficiency of their support for the appropriate therapeutic compliance of their patients is essential for efficient patient care in the future.

The period I spent working for the National Health Insurance Fund Administration of Hungary (hereinafter the NHIFA), dealing with the subsidisation of medications and durable medical equipment, also made a strong impression on me. I had an opportunity to access the payer databases that showed quite clearly and unambiguously that it is not simply the case that the lack of patient adherence is a real and massive problem in Hungary, too, but rather, our country's characteristics in this respect are very poor in international comparison. Working for the Hungarian state health insurance fund, my interests were strongly determined by the realisation that a very significant proportion of the taxes and contributions collected from the tax-paying public is wasted because the subsidised drugs do not bring to desired results, or indeed have no beneficial impacts at all in real life. In the short term, the wastefulness is obviously the result of patients fail to take the subsidised products they purchase for the prescribed period of time, resulting in the medications producing very little benefit or indeed no benefit at all, but the long-term effects can be even more significant. That is because usually, ineffective courses of treatment result in even more costly healthcare having to be provided at a higher level of progression, usually involving institutionalisation. Simply put, this means that failure to take the medicine results in the need for hospital treatment, with all its attendant costs. In the course of my work there, I performed several analyses of the payer databases that made it clear to me that the most important problem of modern pharmaceutical treatments is that patients do not take the drugs prescribed for the prescribed length of time and in the prescribed manner. The research and measurements performed using the payer databases also had a definitive effect on my work as a researcher, as will be evident in the chapter on conditions in Hungary, as in several therapeutic areas, the research and publications that helped to clarify current conditions were in fact efforts that I myself had participated in as a researcher or research manager. I am convinced that in the efficient healthcare system of the future, the payers will play an indispensable role in implementing appropriate therapy management. Payers will not only need to provide feedback to practising physicians in the form of appropriate data, they will also have to

use their own resources, either independently or through cooperative efforts, to take a direct part in the sponsoring of therapy management programmes.

As an advisor to pharmaceutical companies, I became familiar with yet another aspect of the issue of patient adherence. On the one hand, for long decades, those companies have followed the traditional business model and promoted their products very intensively towards the doctors that prescribe them in order to achieve the desired sales volumes. On the other hand, in recent years, the regulatory authorities of almost all developed countries have made efforts to curtail the inordinate promotion of pharmaceuticals, as that type of activity primarily resulted in the generation of new patients, and failed to incentivize pharmaceutical manufacturers to maximize the real-life effectiveness of their products while making them primarily available to patients who actually do need their specific active ingredients. The constraints on promotion towards doctors and the increasing costs of the various remaining techniques resulted in pharmaceutical companies also exhibiting greater interest in the business impact of the loss of sales resulting from patients' failure to cooperate. There is a two-fold effect involved there, as it is not merely a case of the abandonment of therapies causing a short-term direct loss of revenue for the market players: companies also have to face up to the unfavourable secondary impact of unfavourable changes in the attitudes of doctors and the payer towards a particular preparation if therapies are abandoned early and hence fail to produce the desired effect. Today it is quite clear that as a result of the shifting of emphasis in recent years, pharmaceutical companies devote increasing energy to attach therapy management services and IT equipment to their products in order to achieve appropriate patient adherence. I am convinced that in the future, pharmaceutical manufacturers will have to deliver a great deal more than a chemical or biological compound in order to remain successful in business. It is already obvious that intelligent dosing equipment, IT applications and smart blisters have become integral parts of treatment, in it is completely certain that we will see more of that type of solution in the future.

Finally, as the leader and inventor of a start-up creating therapy management programmes, I received confirmation in everyday practice of the view that modern telecommunications and information technologies can be used to educate and motivate large patient populations so as to achieve significant, spectacular improvements in patient adherence. We managed to implement such solutions in practice in a manner that also proved the economic viability and business potential of such activities, if not with scientific rigour, certainly at the level of everyday business.

1.3. Previous research

The experiences described in the previous chapter demonstrate that I have been exposed to the issue of patient adherence from a number of perspectives, and I used those experiences in a number of specific pieces of research. The research I have conducted over the last few years had a stable logical framework and progression. Fundamentally, the research aimed to create an accurate scientific assessment of the international and domestic situation as the first step, followed by an investigation of the explanatory factors and finally the formulation of specific guidelines for practising doctors. The figure below (see Figure 1) is ample demonstration that my scientific work was planned to improve the knowledge of healthcare professionals – primarily doctors and pharmacists – working in Hungary of the significance of patient adherence and the allow them the turn patients into allies with maximum efficiency, so as to achieve the best possible results in their day-to-day work. In the interest of achieving those objectives, our research team cooperated continuously with representatives of the various social sciences, fellow universities, medical professional bodies and the leading medical specialists of the specialist areas involved.

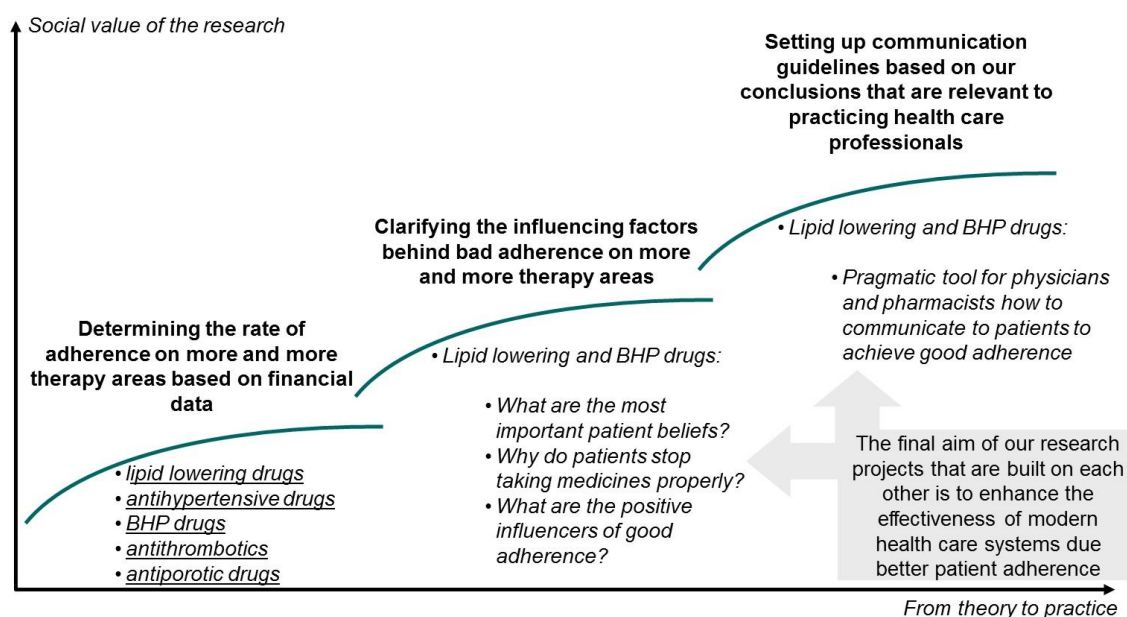


Figure 1: The system of objectives of the research effort (my own figure, used at a meeting of the Hungarian Health Communication Society on 26 January 2011)

The list of therapeutic areas listed as examples in the first column of the figure above. has grown dynamically in recent years, and the number of diseases about which analyses based on payer data have been completed with my assistance has also increased significantly. Many of those analyses were published in domestic journals, a smaller number appeared in the international literature, and we have also produced a number of research papers and presentations that, while not published, still enriched the knowledge of the Hungarian medical and scientific communities in other forms. I participated in the analysis of payer data in the following areas:

- Statins, anti-cholesterol medications
- Fibrates, lipid-lowering medications
- Bisphosphonates, osteoporosis medications
- Medications for BPH (benign prostatic hyperplasia)
- Antithrombotics
- Anticoagulants
- Antidiabetics
- Antihypertensives

These research results, partially my own, are presented in detail in Chapter 3 of my dissertation for the main groups of diseases.

The second column of figure on research activities purposefully goes beyond a descriptive approach, and, going beyond the diagnosis to the effect that in the case of certain diseases, there are serious problems with patient adherence, it aims to find scientific answers concerning the causative factors behind the disappointing data measured. We conducted research in two very different therapeutic areas, using representative samples to discover the beliefs, motivations and ideas in the background of patients' attitudes to cooperation. The two therapeutic areas were the treatment of high cholesterol levels and benign prostatic hyperplasia (BPH). The results of the attitude studies are presented in Chapter 2.4 of the dissertation.

The third column of figure on research activities did not primarily manifest in the form of written handbooks or guidelines, but largely took the form of educational presentations for practising doctors at various professional events and the writing of educational articles for non-scientific periodicals. At the same time, in line with practical requirements, the research strategy was extended to include a fourth column, the scientific measurement of the effectiveness of therapy management programmes. In the practical part of my dissertation, I present the results of two of my research projects in that field.

1.4. A subject on the boundary between scientific disciplines

It would be a justified question to ask what the issue of improving patient adherence is doing in the programme of a doctoral school with a focus on economics, within the framework of a university institution where the subject of study is management. The answer to that question goes beyond the clearly visible verbal parallel, namely that it is no accident that activities aimed at improving patient adherence are called therapy management programmes. The reality is that activities supporting the therapies of patients are located at the boundary between a number of large scientific disciplines, which is in fact the reason why for a long time they were treated rather negligently and received very little attention. First and foremost, we are on the boundary between medical science and economics, but the situation is complicated further, as within each

of those large fields, several specialist areas are involved, and at times, disciplines other than those two major ones also play roles. (ABC Project Team [2012] pp. 166-168)

Of course, scientific interest in patient adherence is far from new. Investigation of the issue goes back to the great scientists of antiquity, such as Hippocrates, who foreshadowed the need to create the scientific concept of patient adherence with the following sentence: *“keep watch also on the faults of the patients which often make them lie about the taking of things prescribed”*. (Fulda et al [2007] p. 568)

The modern focus on the problem of *compliance* itself (for a detailed explanation of concepts, see later chapters) was the result of the work of Robert Koch who in 1882 began to explain the inefficacy of orally administered medications against tuberculosis by the lack of compliance on the part of the patients (ABC Project Team [2012] p. 20). By the end of the 1970's, it was also recognised that the issue of patient adherence is actually a wide-spectrum, complex range of problems, and at that time, therapy-specific analyses and studies began to be published (Vermeire et al [2001]). The complexity of the subject is also highlighted by the fact that according to the WHO, in recent decades, along with healthcare specialists, specialists in behavioural science as well as social scientists have also investigated it (WHO [2003] p. 19). Beginning the 2000's, as cost-efficiency analyses came to the fore, a number of health economists have attempted to quantify the impact of programmes aimed at improving adherence, compliance and persistence using the incremental cost efficiency ratio (ICER) and the quality-adjusted life year (QALY) parameters. For example, Hiligsmann and his colleagues performed a health-economic analysis on the cooperation of patients suffering from osteoporosis (Hiligsmann et al [2012]). These considerations also prove that patient adherence is not simply a medical or healthcare issue, but, rather, an interdisciplinary area on the boundaries of economics, medical science, the behavioural sciences and other management science theories. If, for instance, we begin with the conceptual framework created by Dotar and colleagues, we see that adherence – as a model – can be defined as a socio-cognitive theory, as change management, but also, first of all, as an integrated model (Dotar et al [2009] pp. 8-12).

The integrated nature of this field has the inherent consequence that it is not a central problem for a specific scientific discipline but, rather, a field on the boundaries of several scientific disciplines.

Medical aspects

For a long time, the issue of patient adherence was mostly within the domain of medical science, because practising doctors were the first to recognise the problem of the difficult path to getting patients to accept and comply with the doctor's instructions as regards medications or other components of the therapy. Within medicine, a number of specialist areas began to study the problems of patient adherence.

The behavioural sciences – psychology and communication – began to study the complex psychological process that unfolds in people receiving treatment until awareness of illness and cooperation with the doctor develop, and the ways in which that process can be influenced using suitable verbal and non-verbal communication and techniques. The researchers approaching the field from those disciplines primarily sought motivations, background mental patterns and characteristics in the background of patient adherence, and largely approached the subject holistically, i.e. they studied the doctor-patient relationship in general.

Pharmacological aspects

The representatives of the science of pharmacology began to study a narrower subset of the issue of patient adherence, and in that sense were met with a much more structured problem and – if I may be permitted to put it that way – got a great deal further with mapping the situation. Pharmacology began to study the specific problem of therapeutic adherence in pharmaceutical treatments, the problems of delivering medications. These researchers were not primarily interested in mental patterns: initially, they simply wanted to know what happens if the patient fails to take his medication at exactly 7 in the morning, or he doesn't have exactly two doses every day, or perhaps if he doesn't take the medicine before, during or after eating, or if he

takes two drugs at the same time whose simultaneous use may be contraindicated. Several techniques for measuring patient adherence were clearly the achievements of pharmacological researchers, such as monitoring the levels of individual active ingredients in the blood, or the development and use of various intelligent dosing devices. The therapy management solutions used at the pharmacy, known as pharmacist intervention, also link certain aspects of improving patient adherence and rendering support for pharmaceutical and non-pharmaceutical therapies to pharmacists. This is borne out by the study produced by the Pharmaceutical Group of the European Union (PGEU) in which, on the one hand, the levels of patient adherence were studied within the framework of pharmaceutical care programmes, and on the other hand, an attempt was made to quantify the extent to which pharmacist intervention improves adherence (PGEU [2008]).

Aspects related to economics

While researchers with a medical background started with an investigation of the doctor-patient relationship and pharmacologists wanted to observe and monitor individual pharmaceutical therapies as closely as possible, researchers approaching the problem from the perspective of economics wanted to understand, plan, measure and optimize the purposeful process of organisation that operates within the framework of individual healthcare institutions (hospitals, out-patient clinics), or more commonly the framework of healthcare provision networks, either well or poorly, so as to restore or improve the health of patients. After the medically or pharmaceutically optimal treatment strategy is selected for the patient, supporting the therapy in order to ensure that its effectiveness reaches or at least approaches the theoretical optimum is clearly a management issue. So therapy management is much more of a process management or network management problem, and it is much more amenable to study using the methods customary in the management of business and public service organisations. Therefore all activities aimed at ensuring that a treatment selected on medical grounds is actually implemented as accurately, professionally and successfully as possible can be included in the category of therapy management. Among others, such activities include the following:

- Professional organisation of and IT support for patient journeys both inside and outside the institution
- Professional dissemination of and IT support for information about treatment of the patient and the patient himself, both inside and outside the institution
- Education of the healthcare professionals participating in care
- Patient education in person, using printed material and virtually
- The closest possible monitoring of the therapy, and associated IT support
- Mental guidance for the patient

Alongside the organisational aspect of therapy management processes, it must also be kept in mind that health communication doesn't only develop along the medicine – behavioural sciences – communication pathway: within economics, researchers of marketing communication have also achieved significant results in the field (particularly in Hungary).

Beyond the roots in theoretical science described above it is quite clear that by today, the issues around patient adherence and therapy management have come to constitute a true frontier zone, and that while on the historical scale, the ways of thinking and research interests of the representatives of individual fields of specialisation can be distinguished quite well, today it is much more the case that multidisciplinary research groups are at work on both the theoretical and the practical problems of therapy management, so it is hard to even imagine arriving at the correct scientific answers using a strict categorizing approach. It has become clear in recent years that neither medical science, nor pharmacology, nor economics will be able to furnish appropriate responses to the worldwide catastrophic nonadherence of patients in their own.

1.5. The theoretical background and the structure of the dissertation

The logical progression of my work leads from the general towards the specific. Having outlined my personal connection with and commitment to the subject, I will attempt

to explicate the problem itself, its theoretical background and significance. This includes not only a description of the theories of patient adherence, but also a presentation of international and Hungarian measurement results. I wish to go beyond pure theory and present the specific, palpable medical and economic impact of patient nonadherence, and to justify the necessity and utility of therapy management programmes improving and supporting patient adherence in modern healthcare systems first on a theoretical basis and then also using specific measurements.

As I have shown above, the theoretical background of patient adherence involves a number of scientific disciplines, but today it has become a specialist field in its own right, with its own extensive international and Hungarian literature.

In my dissertation, I will present the core definitions, theories and influencing factors of patient adherence stratum by stratum, based on the literature. In relation to patient adherence, it is necessary to introduce a number of fundamental concepts that are indispensable for a comprehensive exploration of the phenomenon. We are faced with a special situation in which the evolution of the definitions themselves provides a fascinating glimpse of the developmental paths, philosophically and in terms of attitudes, that have transformed the assessment of patients and the system of relationships between doctors and patients in recent decades. After reviewing the definitions, I will present and review the basic literature related to patient adherence and describe our current scientific understanding of the most important factors that determine whether a patient cooperates with his doctor during therapy, and I will also outline the points of intervention at which the situation may be improved. Those theoretical considerations shall provide justification for the therapy management programmes whose effectiveness I will measure in the empirical part of my study.

Illustrating the magnitude of the problem is also part of the theoretical background, so I shall use the examples of a few major chronic diseases to present the measured levels of patient adherence based on international research and, where possible, also Hungarian research, in particular my own research results.

In the last part of the dissertation I will present the objectives, foundations and results of my empirical research. During that research, my fundamental hypothesis was that therapy management programmes improve patient adherence significantly. In addition to providing evidence for that hypothesis, I also investigate a number of secondary hypotheses concerning the economy of therapy management programmes. Is a therapy management programme economical for society? Is a therapy management programme economical for a player in the pharmaceutical market?

2. Review of the theoretical background of patient adherence

2.1. The issue of patient adherence in modern medicine

In the second half of the 20th century, with the development of societies, the creation of modern healthcare systems and general improvement in welfare, the composition of diseases shifted towards chronic conditions. While in previous periods, infectious diseases were the leading causes of death, by today the situation has been transformed completely. In parallel with that, healthcare systems are increasingly devote most of their resources to treating chronic – usually life-long and non-infectious – diseases. Those diseases require long-term pharmaceutical (and non-pharmaceutical) treatment, in contrast with the treatment of rapidly progressing infections, where the cure is also rapid, if there exists one at all. Long-term treatment requires a great deal more from patients in terms of active participation, agreement and attention, so the effect of the lack of those things on the ultimate objective of treatment is much stronger. With chronic diseases, accurate and persistent adherence to the therapy plays an essential role. Adopting a sensationalist approach, we could say that while the epidemics of the 19th century were caused by bacteria and viruses, the epidemic of the 21st century is caused by patient nonadherence. Although we have effective and generally available treatments for most diseases, we do not have the ability to get our patients to actually use them appropriately, and as a result, we eventually lose those patients (McMullen et al [2015]). The healthcare system of the 21st century need to achieve multidisciplinary cooperation and the support of the companies that deliver practical solutions in order to “cure” non-adherent patients, i.e. to secure their cooperation.

As regards the patient adherence data measured in various countries, the literature shows a highly varied picture. Very generally – i.e. without selecting a specific disease, a specific therapy or a specific country of patient demographic – approximately a half of all patients adhere to the prescribed course of medication. It is important to emphasise that without considering the specific factors listed above, we can only establish very general findings, as many publications have reached the conclusion that,

along with other factors, patient adherence is highly linked to the level of development of countries, the specific therapeutic area, the specific treatment and a number of other parameters that I will discuss in detail later. The value of around 50% is valid in the developed world, the level of patient adherence can be significantly worse in developing countries, although we have significantly less information about them. (WHO [2003] p. 7)

In view of the highly unfavourable data the question arises as to the factors that prevent appropriate patient adherence. Most of the factors that can be established are directly related to the character of the cooperation between patients and their doctors, i.e. they are independent of the pharmacological features of the medication used (Hankó [2006]). The scenarios below, and there various combinations, can all be included in the definition of nonadherence (Molnár [2010] p. 4-5):

- *“The patient doesn’t necessarily get the medication prescribed at the pharmacy. This can be caused by forgetfulness, the lack of awareness of illness, or the “overwriting” of the doctor’s instruction for some other reason.*
- *The patient gets the prescription filled, but doesn’t take the medicine, for similar reasons.*
- *The patient does take the medicine, but not with the prescribed frequency, or at the prescribed times or doses, or not using the method specified in the patient information leaflet.*
- *The patient stops or interrupts taking the medicine before the prescribed time, which may be caused by feeling better, regaining a psychological sense of security, a reduced awareness of illness, or experiencing unpleasant side-effects, or it may be simply because the patient is “too busy” for some reason to obtain the next subscription or to get it filled (e.g. holiday, accident resulting in being bedridden, a personal crisis, etc.).*
- *The pharmaceutical therapy doesn’t follow a clear treatment strategy, so the patient switches active substances without justification, begins a parallel auxiliary therapy with a different active substance, changes the dose, etc.”*

As explained above, the level of patient adherence cannot be characterised in general, exact data can only be produced about specific diseases and specific patient populations. The indicative value of 50% specified by the WHO (World Health Organisation) is a rough estimate and it is primarily suitable for illustrating the magnitude of the problem. The great variations that actually exist are characterised well by an analysis performed in 2004 by DiMatteo, which drew its conclusions based on a meta-analysis of 569 previous studies (DiMatteo [2004]). DiMatteo's analysis obtained an average adherence level of 75.2%, ranging from 65.5% to 88.3% in the therapeutic areas reviewed. So that publication reported a more favourable average patient adherence level than the previously published 50%, which may have been partly due to the fact that the fundamental data came from studies before 1998. In Chapter 3 I will provide a detailed description of the likelihood of patients suffering from various diseases discontinuing their medication, but let us look at a few examples from the international literature just to outline the situation.

In the case of asthma, the literature indicates that less than half the patients adhere to the prescribed therapy (Bender [2002]). According to Lerman, the situation doesn't appear to be any better with diabetes, either, the ratio of adherent patients is below 50% there as well (Lerman [2005]). According to the studies performed by Wogen and colleagues, after a year, 63% of patients were taking the prescribed doses of valsartan, while the same figure was 53% for amlodipine and 50% for lisinopril (Wogen et al [2003]). According to another study, 1 year after commencing the therapy, 62% of patients were still taking the prescribed ACE inhibitors, 54% were still taking their calcium channel blockers and 42% were still taking their diuretics (Colin et al [2001]). Data from the United States indicates that in the case of both primary and secondary prevention, 60% of patients discontinue their life-saving anti-cholesterol drugs (Joanne et al [2008]).

2.2. Direct and indirect clinical impacts

The conditions outlined above indicate that therapies that should be life-long are in reality not continued indefinitely, because there is some "defect in the machine", and

the therapeutic process is interrupted. It is also evident that about half of all cases and patients fall in that problematic group, i.e. half the patients do not exhibit appropriate adherence. The meaning of that observation, the significance of that fact is a highly important question. To answer it, we need to understand the causal relationship between the end-result of therapy and appropriate patient adherence.

We have clear scientific evidence that the most frequent cause of a poorly adjusted blood pressure is poor patient adherence (Borghi et al [1999]). Some doctors say there is no such thing as a poorly adjusted blood pressure, only patients who fail to adhere to the prescribed treatment. We also have some studies that indicate that among non-adherent patients, only 18% actually achieve the target blood pressure, while the same ratio was 96% for adherent patients (Waeber et al [2000]). We also know from the work of several authors that appropriate patient adherence improves the effectiveness of the therapy, for instance it reduces the frequency of the complications of high blood pressure and hence the probability of stroke (Marmot et al [2002]) and heart disease (Heller et al [1978]). All of this shows that in the case of cardiovascular disease – where the effects of medication are quite discernible already in the short term – the link between patient adherence and final effectiveness. A 2006 publication used a statistical approach to study exactly that question, and it reached the same results: the authors investigated the relationship between the mortality and the adherence of ischemia and diabetes sufferers. (Ho [2006]) It is quite clear in the figure below that the life prospects of patients not receiving treatment were essentially identical to those of patients who did receive treatment but failed to adhere to the therapy. It is important to note here that the authors treated mortality as a hard limit, so in essence the results say that non-adherent patients dies with the same probability as those who didn't get treatment at all. That is a good illustration of the real stakes involved in improving or achieving patient adherence in modern healthcare systems. The figure below makes it quite clear that, though this may be a slight exaggeration, no matter what new instruments we add to the arsenal of modern medicine if we are unable to get more than half our patients to actually use them as intended. Perhaps the day has come when a unit of the resources of modern healthcare would be more profitably spent on improving patient adherence than on developing a new active substance.

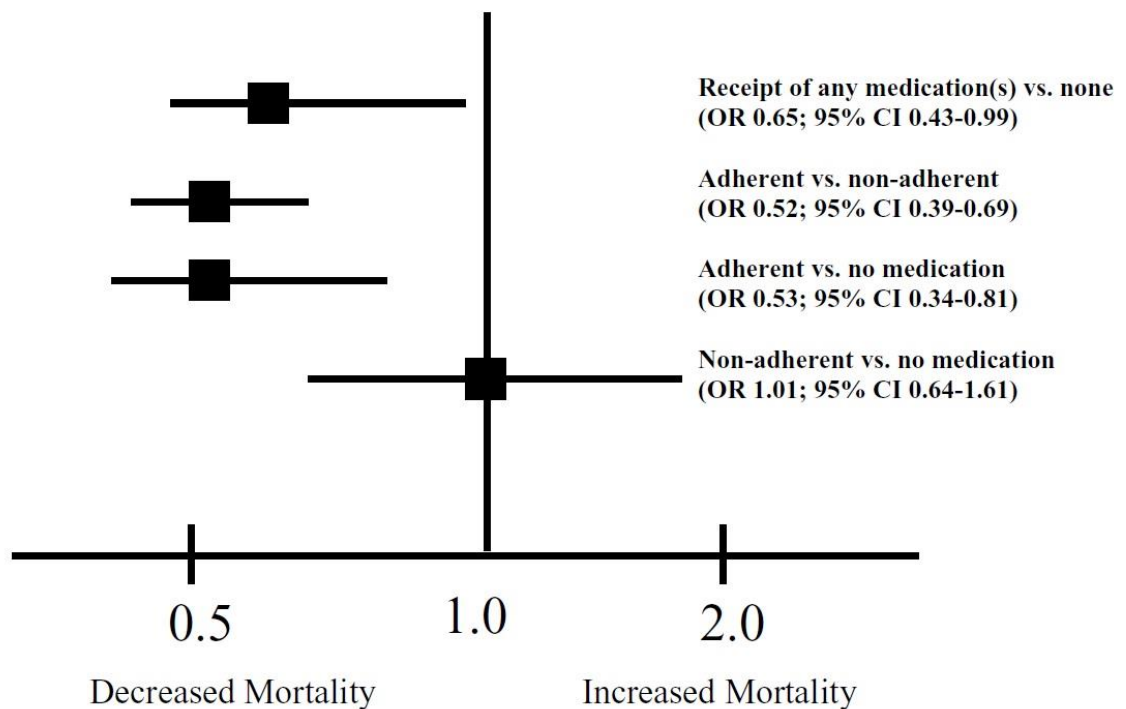


Figure 2: Relationship between adherence and mortality with cardioprotective drugs (Ho [2006])

2.3. Direct and indirect economic impacts at the level of patients, payers and pharmaceutical manufacturers

Poor adherence causes significant extra costs for patients, healthcare systems – which are equivalent to payers, insurance companies or the state – and for pharmaceutical manufacturers both directly and indirectly, through the resulting failure of therapies. In most cases, all three of these three so-called *stakeholders* share the financial loss caused by patient nonadherence in varying shares, so these three stakeholders are also the ones who can benefit from appropriate patient adherence.

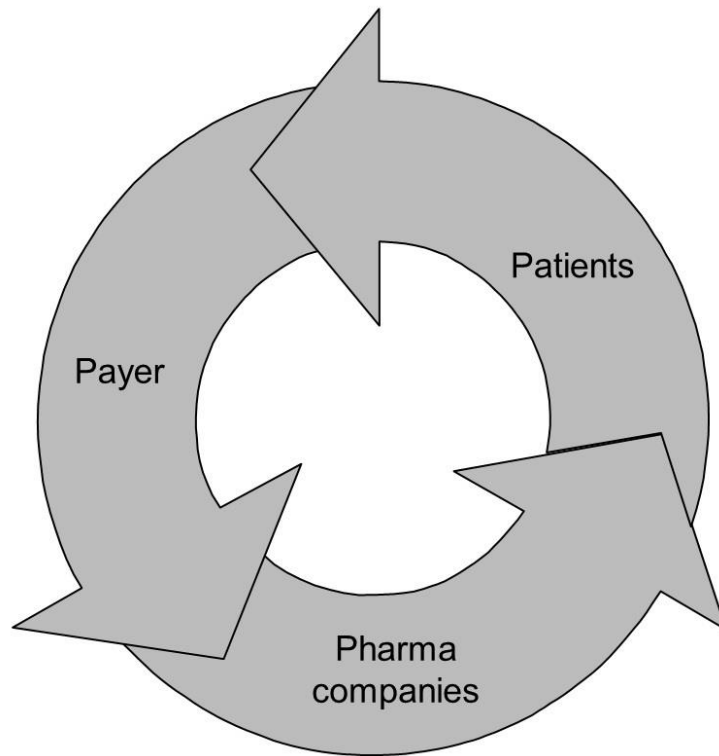


Figure 3: The “victims” of patient nonadherence (own illustration)

Poor adherence leads directly to a loss of economic efficiency if the patient used partly her own funds and partly those of some payer to purchase the medication but doesn't use it, doesn't take it, or uses it in a manner whose effect is significantly below the intended effect. Let's assume a simple and extreme case: the medicine costs 100 units of money, of which the patient herself pays 50 units as a *co-payment*, while the payer pays 50 units as a subsidy. If the patient decides not to take the tablets because after reading the information leaflet she is scared of the potential side-effects, the direct financial loss incurred by the patient is 50 units, and that of the payer is the same. If the drug in question has to be taken specifically during a meal because otherwise stomach acidity prevents appropriate absorption, the result is the same if the patient does take the pills, but does so before eating. It is clear that those two scenarios do not have an economic impact on the pharmaceutical manufacturers, as the product is purchased. Another way to put it is to say that once drugs are purchased, only the patient and the payer have an interest in appropriate use, the manufacturer of the drug no longer has little direct economic interest at that point. The situation is rendered somewhat more complex, however, by the fact that the payer's endeavours

do make the manufacturer interested in ensuring that its products do have a real effect. Once that is taken into account, the pharmaceutical manufacturer is also seen to have an interest in the patient's adherence to the therapy.

It is obvious that the economic impacts of the above scenario can be considered in the short term and in the longer term as well. While the above reasoning primarily concerned the short-term, direct effects, we should not forget the consequence that a drug bought but not taken is not going to have its desired effect, which will result in indirect costs. If, in the above example, if the pills not taken or not taken in accordance with instructions are an antihypertensive, and, as a result, on the day after her failure to take the drug the patient in question suffers a stroke in the early hours of the day, when blood pressure usually exhibits a peak in its normal daily variation, this event, and the costs resulting from that event will also be indirectly attributable to poor patient adherence. In such a case, we can quantify the total cost of treating the stroke for the patient as well as the healthcare system, i.e. the payer. Naturally, the patient's "costs" need to be understood in a wide sense, as the costs of a stroke even include all the actual costs of treatment and rehabilitation, but they may also be considered to include all the lost income due to the incapacitation of the patient and her family. It is exactly those long-term costs that Dankó illustrated in her 2011 article, in which he reached the conclusion that in the case of antihypertensives, the extra cost of drugs resulting from an adherence programme amount to 10.8 million forints in total, the cost of the hospital treatment of just three strokes thus averted could come to 21 million forints. (Dankó [2011])

In the case of the US health care system the following graph illustrates the extent and the composition of indirect costs due to nonadherence.

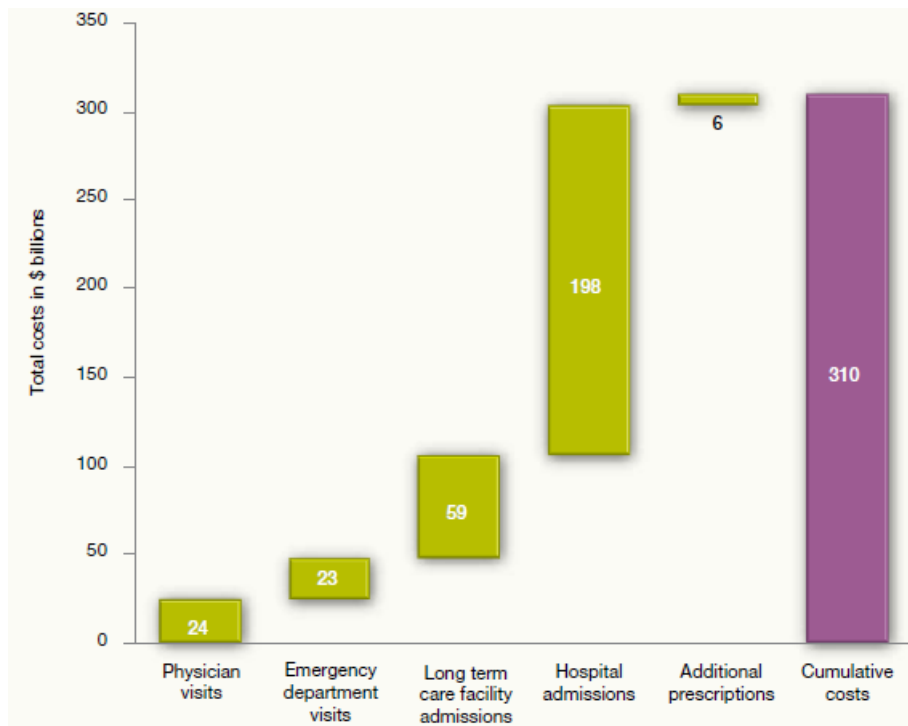


Figure 4: Health care costs due to nonadherence – USA, 2008 (Capgemini Consulting [2011] p.

9)

Naturally, such an analysis of indirect costs is not limited to cardiovascular disease. The same type of analysis can also be applied to respiratory illness, and indeed this has been done by Balkrishnan and his team, who followed 1,595 patients over the age of 65 with chronic lung complaints for two years in a retrospective study. They found that poor patient adherence increased the annual number of registered specialist-patient appointments by 5%, while better patient adherence was able to reduce the number of hospitalisation events by 20%. (Balkrishnan et al [2000])

In summary, we can conclude that if patients get their prescriptions filled but do not actually take the medication or use it incorrectly, there is primary economic damage largely for the patients themselves and the payer, that kind of nonadherence is economically indifferent for pharmaceutical manufacturers. However, it must be noted that due to the provisions of more recent agreements concluded between payers and pharmaceutical manufacturers, and the spread of conditional listing systems, manufacturers also increasingly shoulder a part of the loss. The figure below shows that system of interest relationships:

Stakeholders/ Timeframe	Patients	Payer	Pharma
Short term	Not taking the prepaid pills or doing it without effect means waste of money.	Not taking the reimbursed pills by the patients or doing it without effect means waste of resources.	Indifferent
Long term	Due to missing effect there might be indirect sideeffects, events and costs.	Due to missing effect there might be indirect sideeffects, events and costs.	Indifferent

Figure 5: The system of interest relationships between the three key stakeholders if patient nonadherence takes the form of getting but not taking the drugs (own illustration)

Above, we examined the situation in which the patient gets the drug prescribed from the pharmacy, but doesn't take it, or doesn't take it in accordance with instructions. Let's look at the case in which the patient doesn't get the prescribed medication at all, or gets a product to be taken permanently for a few months, then stops getting it. In that case, the long-term effects are rather similar to the above scenario, but in the short term, things pan out somewhat differently. In this scenario, the patient doesn't get the drug from the pharmacy, so in the short-term, the pharmaceutical manufacturer suffers a loss of sales revenue, while the phenomenon actually causes a gain for the payer as well as the patient. According to certain calculations, the global pharmaceutical industry is losing 36% of the potentially realizable revenue for each individual marketed drug due to nonadherence, though acquiring a new patient costs 62% more than patient retention (Capgemini Consulting [2011], p. 6). Yet the secondary impacts are quite clear in this, case as well: both the patient and the payer will incur significant costs later as a result of patient nonadherence. It follows that the interests and motivations of individual stakeholders may be quite different as a function of the period considered in the case of patient nonadherence in which the patient doesn't even have the prescription filled. This ambivalent network of relationships is also the primary theme of my dissertation, as from the perspectives of patients and payers, the net balance of short-term and long-term impacts needs to be determined in order to assess the economic justification for increasing adherence,

which will certainly result in more pharmacy purchases. The figure below shows the conflicts of interests: in the short term, it appears that there is a conflict of interest between the manufacturers of the drugs on the one hand and the payer and the patient on the other hand, which is resolved in the very fact that the long-term economic interests of patients are in conflict with their own short-term interests as well, while those long-term interests of the patients actually coincide with the short-term interests of the manufacturers.

Stakeholders/ Timeframe	Patients	Payer	Pharma
Short term	Buying the prescribed medication means cost, missing out the refill brings saving.	Reimbursing the prescribed medication means cost, missing out the refill by the patient brings saving.	Missing out the refill by the patient means lower revenue.
Long term	Missing out the refill means missing effect and indirectly unnecessary sideeffects, event and costs.	Missing out the refill means missing effect and indirectly unnecessary sideeffects, event and costs.	Indifferent

Figure 6: Conflicts of interest associated with patients' failure to have prescriptions filled (own illustration)

Despite the above theoretical problems, one thing is certain: the economic costs at the level of society have been quantified in several countries, and extremely shocking results were obtained, particularly as regards the economic impact of the complications and expensive hospital treatments attributable to nonadherence. In the United States, the costs attributable to nonadherence and improper drug selection were estimated in 1995 and in 2000, furnishing a view of the trends in those costs and the dynamics of change. According to a 2001 study by Ernst and Grizzle, in 1995, the drug related problems they described cost 76.6 billion dollars in the United States of America, while calculations using the same model yielded a figure of 177.4 billion dollars for the year 2000. 70% of the 177.4 billion dollars were contributed by hospitalisation costs that would have been unnecessary in case of proper drug selection and appropriate patient adherence. (Ernst-Grizzle [2001]) In 2011, a more

recent calculation has been estimated the yearly economic damage caused by nonadherence at 310 billion dollars (Capgemini Consulting [2011], p. 9).

The literature also furnishes an answer to the question of the relationship between the greater expenditure on drugs caused by better adherence and long-term savings for the payer. A number of studies reached the conclusion that programmes aimed at improving adherence are profitable for the payer even in the short term. Some authors monitoring such programmes report that the ratio of costs to savings is 1:10, i.e. the savings available through the regular taking of drugs are ten times the cost of improving adherence. In the manner described above, Holman and colleagues studied the effects of a complex educational programme, and their highly favourable results were primarily due to the very significant savings resulting from the hospitalisation events that were thereby avoided. They found that members of the control group, who did not participate in the programme, cost 820 dollars more for the US healthcare system than those who did participate in the programme, whose per capita cost was only 70 dollars, of which the cost of trainers was 26 dollars per patient (Holman et al [1997]; [1999]).

2.4. The fundamental concepts of patient adherence

The concepts used to characterise patient adherence have undergone a special evolution in recent decades. The transformation of the concept reflects changes in the understanding of the relationship between doctors and patients over the years quite well. On the one hand, this evolutionary process towards increasingly patient-centred healthcare and medical services is to be welcomed, but on the other hand it must be noted that the desire to avoid various connotations of the definitions has led to an unnecessary proliferation of definitions, so concepts in the field have become rather chaotic, while it is difficult to pinpoint specific differences between the various definitions. It is quite easy to see that the people who formulated the definitions didn't simply wish to describe certain processes, their fundamental objective was to exert an influence, just as working in the field of patient adherence as such reflects the desire to influence patients towards regaining health faster.

The following figure shows how the use of definitions is shifting in the relevant literature each year:

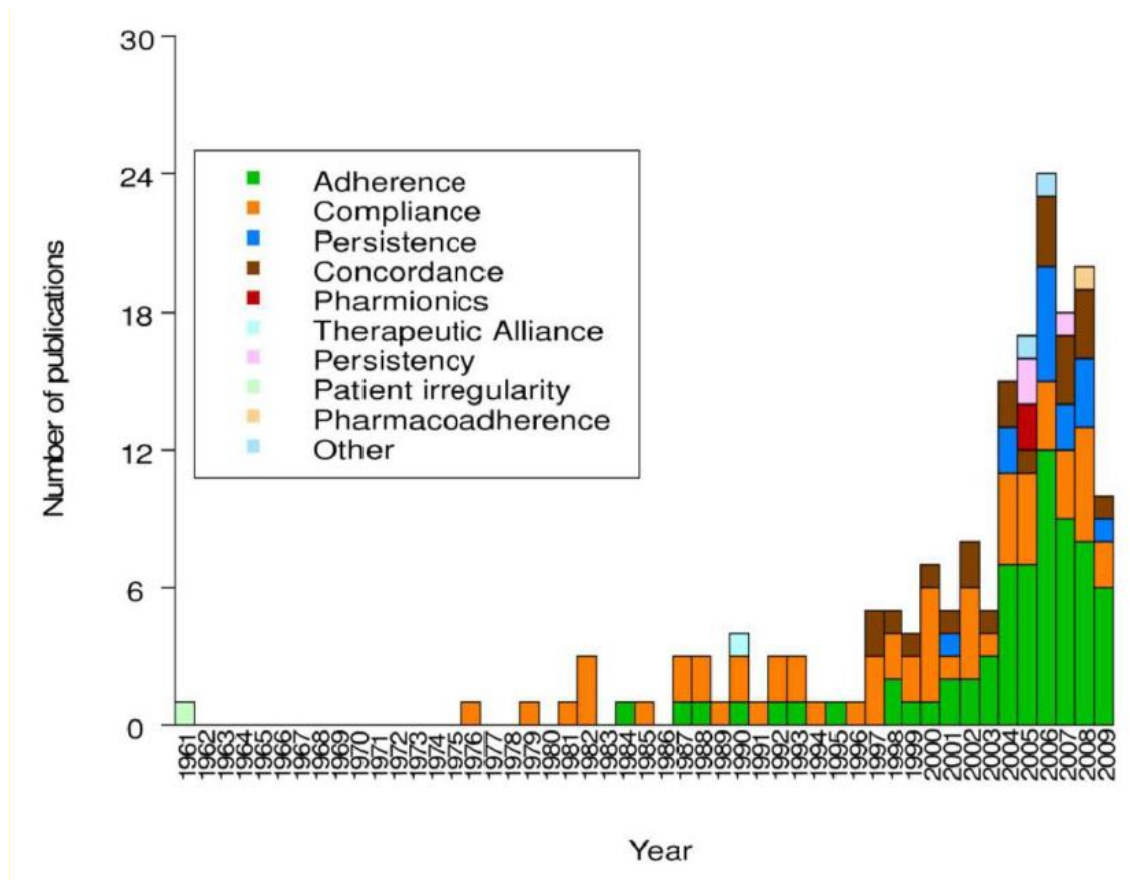


Figure 7: Definitions of adherence-related sciences in the relevant literature (ABC Project Team [2012] p. 19)

In September 2009 the 13th ESPACOMP meeting held in Bangor University Wales had a very interesting electronic vote for theoretical and practical experts engaged in adherence, which showed the existing uncertainties on the field of adherence-related definitions. The results showed that 60% of the experts preferred the term “Medication Adherence” for describing medication habits of patients compared to the term “Patient Compliance”. The chaotic nature of the definitions was clear from the very heterogeneous interpretation of the phrase “the compliance was 90%”. However, there was almost total consensus that the length of therapy and the extent the patient follows the instructions are two different dimensions of adherence. 61% of the voters preferred the term “discontinuation” for stopping the treatment, and only 37% recommended “non-persistence”. (ABC Project Team [2012], p. 23)

Below, I shall present the definitions on the basis of the 2003 WHO study (WHO [2003]), findings of the ABC Project Team (ABC Project Team [2012]), Hankó's 2006 and 2007 overviews (Hankó [2006]; [2007]) and the study by Horne and his colleagues (Horne et al [2005] p. 12).

Compliance

The term first used in the literature to characterise the cooperation of patients was *compliance*, a word that means following rules, or obedience. So in this context, the meaning of compliance is that the patient is obedient towards the doctor, follows the doctor's instructions and the rules shown in the patient information leaflet. The concept of compliance implies a relationship of superior to subordinate between doctor and patient, in which the doctor is the holder of universal knowledge, the healer who will tolerate no contradiction, while the patient is the "sufferer" of the healing process, who has a single right: the right to comply with the doctor's instructions. This pair of roles is most akin to that of father and son or boss and employee, in which the patient is just a patient who has no right to influence his therapy, and he should even be careful about asking questions. The attitude reflected in the word compliance is a definite one in the sense that the doctor is the key to a successful therapy, while the role of the patient is limited to a passive acceptance and following of instructions. Under this logic, patient cooperation is ultimately dependent on the doctor, who plays the "parental" role, while the patient, who relies on the doctor as a "child" either accepts his instructions or, silently or passively, rebels against them. The philosophy behind the definition of compliance is therefore based on the notion that a compliant patient always behaves as "expected" by medical science.

When, without the above philosophical connotations, we refer to inappropriate *compliance*, we are usually referring to the failure to comply with the schematic rules applicable to taking medication, i.e. the irregular taking of drugs (missing out doses, for instance), taking drugs at the wrong time (e.g. in the evening instead of the morning, or before meals instead of after meals), improper dosing (e.g. "pill halving") or the

ignoring of information concerning drug interactions (taking various drugs in parallel or eating foods that should be avoided).

Adherence

Today, the paternalistic doctor-patient relationship that informs the concept of compliance has become obsolete, which has a number of reasons. In the modern consumer and information society, patients are less and less willing to accept the subordinate role in a parent-child relationship, they relate to healthcare services as consumers and demand rights. This is reinforced by the fact that thanks to the Internet, the asymmetry of information between doctor and patient has been transformed, reduced significantly. Today, the thesis that the doctor is an omniscient entity in his ivory tower while the patient is a person wishing to be healed who is at the mercy of the doctor and who is sentenced to death without the doctor's help no longer holds true. It is an increasingly frequent occurrence that patients see their doctors after studying a specialised topic, armed with more knowledge than the doctor has about that particular issue. The general practitioner, on the other hand, increasingly assumes the role of a mentor, who provides support in the process of healing and, over and above rote instructions, attempts to nurture the patient's inner motivation, his ability and his will to cooperate.

Due to the trends described above, a patient cooperation model that places the treating physician in the centre is no longer viable. It was in response to that realisation that the concept of adherence was adopted in the literature at the initiative of the WHO, which, today, goes beyond the definition of compliance, although it was earlier adopted as a synonym for the previous term. This term also describes patient cooperation, therapeutic adherence, but with connotations of an equal relationship between doctor and patient, and it does not limit the cooperation of the patient to simply following rote instructions, but implies, in a significantly more complex manner, following the entire course of therapy in the long term. The WHO defines adherence as follows: *"the extent to which a person's behaviour - taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a*

health care provider". (WHO [2003] p. 3.) If we wish to capture the difference between the two concepts with maximum accuracy, it is perhaps best to focus on the agreement between doctor and patient. While in the case of compliance, the doctor instructs and the patient accepts the instructions, here there is a process of coordination, which results in the doctor and the patient reaching a consensus, an agreement about the best path towards achieving a cure.

Concordance

The concept of concordance goes further along the path marked out by the progression from compliance to adherence, it is best viewed as a future model of patient adherence. The concept first came into use in the United Kingdom, the theory initially placed the emphasis on the process of consultation between doctor and patient and investigated how doctor and patient are able to reach a full consensus while fully respecting each other's opinions and positions. Today, it is largely meant to refer to the idealistic process that involves continuous support from the prescription of the drug to the end of therapy. (Horne et al [2005] p.12.)

Persistence

The concept of persistence describes the temporal dimension of patient adherence, i.e. it indicates the period of time for which the patient actually receives the therapy prescribed. The concept of persistence is exceptionally important in a number of respects. Firstly, in contrast with the above concepts, persistence is a completely objective quantity, and as such is it easily measured in an exact fashion. We simply need to find out the number of days, beginning with the first day, for which the patient adheres to the therapy. The significance of persistence is therefore primarily associated with its measurability, and hence it may be the best parameter to effect comparisons of adherence between various diseases, countries or patient groups. Persistence is measured and described using persistence curves, which will be described in detail in the section on measurement.

2.5. The factors influencing patient adherence

As I explained in previous chapters, insufficient patient adherence can have a very large variety of underlying factors. Those factors may be categorised in a number of different ways, largely depending on the background scientific discipline of the people doing the categorising. In the present chapter, I shall categorise the factors influencing adherence on the basis of Chapter 5 of the 2003 WHO study (WHO [2003] pp. 27-38) and Chapter 3 of the 2012 Report of ABC Project Team (ABC Project Team [2012] pp. 40-145), as that classification was subsequently used as the basis for most scientific research in the field. The following figure is an illustrative presentation of the sets of factors defined by the WHO:

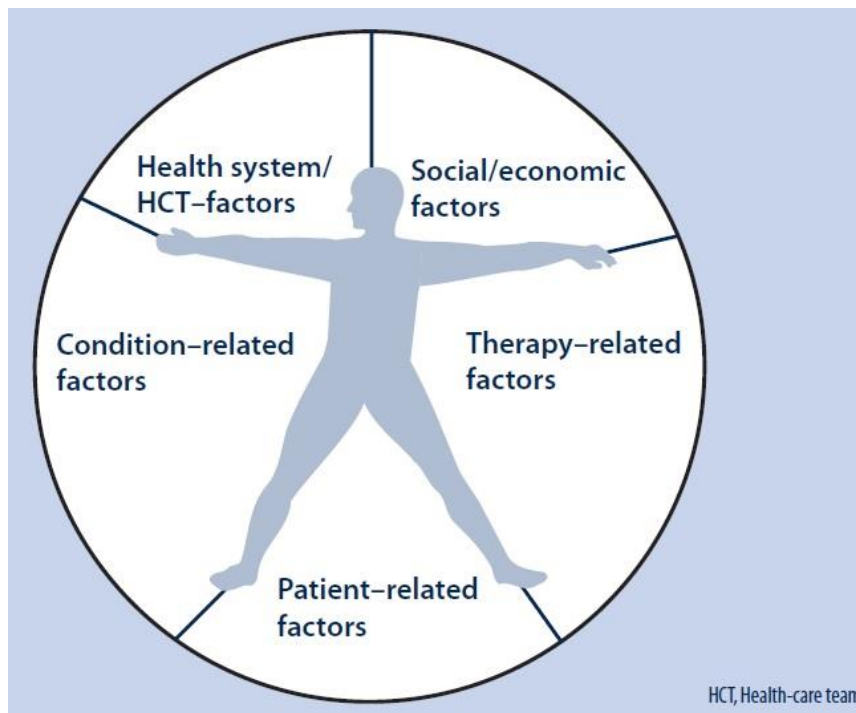


Figure 8: The five sets of factors influencing patient adherence according to the WHO (WHO [2003] p. 27)

Social/economic factors

I have mentioned before that adherence conditions in developing countries are significantly worse than in developed nations. This fact in itself indicates that the level of economic development exhibits a negative correlation with adherence. Naturally, there are direct as well as indirect links, and, naturally, economic factors may be interpreted at the level of individual patients as well as at the level of entire countries.

If we examine direct effects and look at the impact of economic factors at the level of the patient, it is obvious that therapeutic adherence is decisively influenced by whether the patient is actually able to purchase the medication that his doctor prescribed on a continuous basis. If that fundamental condition is not met, we will clearly get poor adherence. At the level of societies, direct economic influences include, for instance, the quality, operation and the existence of the drug reimbursement system. It stands to reason that without a drug reimbursement system, patients are much less likely to be able to exhibit appropriate adherence. Indirect economic impacts are at work, for instance, if the healthcare system operates in a deficient manner due to economic reasons, which will indirectly result in poor therapeutic adherence in certain countries.

Social factors can be highly complex and variable. The level of social and human development of a society along with its general sociocultural features play premium roles in determining the ways in which people think about health and illness, their lifestyles and the extent to which they take responsibility for their own state of health and what they do to protect it. Social aspects include, for instance, trust in conventional medicine, as well as its opposite, the strength of belief in alternative medicine. Naturally, a society in which patients entertain strong doubts about conventional medicine is less likely to be able to cooperate with conventional doctors. Similarly, another social factor is constituted by the extent to which several generations tend to live together in a society, or the extent to which older generations, who are most susceptible to chronic disease, do not live alone and hence are able to get assistance from younger generations living in the community with having prescriptions filled and taking their medications accurately. A very special and interesting type of social factor concerns the attitudes towards the colours, shapes and sizes of tablets, and the work of Hungarian researchers has already demonstrated that those properties of drugs play a very important role in achieving the desired outcomes (Köteles-Komsa-Bárdos [2010]). The effects are strongly determined by the perceptions that various cultures associate with various colours and shapes. A yellow tablet, for instance, clearly means something different to a European and an Egyptian person. While in Europe, the colour yellow generally connotes hope, happiness and

warmth, in Egypt, yellow is the colour of mourning. Therefore in Egypt, a yellow tablet may give rise to associations similar to those elicited in Europe by black pills.

Therapy-related factors

Therapy itself is an exceptionally important factor for establishing suitable patient adherence, or, looking at it from the other side, lack of adherence is often attributable to the characteristics of the therapy. Patients fail to adhere to many therapies because those treatments are simply very difficult to adhere to due to their complexity, painfulness, side-effects or the dosing involved. It stands to reason that a patient will find it very difficult to follow a drug dosage scheme that involves taking two large, difficult-to-swallow pills five times a day. The situation is even worse if, instead of pills, the patient has to self-administer painful injections under the dosage scheme.

A number of chronic diseases are often called silent killers, because they cause no spectacular symptoms, although they are life-threatening. Typical conditions of that type include hypertension and hyperlipidaemia. With those diseases, drug therapy is characterised by the fact that the therapy does not have any specific, perceptible and obvious positive effects that would motivate the patient to insist on taking the medication. It is simply a feature of the therapy that it does not result in benefits that are perceptible, immediately obvious to the patient.

Patient-related factors

A number of attributes that specifically characterise the patient are fundamentally important for establishing good adherence. These factors include the general state of health of the patient, his level of mental and physical activity, family relationships, motivations, general attitude towards getting better, towards the illness and towards medical personnel. The patient's educational level, his knowledge of his own disease and basic information about the therapy also fall in this category. While discussing the factors related to the patient it is important to mention the fact that on many occasions, nonadherence is the result of a completely purposeful process, i.e. the patient actually decides not to cooperate, even if he is fully aware of the

consequences. This phenomenon is called intentional nonadherence, and it usually comes from motivation problems, personal explanations, negative attitude to life or the lack of ambition.

Berger and Felkey produced a good summary of the patient-level prerequisites for appropriate adherence. Those factors are shown in the list below (Berger-Felkey [2001]):

- Show interest in his or her health and understand the diagnosis and the potential impact of the diagnosis
- Believe that the prescribed treatment will help
- Know exactly how to take the medication and the duration of therapy
- Find ways to fit the medication regimen into his or her daily routine
- Value the outcome of treatment more than the cost of treatment
- Believe that he or she can carry out the treatment plan
- Believe that the health care practitioners involved in the treatment process truly care about him or her as a person rather than as a disease to be treated

Factors related to the healthcare system and the healthcare team

Everyday thinking largely lays the emphasis on this group of factors when attempting to explain the lack of patient adherence using everyday answers. Lay explanations often include arguments to the effect that the healthcare system is unsuitable, that it is not possible to get a referral in time, that the doctor doesn't explain the necessary information and that there are no competent nurses. Naturally, those stereotypical assertions may all be true in practice, i.e. those negative perceptions do have a negative effect on the level of adherence. This is true despite the fact that few studies have investigated the links between specific parameters and the level of patient adherence. In general, the factors related to the healthcare system fall in the following categories:

- Factors establishing the general trust of patients (e.g. quality of the infrastructure, the doctor's style and quality of communication, lack of

contradictions between the recommendations of healthcare professionals, presence of trust-building rituals, lack of information that later proves false)

- Factors that shape the objective knowledge of patients (e.g. the level of organisation of patient education, the availability of suitable specialists for it, the degree of importance of that dimension for healthcare professionals, the availability of financing for pharmacy care and patient education)
- Appropriate organisation of patient journeys (does the patient reach the specialist who will indicate appropriate therapy and prescribe the required drug, or issues the instruction to continue the treatment, or provides the required prescriptions or continuously provides the required product in time?)

Factors related to the medical status of the patient

Generally speaking, the mental process that shapes patient adherence is always similar, yet in the case of a few specific diseases it is worth measuring adherence and researching the background factors, because individual diseases can be quite different in this respect. The main reason for that is that the disease itself, the therapeutic area has a number of features that influence the level of adherence. In addition to the fact that the patient's main diagnosis has a definitive effect on the degree of adherence exhibited towards the corresponding treatment, it is also important to take into account that in many cases a secondary condition or health condition that is not actually caused by the disease established by the main diagnosis that also has a decisive effect on therapy adherence.

In view of the above it is obvious that in the case of a psychiatric illness, for instance, accompanied by lack of motivation and forgetfulness, we may expect much poorer adherence than with a bacterial infection. Or, rather, in the case of the bacterial infection, the primary factors deteriorating adherence will not be those related to the medical status of the patient. In the same way, in the case of a neurological syndrome whose main symptom is memory impairment, we cannot expect the patient to remember a complicated drug administration schedule and to follow it accurately. As I mentioned above, it is also often the case that a secondary condition determines the

adherence to the therapy for the primary disease. An example may be the depression and lack of motivation accompanying a terminal condition resulting in poor adherence to the therapy for a terminal oncological disease.

It is also worth mentioning the situation in which the primary disease-related factor influencing adherence is the lack of awareness of illness. Typically in cases in which the disease does not cause obvious and intrusive symptoms for the patient, the appropriate awareness of illness is not formed, therefore the patient feels that it is not particularly important to adhere to the therapy exactly, which in the end leads to nonadherence. This very situation obtains with a number of chronic conditions, where the long-term maintenance of abnormal lab values that, however, do not cause a complaint as such leads to sudden, catastrophic deterioration year later, as for instance with high lipid levels and cardiovascular crises (Hankó [2007]).

2.6. Factors determining patient adherence as reflected by patient perception research in Hungary

In the previous section I presented the factors that may determine the level of patient adherence based on the international literature. The present chapter describes the factors that the attitude studies of our research group identified as playing an important role in the therapy adherence of the patients we have surveyed. The studies were prepared in 2010 and 2011, and the first publication based on them appeared in 2012 (Csóka et al [2012]), along with a summary research report (Dankó-Molnár [2011]). I shall use those two sources to provide a brief overview of the factors whose significance our research, conducted in cooperation with other universities, established using a Hungarian sample.

Patient attitudes in statin therapy based on the research published by Csóka et al. in 2012

In the course of this study, we contacted a random, phonebook sample of 3000 people and asked them whether their physicians had prescribed any statins for them over the

previous 5 years. The methodology produced a representative sample of 650 people, they were the patients who had recently received prescriptions for statin medication, and either never actually purchased the drugs, or started them but stopped, or were still taking them at the time of the interviews. We wanted to find out how those groups differed statistically, what distinguishing characteristics could be ascribed to the individual populations.

One of the conclusions of the study was that according to self-reporting, Hungarian patients don't take the prescribed drugs regularly, as only 47% claimed to follow the prescribed therapy accurately.

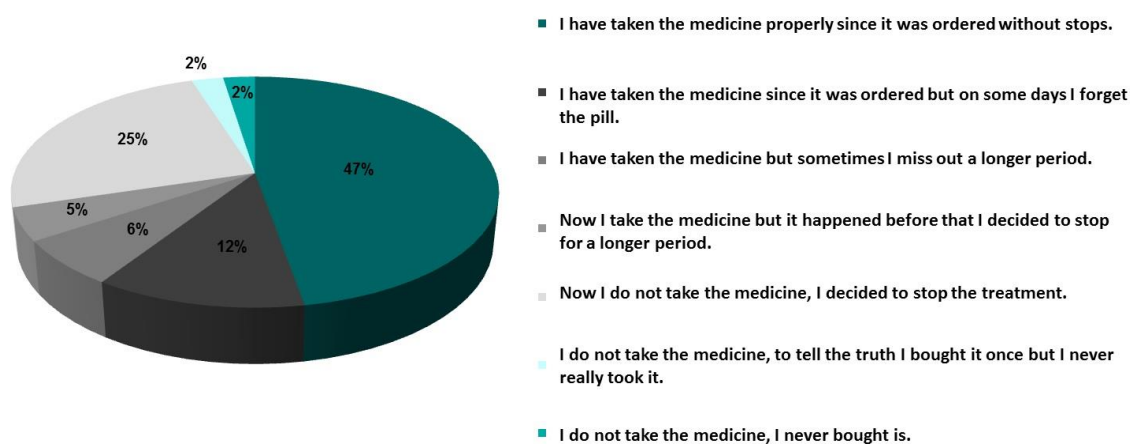


Figure 9: Frequency / regularity of taking statins (Csóka et al [2012] p. 1)

Among the patients who were no longer taking their medication, only 4% claimed never to have had their prescriptions filled. Most of them claimed that they were scared of the side-effects, and that they felt it was a good solution to pay more attention to their diets or that they had more faith in alternative therapies. Among the patients who had started the treatment but later stopped, most of them stopped taking their drugs because they felt that their improving test results meant they no longer needed the treatment, or they were actually instructed to discontinue the medication by their doctors, or they felt that they suffered from side-effects.

In previous sections I have repeatedly emphasised that the awareness of illness has a strong impact on the commitment, motivation and adherence of patients. This theory,

which occurs in the literature, was confirmed by our study, as we have shown that those in the category of patients who no longer take the drugs at all – i.e. those who had discontinued the therapy at some time – are also the group with the highest proportion of people who don't think they have high lipid levels any more.

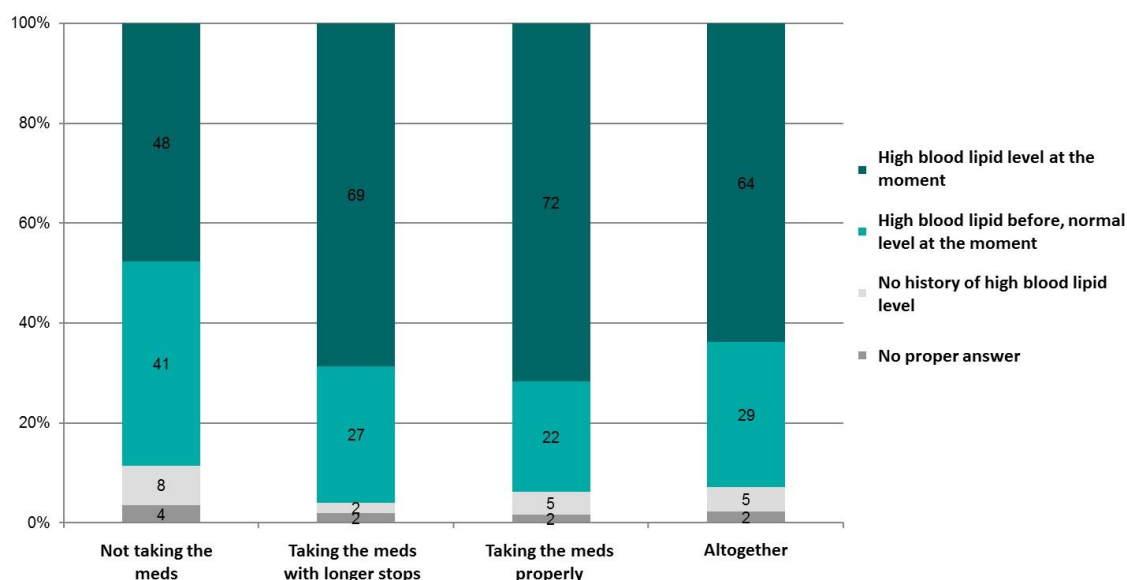


Figure 10: Relationship between adherence and patients' own perceptions of their lipid levels (Csóka et al. [2012] p. 3)

Another, similar link that we observed was that those taking their medication regularly attribute greater significance to and are more worried about potential complications.

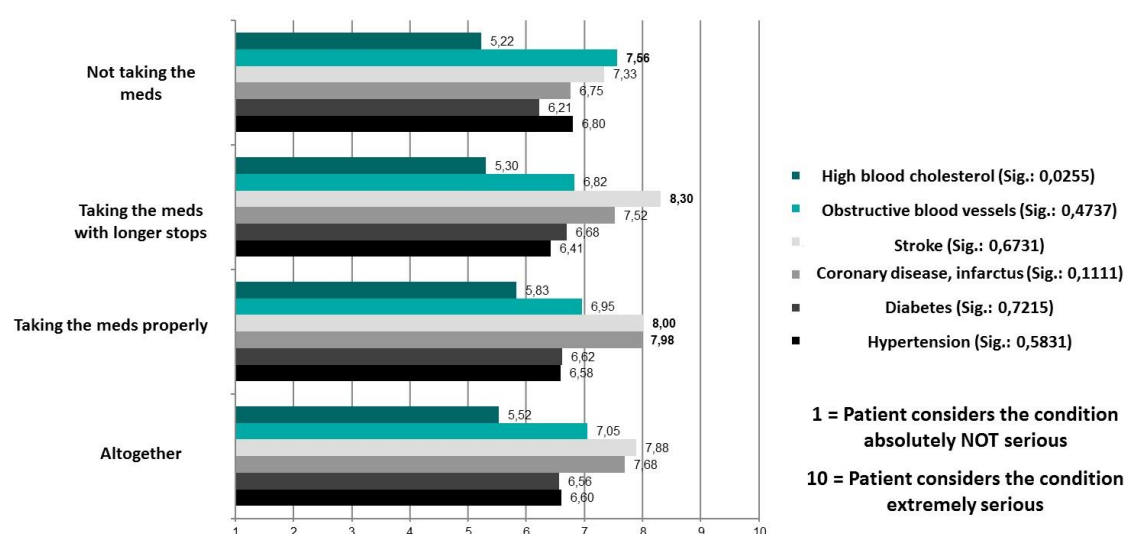


Figure 11: Relationship between significance ascribed to potential complications and patient adherence in statin therapy (Csóka et al. [2012] p. 3)

The results of the research have also underlined that trust in the doctor and the provision of appropriate, professional and objective patient information are also highly significant for establishing adherence, while contradictory instructions received from healthcare professionals can degrade the patient's faith and trust in the people treating him very quickly. Our question about generic drugs had a somewhat surprising result: it was our clear hypothesis that switching between products with the same active substance has a detrimental effect on adherence, but we had to discard that hypothesis because we found no data to support it at all. For statin therapy in particular, our study indicates that it is very important to emphasise that this is a life-long form of therapy and that taking the drug irregularly has no effect whatsoever, while on the other hand, side-effects are exceedingly rare.

Patient attitudes in therapy for benign prostate conditions, based on the research published by Dankó and Molnár in 2011

Several of the underlying factors behind adherence are specific to a particular therapeutic area or disease. That was our focus of interest when we adapted the attitude study performed on statins (Csóka et al [2012]) to the treatment of prostate disorders. (Dankó-Molnár [2011]) In that study, we also used phonebook sampling to identify 156 patients for whom their physicians ordered medication for benign prostatic hypertrophy (BPH) in the last five years.

The results showed quite definitely that the general conclusions drawn earlier about the required trust between doctor and patient, patient education and awareness of illness were fully applicable with this disorder, too. In addition, it was confirmed that the price of medication has a much smaller effect on adherence than it is often thought on theoretical grounds, and we also saw that younger people were more likely to discontinue taking their drugs.

2.7. The possibilities of measuring patient adherence

There are several methods available for measuring patient adherence, and those methods of measurement can be categorised from a number of perspectives. The main significance of those methods is that comparable and reliable measurement is indispensable for giving the issue of adherence the attention that it deserves on the grounds of the magnitude of the problem. The measurability is a key challenge of adherence-related sciences, as there are many aspects of adherence that are extremely hard to quantify. In addition, it is possible to measure the initiation, the discontinuation and the implementation of the therapy, moreover it is necessary to know all the three aspects. These three phenomena are markedly different, so it is not possible to find any method of measurement or unit of measure, which perfectly characterizes the degree of all three at the same time. (ABC Project Team [2012], p. 27) I summarised the applicable methods of measurement in a paper in 2010, the present section is based on that summary article. (Molnár [2010])

If we wish to quantify, monitor or track the level of adherence, we must certainly determine the objective of the measurement, the feature of adherence that we wish to measure, and whether we wish to measure prospectively or retrospectively. The purpose of the measurement may be of a therapeutic type, for instance with all active substances with which the therapeutic window is very narrow, i.e. fluctuations in blood levels have a strong impact on the effectiveness of the drug. An example of such a situation is the case of immunosuppressants administered after transplantation, where the dose of the medication is actually determined on the basis of blood level. Naturally, in most cases the measurement is not for a therapeutic but for an analytic purpose. It is possible to measure the blood level of the active substance being studied directly, it is even possible to monitor blood levels continuously. Discipline in complying with drug administration instructions can be monitored using electronic equipment or logging, and patient logs or databases can be used to determine the period of time for which patients comply with the rules applicable to the taking of medications, or, for a given population, it is possible to quantify the proportion of the group concerned that are still adhering to the therapy at the end of a specific period of time.

Discipline in compliance with dosing instructions is most frequently measured using the parameter MPR (*Medication Possession Ratio*; the ratio of days during which the drug is taken). MPR is the ratio of daily doses prescribed and the number of days until the next prescription is filled, so MPR is a percentage value indicating ratio of days between two consecutive pharmacy purchases that were actually covered by the quantity of the drug obtained. In general, MPR below 80% is said to constitute nonadherence. (Dóczy-Mészáros [2013])

Prospective measurement options

Prospective measurements are primarily facilitated by electronic dosing devices and patient logs that can be placed in the patient's home. Those solutions are simple, not costly, and today applicable to larger patient populations. With the development and spread of technology, electronic dosing devices are increasingly affordable and ever smaller, so they are increasingly becoming everyday items, or indeed standard packaging for medication. Those devices are primarily suitable for the exact monitoring of compliance, as they are able to furnish data about the extent to which the patient took the prescribed doses of the medication at the prescribed times. It is obvious that the patient's lack of cooperation may manifest during the measurement, i.e. we cannot entirely rule out the possibility that the entries in the patient log don't actually reflect reality, or that the opening of the dispenser wasn't actually followed by the patient taking the pill.

It is a very important advantage of prospective measurement that over and above the purpose of the measurement, it is in itself a very effective means of improving adherence. The attitude study about statin therapy (Csóka et al [2012]) already showed that close monitoring improves adherence, and this is a reliable effect. If the number of pills that the patient has forgotten to take is continuously measured, this provides an incentive to the patient not to forget to take the pills.

Retrospective measurement techniques

Prospective measurement techniques are accurate, modern equipment is now available, and this form of measurement also improves adherence, yet the technique requires a high level of awareness and foresight, so in many cases we are more likely to want to gather information about periods in the past. In such cases, asking the patients themselves may be the obvious solution, or we may access a healthcare database of some sort which has information available about prescriptions and the filling of prescriptions in the past period under review. The technique of asking the patients for self-reporting is always feasible, but it has the great disadvantage that we need to prepare for significant distortion in patient responses. Failure to comply with the dosing instructions results in the patient feeling the need to meet certain expectations when responding to our questions, so they will distort the information to present a more favourable view than the actual reality. The difference is illustrated quite well by the fact that while in the attitude study, 47% of patients claimed to be taking their drugs regularly (Csóka et al [2012]), the payer data indicates that only 20.1% of Hungarian patients still adhered to their therapies at the end of the 12th months from the commencement of therapy. (Kiss et al [2013])

So the self-reporting technique may result in a distortion of up to 30%, presenting that much more favourable a view than reality as reflected in hard data. Luckily, today the prescription of medication and the filling of prescriptions at the pharmacy are both controlled by computers, so databases are available that can tell us how long individual patients actually obtained the medication, how long the number of doses obtained was sufficient for, how long they had a supply of the medication. Database analysis has the advantage of simplicity, but it has the disadvantage that it will not shed light on certain dimensions of adherence at all. In a significant ratio of cases, it is difficult to obtain exact information about the prescribed dosing regimen, and we practically never have accurate information as to whether the drug was actually taken or how it was dosed.

Database analysis is most often used to measure persistence, i.e. we study the proportion of patients who continue the therapy after a specific period of time, usually 6 or 12 months, and we obtain specific persistence curves for the therapy under

review. In order to facilitate the comparison of data measured in different countries, by different research groups and in various therapeutic areas, today there are recommended analytical methodologies, which are worth observing, and certain initial assumptions must also be specified for all such analyses. It is important to declare clearly the type of therapy for which we are examining persistence, as it is clearly not indifferent whether we consider a patient who switches from one statin to another statin active substance and continues taking that to have remained adherent or become nonadherent. We must also determine well in advance, given that we do not have information about the exact dosing instructions of all the individual patients, what we will consider a daily dose when trying to determine the period for which a quantity of the drug obtained is sufficient for. We can choose to use the average dose defined by the WHO, use an estimate obtained from the medical profession, or estimate the actual average dose for the population we are studying. The third very important parameter of such an analysis is the so-called “grace period”, i.e. the number of days off the drug (known as a *drug holiday*) that we permit patients before we consider them to have abandoned the therapy. The International Society for Pharmacoeconomics and Outcome Research (ISPOR) recommends that a holiday of 60 days be permitted in analyses, but determining the optimal grace period in view of the characteristics of the specific treatment under consideration, and possibly running calculations with several values, may also be advisable.

3. Levels of adherence for major chronic diseases around the world and in Hungary

The 2003 WHO study I refer to repeatedly in my dissertation began with the assertion that poor adherence is not only a problem in our country, but it has become a worldwide problem, an epidemic (WHO [2003]). In the previous chapter, I used a literature review to describe the possible consequences of poor patient adherence, ranging from ineffective treatment through inappropriate quality of life to financial losses for the payer, the patient and the manufacturers of drugs. It is clear that those harmful effects and the benefits expected from improved adherence are related to the exact, quantified facts that characterise the quality of adherence in specific therapeutic areas. The previous sections of the dissertation unavoidable included references forward in order to illustrate the magnitude of the problem, but in the present chapter I shall describe, on the basis of data from the literature, the adherence and persistence values measured for the most important chronic diseases. I selected the diseases to examine in detail primarily on the basis of the sizes of the populations affected in modern societies, the importance of long-term continuous treatment in relation to the diseases, and the extent to which the individual therapeutic areas are covered in Hungarian and international research.

In the sections that follow, I shall use the same structure to review the chronic disorders selected, giving a brief overview of their epidemiological backgrounds to give an idea of their significance for the health of the general population, followed by a description of the levels of adherence established in studies around the world, and – to the extent possible – I shall also present domestic results from my own research, or if that's not possible, the research of other Hungarian scientists.

3.1. Hypertension

Background, epidemiology

In Europe as a whole, 44% of the population suffer from hypertension, and about 2/3 of those with hypertension do not have their blood pressure appropriately controlled

(PGEU [2008] p. 12). High blood pressure is a chronic condition without symptoms shared by 25% of the adult population of the US. A number of severe illnesses and mortalities are the result of patients suffering from untreated or mistreated high blood pressure for years. 30% of patients are not even aware of their condition, there is no awareness of illness, which is strongly correlated with the lack of symptoms. About 11% of patients are not receiving treatment at all, while 58% of those who do receive treatment have poorly controlled blood pressures. (Wogen [2003] p. 424)

About 50% of the Hungarian population have the condition, and among them, the same proportion never achieve the desired target blood-pressure value. (Simonyi [2013a])

This therapeutic area is of primary importance because, while the cost of treating high blood pressure is not high in itself, the public health expenditure on the complications caused by insufficiently controlled blood pressure is significant, contributing some 12.6% of all public healthcare expenditure according to the WHO. In the long term, reduction of public expenditure would certainly require improvements in patient adherence. (WHO [2003] p. 12)

International overview

As I explained above, the level of economic development of a country correlates with the measurable level of adherence. (WHO [2003]) Perhaps we could even go as far as to say that in the developing countries, today the problem of nonadherence has outgrown the problems caused by scarce healthcare resources or the inequalities in access to healthcare services. For example, measured adherence levels among patients with high blood pressure were 43% in China, 27% in Gambia and 26% in the Seychelles. The 51% adherence level measured in the United States may appear to be better at first glance, but it is clearly far from sufficient if half the patients do not exhibit sufficient adherence in the course of therapy. Despite the availability of effective treatments, a number of studies reached the conclusion that among those receiving antihypertensive therapy, only 25% of patients actually achieved good target blood-

pressure values, implying that in the case of one of the most important widespread diseases, despite the fact that we do have working drugs, the disorder is clearly not under control. The proportion of patients with blood pressure under control is 30% in the US, 7% in the United Kingdom and 4.5% in Venezuela, according to the measurements. The failure to reach target blood-pressure values is largely attributable to poor adherence, which eventually leads to the occurrence of costly and severe complications. (WHO [2003] pp. 7, 12)

The adherence of cardiovascular therapies is estimated at 50% even in developed countries. (Simonyi-Kollár [2013]) Analogously, the 1-year persistence of antihypertensive therapies is also 50%. (Simonyi [2013a]) The adherence of specifically antihypertensive therapies is between 50-70% depending on the type of therapy (Cortet et al [2006]). However, in order to assess patient cooperation, it is also worth examining persistence and compliance data: Wogen's study indicates that after 12 months of monitoring, 63% of patients taking valsartan, 53% of those taking amlodipine and 50% of those taking lisinopril were still in therapy. In addition to persistence data, Wogen also studied compliance values: the values measured were 88.5% for valsartan, 86.7% for amlodipine and 86.3% for lisinopril. (Wogen [2003] pp. 426-427.)

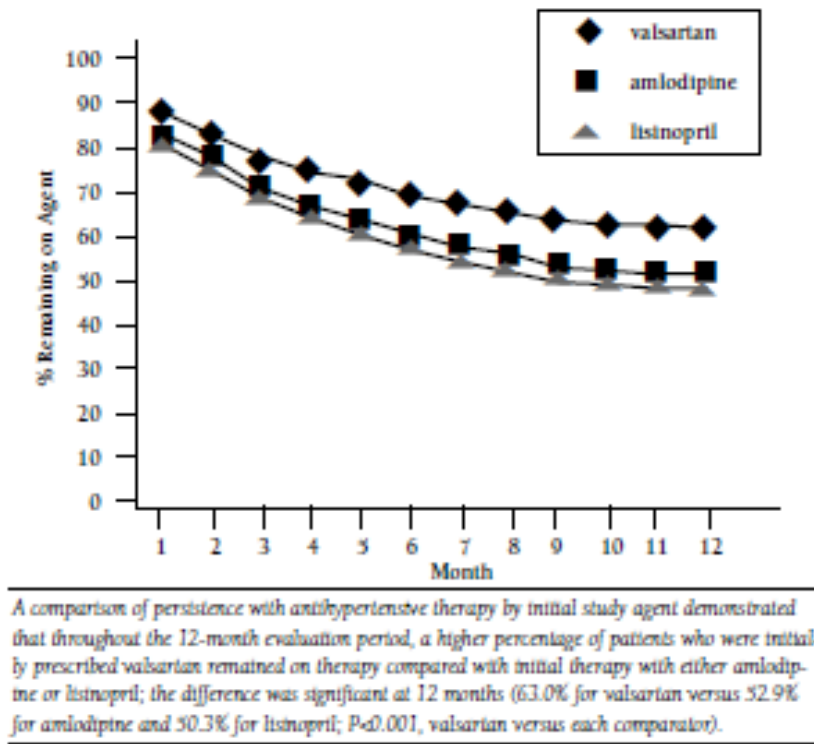


Figure 12: Persistence of antihypertensive therapies (Wogen [2003] p. 427)

According to an American study, patients who had received several different drugs previously for their disorder exhibited progressively worse adherence. (1-41%, 2-35%, 3-30%) If over 10 different drugs had been given previously, persistence dropped to 20% by the end of the 12 months. (Marrs JC. [2010] p. 15-16)

Ho and colleagues examined the level of adherence in patients with cardiovascular disease. Although their research was not specifically focussed on antihypertensive drugs, they still obtained results about several of those drugs as well. They essentially included diabetics in their study, but some of them were also taking at least one cardioprotective drug, most of them antihypertensives: angiotensin-converting-enzyme inhibitors (ACE blockers), angiotensin-receptor inhibitors (ARBs), beta blockers or HMG-CoA reductase inhibitors (statins). The following adherence data were measured for the individual medications: statin: 81.9%; ACE blockers: 80%; beta blockers: 76.6%: (Ho et al [2006])

According to a Dutch study, some 39% of patients taking drugs to treat high blood pressure were still on some form of antihypertensive therapy after 10 years, while 22% stopped and then recommenced therapy and 39% discontinued it for good. The ratio of those that discontinued the therapy was lower in the case of ACE inhibitors and combination therapies than with diuretics and beta blockers. Discontinuing beta blocker treatment actually increases the risk of coronary disease by a factor of 4.5. (Simonyi [2013a])

In the case of antihypertensive therapies, the negative effect of other drugs taken in parallel on adherence was also confirmed, so over a period of 12 months, fixed dose combination products exhibited a 20% improvement of adherence relative to plain therapies. With one dose a day, adherence was 79%, with two doses 69%, three doses 65%, while with four doses a day, adherence dropped to 51%. As regards gender, women have a higher risk of nonadherence with respect to high blood-pressure therapies. (Simonyi [2013a])

Between January 2000 and December 2001, Lachaine and colleagues studied the persistence of antihypertensive drugs obtained with reimbursement. They obtained their raw data from the RAQM database of the *Quebec* insurer, and they obtained results about most of the frequently used antihypertensive active substances. The two-year persistence data obtained are shown in the following figure (Lachaine et al [2006]):

Antihypertensive therapy	2 year persistence	2 year adherence (80%≤MPR)
diuretics	52.8%	50.9%
β-blockers	69.3%	60.3%
calcium-channel-blockers	64.3%	64.2%
angiotensin-II receptor blockers	60.9%	65.0%
ACE-inhibitors	58.9%	64.9%

Figure 13: Persistence of antihypertensive therapies I (my figure based on Lachaine et al [2006])

It is clear from the above table that in the case of diuretics, both two-year persistence and the ratio of patients with good adherence are lower relative to the other antihypertensive therapies (Lachaine et al [2006]). Gogovor and colleagues studies the persistence of ACE inhibitors in primary and secondary prevention, i.e. in patients with disorders of varying severity. Surprisingly, they actually measured poorer adherence data for patients in secondary prevention. (Gogovor et al [2007])

Antihypertensive therapy	1 year persistence (primary prevention)	1 year persistence (secondary prevention)
enalapril	66%	66%
fosinopril	72%	64%
lisinopril	71%	69%
quinapril	72%	65%
ramipril	75%	72%

Figure 14: Persistence of antihypertensive therapies II (my figure based on Gogovor et al [2007])

According to the studies of Gogovor and Lachaine, persistence values are around 65-70% for antihypertensive therapies, but as we saw in a previous chapter, the literature features highly varied data depending on country, measurement methodology and research results. This is consistent with the findings I mentioned in the section on methods of measurement concerning the strong demand for the development of uniform and comparable international methodologies. To a certain extent it also serves to show that the around 50% adherence value stated by the WHO (WHO [2003]) – which may have seemed a rather careless estimate – is not so careless after all.

Hungarian data

In a study based on the reimbursement data of the NHIFA, we examined persistence associated with fosinopril and fosinopril HCT products dispensed between 1 January 2007 and 31 December 2010. The active substance fosinopril is an ACE inhibitor, and although the use of that class of drugs is decreasing today, according to the international literature, the persistence characterising the group of active substances provides a good indication to patient cooperation conditions in the entire antihypertensive group. I shall present the results of our research on the basis of our research report. (Molnár-Dankó [2011])

The patients participating in the study were therapy naive, who had not had drugs containing fosinopril dispensed to them in the previous one-year period. The analysis was not performed on a sample, we included the entire Hungarian population. Our main objective was to determine one-year persistence with a 60-day *grace period*. In the study, we considered a change of therapy to be a discontinuation if the patient began to take an other active substance instead of fosinopril, but not if the patient switched to an other product which also contained fosinopril. Along with active substance level persistence we also examined product-level persistence, and there we only considered patients adherent if they took the active ingredient in the same product throughout.

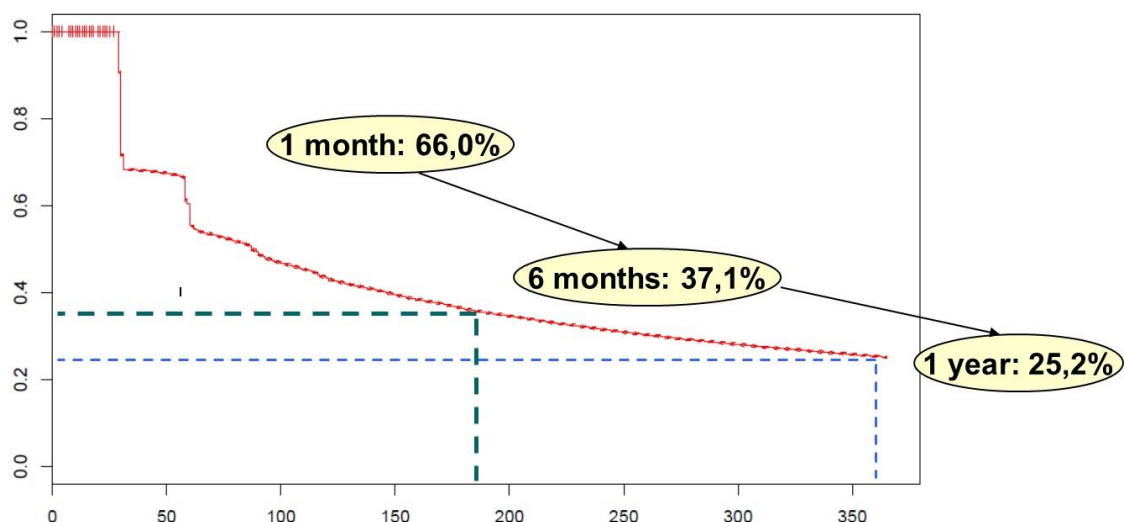


Figure 15: The one-year fosinopril persistence of Hungarian patients (Molnár-Dankó [2011])

The above figure shows quite well that, according to the curve, patients discontinue the therapy at the highest rate in the first two months, while patients who stick with the therapy for two months are more likely to remain adherent. According to our results, after 12 months, only 25 out of a 100 patients still comply fully with the doctor's instructions for the therapy. The long-term persistence study indicates – as shown in the figure below – that after 4 years, barely 10% of patients persist with the therapy.

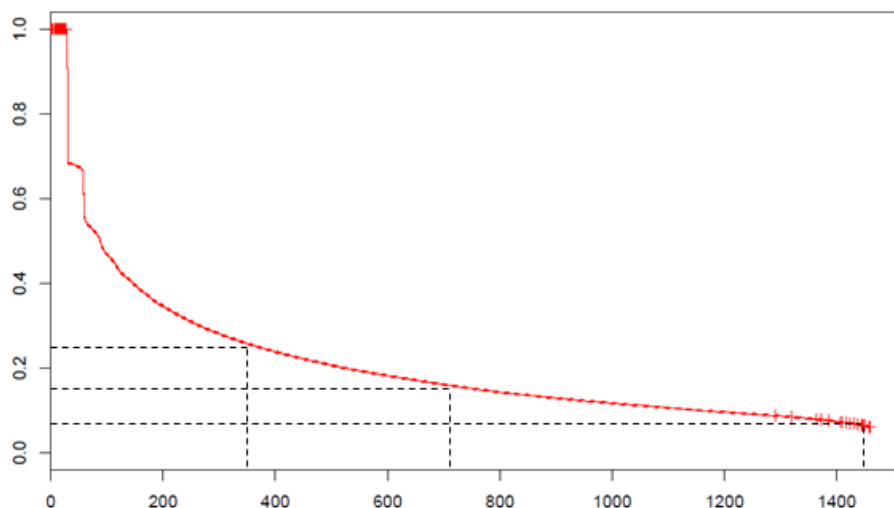


Figure 16: Four-year foscinopril persistence of Hungarian patients (Molnár-Dankó [2011])

The examination of brand names revealed that the persistence curves of various brands containing the active substance foscinopril are very similar. We identified somewhat worse adherence conditions with the original products, but we may assume that this was due to the increased price of the originals once generics appeared in the market. In the case of the originals Monopril and Duopril, the 12-month persistence value was 23.2%, while for the generic products Noviform and Noviform Plus, we measured 32.1%.

Based on the data from lipid-lowering drugs, we had previously estimated adherence at 35-45% for high blood-pressure treatments as well. (Molnár-Dankó [2010] p. 16) But the above analysis shows that a study of specific active substances revealed even poorer patient cooperation. In summary, we can conclude that the one-year active substance persistence of 25.2% is significantly below the generally measured

international persistence values (> 50%) measured for antihypertensive therapies that were presented in the first half of this chapter.

A recent international study based on the same methodology in several European countries also brought home a very unfavourable result for Hungary. One of the key conclusions of the research was that the Hungarian patients have much worse adherence level, than Western European and even neighbouring countries. (ABC Project Team [2012], p. 91)

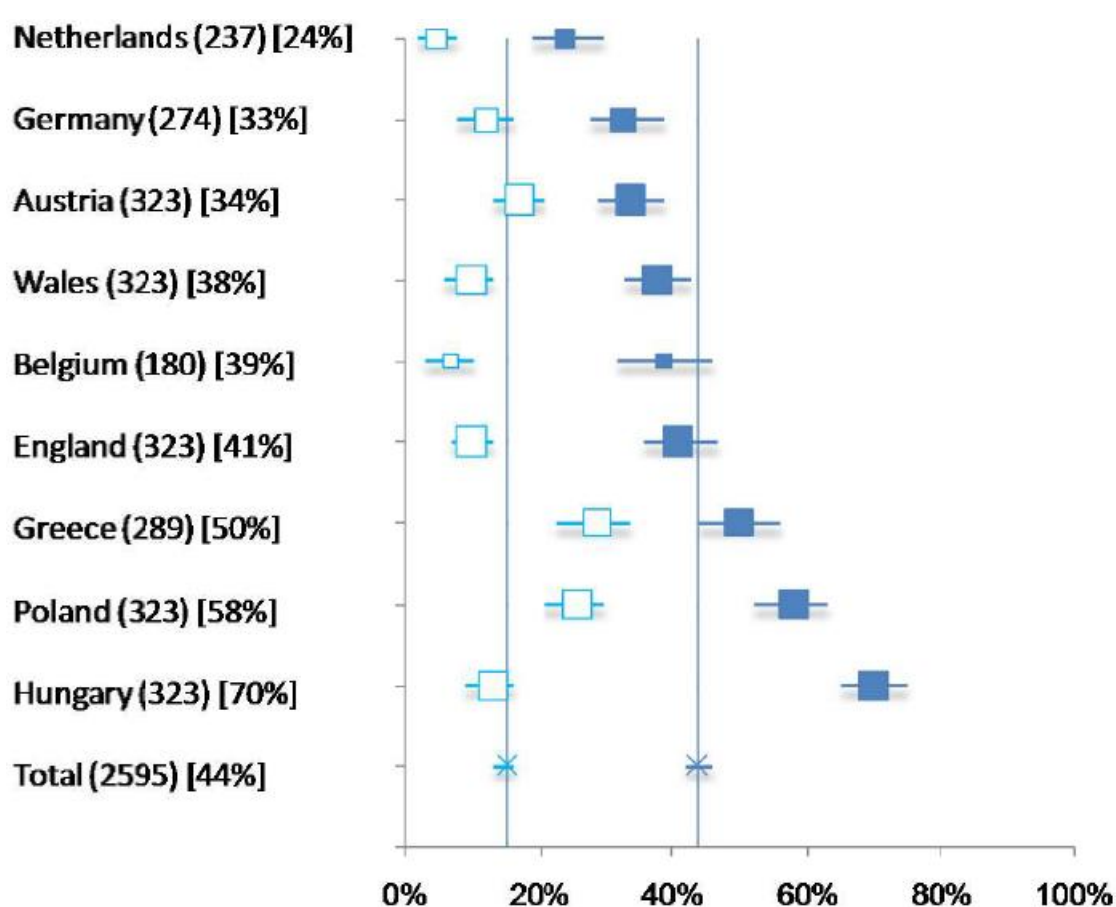


Figure 17: Proportion of non-adherent patients in European countries (ABC Project Team [2012]

p. 91)

3.2. Lipid disorders

Background, epidemiology

Lipid disorders play a significant role in the development of cardiovascular diseases, which are in turn among the leading causes of death in the countries of the developed world, including Hungary. High levels of lipids in the blood are largely the result of the dietary habits and low-exercise lifestyles that characterise developed societies. Normalising lipid levels has a positive effect on the frequency of diseases as well as mortalities, therefore the appropriate control of lipid levels – in particular, but not exclusively, so-called LDL cholesterol – is exceptionally important. The most common lipid disorder is hypercholesterolaemia, i.e. excessively high concentration of LDL cholesterol. About 66% of the Hungarian population have high cholesterol levels, i.e. for two-thirds of the Hungarian population, lab results are above the target values prescribed in international guidelines. Lipid levels can be reduced over a long period by following a regularly monitored course of drugs, but appropriate changes of lifestyle, i.e. weight loss, low-fat diets and regular exercise are even more important. (Health professional guidelines – lipid metabolism disorder, [2010] pp. 2-3)

International overview

Most research from around the world draws attention to the fact that there are a number of obstacles that render the successful management of lipid levels difficult. Or, to put it another way, anticholesterol therapy is the perfect worst case scenario for researchers of adherence, because it is concerned with a disease that requires continuous, long-term medication, the disorder itself has no symptoms whatsoever, taking the drug doesn't cause any perceptible changes, and there is usually no awareness of illness at all. Yet at the same time, hyperlipidaemia can have very serious consequences, as I have described in detail above.

The primary cause of the failure of lipid therapies is the low level of adherence. According to research, only 50% of patients are still taking hypolipidemic drugs 6 months after the first prescription, and that value drops to 30-40% by the end of the 12th month. In Portugal, 1270 patients were monitored, resulting in a 3-month persistence of 33.7%, and a 48.8% value for 6 months. Pharmacist intervention in itself improved both persistence and adherence, and that also resulted in favourable

changes in the patients' cholesterol levels. Similar results attesting the benefits or pharmacist intervention were also obtained during the ImpACT study in America. (PGEU [2008] pp. 14 -15)

According to an American study, in the case of hypolipidemics, nonadherence was 57.3%, of which below-optimal doses or poor titration caused 31.7%, while 14.1% was attributable to various, hard-to-tolerate combinations of drugs. Taking several drugs at the same time has a significant negative effect on adherence: the more pills a patient is required to take, the more likely he is to discontinue the treatment. According to a study by Marrs, adherence was 41% with monotherapies, 35% when two drugs were prescribed and 30% with three drugs. When more than 10 different medications were prescribed, the 12-month persistence value was only 20%. (Marrs [2010] pp. 15-16.) Corten and colleagues put persistence for statin therapy at 25 to 40% depending on the specific therapy chosen. (Cortet et al [2006])

In the previous section we saw that the results of studies around the world exhibited significant variation in the hypertension therapeutic area, and it is clear that the situation is no different with antihyperlipidemic treatments. Several studies have looked at statin therapy persistence internationally, I present the results below based on the summary paper by Gábor Simonyi.

Study	Timeframe (years)	Persistence (%)
WOSPCOPS (West of Scotland Coronary Prevention Study Group)	5 years	26%
CARDS (Collaborative Atorvastatin Diabetes Study)	5 years	9%
EXCEL (Expanded Clinical Evaluation of Lovastatin)	1 years	16%
ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm)	3 years	13%
AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study)	5,2 years	29%

Figure 18: Statin persistence measurement results (my figure based on Simonyi [2013b]) p. 8)

Simonyi's work also shows that fixed dose combinations dosed once daily have a positive effect on adherence, they increase it. According to a HIRD (*HealthCare Integrated Research Database*) study, fixed dose combinations (simvastatin/ezetimibe, simvastatin/niacin, lovastatin/niacin) result in 32% better adherence values relative to free-dose combinations (simvastatin+ezetimibe, simvastatin+niacin, lovastatin+niacin). (Simonyi [2013b])

Hungarian data

Over the last few years, our research group has done extensive work on the adherence conditions of hypolipidemics. An analysis of the prescription dispensation data from the NHIFA has yielded measurement data about the statins and fibrates in most common use, which we have published. In general, we measured highly unfavourable persistence data for the hypolipidemics, too, below the data published in the international literature. That is a particularly serious problem because due to low persistence, a significant part of the patients do not get any practical benefit from the therapy, as those medications are only able to exert a beneficial effect with long-term use. (Molnár-Dankó [2010] pp. 15-16)

Fibrates: While statins primarily effect the level of LDL cholesterol, fibrates influence the lipid metabolism directly, therefore they reduce the incidence of the main types of cardiovascular episodes by 13%. In addition to the relationship with cardiovascular disease, it is important to mention that fibrate therapy also plays a role in the treatment of metabolic syndrome and type 2 diabetes mellitus. On that basis, although fibrates are used much less frequently than statins, they have an indispensable role in that therapeutic area. During our analysis, we primarily wanted to see whether fibrates exhibited different persistence values to statins. We expected to see similar values for fibrates as for statins, so in advance we estimated 12-month persistence to fall between 20 and 25%. (Simonyi-Molnár-Pálosi [2014])

We used the reimbursement data of the NHIFA for the study, and included 48,314 patients taking fibrates, who had not received that active substance previously. We

defined the relevant period to be 1 July 2009 to 30 June 2010, i.e. we tracked patients in the database who had a prescription for fibrates filled for the first time during that period. We tracked patients for 14 months, with a 60-day grace period, i.e. we considered those patients to have abandoned the therapy who were without their medication for a period in excess of 60 days. Our results indicated that by the end of the 12th month, only 22.51% of the patients were still on fibrates, while the rest had interrupted their therapies for periods in excess of 60 days for some reason. In the case of fibrates as well, we found that patients dropped out at the highest rate during the first three months, with the persistence curve growing much “flatter” afterwards. (Simonyi-Molnár-Pálosi [2014])

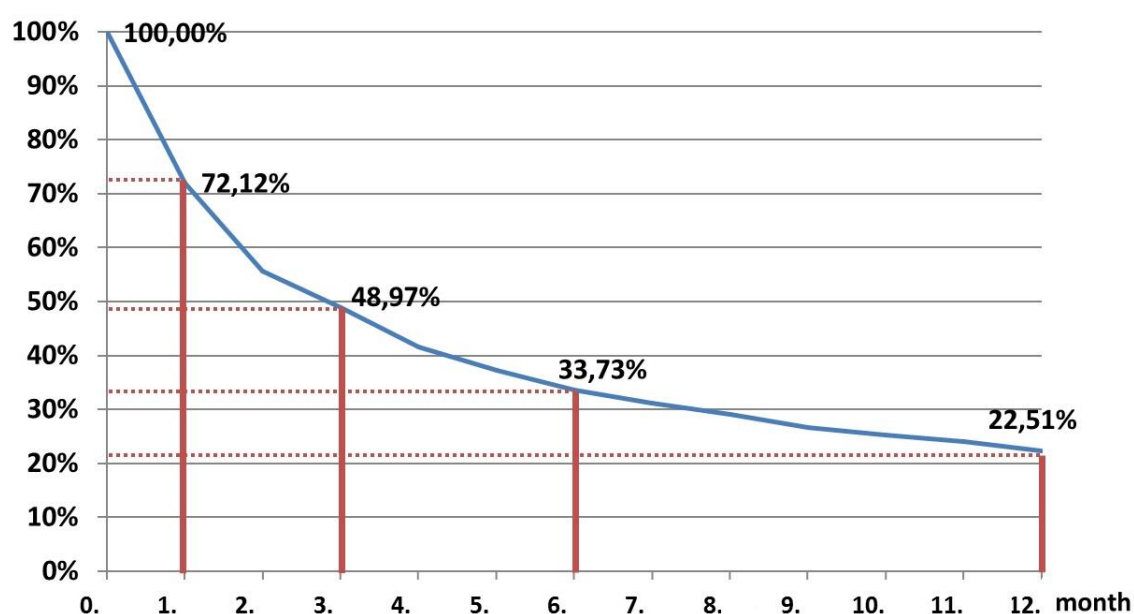


Figure 19: 12-month fibrate persistence (Simonyi-Molnár-Pálosi [2014] p. 95)

A comparison of the persistence data for fibrates and statins indicates that in aggregate, very large proportions of patients receiving both types of drug abandoned the therapy early, and our initial hypothesis was also confirmed, as we found no significant differences in the levels of patient cooperation between the two etiological groups.

Statins: The pharmacological group of statins provide the most common therapy for high cholesterol levels, so if we wish to measure the level of patient adherence to

treatments of high lipid levels, we primarily need to look at statin adherence. Our research group has participated in a number of analyses aimed at quantifying the adherence of patients taking statins in Hungary, I shall summarise them below. The main justification for the measurements was that even the early calculations had suggested that the adherence of Hungarian patients is a great deal worse than that of patients in other countries.

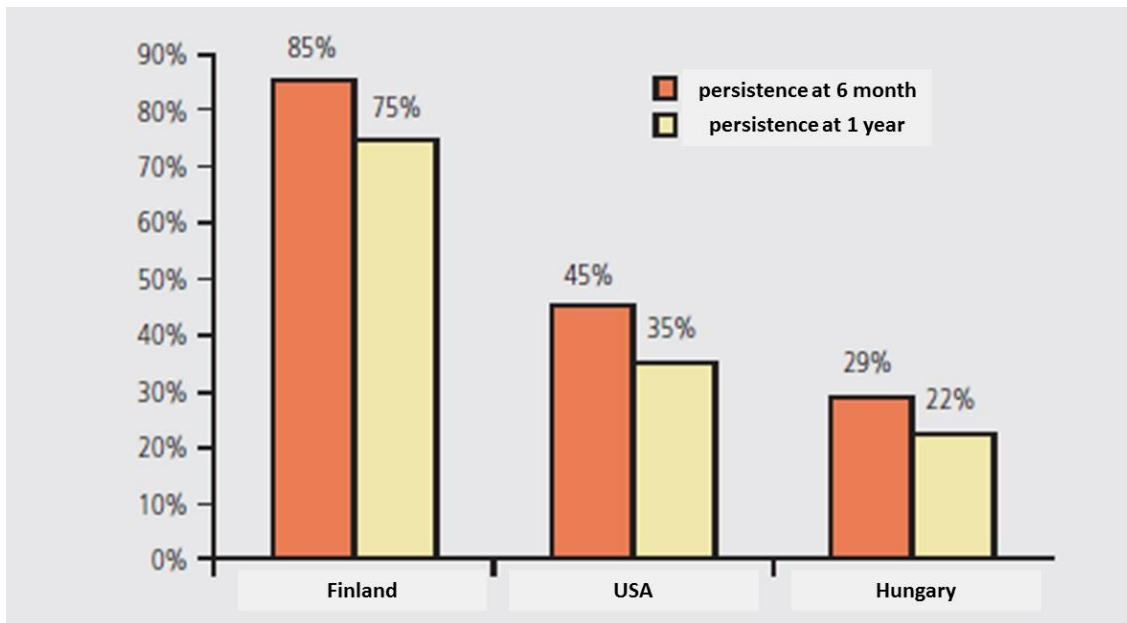


Figure 20: 6 and 12-month persistence of lipid-lowering drugs (Molnár-Dankó [2010] p. 16)

In our 2010 study we analysed the entire Hungarian population taking lipid-lowering drugs based on reimbursement data from the NHIFA and published our findings internationally in 2013 (Kiss et al. [2013]). We primarily wished to determine the average persistence of statins and the active substance ezetimibe in a number of subgroups we defined. The study period was 1 January 2007 to 31 March 2009, i.e. we tracked patients who obtained some lipid-lowering drug for the first time during that period. We identified a total of 459,034 patients, and we analysed their subscription dispensation data in detail. 8,893 of those patients were taking ezetimibe along with a statin. We set the grace period at 60 days. (Kiss et al. [2013])

The statin persistence curve we obtained from our analysis was a typical one: patients were dropping out at a dynamic rate during the first three months, after which the

curve grew increasingly flat. Only 20.1% of patients receiving statin therapy were still taking the drug at the end of the 12-month period. Changing the grace period of 180 days increased persistence to 27%, a significant difference. Such a large difference between the results obtained with the two different grace periods indicates that many Hungarian patients stop taking statins but return to the therapy later on. (Kiss et al. [2013])

We considered patients who had suffered some sort of a cardiovascular episode before, i.e. those receiving lipid-lowering treatment as secondary protection, separately. That subpopulation included 5,590 patients, and they exhibited significantly better cooperation, as in that subgroup, the 12-month persistence level was 50%. This is strong support for the thesis that awareness of illness is a factor motivating adherence. (Kiss et al. [2013])

The analysis of various subgroups defined in advance yielded support for a number of hypotheses that we had determined in advance, based on the literature; for instance, we saw that younger patients exhibit poorer adherence, while patients with more serious conditions, who were also taking ezetimibe, had better adherence. We were unable to identify any important or significant differences between individual active substances, dose strengths and brand names. (Kiss et al. [2013])

There was a difference between patients who were receiving statin therapy as primary prevention and those receiving it as secondary prevention. We found higher persistence values with secondary persistence. (Kiss et al. [2013]; Márk et al [2013])

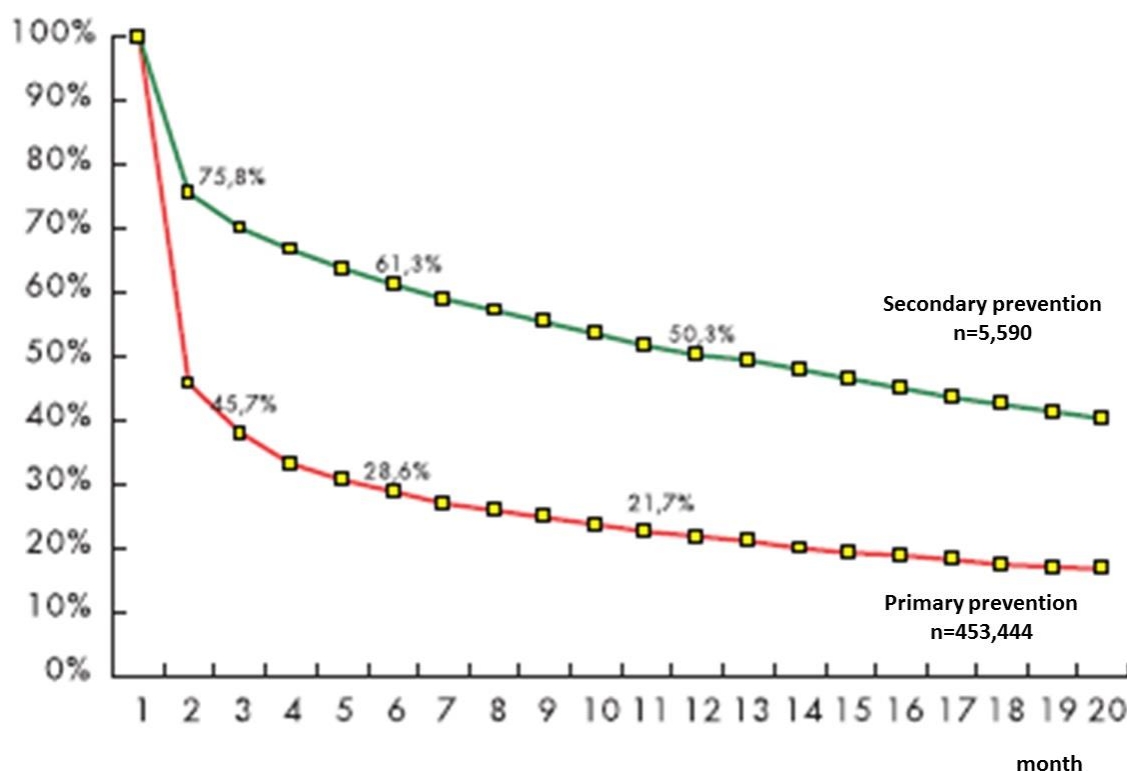


Figure 21: Statin persistence in primary and secondary prevention (Márk et al [2013] p. 172)

3.3. Diabetes

Background, epidemiology

My overview of the chronic diseases with the greatest significance for public health in this chapter cannot be complete without a consideration of diabetes. Many authors claim that diabetes is indeed the so-called “disease of civilization” with the greatest impact on public health. That opinion is shared by Jermendy in the Hungarian healthcare guidelines compiled in 2009, in which he published summary data about the international epidemiology of diabetes as well. According to his data, in the year 2000, the global number of diabetics over the age of 20 was around 171 million, and that figure is expected to increase to 366 million by 2030. Today, a significant proportion of diabetics suffer from type 2 diabetes, and not type 1, the diabetes that manifests at an early age and that is always insulin-dependent. Type 2 diabetes has causal links with lifestyle characteristics and it only becomes insulin-dependent at a late stage. (Jermendy [2009] p. 4) Prevalence measured in Hungary in 2003 was 9.7%, which is extremely high in European comparison. (Doró [2005] p. 893)

The study entitled “CODE-2 – The cost of diabetes Type 2 in Europe” has shown that the treatment of the over ten million patients with type 2 diabetes costs almost 29 million dollars, equivalent to approximately 5% of the total healthcare expenditure of the countries included in the study. (WHO [2003] pp. 11-12) According to another European study, type 2 diabetes is the single therapeutic area with the greatest per capita cost within public healthcare expenditure, the estimated per patient cost is €3,000/year. (PGEU [2008] p. 12)

International overview

A meta-analysis of twenty studies has reached the conclusion that among diabetics, those taking oral antidiabetics (OAD) exhibit adherence ranging from 36 to 93%. (Doró [2005] p. 893) Although that is a very large range, we can certainly conclude on the basis of just the lower bound of that range that nonadherence is a serious problem in the area of diabetes therapy as well. The conclusion of the CODE-2 study, to the effect that only 28% of the patients receiving antidiabetic treatment are able to achieve good glycaemic control values, i.e. that only a fraction of all patients are receiving effective therapy, correlates well with that result. According to the WHO study, the development of most of the complications associated with diabetes is also attributable to low patient adherence. (WHO [2003] pp. 11-12)

In their study, Farsaei and colleagues used the 8-component Morisky scale (MMAS) to assess the adherence of diabetics, where 8 indicates good, 6-8 medium and below 6 poor adherence. According to their results, among those suffering from type 1 diabetes, 22.3% had good adherence, 63.4% had medium adherence and 14.3% had poor adherence. The same values for type 2 diabetes were 24.9%, 46.3% and 28.8% respectively. The results, once again, are a good indication that only a fraction of all diabetics achieve good adherence. (Farsaei et al [2014])

A study by Colombo and colleagues proves that in the case of type 2 diabetes, the lack of patient adherence has a great economic and social impact. In the study, they

measured the adherence of several specific orally administered active substances, as well as fixed dose combinations. As a general conclusion, they found that adherence ranges from 40% to 80% among the various orally administered drugs. The results of their analysis are shown in the following two charts:

(Colombo et al [2012])

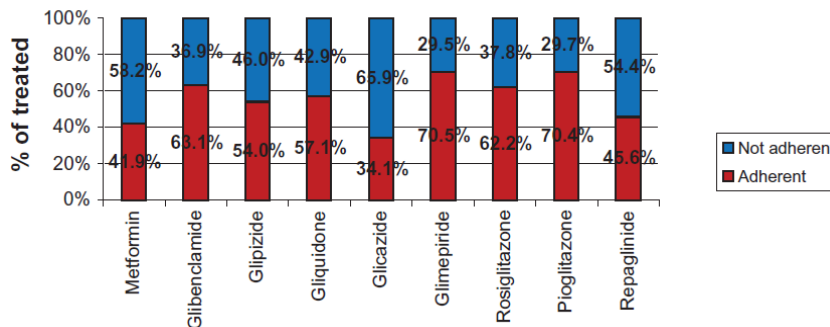


Figure 22: Monotherapies of diabetes: adherence values for each active substance (Colombo et al [2012] p. 658)

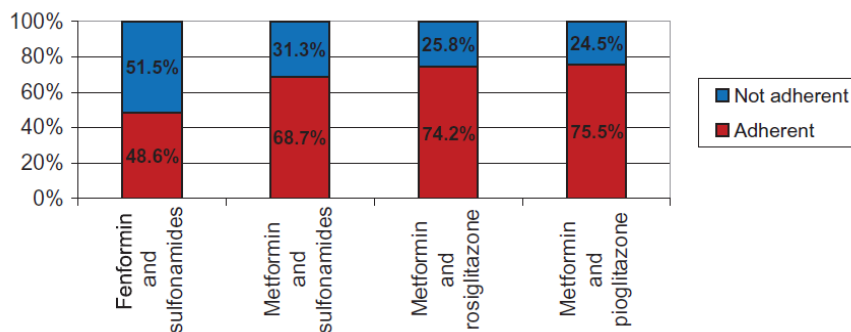


Figure 23: Fixed dose combination therapies for diabetes: adherence values for individual combinations (Colombo et al [2012] p. 658)

Daily and colleagues studied the persistence of antidiabetics with a 60-day grace period. The study was conducted between 1996 and 1998, the one-year drug-dispensing data of 37,430 and the two-year drug-dispensing data of 16,452 patients was analysed. The study's results showed that when metformin and sulfonylurea were used as monotherapies, their one-year persistence levels were similar at around 20%, but when metformin and sulfonylurea were used in combination, persistence was much lower, below 10% (!), if they only considered those patients who maintained that specific combination to be adhering. (Dailey et al [2001])

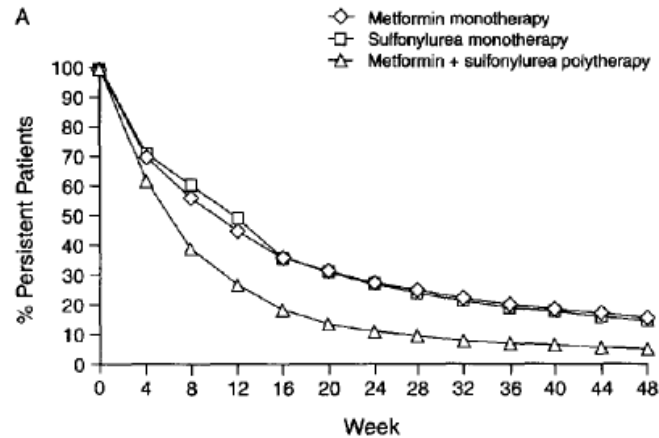


Figure 24: Metformin, sulfonylurea monotherapies and metformin + sulfonylurea combination, 1 and 2-year persistence values (Dailey et al [2001] p. 1317)

Hungarian data

Péter Doró and his colleagues examined the data for 1998 to 2004 of a population of 38,855 patients in Csongrád County. Their results indicated that the adherence of diabetics on orally administered drugs was between 47.9% and 49.2%, and women are more adherent than men (51.3% and 45.5%, respectively). In addition to the difference between genders, the adherence of combination therapies was also much better (67%) than that of monotherapies (40%). (Doró [2005] pp. 893-896)

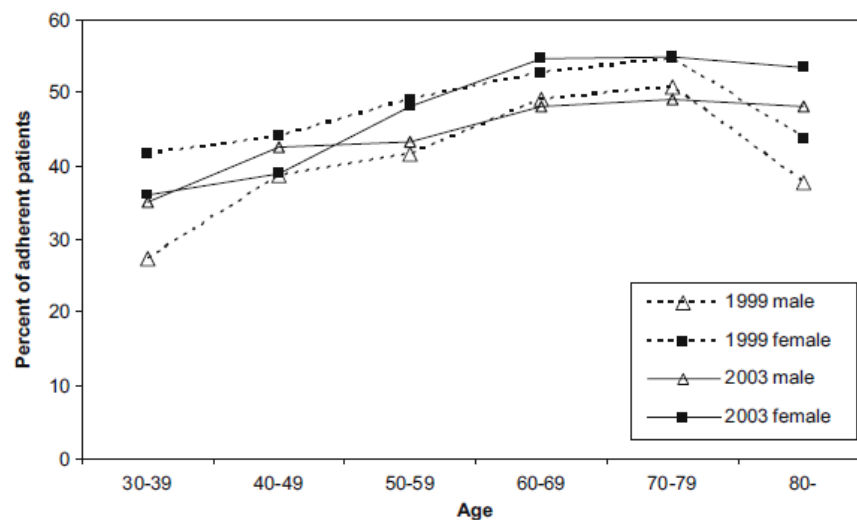


Figure 25: Adherence of diabetics between 1999 and 2003, % (Doró [2005] p. 895)

Jermendy and colleagues studied the Hungarian persistence of orally administered drugs for type 2 diabetes based on reimbursement data from the NHIFA. The one-year

data indicated that the persistence of metformin, sulfonylurea and metformin + sulfonylurea therapies was 47.7%, 45.4% and 55.8%, respectively. In the group of sulfonylurea drugs, adjusted release tablets exhibited an advantage against conventional tablets (47.8% vs 42.2%). An outlier result was obtained for the packaging containing 60 1000 mg doses of metformin against both other dosages and smaller packages (60.4% vs 47.7%). (Jermendy et al [2012])

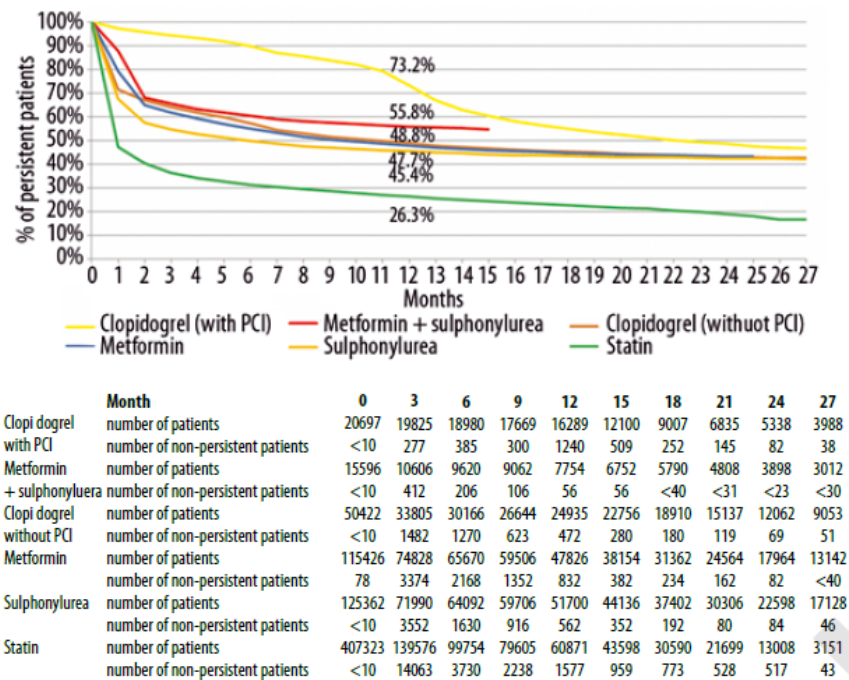


Figure 26: 12-month OAD persistence (Jermendy et al [2012] p. CR75)

3.4. Benign prostatic hyperplasia (BPH)

Background, epidemiology

BPH is the benign enlargement of the prostate, characteristically a progressive disorder of older men, which primarily impacts the quality of life of patients as it makes urination difficult. Symptoms usually appear over the age of 40, among those over the age of 60, over half of the male population are affected by medium or intense symptoms, while prevalence is over 90% among men over the age of 85. Men in their 50's usually exhibit mild symptoms, while those over 60 usually have medium or intense symptoms that have a detrimental impact on everyday life. In view of its prevalence and the expenditure associated with treatment, BPH is an endemic disease. The treatment of BPH depends on the degree of progression of the disease and the

severity of symptoms. Therapy largely consists of pharmacological treatment, required in the long-term. (Healthcare Professional Guidelines – BPH, [2010] p. 2)

International overview

Auffenberg and colleagues analysed the electronic patient data of BPH patients generated between 1 January 2008 and 31 December 2012. According to their results, adherence ranged from 53.0% to 92.8%. (Auffenberg et al [2014])

In the Netherlands, Verhammea and colleagues analysed the anonymised data of 500,000 male patients over the age of 45 who were diagnosed with BPH during the period 1995-2000. According to their measurements, adherence was 67% for alpha blockers, 73% for 5-alpha reductase inhibitors and 71% for combination therapies. So about a third of all patients had poor adherence, irrespective of the active substance prescribed. The analysis also found that the less complications a patient suffers, and the less other disorders are present, the more likely they are to abandon the therapy prematurely. In addition, the study showed that patients are less likely to abandon the therapy if they only have to take one dose per day, but the difference was not significant. In summary, they reached the conclusion that the average adherence level is around 70%, but 12-month persistence is very low, only 26%. The occurrence of side-effects and insufficient effectiveness were considered the main causes of low persistence. (Verhammea et al [2003])

Nichola and colleagues studied the data of Californian BPH patients from the period 1995-2004. They included men over the age of 40 who had had at least one diagnosis of BPH and who had had prescriptions filled for drugs with a BPH indication at least twice. Irrespective of the type of treatment, 40% of patients were considered adherent. Patients who took more drugs had significantly better, 50-60% adherence values. As in a previous study, younger patients proved less adherent, and, similarly to the Dutch study, those taking alpha blockers proved less adherent than those on 5-alpha reductase inhibitors or other combination therapies. It also transpired that the complete therapeutic effect of 5-alpha reductase inhibitors is only exerted if patients

remain on the treatment for 6-12 months. In summary, 60% of the Californian population were not adherent to either form of BPH therapy, and the type of therapy determines both persistence and adherence levels. (Nichola et al [2009])

The work of Davis and colleagues has established that 2/3 of BPH patients receiving tamsulosin treatment stop the therapy within 6 months, while by the end of the 12th month, 86% of patients no longer take the drug as prescribed. (Davis et al [2006])

Hungarian data

In our study, we analysed the drug-dispensing data of patients who commenced treatment for BPH between 1 January 2007 and 30 June 2009 using the reimbursement database of the NHIFA, with a view to determining patient adherence levels for the main active substances used for treating BPH (alpha-receptor blockers: alfuzosin, tamsulosin, terazosin, silodosin; 5-alpha reductase inhibitors: finasteride, dutasteride). Our analysis yielded the following results for the active substances used for the treatment of BPH: one-month persistence: 63%, six-month persistence: 34.8%, one-year persistence: 22.3%. Our study also showed that the persistence curves of the individual active substances are similar, there were not significant differences, and they all had low 12-month levels, with the highest rate of dropouts realised in the first phase of therapy. (Dankó-Molnár-Piróth [2011])

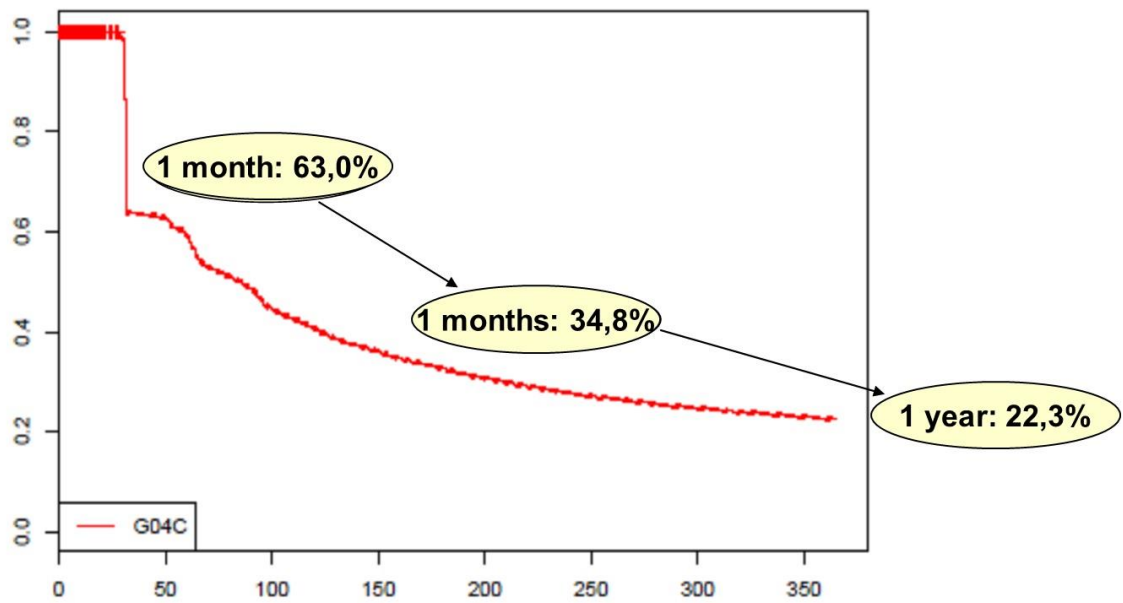


Figure 27: One-year persistence in the pharmaceutical treatment of BPH (Dankó-Molnár-Piróth [2011])

In summary we can conclude that the Hungarian situation does not differ significantly from the data in the international literature, but in the case of BPH it is once again true that the adherence-level of patients is very poor in Hungary.

3.5. Atrial fibrillation

Background, epidemiology

Atrial fibrillation is an abnormal heart rhythm in which the atrial part of the heart exhibits high frequency electrical activity, which inhibits the normal movement of the wall of the atrium and hence decreases the efficiency of blood flow significantly. Atrial fibrillation is one of the most frequently treated abnormal heart rhythms, it is responsible for 30% of hospital care events associated with abnormal heart rhythms. According to data from the NHIFA, the prevalence of atrial fibrillation was 2.37 to 2.67% in the Hungarian population (Simonyi [2012]) It is generally a disorder of old age, prevalence grows to 3-5% in the over 65 age group, and prevalence increases exponentially with increasing age. The probability of atrial fibrillation is increased by other disorders such as hypertension, coronary artery disease, circulatory failure, problems with the mitral valve, hyperthyreosis, infarctions, disorders of the sinoatrial

node, congenital heart disease, heart surgery, pericarditis, alcohol, lung disorders, disorders of the vegetative nervous system, tachycardia-induced atrial fibrillation and idiopathic atrial fibrillation. Atrial fibrillation can be treated in a large number of different ways depending on its etiology and severity, but long-term anticoagulants are generally used to prevent clot-formation caused by atrial fibrillation. Traditional forms of those drugs, with long histories of usage are the vitamin K antagonists (VKA). (Healthcare Professional Guidelines – atrial fibrillation, [2006] p. 1) VKAs are used with the objective of achieving good INR values, and in general, the patient population over the age of 75 can profit the most from it. The worst adherence levels are exhibited by patients receiving VKAs, with the result that about half the patients don't achieve the desired INR target value, which causes further complications. (Simonyi [2012])

International overview

Coleman and colleagues analysed 29 primary studies that examined adherence in the field of cardiovascular disease, among others in relation to atrial fibrillation. The authors produced a meta-analysis of 29 studies, and the results indicated, in general, that the adherence of patients with cardiovascular disorders is influenced by the frequency of doses, i.e. drugs taken once a day have better adherence than those taken several times a day. Using a therapy involving several doses of the drug per day may reduce patient adherence by as much as 30% relative to single daily dose regimens. (Coleman et al [2012])

Carrasco and colleagues specifically studied the adherence and persistence of VKA treatments. The results indicated that the median period between starting and stopping VKA therapy is 0.78 years in Germany, 1.00 years in Italy, 1.34 years in France, 1.99 years in Germany and 1.92 years in Great Britain. As regard adherence (MPR), the following results were measured: Spain: 0.54, Italy: 0.56, France: 0.57 and Germany: 0.59. Good adherence was defined as $0.80 \leq \text{MPR}$, i.e. in summary, VKA therapies do not exhibit good adherence in any of the countries reviewed, which increases the risk of strokes for patients. (Carrasco et al [2013])

In an American study, Patel and colleagues analysed warfarin dispensing data between 1 April 2007 and 1 December 2008. Based on the data, they measured persistence with a 60-day grace period. The result showed that after 90 days, only 71.2%, after 180 days, 61.4%, while after 360 days, only 44.2% of patients were still continuing the therapy. (Patel et al [2013])

Kim and colleagues looked at the persistence data of people who were dispensed amiodarone and sotalol between 2004 and 2007. The one-year persistence for amiodarone was 30.6%, while for sotalol it was 53.2%. (Kim et al [2011])

Hungarian data

In a study I completed with Gábor Simonyi, we studied the persistence of people who began VKA therapies (acenocoumarol and warfarin) between 1 June 2011 and 31 May 2012. The average one-year persistence for VKA therapies we found was 30%, which can be considered very low, but it is not a surprising result in the light of international data. (Simonyi-Molnár [2014])

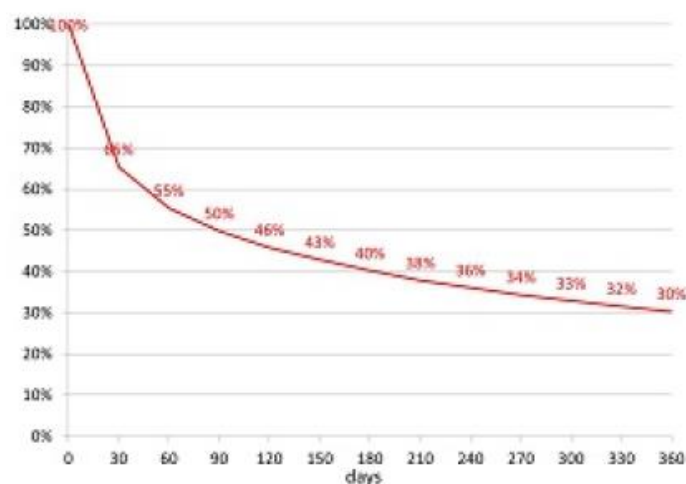


Figure 28: Persistence curve of VKA therapies (Simonyi-Molnár [2014])

In summary, we can conclude that according to the international literature, the persistence of oral coumarin-derivative anticoagulants ranges from 30% to 50%, and the persistence measured for Hungarian patients for KVA therapies is at the bottom of that range.

3.6. Osteoporosis

Background, epidemiology

8 to 10 percent of the Hungarian population suffers from primary or secondary osteoporosis. Osteoporosis is said to be primary when the disorder of bone metabolism does not have a secondary, underlying cause that leads to the pathological physiological process. Such secondary causes may be a vitamin D deficiency, a problem that impacts 30% of all people over 50, or primary hyperparathyreosis, of which 2000 new cases are found in Hungary each year. In Hungary, in the over 50 age group, 600,000 women and 300.000 men suffer from osteoporosis. (Healthcare Professional Guidelines – osteoporosis, [2005] p. 1-3) The significance of this group of diseases is that after an initial symptom-free period, patients face significant reductions of their quality of life, complications and various concomitant diseases. A well-known example of the cascade of consequences of osteoporosis is the scenario in which a femoral fracture suffered in old age that may result in a long bedridden period, which can then result in severe thromboembolism, possibly with a fatal pulmonary embolism at the end of it. The disease can certainly be considered endemic on the basis of the number of sufferers, and while we do not have specific, quantified data about its social and economic impact, we do know that the healthcare expenditure associated with the primary traumatological care of limb fractures reaches HUF 12 billion in Hungary. The cascade outlined above is present to some degree in most cases involving a fracture of the femoral neck, so if take the costs of the consequences into account as well, the sum total expenditure thus obtained is probably a highly significant cost factor for the healthcare system as a whole. The fundamental therapy of osteoporosis is long-term drug treatment, including replacement of calcium and vitamin D, and various other pharmaceutical products used in more severe cases. (Healthcare professional guidelines – osteoporosis, [2005] p. 3)

International overview

In previous sections I have explained that suitable patient adherence is particularly significant with diseases for which treatment is largely long-term drug treatment. In addition, the diseases with poor adherence are generally those that don't have any alarming symptoms, so the appropriate awareness of illness is not established. Osteoporosis is certainly in that category, as it is largely treated using drugs, and prior to the resulting fractures, it essentially doesn't cause any complaints at all. Therefore osteoporosis became a focal subject for adherence research quite early on, also partly because with that disease, fractures have measurable consequences in the shorter term already.

It is consistent with the above considerations that several studies have found that about 50% to 75% of people taking medications for the treatment of osteoporosis abandon the therapy within 12 months. It can be seen clearly in the figure below that in Ireland, even in the group of patients with quite good adherence, only half the patients maintained the therapy. (Hilgsmann et al [2012])

	Follow-up					
	6 mo	1 y	1.5 y	2 y	2.5 y	3 y
Women						
Nonpersistence	26.2%	35.7%	41.9%	47.3%	51.9%	55.0%
Poor adherence	13.1%	7.7%	5.9%	4.7%	4.1%	3.5%
High adherence	60.8%	56.6%	52.2%	48.0%	43.9%	41.5%
Number of persistent cases	52,192	42,819	35,925	30,051	24,983	20,781
Men						
Nonpersistence	40.0%	51.8%	58.9%	64.0%	68.1%	70.6%
Poor adherence	10.0%	5.1%	3.4%	2.6%	2.3%	2.1%
High adherence	50.0%	43.2%	37.7%	33.5%	29.6%	27.3%
Number of persistent cases	7,569	5,557	4,246	3,323	2,567	1,991

* Refill gap period of 9 wk; medication possession ratio of ≥ 0.8 to define high compliance, < 0.8 to define poor adherence.

Figure 29: Adherence and persistence values for osteoporosis medicines (Hilgsmann et al [2012] p. 608)

According to an American study, $\frac{3}{4}$ of women with osteoporosis receiving bisphosphonate therapy are nonadherent, and in the same population, 50% of patients terminate the therapy by 12 months. That poor adherence clearly leads to deterioration of practical efficiency, i.e. lower bone density, which results in a larger number of fractures. Overall, the adherence measured for osteoporosis therapies is too low, not optimal. A European study has found that 43.5% of women taking bisphosphonates (alendronate) discontinue the treatment within 6 months. An

additional 18.1% and 13.9% abandoned the therapy within 1 and 2 years, respectively, so only 25.5% were still receiving the treatment after 3 years. As in the other studies, an MPR value over 80% was considered to indicate good compliance. Results indicated that low compliance increased the rate of fractures in the hip area by 35%. (Hilgsmann et al [2010])

Cortet and colleagues performed a meta-analysis, which indicated that when raloxifene use is monitored for two years, only 53,7% of patients are still on the drug. (Cortet et al [2006])

In a very interesting piece of research, Curtis and colleagues analysed the pharmacy databases of 14 American states. The essence of the study was that they measured adherence and persistence on the basis of the data, then compared the results with the results obtained from interviewing patients. The charts below show that the adherence as perceived by patients always differs from the adherence levels measured using the database (in some cases, a factor of 6 or 7 separates the two values), and doctors are also susceptible to overestimating the adherence of their patients. While the doctors' estimate of the proportion of their adherent patients was 67.2%, the database showed that the actual value was 40%. (Curtis et al [2013])

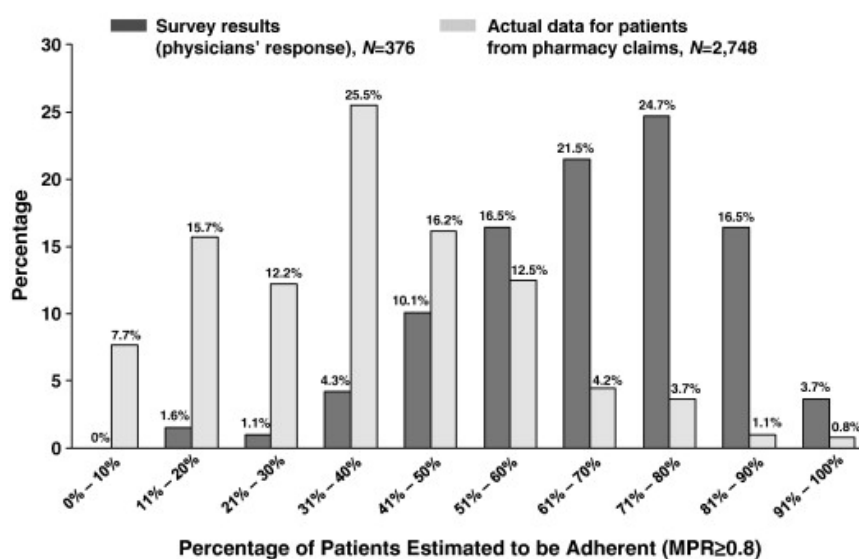


Figure 30: Adherence values for osteoporosis medications I. (Curtis et al [2013] p. 4)

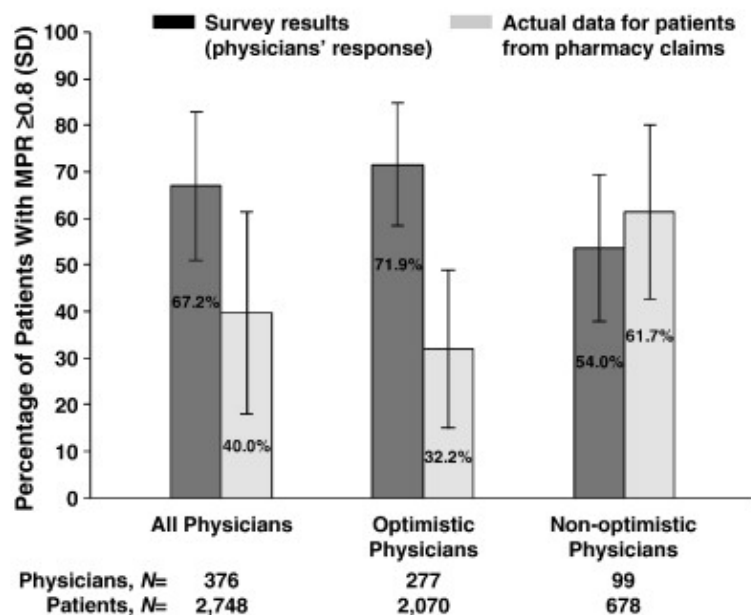


Figure 31: Adherence values for osteoporosis medications II. (Curtis et al [2013] p. 4)

Cheng and colleagues studied alendronate, raloxifene and calcitonin dispensing data between 2001 and 2007. Their results included persistence and over 80% MPR as well. The figure below makes it clear that they measured the worst 12-month persistence (32.9%) for calcitonin, with somewhat better values for the other two active substances (alendronate: 57.1%; raloxifen: 50.2%). (Cheng et al [2013]):

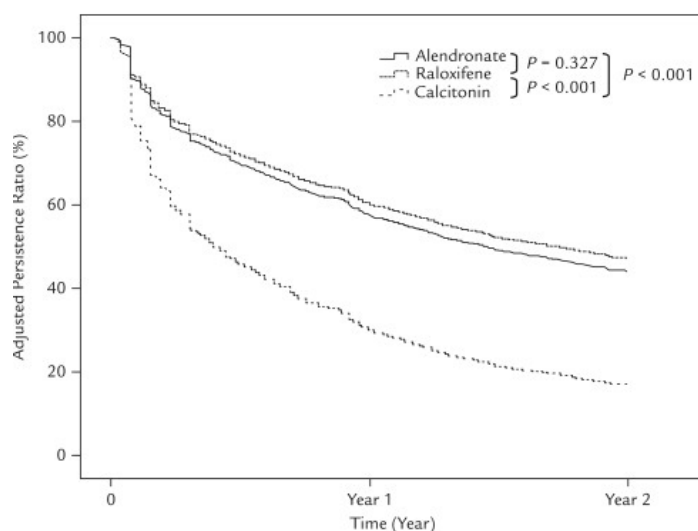


Figure 32: Persistence of antiporotic drugs (Cheng et al [2013] p. 1010.)

Hungarian data

In a study of my own, I analysed the dispensing data of oral medications for osteoporosis using the reimbursement database of the NHIFA. I monitored patients who commenced the therapy between 1 April 2007 and 2009; the results are presented in the chart below. 12-month persistence was around 30% (29.2%).

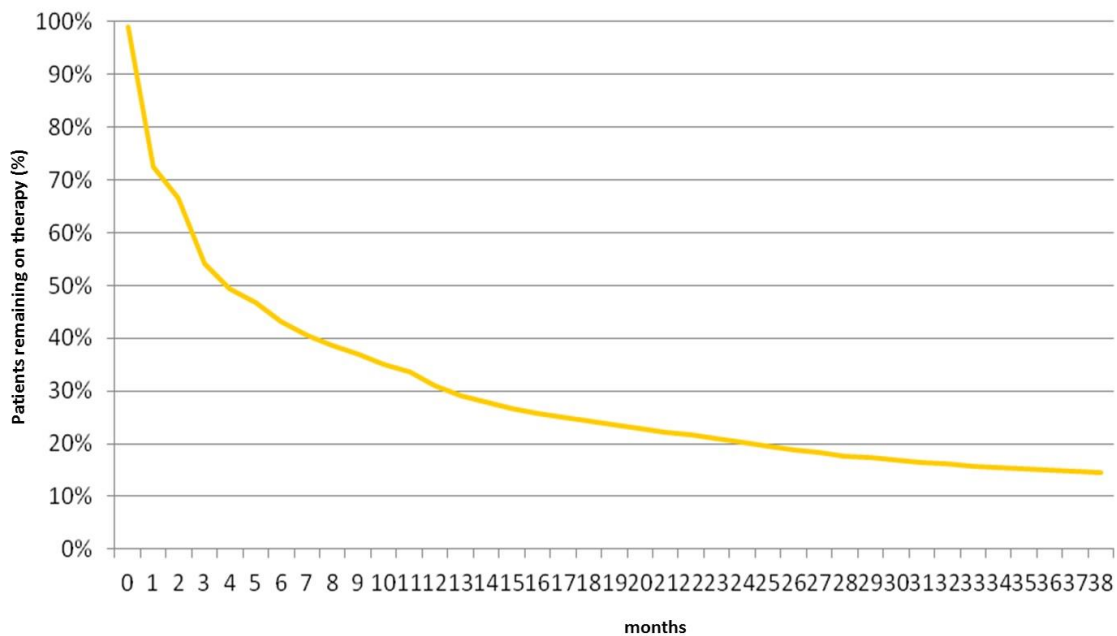


Figure 33: Full therapeutic persistence of medications used for the treatment of osteoporosis (60-day grace period) – 1 April 2007 - 2009 (my figure from a meeting of the Hungarian Health Communication Association on 26 January 2011)

In summary, we can conclude that relative to the international persistence data (30-60%), Hungarian patients are at the bottom of the range (30%). Therefore we can conclude that the persistence and adherence of Hungarian osteoporosis sufferers is very low in international comparison.

4. The possible ways of improving patient adherence

In previous chapters I presented evidence to the effect that patient adherence is below the desirable level for both drug and non-drug treatments, and I also pointed out that the direct and indirect impacts of that phenomenon are highly significant in modern healthcare systems. In view of that result, it seems logical that we should not only attempt to influence adherence indirectly, but we should develop and operate complex activities with the specific objective of supporting therapy, improving the adherence of patients. In the present chapter, I shall define therapy management programmes to include all activities whose objective is the improvement of adherence, irrespective of the complexity, the specific focus and the special components of such activities. In this chapter I define therapy management programmes as the sum of activities aimed to measure and improve adherence in order to optimize therapy, to achieve the maximum possible benefit with the least harmful effect, regardless of the complexity or the specific focus of the activity. In the material I use the English terms of "therapy management", "management of adherence" and "adherence management" as synonyms (ABC Project Team [2012], p. 26). In the present, 4th chapter of my dissertation I shall present a theoretical overview of the types of methods than can be expected to improve adherence, and I shall also outline how therapy management programmes can be developed by integrating those methods into an integrated framework. After that I shall propose that it is worth measuring the effectiveness of such programmes, and, based on the international literature, I shall present a few therapy management programmes whose effectiveness has been measured.

4.1. The possible points of intervention

In chapter 2.5 I described how the factors influencing patient adherence can be categorised into five main groups on the basis of the summary WHO study from 2003. It seems logical to use that classification of underlying factors to outline a few specific potential interventions, theoretical points of intervention that can assist us in improving adherence.

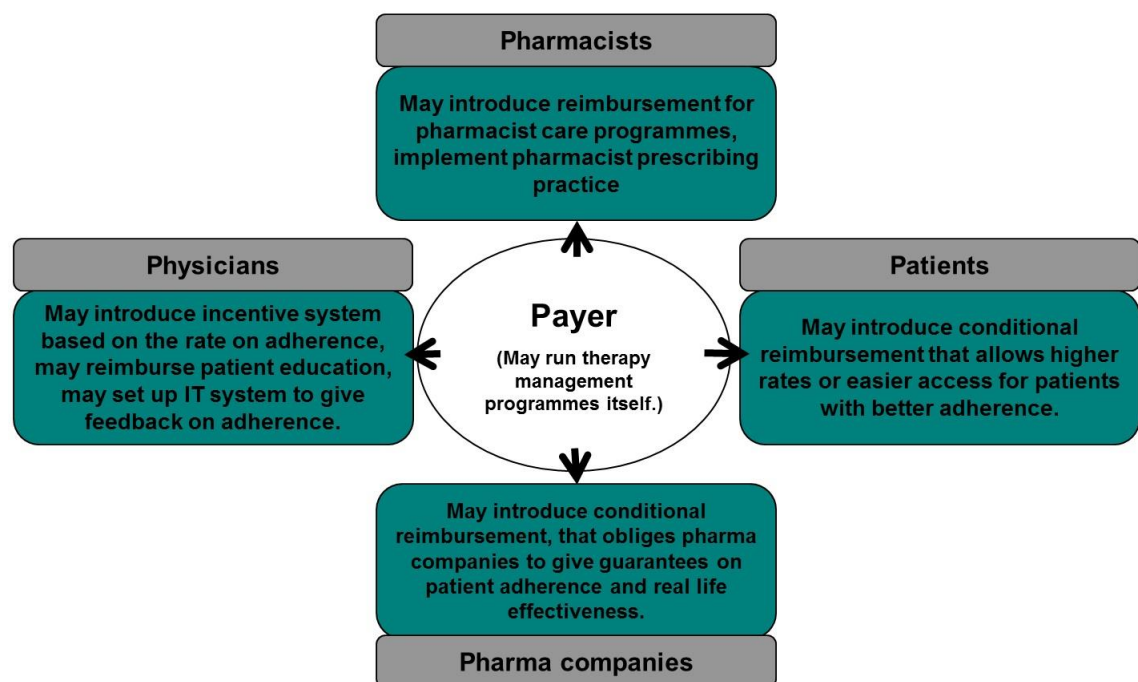
Influencing social and economic factors

As I previously outlined, this group primarily includes the system-level factors that are very difficult to influence, particularly in the short term, as a programme. It is clear that when the two most fundamental economic factors, liquid resources and an appropriate reimbursement system are both lacking, the patient is unable to afford to medication, i.e. he will exhibit poor adherence. It is a logical conclusion from that that the establishment of a functional reimbursement system will improve patient adherence, but however correct that assertion may be, it is unlikely to permit the drawing of any functional conclusions. Perhaps it is worth mentioning for developing countries that keeping co-payments at a level that makes medication available to a wide spectrum of the population is the foundation for good adherence.

We are much more likely to obtain some practical conclusions if we extend the above reasoning in the direction of attempting to use suitable reimbursement rules and financing incentives to urge patients and society as a whole to behave in a more adherent manner (Molnár-Dankó [2009]; Molnár [2011] p. 5). That intention can be realised in a number of different ways, the most important ones are as follows:

- Conditional reimbursement techniques can be introduced in which the co-payments required from patients are somehow linked to their levels of adherence. For instance, a patient can only get an anticholesterol drug with a high level of reimbursement if their body mass index does not exceed a certain limit value determined in advance. Only allowing reimbursement of a COPD medication if the patient gives up smoking is a similar solution.
- The payer can conclude agreements with pharmaceutical manufacturers that improve patient adherence in the long term:
 - o The manufacturer of the drug issues a guarantee of a certain level of real-world effectiveness, i.e. it acquires an indirect interest in appropriate adherence.

- The manufacturer issues a guarantee of a certain level of adherence, i.e. becomes interested in marketing methods and drugs that support adherence, and in financing therapy management programmes.
- The manufacturer undertakes to operate a therapy management programme.
- The payer can operate therapy management programmes directly.
- The payer introduces reimbursement and access rules and regulated patient journeys that specifically support appropriate patient adherence. Such solutions may include removing the payer obstacles to access to drugs, i.e. rethinking the domestic system based on medical specialist recommendations, introducing pharmacist prescriptions for chronic illnesses, where, after a medical diagnosis and initiation of the therapy, regular doctor-patient meetings are no longer required, as refills can be issued independently by pharmacists.
- The payer can establish a system of incentives and feedback that provides information to individual doctors about the adherence of their patients, and other incentives can also be involved.



*Figure 34: Points of intervention for payers in order to improve patient adherence
(own illustration)*

In addition to the examples listed above, a further possible system-level intervention is the provision of active support for the NGOs that at present hardly exist at all in Hungary, but exist to highly varied degrees in other countries, and which could play a very important role in patient education and training.

Influencing therapy-related factors

The 2003 WHO paper repeatedly asserts that the pharmaceutical industry does not sufficiently consider the establishment of suitable patient adherence to be an important matter, and that the knowledge-level of pharmaceutical industry stakeholders should be improved in this area (WHO [2003]). The publication of Kreps et al, to be described in detail later, also contains the thesis that the patient education material produced by pharmaceutical manufacturers has little significance. (Kreps et al [2011]) Despite all of that, however, it is still the case that in pharmaceutical development, the pharmaceutical industry has recognised the significance of suitable adherence for quite a long time. Accordingly, for those companies, the development of drugs and formulations that facilitate better adherence is a research directive, an important objective of innovation. Today, it is almost unheard of for a new product to appear in the market in a formulation requiring two or three doses per day, the era of those difficult dosage regimens is over. Drugs that used to be administered several times a day have been replaced by new formulations, version with long-term absorption, which are able to maintain stable drug levels with fewer doses. In the case of orally administered products, developing formulations allowing taking of the drug “less times a day” became a trivial development direction. In addition, we see a number of examples of drugs in daily doses being replaced by depot injections and implants that only need to be applied weekly, monthly or even less frequently, which are also aimed at improving adherence.

A third major direction of adherence focused pharmaceutical development is the development of fixed dose combinations (FDC). As I explained in previous chapters, increasing the number of different drugs to be taken at the same time has a significant detrimental effect on adherence, so putting two or more active substances that can be

taken in parallel into a single pill can have a significant positive effect on it. (Molnár [2011] p. 5)

Influencing patient-related factors

Many of the patient-related factors are associated with the personal characteristics of the patient, so they are difficult to change. So, instead, we may find ways to take those personal characteristics, habits and features into account when we wish to influence the factors that determine patient adherence. In addition, in previous chapters we also learned that well-informed patients are more likely to follow the doctor's instructions. Accordingly, whatever form the education of patient takes, it always improves adherence. The beneficial effect of education is largely caused by the fact that, as I described in Section 2.5, discontinuation of the treatment is often caused by lack of information, unfounded fears or beliefs, and education is able to counteract, dispel those. Ensuring that the patient actually knows how exactly to dose and to use the medication requires patient education in itself. Education can also generate motivation in the patient by calling attention to the unwanted events, complications that should be avoided as well as the benefits that can be achieved. If the patient knows clearly why it is important to take the lipid-lowering medication regularly so as to avoid a cardiac infarction, there will be a much better chance that this will motivate the patient during treatment.

Patient education can be performed by a number of stakeholders, but regardless of the way in which the patient acquires new, important information, it will have a beneficial effect on subsequent adherence (Molnár [2011] p. 5). Patients may be educated by:

- Healthcare personnel,
- Patient organisations, associations, clubs
- Other non-governmental organisations
- Central government
- The insurance company or payer

- State or commercial telecommunications outlets, the media
- Market stakeholders (for example pharmaceutical companies)

Influencing factors related to the healthcare system and the healthcare team

We have seen that the attitudes of the healthcare system supporting the patient – and its many stakeholders – towards the patient's healing constitute a key issue. Therefore the establishment of a patient-centred healthcare system is a key point of intervention for achieving appropriate patient adherence. It is quite clear that doctors play a definitive role in reaching patients, in improving their awareness of illness and improving adherence, as it is primarily doctors who can gain the trust of patients to an extent that actively shapes patient motivation and beliefs (Molnár-Dankó [2010]). I have already discussed a part of the system-level issues under economic and social factors, such as the issue of patient journeys, or some aspects of the financing of healthcare. In this section, I shall primarily discuss the relationship and the communication between healthcare staff and patients.

A number of studies have examined the factors that influence patient adherence in order to identify those that may have a direct effect in the establishment of adherent behaviour. Kreps and colleagues identified the exceptional importance of direct, personal consultation with pharmacists and doctors, and they also showed that the channel of communication may play an important role, i.e. it is important to ensure that the patient receive information using the channel and with the regularity the patient prefers, also involving being contacted by healthcare staff concerning their medical condition. (Kreps et al [2011])

Therefore, the communication skills and routine of healthcare professionals are particularly important, but graduate training in Hungary today places undeservedly little emphasis on those subjects. That is the case despite the fact that from the perspective of adherence conditions in a specific country, the knowledge and communication skills that the people working on the healthcare system acquire during their graduate and postgraduate education are of key significance. Therefore in our

country, one of the most important directions for the improvement of therapy adherence would be to provide more intense training to our healthcare professionals in order to improve their communication skills. Modern infocommunications equipment could also play a key role in establishing better communication. During medical work, there is often very little time for appropriate communication, dialog, so the communication opportunities provided by modern technology could also provide significant assistance with improving therapy adherence. (WHO [2003] p. 4)

The extent to which healthcare professionals are aware of and understand the theories and problems associated with adherence also seems to be an important issue. The attitudes of healthcare personnel could be significantly improved by simply convincing them that nonadherence is a real and serious problem. As we saw in previous chapters, doctors generally overestimate the adherence of their own patients significantly. Even if they accept the fact that, for instance, national persistence data are poor, they typically assume that those problems are only present in the practice of their medical colleagues, but not themselves.

Although in the previously quoted study, Kreps belittled the importance of patient information leaflets issued by pharmaceutical manufacturers relative to personal consultation with a doctor or pharmacist (Kreps et al [2011]), that does not mean that that material is not highly important from the perspective of patients. Manufacturer-provided material can assist the doctor during the education of patients and support the establishment of a good doctor-patient relationship. For that very reason, most pharmaceutical companies recruit the help of practising physicians to formulate their patient support programmes and materials.

Influencing factors related to the medical status of the patient

In Section 2.5 we saw that the factors related to the medical status of the patient are primarily related to diseases, or concomitant diseases that are characterised by a lack of awareness of illness. The lack of awareness of illness is partially caused by the patient and partially by the disease itself, so the patient education activities described

in the section on patient-related factors are also important here. If the lack of awareness of illness – for instance with hypertension – is attributable to the fact that the patient is not aware that hypertension, which has no symptoms in itself, can cause a stroke, a comprehensive educational programme can be the right solution to improve the patient's adherence. If the lack of awareness of illness is due to the fact that the patient refuses to consider his addiction to be a disease, education in itself is clearly not going to be sufficient; psychological guidance of a much more robust form will be required to achieve adherence. A similar active psychological intervention is required when nonadherence is caused by a concomitant disease, such as the depression associated with a cancer diagnosis. It is obvious that without appropriate treatment of the depression, it is impossible to restore the motivation required for suitable adherence.

4.2. Therapy management programmes and patient education

Based on the complex motivations and influencing factors that underlie adherent conduct we may conjecture that improving patient adherence is a highly complex task. As many as possible of the five groups of factors defined by WHO and described in detail in Section 2.5 (and referred to in the previous section) should be targeted for intervention if we wish to achieve really good results (WHO [2003]). It is not sufficient to simply adjust the therapy – for instance by switching from three daily doses to just one tablet a day – it is expedient to exert an influence on other factors, too, for example by giving the patient a printed package of educational material at the time of the switch, or starting a patient log in cooperation with the patient. That is how the complex therapy management programmes that modern healthcare systems truly need are built up. (Molnár [2011] p. 5.)

On the basis of the foregoing, an ideal therapy management programme would be a comprehensive initiative that targets all five of the groups of factors defined by the WHO. Obviously, an individual stakeholder in the healthcare system can rarely exert an activity that is able to influence all five groups of factors, so we can consider any

solution that targets at least two of the groups of factors at the same time in order to improve patient adherence to be a therapy management programme.

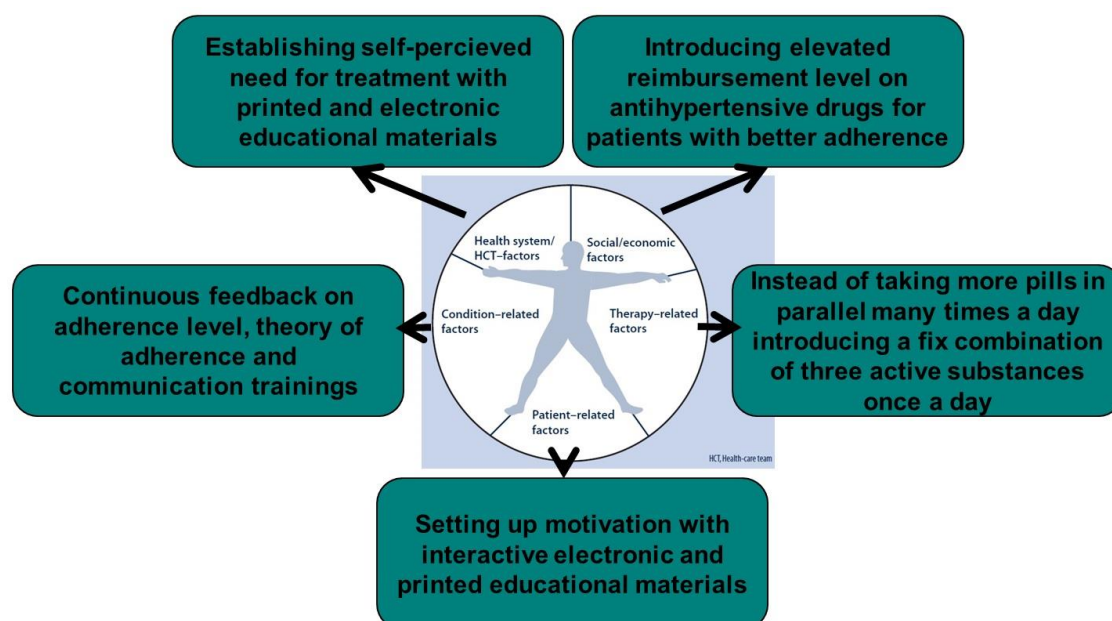


Figure 35: An ideal therapy management programme for the treatment of hypertension, which targets all five groups of factors (own illustration)

At present, the only stakeholders that are willing to finance such therapy management programmes are the pharmaceutical manufacturers, but due to the benefits for society and for the payer, the participation of the social insurance system in the operation of such programmes is not out of the question. In developed countries, especially where the payers have complex, long-term interests, the insurance institutions already participate regularly in the organisation of therapy management programmes, in a manner similar to prevention programmes. There are many such examples among German insurance companies (Stock et al [2010]), but American managed care organisations (MCOs) and health maintenance organisations (HMOs) have also been operating such initiatives professionally and monitoring them scientifically for decades. (Wilson-Pessaro et al [1987]; Bachman et al [2007])

The operation and financing of therapy management programmes by pharmaceutical manufacturers is increasingly common around the world. This statement might be partly contradict the research, where only four pharmaceutical companies out of the

interviewed nine indicated that improving adherence is their key strategic objective, and only four indicated that they are actively engaged in such activities. (ABC Project Team [2012] pp. 184-190) As I explained above, a number of background factors can be identified to explain the phenomenon. Firstly, increasingly stringent drug promotion regulations have transformed the attitudes of pharmaceutical manufacturers, and the emphasis has shifted from getting new patients to retaining the existing ones. Although that process is forced on the manufacturers, in recent years the pharmaceutical industry has voluntarily taken steps, towards the concept of “health companies”, and increasingly away from just selling pills towards supplying complex healthcare solutions, including the monitoring of treatment, patient education, and the development and supply of intelligent devices and IT solutions. The third pillar of the process is also a factor forced onto the players in the pharmaceutical market: payers are less and less interested in paying for medications that do not actually work in the real world. As a result of that, pharmaceutical companies increasingly need to assume shared risks with the payers as regards real-world effectiveness, and patient adherence is one of the main factors involved there.

4.3. Measuring the effectiveness of therapy management programmes

As we saw in the previous section, effective therapy management programmes are highly complex and impact as many of the factors that influence adherence as possible simultaneously. Clearly, the cost of programmes increases proportionally to their complexity. For example, Vegter and colleagues measured the cost of a pharmacist intervention programme applied to lipid-lowering drugs to be EUR 443,000 (Vegter et al [2014]). That illustrates that a therapy management programme can be very resource-intensive, which raises the issues of the effectiveness and cost-efficiency of such programmes and, as a closely related issue, the necessity of measuring those parameters.

The easiest way to evaluate the improvement of adherence achieved is a direct comparison of measures, for instance the MPR used to measure adherence, the adherence derived from it, or the persistence of a patient population at the end of a

specific period. In effect, during the measurement and the evaluation of the effectiveness of therapy management programmes, the measurement techniques described in the chapter of my dissertation on measurement techniques need or might to be applied in practice so as to be able to evaluate the effectiveness, efficiency or success of an individual programme. It is possible that we may try to quantify the results of an activity in itself, and we wish to know how many of a group of patients who had received education discontinued their therapy one year on. However, we get more realistic results if we compare the effect of our intervention with some sort of baseline value, and in that case we need to select a basis for comparison to which the new measured values are to be compared. Ideally, we perform prospective measurements of the adherence or persistence of two groups of patients, one that received the intervention and one that did not, in parallel and using exactly the same methodology. If that is not feasible, we can also generate an artificial basis for comparison using adherence data from an earlier period or a different population. Although the measurement of the effectiveness of such programmes seems to be easy from theoretical perspective, but in reality a very significant number of pitfalls need to be overcome. The measurement methodologies are diverse, and the therapy management programmes are using very different technics to improve adherence, the interventions are complex, and it is very difficult to compare them. For this reason, most of recent research findings, conclusions are irrelevant for other settings and other therapy management programmes, it is not possible to extrapolate. (ABC Project Team [2012], pp. 270-271.)

4.4. International results concerning the effectiveness of programmes aimed at improving adherence

I defined the therapy management programmes that may have a material effect on therapy adherence above. I also demonstrated that those programmes are often highly costly, so it is very important to be able to quantify their results. Below, I shall present international research results about the effectiveness of programmes aimed at improving adherence.

Kreps and colleagues studied the effects of so-called motivational messages sent to sufferers of chronic diseases on the patients' adherence. They sent patients motivational messages that influenced their anxieties and uncertainties so as to provide incentives for adherent behaviour. The messages were developed as the first step of the study in personal in-depth interviews and focus group interviews. Patients found the messages they received from doctors and nurses in personal consultation the most effective in terms of impact on adherence. The messages coming from pharmaceutical manufacturers and insurers were placed last. Patients also preferred messages in email format to telephone calls or text message delivered to mobile phones. (Kreps et al [2011])

The researchers drew attention to the fact that in relation to asthma, patient education and self-management play the larger roles in achieving long-term controllability of the disorder. (WHO [2003] p. 55) The study produced by Yeung and colleagues indicated that the simple fact that the patient knew that adherence would be monitored during the treatment in itself resulted in 60% of patients becoming fully adherent, following instructions in full, 20% was partially adherent, i.e. they took at least 70% of the doses prescribed, while the remaining 20% remained nonadherent. When patients didn't know about the monitoring, 55% only took 30-51% of the prescribed doses. (Yeung et al [1994])

According to a study performed in Germany, consultation between the patient and the pharmacist can reduce the improper use of the inhalation equipment provided for the treatment of asthma by 65%, which had the end result of better therapeutic results. (PGEU [2008] pp. 13-14)

Nayeri and colleagues investigated the effect of family-centred patient support programmes on adherence in patients who had suffered a stroke. According to the research methodology, the control group received the usual hospital treatment, while those in the research group also participated in a four-step, family-centred support programme along with the traditional hospital treatment. The content items of the four-step therapy management programme were as follows:

- Assessment of the patient's unique needs
- Education of family members on the basis of the unique needs surveyed about what the patient who suffered a stroke needed
- Follow-up phone calls
- Patient guidance services as required

Adherence was measured using a questionnaire, i.e. it was self-reported. The results indicated that the patients participating in the therapy management programme produced significantly better adherence values relative to the control group, i.e. similar initiatives may play an important role in providing tailored care to stroke patients. (Nayeri et al [2014])

Ho and colleagues investigated the methods for improving the adherence of cardioprotective therapies. The therapy management programme they studied had a mechanism with multiple pillars:

- They provided pharmacist intervention to ensure that patients accepted their illness.
- They educated the patients.
- They established cooperation between the pharmacist and the cardiologist providing primary care to the patient.
- They sent voice messages to patients to educate them and to remind them to take their drugs.

Adherence in the experimental group was 89.3% while in the control group it was only 73.9%. Clopidogrel, statins and ARBs all yielded better adherence values than beta-blockers. In summary, we can conclude that pharmacist intervention, patient education and voice messages, along with active cooperation between the treating physician and the pharmacist has a positive effect on adherence. (Ho et al [2014])

Guiraud and colleagues wanted to measure the effectiveness of telephone therapy management programmes aimed at improving the level of physical activity of patients with cardiovascular disorders. They reached the conclusion that telephone support programmes are effective, they improve the adherence of nonadherent patients, therefore this solution can be considered a useful strategy that can be implemented easily and at a low cost, and applied simply after institutional cardiac rehabilitation. (Guiraud et al [2012])

Pladevall and colleagues studied the effectiveness of patient education programmes for high cardiovascular risk patients receiving antihypertensive therapy. Their end result was that patient education programmes result in a higher probability of patient adherence. (Pladevall et al [2010])

They reviewed the results of several adherence programmes associated with hypertension therapy, and they found that, looking at the data of the patients included in the adherence programmes for five years, the total mortality rate – irrespective of the causes of death – was 57.3% lower than that of the control group, who didn't receive any support during their therapies. The mortality rate associated with hypertension was 53.2% lower among the patients included in the adherence programme. The differences in the mortality data were clearly caused by well-adjusted blood pressures, and this was borne out by the data: 39.7% of the patients included in the programme had acceptable blood pressures, while the same parameter was only 24.8% in the control group. (WHO [2003] pp. 40-41)

In Portugal, patients were given cards reminding them of the most important details of the treatment within the framework of complex pharmacist intervention. Finally, they examined the effect of the activity on persistence and adherence. The results indicated a clear positive correlation, i.e. the interventions had a clearly positive effect on adherence, which contributed to an improvement in the state of health of the patients. (PGEU [2008] p. 12)

Vegter and colleagues examined the results of pharmacist intervention applied in conjunction with lipid-lowering drugs. They found that pharmacist intervention aimed at monitoring and optimising the therapy improved the adherence of statin therapy, and as a result, reduced the probability of cardiovascular incidents. The cost of the programme was measured at EUR 411,000, while the quantified cost saving resulting from there being less cardiovascular incidents was calculated as EUR 443,000. In addition to the net saving of EUR 32,000, the programme also generated a saving of 84 QALY, i.e., to use the terminology of health economics, it proved dominantly cost-efficient. (Vegter et al [2014])

Taitel and colleagues measured the effectiveness of adherence programmes administered by local pharmacists by means of personal consultations to accompany statin therapy. At the 12-month follow-up they found that in the experimental group, MPR was 61.8%, while in the control group – i.e. in patients not participating in the programme – it was only 56.9%. This indicates that programmes based on personal intervention by pharmacists can successfully increase the MPR value, used to measure adherence, in statin therapy. (Taitel et al [2012])

Stuurman-Bieze and colleagues also investigated the results of pharmacist intervention aimed at monitoring and optimising lipid-lowering treatment. The main part of the intervention involved personal consultations with nonadherent patients. Of those that participated in the programme, 13.6% terminated therapy within a year, while the same ratio was 25.9% in the control group. On-going but non-adherent therapy occurred in 3.2% of the experimental group and 7.6% of the control group, i.e. the programme didn't only have a beneficial effect on persistence, but persistent patients also took their drugs with much better compliance with instructions. Overall, the programme reduced the probability of discontinuing the therapy by some 51%. In summary, we can conclude that therapy management programmes can be used effectively to improve the adherence of lipid-lowering drugs. (Stuurman-Bieze et al [2013])

Stuurman-Bieze and colleagues also performed a study similar to the above analysis about osteoporosis. Once more, they analysed the results of pharmacist intervention, and the results were as follows: 32.8% of the control group stopped the therapy prematurely, while in the experimental group the same ratio was only 19.0%. Those in the experimental group received consultancy along with monitoring. It is an interesting feature of this study that 31% of the patients in the experimental group actually noted that it was the first time they met a pharmacist who provided any information at all about their disease and its drug therapy. (Stuurman-Bieze et al [2014])

Foreman and colleagues studied the adherence impact of educational text messages. In order to measure adherence, they analysed the medication possession ratio. They found that the messages improved adherence, irrespective of the specific form of treatment that the patients were receiving. The greatest difference between the experimental and the control groups was measured in the patient populations taking antidiabetics and beta-blockers. In summary, we can conclude that in the case of orally administered, long-term medication treatments, those receiving therapy-specific messages exhibited significantly better adherence values. (Foreman et al [2012])

Henry and his team investigated the effects of a complex education programme for diabetics. The core feature of the programme was a personal doctor-patient consultation following a fixed script, during which the doctor and the patient discussed the reason for starting the therapy, and the doctor provided education to the patient about a number of subjects in order to establish appropriate awareness of illness and motivation:

- The significance and content of lifestyle changes
- The possible causes and consequences of terminating the therapy prematurely
- The necessity of potential dose adjustments
- The importance of continuous blood pressure measurements
- The necessity to monitor the blood-sugar level continuously

The programme was developed with a team of carers. The team consisted of four specialist doctors, a practising nurse, two pharmacist residents, two clinical pharmacist trainers, pharmacology students, registered nurses and doctor's assistants. Thanks to the work of the team, the programme proved successful, they were able to reduce the primary indicators in diabetes care, such as the HgA1c and LDL values. (Henry et al [2013])

Dale and colleagues are currently studying the impact of mobile applications for the self-management of coronary heart disease on adherence, as compared to the traditional forms of cardiac rehabilitation. Their study has one of the widest ranges of data among studies available in the literature about the effectiveness of modern educational activities, but the results are not available yet. Cardiac rehabilitation itself is considered secondary prevention, in the course of which education and support is provided to those suffering from coronary heart disease. Only a very small proportion of patients participate in programmes that are offered at centres to patients who are present in person. Therefore, a two-arm study is being conducted in New Zealand to examine the results of patient education programmes supported by new mobile technologies. Members of the group receiving education will receive personalised educational messages in addition to traditional rehabilitation, and they will also have access to a supporting website. The members of the experimental group will receive 5-7 messages per week for 24 weeks. The messages will be primarily aimed at reinforcing awareness of illness, to ensure that patients take prevention seriously. Participants will also receive messages to provide support with lifestyle changes, urging them to exercise, to maintain the diet required for a healthy heart, to promote stress management and to support patients with giving up smoking. The support website will provide as much interactivity as possible. In contrast, the control group will only receive traditional rehabilitation. Patients are currently being enrolled in the study, once they reach the requisite number of patients they will analyse a number of primary and secondary parameters, including six-month adherence. (Dale et al [2014])

5. The empirical study

5.1. Gaps in international and Hungarian literature

In previous chapters, I demonstrated that since the 1970's, the range of issues around patient adherence has increasingly garnered interest from theoretical specialists of several scientific disciplines and the practical specialists of a number of very different professions. In the last few decades, a large number of studies and theories have been published about the background of appropriate or indeed inappropriate adherence, the underlying factors, and the process of patients achieving adherence. It was in relation to that that I also demonstrated, in Chapter 3, that today, we have a great deal of scientific evidence about all the large chronic diseases concerning the exact levels of adherence in various countries, as we have analyses available about both the MPR-based approach and the determination of persistence. In addition to studies about adherence levels, an increasing number of publications also attempt to determine the direct and indirect costs associated with nonadherence. Hungary is keeping up with international trends, so a number of Hungarian researchers have gained international recognition in the field as representatives of marketing communication, medical psychology or the behavioural sciences.

On the other hand, despite the wealth of literature detailed above, it is also quite clear that the scientific study of the effectiveness and cost-efficiency of therapy management programmes is still in its infancy, there are few scientific studies available about the subject, and it is also apparent that a number of international research groups are currently working on studies of that type. In 2005, Elliott et al. attempted to review the relevant literature on the economic effectiveness of therapy management programmes, but they had to state that none of the analysed publications met the minimum criteria for real economic analysis, and therefore they could not comment on the economics of these interventions. In 2009, the British NICE updated the review led by Elliott et al, but all they could conclude was that further research is needed in the area. (ABC Project Team [2012], p. 301)

So at present, results of that sort are in short supply internationally, too, but I expect that in the near future, an increasing number of research papers will be published, including the New Zealand study currently underway – as described in the previous section – by Dale and colleagues (Dale et al [2014]). The results of those studies will no doubt attract a great deal of international attention, and they will determine the conceptual framework to be used by the multidisciplinary scientific community working on patient adherence for a long time.

5.2. Research objective, hypotheses

With my empirical research, I will try to establish how to assess the effectiveness of a comprehensive therapy management programme using objective, scientific methods, that is to say I will try to measure how the implementation of such a programme impacts the levels of patient adherence. In the course of my research, I will endeavour to apply the theories presented in my dissertation in practice, i.e. I will measure the effectiveness of a therapy management programme that influences as many different factors driving therapy adherence as possible, as explained in Chapter 4. In addition, I will use the methodologies presented in the chapter on the measurement of adherence during the measurement of the effectiveness of the programme, and I will try to establish the relationship of the 3, 6 and 12-month persistence values of the patients that participate in the therapy management programme with those of the control group.

So my fundamental research question concerns the effectiveness, the impact on adherence of the therapy management programme investigated. In addition, I also want to determine the economy of the programme as seen from the perspective of the pharmaceutical manufacturer that finances the programme and the insurance fund that finances the medications themselves.

My hypothesis is that the complex therapy management programme examined has a beneficial effect on the level of patients' adherence, i.e. the 3, 6 and 12-month persistence of the patient population participating in the programme will exceed the

values characteristic of the population that does not participate in the programme. If I am able to confirm my hypothesis with the results of my study, I will be able to conclude that programmes similar to the one examined are effective in improving adherence.

As an auxiliary hypothesis, I will also posit that *the costs of the programme will be below the increase in the turnover of the drug therapy that the programme focuses on, so the initiative is highly likely to result in a financial profit for the pharmaceutical manufacturer that finances the programme.*

Finally, my third hypothesis shall be that *the unfavourable effect of the increase in drug consumption resulting from the therapy management programme on social insurance expenditure will be below the savings made by the payer by not having to finance the hospitalisation events and the treatment of other consequences that it would have incurred if the programme had not been implemented.*

5.3. Research methodology and therapeutic area

The therapeutic area selected

I wish to conduct my research in a therapeutic area about which there are plenty of international and Hungarian evidence, preferably including the results of my own previous research. The figure shown in Chapter 1 about the research strategy was most applicable to lipid-lowering therapy and the treatment of prostate disorders, as it was in relation to those disorders that in recent years, international and Hungarian persistence conditions were the most fully mapped out, and those were also the treatment areas in which patient attitude studies were also conducted. Of those two areas, cholesterol-reducing treatments are already in the focus of a number of studies in progress, so I decided to perform a detailed analysis of a complex therapy management programme in the therapeutic area of *prostate disorders*.

Of course the decision related to the focus therapeutic area was complex, and I had to consider and weight several pros and cons. It was an argument for prostate disease, that this disease essentially affects every older men in developed societies, which means that the prevalence, the size of population affected and the disease burden are very significant. Nevertheless, the most obvious treatment of the disease is chronic medication, therefore adherence is a key issue in the effective and efficient management. It was an argument against the disease that its consequences – like hospitalization – that can be avoided by appropriate treatment are not too complicated or costly. It was also an argument against the disease that it only affects one gender, and the target population might not be very open for electronic methods of influencing or educating. I had to identify the disadvantage, that the disease is often treated with prescription-free products, which might be used as a substitute of prescription drugs. Overall, I analysed all the advantages and disadvantages and as a result I decided to link my analysis to BPH.

The structure of the therapy management programme

In the course of my research, I studied the drug consumption habits of patients treated with benign prostatic hyperplasia (BPH) who had participated in a complex therapy management programme aimed at increasing adherence. The complexity of the programme was a theoretical advantage in terms of expected results, however, this fact is a significant limitation on the other hand to extrapolate the findings for other therapy management activities, or use the research outcomes as general rules. The structure of the therapy management programme reflected the requirements detailed in a previous chapter, i.e. it attempted to improve as many underlying factors of adherence as possible at the same time. The programme was implemented within the framework of the PraxisPlatform™ patient education system, and it concerned a pharmaceutical product containing a fixed dose combination of dutasteride and tamsulosin, i.e. it was available to patients using that medication for the treatment of BPH, and their doctors. This fact is a limitation of my study, which was linked to an existing therapy management programme linked to a specific pharmaceutical product.

In every instance, the patient was introduced to the therapy management programme by the doctor, i.e. the doctor and the patient made the mutual decision about enrolling the patient in the programme. This act was legally implemented by having the patient sign a consent form authorising his doctor to initiate the programme for him, and authorising our research group to submit the Social Insurance Number (hereinafter the SIN) that identifies the patient to the NHIFA in order to obtain aggregate data about medication consumption habits. I have to emphasise that my study method has a limitation related to the selection of physicians and patients and the positive bias of this selection process. Firstly, the requested and cooperative physicians who took part in the initiative were apparently more open and more sensitive to issues of adherence, which in itself raises the possibility that their patients were already more adherent to therapies. The second level of positive selection was on the level of patients, who had the opportunity to participate in the intervention voluntarily, thus it can be assumed that due to the openness to participate these population might have had already better adherence before the programme.

The programme itself contained the following main components in order to achieve the desired effect on patient adherence:

1. *Educational opportunity for the patients' doctors:* Within the programme, doctors will have two types of opportunity to extend their knowledge. On the one hand, the doctor will be given a presentation about the programme as part of a personal consultation, where we will not only describe legal, administrative, IT and technical issues; we will also discuss the unfavourable adherence levels measured in the therapeutic area. On the other, in the PraxisPlatform™ system, doctors will have unique identifiers which they can use to log in and access professional information in electronic format that can assist with their work.
2. *Surveying individual patient needs using a questionnaire:* The first step of the programme, the enrolment of the patients in the programme followed by registration, will take place within the scope of a meeting in person. During that meeting, we will discuss legal and technical information, and it will also provide an

opportunity to the doctor to provide to the patient the basic information about the disorder and the therapy, and to record the individual patient needs on whose basis the educational part of the therapy management programme can be customised later on. During the conversation, the treating physician will record the following information:

- a. During which part of the day would the patient like to receive educational and motivational messages, when would such messages fit into his daily routine the best?
- b. What channel of communication would the patient prefer for receiving information (email, telephone voice messages or text messages)?
- c. Do the patient and his doctor use the informal or the formal mode of address?
- d. By what name does the doctor address the patient when they meet in person?
- e. What stage BPH does the patient suffer from (severe or medium severity)?
- f. When did the patient start the treatment, how important is it to start the educational content from the very basics?

3. *Educational opportunity for the patients:*

- a. The main component of the therapy management programme will be the customised educational messages that patients will receive through the channel they selected, at the time of day they selected, for a period of 6 months from being enrolled in the programme. A total of 46 such messages will be sent to the patients enrolled in the programme that provide both mobile phone and email contact details to their doctors. Patients will receive 1-2 educational messages per week on average, about the following subjects:
 - i. The causes, essential features and characteristics of the disease
 - ii. Characteristics of the therapy, the prescribed dosage regimen
 - iii. Information about the significance of the doctor's instructions, the potential consequences of not complying with the instructions
 - iv. Lifestyle recommendations
 - v. Practical advice about taking the drugs.

As examples, here are the messages sent to patients participating in the programme on the 14th, the 35th and the 63rd day, as text messages to their phones:

“Dear [the name specified by the doctor that he uses to address the patient], Did you know how the enlargement of the prostate causes problems with urination? As the prostate grows larger and larger, it becomes tighter around the urethra, compressing it, which slows down or even blocks the passage of urine. [signature provided by the doctor]”

“Dear [the name specified by the doctor that he uses to address the patient], BPH occurs in 40 percent of men over the age of 60, so you are far from alone with the problem. Almost all men over the age of 80 suffer from the disorder. Benign prostate hyperplasia becomes increasingly common and severe with age. [signature provided by the doctor]”

“Dear [the name specified by the doctor that he uses to address the patient], I am sure you have heard at the surgery that you have medium severity BPH. But did you know what exactly that means? In that condition, beginning to urinate is much harder than normal, and the stream of urine is weak. Urination becomes much more frequent. Discharging urine through the compressed urethra puts a strain on the musculature of the bladder, which may lead to fatigue. When the stream of urine ceases, there may still be up to 1 – 2.5 dl of urine left in the bladder. [signature provided by the doctor]”

- b. In addition to the messages, patients will also receive access to the PraxisPlatform™ website, where a number of pieces of partly interactive educational content will be made available.

- i. The messages described in the previous section, for reading or listening at any time
- ii. Electronic educational material
- iii. A playful quiz to practice and repeat the knowledge dispersed
- iv. A possibility for patients to use the International Prostate Symptom Score (IPSS) for assessing and monitoring their own condition, and to share the results with their doctors

Measuring the effectiveness of the therapy management programme

I intended to follow and analyse the drug consumption of the total Hungarian population taking the specific pharmaceutical product in the relevant timeframe to determine the effectiveness of the therapy management programme. To do this, the SINS of the patients participating in the therapy management programme were submitted to the specialists of the NHIFA (in compliance with data protection rules; see section “Data privacy aspects” later in this chapter), who filtered out those patients who had been still alive at the end of the study period and had at least one package of the product studied dispensed to them during that time. Using those filters, the NHIFA established a specific range of patients, and that became my test population. The difference between the two sets of the SINS consisted of the patients who died during the study period, and those who, despite the doctor’s instructions, never had a single prescription filled. At my request, based on the SINS I submitted and the set of patients who had the drug dispensed to them at least once during the study period, the NHIFA also determined the complete population who had the drug studied dispensed to them but definitely didn’t take part on the therapy management programme. That set of patients became the control group of my study.

In the course of the measurement, I analysed the itemised drug-dispensing data of the population participating in the education (experimental group), and the control group, i.e., using a 60-day grace period, I determined the proportion of patients that maintained the treatment as a function of the days elapsed from the commencement

of treatment. By producing a graph representation of the results, I obtained the persistence curves of the experimental group and the control group.

Determining economy from the perspective of the pharmaceutical manufacturer

In the course of my study, I obtained an accurate view of the content of the therapy management programme, its costs of development and operation, and the medication consumption habits of the patients participating and not participating in the programme. Based on that, I was able to establish accurately the overall incremental costs of the programme for the financing pharmaceutical manufacturer relative to the “do nothing” scenario, and also the incremental revenues realised specifically as the result of improved adherence. The comparison the expenditure and the palpable positive effects of the programme allowed me to determine the economy of the programme from the perspective of the pharmaceutical company. The calculations did obviously not include any potential additional effects of the programme that did not influence the turnover of the drug through the improvement of adherence but in some other way (for example: better company image).

Economy from the perspective of the social insurance fund

The third – and the most uncertain – research question of my study was the question of economy from the perspective of the payer. As the aggregate result of the complex network of short-term and long-term effects outlined in the previous chapters, the therapy management programme is *certainly* economical (that is to say, dominantly cost-efficient or cost-effective) for the payer if the total of the extra reimbursements resulting from increased consumption of the drug is less than the saving the payer realises from avoiding medium-term costs. As my study will gave me a completely accurate view of drug consumption, it was possible to calculate the incremental reimbursement outflow caused by the programme. Determining the costs avoided was a much more difficult task, and I certainly had to use some estimates:

- As a first step, I used the available clinical studies to establish the basic cost events that the combination drug therapy can prevent, and the prevalence of those events in the experimental and the control groups.
- Afterwards, based on the different proportions of patients receiving those treatments in the two groups, I modelled the number of cost events that occurred, and I attached specific costs to them based on Hungarian reimbursement data.
- Based on my calculations, finally I was able to compare the cost savings resulting from the therapy management programme with the extra reimbursement outflow caused by the increased consumption of the medication.

Data Privacy Aspects

During the research I all the way kept in mind that I was working only on statistical level, but with health data, that should always be treated with caution. My basic principle was to develop a research methodology and research framework that does not handle any personal identification data or health data which belongs to any specific person. The company – managing the programme itself – handled the patients' personal, contact and health data on the basis of voluntary and written consent outside the research framework, and they transferred – also based on the consent of the patients – the SINS to the NHIFA for running the data analysis. Following this essential part of the research the NHIFA gathered all the raw data, run the specified analysis and issued the final results. All these results were based on sensitive unique personal data, but all the issued information was only statistical data from which was never possible to trace back the individual patient level.

Health data analysis delivered by the NHIFA is clearly regulated by law. According to the Act No. CXII of 2011 on the right of informational self-determination and freedom of information the data handled by NHIFA is considered to be public information. According to the Act the information is public, if "it is created in the context of public duty of the state or the local government or other public duties defined by the law, it is

not personal data, whatever method it was used to record, however it was created, handled, collected. The data is highly public if it is related to the competence, organizational structure, professional activity, possessed data, general operations, contracts of a public organization including the assessment of its effectiveness.” This means that all data created and collected by the NHIFA is public data in the form that does not contain any sensitive, personal information. Therefore on proper request NHIFA has the obligation to deliver the required data for research, analysis and other functional purposes. This obligation is declared in Act No. LXIII of 2012 on disclosure and recycling of public information.

The NHIFA – as a public body – fully adheres to the regulation and publishes or provides all public information related to the health care system or to its own operation if it is not considered as private personal data. State organizations are not obliged to produce a new, qualitatively different data only to meet the research needs. If the requested information is not managed naturally by the state organization in the required form, it is not necessary to fulfil the request. On the other hand If data collection according to the criteria specified in the claim requires more costs and resources, the authorities may apply an additional fee and deliver the analysis as a service (Resolution of Ombudsman for Data Protection: 974 / K / 2008-3). Based on the data claim the NHIFA declares the service fee, which has to be paid upfront, then they generate the requested data within the specified time limit, and they send the data to the customer with a receipt. The NHIFA handles all private and health data according to the general legal regulations in respect of the protection of personal data. Therefore all incoming data request is subject to peer review from the aspect of data privacy. I followed during my research this procedure, NHIFA investigated my claim from data privacy aspects, and they delivered the results after this investigation generally based on the Act No. CXII of 2011 on the right of informational self-determination and freedom of information and the Act No. LXIII of 2012 on disclosure and recycling of public information.

Schedule

My research was based on the long-term monitoring and assessment of the drug dispensing data of large population, using a methodology that did not involve sampling. Therefore I already began preparing for the study in 2011. I performed the final analyses in 2015.

5.4. Presentation and interpretation of research findings

The effectiveness of the therapy management programme

All together 1,358 pieces of various SINs were handed over to the NHIFA. This patient population entered the therapy management programme sometime between 31 November 2011 and 2 December 2012. I asked the NHIFA to filter out those patients who were alive during the entire study period from 1 July 2011 until 31 December 2013 and started the therapy at any time – bought at least one unit from the study medicine. The data analysis resulted 934 SINs, which determined the relevant study population. The following factors were responsible for the difference between the two groups; the patients passed away during the study period, patients recorded by doctors with invalid SINs, and patients participating in the programme but not buying even one single dosage from the study drug. It is not possible to gather credible information on the composition of the three subgroups. Based on our former research related to cholesterol lowering drugs (Csóka et al [2012]) I assumed that the rate of primary nonadherence might have been low, therefore the main reason behind the difference might have been the administrative error or death of patients. Based on the patients participating in the programme and the patients buying the study pill, NHIF was able to determine the total population that certainly did not take part in therapy management programme, but indeed consumed the tablets. NHIF identified 9,403 persons in this group respectively.

In the course of the measurement, I analysed the itemised drug-dispensing data of the 934 patients participating in the education and taking the study drug (experimental group), and the control group, i.e., using a 60-day grace period, I determined the proportion of patients from each group that maintained the treatment, and obtained the persistence curves of the experimental group and the control group.

In Chapter 3.4 based on international studies I showed that the 12-month persistence of BPH is a wide range, the average rate is between 20% and 30%. I also pointed out that based on our research the Hungarian patients have similar measures with 12-month persistence of 22.3% (Dankó-Molnár-Piróth [2011]). The therapy management programme in my research was linked to a fixed dose combination medicinal product, so this factor had obviously a significant positive effect on patient cooperation, and baseline 12-month persistency as it is visible on the following graph.

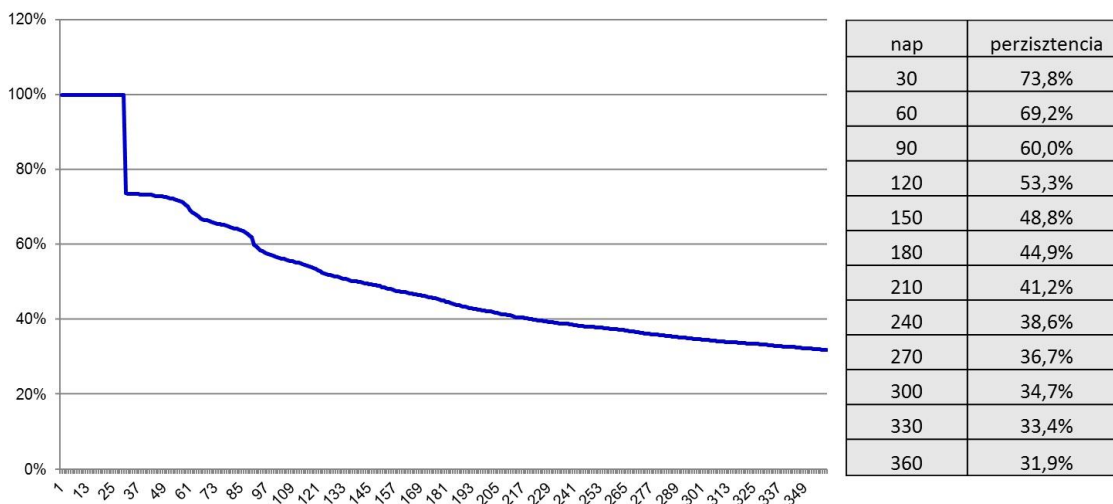


Figure 36: 12-month persistency of the total population treated with dutasteride and tamsulosin fixed dose combination (own illustration)

As it is shown in the graph above, the tamsulosin and dutasteride fixed dose combination has 12-month persistence of 31.9%, which is far better than the baseline from the literature. This data is valid for the total population taking tamsulosin and dutasteride fixed dose combination in the study period, which means 10,337 patients in total (9,403 patients left out of the programme, 934 patients taking part in the programme). The figure below shows the co-operation level of the patient group certainly left out from the therapy management programme. The results showed that without programme the average level of 12-month persistence is 31.0% among these 9,403 patients.

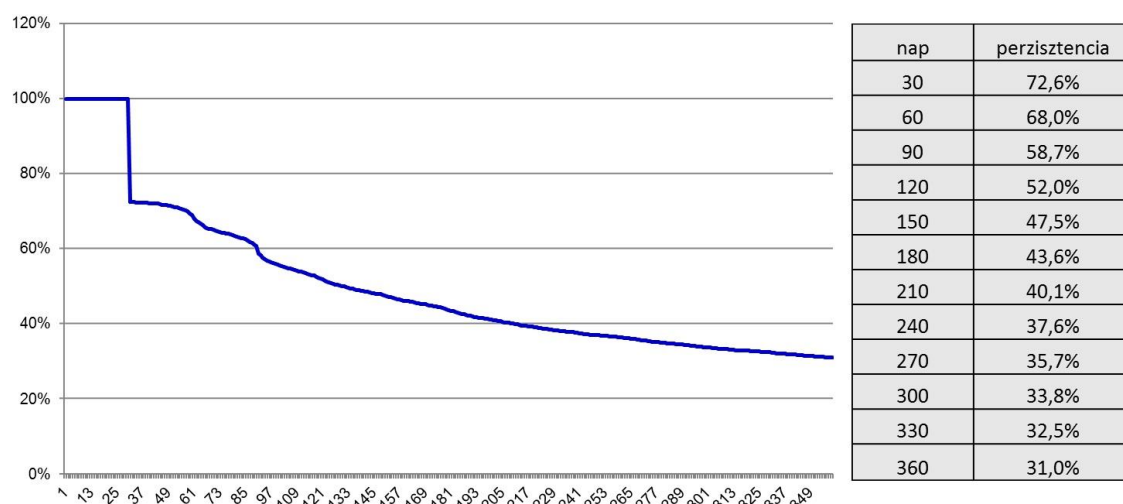


Figure 37: 12-month persistency of the population treated with dutasteride and tamsulosin fixed dose combination but certainly left out of the programme (own illustration)

As shown in the next graph, the 12-month persistence of the 934 patients taking tamsulosin and dutasteride fixed dose combination and in parallel certainly taking part in the therapy management programme was 41.2%

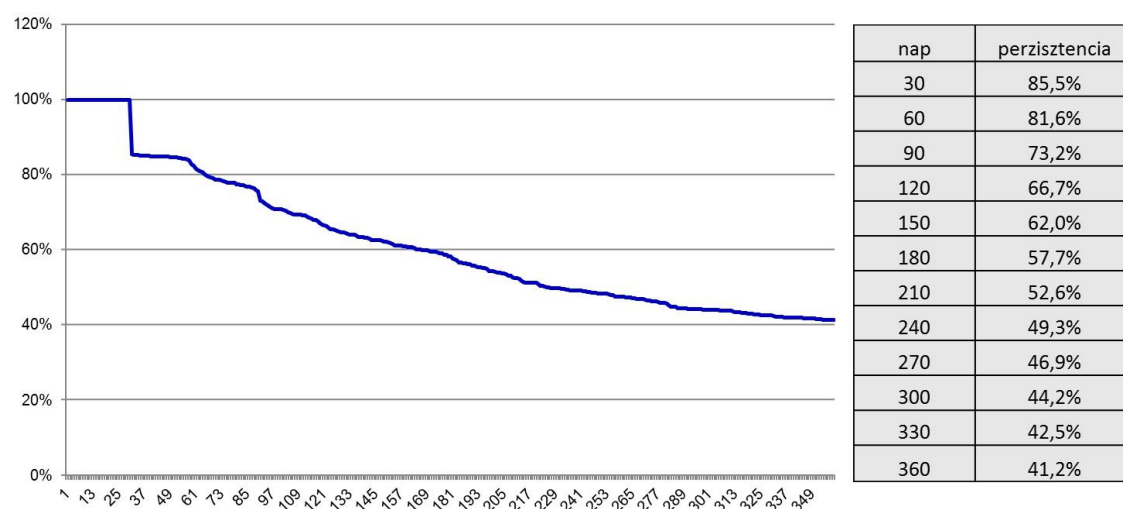


Figure 38: 12-month persistency of the population treated with dutasteride and tamsulosin fixed dose combination and certainly took part in the programme (own illustration)

Thus, I arrived at the persistence curve of the total population taking the study drug and participating in the therapy management programme, as I had the discontinuation rate of treated patients who did not participate in the programme as well. I used the simplifying assumption that the only decisive difference between these two groups is

whether the patients did or did not take part in the investigated programme. In this way, I built up research on the assumption that the different persistence of the two populations is due to the effect of the therapy management programme. I needed to use this assumption, but its simplistic nature is a limitation of my research methodology, which is pointed out in detail later on. The figure below shows the measured difference in term of persistence between the control and the examination group.

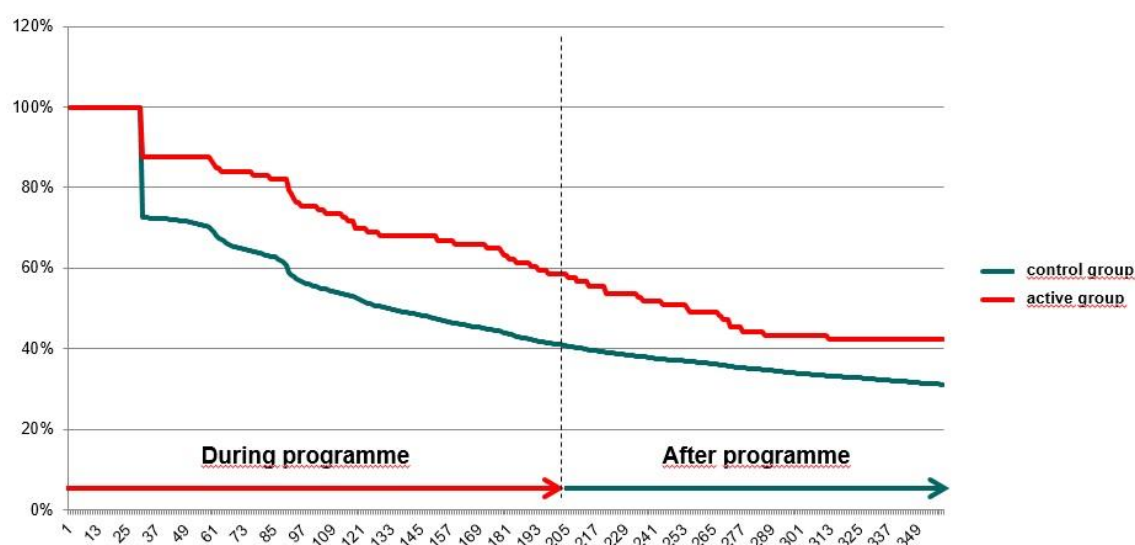


Figure 39: Comparison of persistence curves from the control and the examination groups (own illustration)

I quantified the visible difference on the graph above between the two patient groups. As the graph shows the advantage of the educated group in terms of persistence remained stable all the way long, and the difference in percentage points ranged from 10.0 to 14.7. I was not able to justify any clear trend in the extent of the difference, though in the first 120 days it showed an increase, then a decrease could be observed. The last third of the curve showed a stable difference at around 10 percentage point. It is worth to underline that the therapy management programme lasted only six months, so its effect on persistence seemed to last longer than the intervention itself. The characteristics of the curves allow us to extrapolate, that the programme has a long term effect on persistence, which is maintained well beyond the period.

Based on the results I confirmed my first research hypothesis, therefore I proved that the investigated therapy management programme was able to improve patient adherence significantly in long term period, the intervention was effective.

Effectiveness from the pharmaceutical manufacturer's perspective

Determining the economic effectiveness of the programme from the perspective of the financing pharmaceutical company I used the results of programme effectiveness analysis from the previous chapter. In parallel I used the drug prices of the studied fixed dose combination and programme cost of PraxisPlatform™ that were publicly available. Thus, the cost of therapy management programme was calculated as 5,000 Hungarian forint (hereinafter HUF) per enrolled patient, and the cost of the drug was 5,832 HUF on the basis of ex-factory price per box which contained medicine sufficient for 30 days. The reimbursement amount for the box was 1,125 HUF, respectively.

Along the outlined conditions the 12-month revenue of the pharmaceutical company from the 934 patients assuming the adherence measured for the non-educated group would be 33.9 million HUF. With the therapy management programme, the dropout rate would be lower, at 12 months the manufacturer would realize 41.5 million HUF as net income, however it should finance the programme itself. The total programme cost for educating the 934 patients would be 4.67 million HUF.

To fully determine the economics of the intervention I missed the data related to manufacturing costs of the drug, therefore I was not able to clarify the specific additional margin due to the programme. All I could conclude from the model calculation was that if the drug with 5,832 HUF ex-factory price has a lower than 2,264.3 HUF manufacturing cost per box, the therapy management programme's favourable impact on revenue certainly offsets the expenses. According to my assumptions there is a very high degree of certainty that my second hypothesis is also been supported by hard evidence, therefore we can conclude, that it is worth to run, initiate or support a therapy management programme by a pharmaceutical company, because it certainly may realize economic benefits as a result of the intervention. The

statement is valid even regardless the fact, that the pharmaceutical company supporting such a programme may gain other, intangible benefits also – like better company image – which are hard to quantify.

Effectiveness from the payer's perspective

To analyse the effectiveness from payer perspective I had to determine two main financial factors; the cost saving due to avoided events and the extra cost of additional drug consumption. First I estimated the frequency of avoided costly events due to the therapy management programme. To do so, I used a double-blind, long follow-up study analysis published by McDonnell et al, which was investigated 3,047 patients treated with BPH. The study demonstrated that on the placebo arm 5% of patients had to be treated with invasive interventions due to BPH, on the active arm with oral combination therapy this probability was only 1% during the 4-year follow-up. (McDonnell et al [2003], p. 2391)

I had the assumption that the costly adverse events occurred with the frequency published by McDonnell et al and that these events show equable distribution within the 4-year period. I weighted the probability of having invasive treatment events within 12 months to the dropout rate from the persistence curve. My calculation was based on the fact that chance of having invasive treatment of patients discontinued the drug treatment is equal to the probability of patients without treatment in the McDonnell study. As clinical data from the study referred to a 4-year period I extrapolated the difference between the two discovered persistence curves and considered the gap constant from the 12th month till the end of the 4-year period.

According to my model calculations in the control group assuming baseline persistence from my research 32.7677 invasive procedures is needed over a period of 4 full calendar years due to BPH, while for patients taking part in the therapy management programme, this value is 28.8575 respectively assuming the measured better persistence. This means that over a period of 4 years the 934 patients involved in the

programme avoid nearly four full-invasive intervention thanks to the participants' better adherence.

In the next section I defined which official costs can be associated with events avoided. I took the following official DRG and German Point values as reference to calculate the payer's expenditures related to one invasive treatment event:

OENO code	Description	German Point in out-patient care	HUF
	Treatment	750	1 125
	Control, conciliar	354	531
42162	define creatinine	108	162
2662C	Prostate specific antigen (PSA)	983	1 475
3617D	Duplex UH, kidney	1 383	2 075
36130	Stomach (overview, complex) UH	944	1 416
36180	Urination examination with UH	284	426
13305	Combined lower urinary tract function test (cystometria + pressure-flow examination)	15 511	23 267
Costs of out-patient care á visit			30 476
Costs of out-patient care á 5 visits			152 378
DRG code	DRG description	Treatment cost/DRG weight	HUF
11P 608Z	Kidney and urinary tract surgery (exception: serious surgeries) with serious co-morbidities	2,30155	345 233
In-patient cost:			345 233
Total cost:			497 610

Figure 40: Estimated cost of an invasive urological treatment

As shown by the above table I estimated the cost of an invasive urological treatment based on the DRG value of a urological surgical event and on the other hand 5 urological out-patient visits. Based on these expenditures the cost of 3.9 hospital treatment avoided turned out to be 1,940,783 HUF all together. In parallel the payer has to face additional drug consumption in form of additional reimbursement cost due to better adherence for the total 4-year period. This reimbursement amount is 5,265,283 HUF for the whole period.

The result of my calculations concluded that a total of 3,324,500 HUF additional expenditure might arise on the payer side due to the programme as a balance.

Approximately four hospital treatments can be avoided in exchange for this expenditure. It is clear that however my research could not underline that the therapy management programme is a budget saving tool, but the costs and benefits seem to be in line with the cost-effectiveness parameters of modern pharmaceutical treatments. Based on my model it can be stated, that the cost-effectiveness of such interventions primarily determined by cost of the investigated drug, cost the programme and the cost and frequency of the avoided events. In the field of BPH I have to point out that these main factors do not drive into to direction of cost-effectiveness, so it is very difficult to set up a budget saving adherence improving intervention from payer perspective in the Hungarian context. In Hungary the reimbursement level of hospital interventions is very low, therefore the avoided cost due to such an intervention is lower than in most Western-European setting they would be. The higher hospitalization cost we assume, the more certain the intervention will be cost-effective.

5.5. Validity, reliability and generalizability of the results

My research methodology has several advantages and strengths, therefore the results can be extrapolated for other therapy management programmes with similar design and cost on other chronic therapeutic areas. It should be emphasized that I used no sampling technique in my research, but I analysed the whole relevant patient population taking the specified fixed dose combination drug in the study period. This statement is valid for the selected patients participated in the programme and for the total patient pool left out of it. The active group was about 10% of the total population, so the model was robust enough to reach legit and generalizable results. I believe my research design and methodology with large patient populations allow me to draw conclusions for the total Hungarian patient population taking the investigated drug without extrapolation.

On the other hand there are some limitations due to study methodology as well, which should be highlighted during the interpretation of the results. I noted the key limitations in the chapters before, in this section I summarize them.

The selected therapeutic area seemed to be an appropriate choice for several reasons (prevalence, chronic drug therapy), but at the same time it can be stated that its consequences are not serious, most of the necessary interventions are not very expensive. The final conclusions are tinged by this fact and presumably in case of such a chronic disease, where the avoided consequences are more serious, the cost-effectiveness of the programme can be easier to quantify with the same methodology.

The therapy management programme was complex and unique, so its efficacy and cost-effectiveness results are difficult to extrapolate to other interventions that consist different elements.

However I needed to use the assumption during the measurement of therapy management programme's efficacy, that the only difference between the two compared patient groups is the education programme, but it has to be noted, that this is a simplification. As explained before, the patient selection of physicians and self-selection of patients regarding the participation can be a factor which leads to bias in final results. There is a mechanism of positive selection, as the doctor enrolling patients into the programme knows more about the importance of patient education, therefore his/her patients might have better adherence regardless of the programme itself. On the other hand it can be assumed that the adherence level of a patient voluntarily participating in a therapy management programme is also superior to patient who follows his/her own insights and decide not to participate in such an initiative because he/she considers such initiatives pointless.

The selected therapy management programme was linked to a particular drug, so generalizability of final results may be limited by its characteristics. The selected product was a fixed dose combination that can be associated with a higher level of adherence even without a therapy management programme. This was also confirmed in the research. It has to be noted, that this factor made it even more difficult to achieve better results in terms of improvement from a higher baseline. Another

specificity of investigated drug was the high co-payment level that – in theory – could harm the adherence level. It is obvious that the impact of unaffordability cannot be offset by the education or this effect is very limited.

Finally, in case of the economic calculations it is also important to point out the limiting factors that distort the generalizability of outcomes. The expedience of economic calculations performed from pharmaceutical manufacturer's perspective is distorted by the fact that indirect benefits and improved company image could not be quantified. It has to be stated, that the initiative is very likely to have additional advantages beyond the quantified ones. Even more significant methodological limitations exist related to the analysis made from sick fund's perspective, as it is not possible to predict the avoided complications in long term with a very high degree of certainty. On one hand I could quantify the likelihood of invasive hospital treatments based on clinical trials, on the other hand I had to associate the frequency of these events with the Hungarian DRG and German Point tariffs, which do not reflect in all cases the real costs. I assume that I could realize and identify several other cost components monitoring the real and total health care costs of the followed patients.

5.6. Conclusions, areas for further research

My results showed that the investigated therapy management programme was effective to improve patient adherence in the field of BPH, it was economically rational investment from the financing pharmaceutical company, however from payer's perspective the programme did not turn out to be predominantly cost-effective, because I could not prove its budget saving nature. Nevertheless, it should be noted that the programme was able to avoid complications, adverse events and hospitalizations, therefore it could avoid additional expenditures and improve the patients' quality of life. Due to methodological limitations I could not quantify all the avoided costs, and determine the degree of improvement in quality of life. To be able to measure the cost-effectiveness more precisely, further researches are needed. These further investigations might focus on measuring avoided costs more properly and calculating the quality of life improvement due to therapy management

programmes. My measurement methodology seems to be appropriate in field of other chronic diseases not only in BPH. In further researches applying this methodology for other diseases might help to detect how treatment- and disease specific attributes may influence the results. Based on my model calculations it has become clear that there is conceptual correspondence among drug costs, programme costs, avoided costs of complications and the cost-effectiveness of therapy management programme. Lower drug and programme costs, and more expensive avoided complications lead to more cost-effective therapy management programmes in the field of chronic conditions.

6. References

- ABC Project Team [2012]: Ascertaining Barriers for Compliance: Policies for safe, effective, and cost-effective use of medicines in Europe. Final Report of the ABC Project (Deliverable 7.1). FP7 Theme Health, 2007-3.1-5, grant agreement number 223477. Epub 2012 June. <http://www.ABCproject.eu>
- Auffenberg GB., Gonzalez CM., Wolf JS., Clemens JQ., Meeks W., McVary KT. [2014]: An observational analysis of provider adherence to AUA guidelines on the management of benign prostatic hyperplasia. *THE JOURNAL OF UROLOGY* 2014 Nov; 192(5): p. 1483-1488. doi: 10.1016/j.juro.2014.06.016. Epub 2014 Jun 12
- Bachman KH., Histon TM., Remmers C. [2007]: Obesity in the Kaiser Permanente Patient Population and Positive Outcomes of Online Weight-Management Programs. *Perm J.* 2007 Spring; 11(2): 25–30.
- Balikó Z. [2007]: Persistence on tiotropium treatment [A tiotropiumkezelés perzisztenciája]. *LAM* 2007;17(8–9): p. 585–586.
- Balkrishnan R., Christensen DB. [2000]: Inhaled corticosteroid use and associated outcomes in elderly patients with moderate to severe chronic pulmonary disease. *Clinical Therapeutics*, 2000, 22:452-469. DOI: [http://dx.doi.org/10.1016/S0149-2918\(00\)89013-X](http://dx.doi.org/10.1016/S0149-2918(00)89013-X)
- Medical College of Internists [Belgyógyászati Szakmai Kollégium] [2010]: Medical guideline of Ministry of National Resources on lipid disorders [A Nemzeti Erőforrás Minisztérium szakmai irányelve a zsíryanagcsere-zavarokról (dyslipidaemiákról)]. 2010. EÜK 10.
- Bender BG. [2002]: Overcoming barriers to nonadherence in asthma treatment. *J Allergy Clin Immunol* 2002;109(Suppl 6): p. 554–559
- Borghi C. et al. [1999]: Effects of the administration of an angiotensin-converting enzyme inhibitor during the acute phase of myocardial infarction in patients with arterial hypertension. *American Journal of Hypertension* (12) p. 665-672.
- Capgemini Consulting [2011]: Patient Adherence: The next Frontier in Patient Care, Vision & Reality 9th Edition, Global Research Report.
- Carrasco J., Cotté FE., Lomon ID., Letierce A., Huguet M., Marchant N. [2013]: PCV24 – Adherence to Treatment and Persistency in Patients Treated with VKA in France, Italy, Germany, Spain and the United Kingdom. *ISPOR 16th Annual European Congress and 4th Latin America Conference Research Abstracts, Value in Health, Volume 16, Issue 7, November 2013*, p. A516. doi:10.1016/j.jval.2013.08.1223
- Cheng T-T., Yu S-F., Hsu C-Y., Chen S-H., Su B.Y-J., Yang T-S. [2013]: Differences in Adherence to Osteoporosis Regimens: A 2-Year Analysis of a Population Treated Under Specific Guidelines. *Clinical Therapeutics* Volume 35, Issue 7, July 2013, p. 1005–1015. doi:10.1016/j.clinthera.2013.05.019
- Coleman CI., Roberts M., Sobieraj D., Lee S., Alam T., Kaur R. [2012]: Effect of dosing frequency on chronic cardiovascular disease medication adherence. *Journal of*

- The American College of Cardiology Volume 59, Issue 13s1, March 2012. p. E1808-E1808. doi:10.1016/S0735-1097(12)61809-9
- Colin PR., Gerth WC., Fox J. et al. [2001]: Four year persistence patterns among patients initiating therapy with angiotensin II receptor antagonist losartan versus other antihypertensive drug classes. Clin. Ther. (23), p. 1999-2010.
- Colombo GL., Rossi E., De Rosa M., Benedetto D., Gaddi AV. [2012]: Antidiabetic therapy in real practice: indicators for adherence and treatment cost. Dovepress, Patient Preference and Adherence 13 September 2012. p. 653–661. doi http://dx.doi.org/10.2147/PPA.S33968
- Cortet B., Bénichou O. [2006]: Adherence, persistence, concordance: do we provide optimal management to our patients with osteoporosis? Joint Bone Spine Volume 73, Issue 5, October 2006, p. e1–e7. doi:10.1016/j.jbspin.2006.02.006
- Curtisa JR., Caib Q., Wadec SW., Stolshekd BS., Adamse JL., Balasubramaniand A., Viswanathand HN., Kallich JD. [2013]: Osteoporosis medication adherence: Physician perceptions vs. patients' utilization. Bone Volume 55, Issue 1, July 2013, p-1–6. doi:10.1016/j.bone.2013.03.003
- Csóka I., Dankó D., Soós Gy., Molnár MP. [2012]: Patient adherence in statin therapy [Beteg-együttműködés sztatinterápiában]. Pharmacology [Gyógyszerészet] 56. 2012. May p. 1-8.
- Dailey G., Kim MS., Lian JF. [2001]: Patient Compliance and Persistence with Antihyperglycemic Drug Regimens: Evaluation of a Medicaid Patient Population with Type 2 Diabetes Meilitus. CLINICAL THERAPEUTICS*/VOL. 23, NO. 8, 2001. p. 1311-1320. doi:10.1016/S0149-2918(01)80110-7
- Dale LP., Whittaker R., Jiang Y., Stewart R., Rolleston A., Maddison R. [2014]: Improving coronary heart disease self-management using mobile technologies (Text4Heart): a randomised controlled trial protocol. Trials. 2014 Mar 4 p. 15-71. doi: 10.1186/1745-6215-15-71.
- Dankó D., Molnár MP. [2011]: Patient adherence in benign prostate hyperplasia (BPH) – reasons and influencing factors [Terápiahűség a benignus prosztata hyperplasia (BPH) gyógyszeres kezelésében – Okok és befolyásoló tényezők]. Research report [Kutatási Jelentés]. Budapesti Corvinus Egyetem. 2011. January 17.
- Dankó D., Molnár MP., Piróth Cs. [2011]: Patient adherence (persistence) in benign prostate hyperplasia (BPH) [Beteg-együttműködés (perzisztencia) a benignus prosztata hyperplasia gyógyszeres terápiájában]. Hungarian Urology [Magyar Urológia]. - ISSN 0864-8921. - 2011. 23/1, p. 7-12.
- Dankó D. [2011]: Adherence Cyclopaedia [Adherencia Tudástár] 7. Economic impact of patient adherence [A beteg-együttműködés gazdasági jelentősége]. Medical Tribune 9/5. 2011. March 17. p. 6.
- Davis KL., Mauskopf JA., Chow W.,Chao J., Seal B. [2006]: Titration and Persistence with Tamsulosin Among Men with Benign Prostatic Hyperplasia in a Large Managed Care Population. AMCP 18th Annual Meeting and Showcase, Seattle, 2006

- DiMatteo MR. [2004]: Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. *Med Care* 2004; 42(3): p. 200–209
- Dóczy V., Mészáros Á. [2013]: Methodological questions of patient adherence and national research findings [Beteg-együttműködés, módszertani kérdések és hazai vizsgálatok]. *Acta Pharmaceutica Hungarica*, 2013/1. 83., p. 13-27.
- Doró P, Benkő R, Kosik E, Matuz M, Tóth K, Soós Gy. [2005]: Utilization of oral antihyperglycemic drugs over a 7-year period (1998–2004) in a Hungarian population and adherence to drug therapy. *Eur J Clin Pharmacol* 2005; 61: p. 893–897.
- Dotar D. [2009]: Promoting adherence to medical treatment in chronic childhood illness. Concepts, Methods, and Interventions. Lawrence Erlbaum Associates, Inc. Publishers 10 Industrial Avenue, Mahwah, New Jersey 07430. p. pp. 8-12.
- Medical College of Pulmonologists [Tüdőgyógyászati Szakmai Kollégium] [2014]: Medical guideline of Ministry of National Resources on adult asthma diagnostics, treatment and chronic care [Szakmai irányelv az asztma diagnosztikájának, kezelésének és orvosi gondozásának alapelveiről felnőttkorban]. 2014. EüK 7.
- Ernst FR, Grizzle AJ [2001]: Drug-related Morbidity and Mortality: Updating the Cost-of-Illness Model. *Journal of the American Pharmaceutical Association*. 2001, 41(2):192-199
- Farsaei S., Radfar M., Heydari Z., Abbasi F., Qorbani M. [2014]: Insulin adherence in patients with diabetes: Risk factors for injection omission. *Primary Care Diabetes* Volume 8, Issue 4, December 2014, p. 338–345. doi:10.1016/j.pcd.2014.03.001
- Foreman KF., Stockl KM., Le LB., Fisk E., Shah SM., Lew HC., Solow BK., Curtis BS. [2012]: Impact of a Text Messaging Pilot Program on Patient Medication Adherence. *Clinical Therapeutics/Volume 34, Number 5, 2012*. p. 1084–1091. doi:10.1016/j.clinthera.2012.04.007
- Fulda TR., Wertheimer AI. [2007]: Handbook of Pharmaceutical Public Policy. Haworth Press Inc., 10 Alice Street, Binghamton, NY 2007. p. 568.
- Gillissen A. [2007]: Patients' adherence in asthma. *Journal of Physiology and Pharmacology* 2007, 58, Suppl 5., p. 205-222.
- Gogovor A., Dragomir A., Savoie M., Perreault S. [2007]: Comparison of persistence rates with angiotensin-converting enzyme inhibitors used in secondary and primary prevention of cardiovascular disease. *Value in Health* Volume 10, Issue 5, September–October 2007. p. 431-441. doi:10.1111/j.1524-4733.2007.00247.x
- Guiraud T., Granger R., Gremeaux V., Bousquet M., Richard L., Soukarié L. Babin T., Labrunée M., Sanguignol F., Bosquet L., Golay A., Pathak A. [2012]: Telephone Support Oriented by Accelerometric Measurements Enhances Adherence to Physical Activity Recommendations in Noncompliant Patients After a Cardiac

- Rehabilitation Program. Archives of Physical Medicine and Rehabilitation Volume 93, Issue 12, December 2012, p. 2141–2147. doi:10.1016/j.apmr.2012.06.027
- Hankó B. [2006]: Current issues on patient adherence Part I. [A beteg-együttműködés aktuális kérdései I. rész]: Pharmacology [Gyógyszerészet], 2006. October, p. 619-623.
- Hankó B. [2007]: Current issues on patient adherence Part II. [A beteg-együttműködés aktuális kérdései II. rész]: Pharmacology [Gyógyszerészet], 2007. March, p. 152-157.
- Heller RF. et al. [1978]: Blood pressure measurement in the United Kingdom Heart Disease Prevention Project. Journal of Epidemiology & Community Health (32) p. 235-238.
- Henry TM., Smith S., Hicho M. [2013]: Treat to goal: impact of clinical pharmacist referral service primarily in diabetes management. Hosp Pharm. 2013 Sep;48(8) p. 656-661. doi: 10.1310/hpj4808-656
- Hilgsmann M., McGowan B., Bennett K., Barry M., Reginster J-Y. [2012]: The Clinical and Economic Burden of Poor Adherence and Persistence with Osteoporosis Medications in Ireland. Value in Health Volume 15, Issue 5, July–August 2012, p. 604–612. doi:10.1016/j.jval.2012.02.001
- Hilgsmann M., Rabendab V., Bruyèreb O., Reginster J-Y [2010]: The clinical and economic burden of non-adherence with oral bisphosphonates in osteoporotic patients. Health Policy Volume 96, Issue 2, July 2010, p. 170–177. doi:10.1016/j.healthpol.2010.01.014
- Ho PM., Magid DJ., Masoudi FA., McClure DL., Rumsfeld JS.[2006]: Adherence to cardioprotective medications and mortality among patients with diabetes and ischemic heart disease. BMC Cardiovascular Disorders 15 December 2006, 6:48, p. 1-9. doi:10.1186/1471-2261-6-48
- Ho PM., Lambert-Kerzner A., Carey EP., Fahdi IE., Bryson CL., Melnyk SD., Bosworth HB., Radcliff T., Davis R., Mun H., Weaver J., Barnett C., Barón A., Del Giacco EJ. [2014]: Multifaceted intervention to improve medication adherence and secondary prevention measures after acute coronary syndrome hospital discharge: a randomized clinical trial. JAMA Intern Med. 2014 Feb 1;174(2) p. 186-193. doi: 10.1001/jamainternmed.2013.12944
- Holman HR. et al. [1997]: Evidence that an education program for self-management of chronic disease can improve health status while reducing health care costs: a randomized trial. Association for Health Services Research (14), p. 19-20.
- Horne R. et al. [2005]: Concordance, adherence and compliance in medicine taking. Report for the National Co-ordinating Centre for NHS Service Delivery and Organisation R&D (NCCSDO).
- Iyengar RN., Balagere DS., Henderson RR., LeFrancois AL., Rabbitt RM., Frazee SG. [2014]: Association between dispensing channel and medication adherence among medicare beneficiaries taking medications to treat diabetes, high blood

pressure, or high blood cholesterol. J Manag Care Pharm. 2014 Aug;20(8), p. 851-861.

Jermendy Gy. [2009]: Diagnostics, treatment and chronic care of adult diabetes mellitus [A diabetes mellitus kórismézése, a cukorbetegség kezelése és gondozása a felnőttkorban]. Medical guideline of Hungarian Association of Diabetes [A Magyar Diabetes Társaság szakmai irányelve], 2009.; 2009. EÜK 21.

Jermendy Gy., Wittmann I., Nagy L., Kiss Z., Rokszin Gy., Abonyi-Tóth Zs., Katona L., Paragh Gy., Karádi I., Merkely B. [2012]: Persistence of initial oral antidiabetic treatment in patients with type 2 diabetes mellitus. Clinical Research Med Sci Monit, 2012; 18(2): p. CR72-77. PMID: 22293880. doi: 10.12659/MSM.882459

Joanne M., Amie T., Amy E., Larry Z., Joshua S. [2008]: Persistence of atorvastatin and simvastatin among patients with and without prior cardiovascular diseases: a US managed care study. Current medical research and opinion 7(24), p. 1987-2000.

Medical College of Cardiologists [Kardiológiai Szakmai Kollégium] [2006]: Medical guideline of Ministry of National Resources on atrial fibrillation and flutter [Szakmai irányelv: Pitvarfibrilláció és flutter]. 2014. EÜK 7.

Kim MH., Smith PJ., Jhaveri M., Lin J., Klingman D. [2011]: One-Year Treatment Persistence and Potential Adverse Events Among Patients With Atrial Fibrillation Treated With Amiodarone or Sotalol: A Retrospective Claims Database Analysis. Clinical Therapeutics. Volume 33, Issue 11, November 2011, p 1668–1681. doi:10.1016/j.clinthera.2011.10.005

Kiss Z., Nagy L., Reiber I., Paragh Gy., Molnar MP., Rokszin Gy., Abonyi-Toth Zs., Márk L. [2013]: Persistence with statin therapy in Hungary. Clinical research 2013; Arch Med Sci 2013; 9, 3: p. 409-417; DOI: 10.5114/aoms.2013.35327

Köteles F., Komsa I., Bárdos Gy. [2010]: The effect of perceptual characteristics of tablets upon patient's choice. Clinical and Experimental Medical Journal. Vol 4., Number 1. p. 99–104. DOI: 10.1556/CEMED.4.2010

Krepsa GL., Villagrana MM., Zhao X., McHorneyb CA., Ledforda C., Weathersa M., Keefec B. [2011]: Development and validation of motivational messages to improve prescription medication adherence for patients with chronic health problems. Patient Education and Counseling Volume 83, Issue 3, June 2011, p. 375–381. doi:10.1016/j.pec.2011.04.029

Lachaine J., Petrella RJ., Merikle E., Ali F. [2008]: Choices, persistence and adherence to antihypertensive agents. Evidence from RAMQ data. Canadian Journal of Cardiology, April 2008 Volume 24, Issue 4, p. 269–27. [http://dx.doi.org/10.1016/S0828-282X\(08\)70175-2](http://dx.doi.org/10.1016/S0828-282X(08)70175-2)

Lerman I. [2005]: Adherence to treatment: the key for avoiding long-term complications of diabetes. Arch Med Res. 36(3), p. 300-306.

Márk L., Reiber I., Paragh Gy., Karádi I., Pados Gy., Kiss Z. [2013]: Lipid lowering treatment – multi gap 2012 [Lipidcsökkentő kezelés – multi gap 2012]. Patient adherence, statin persistence [A betegek terápiás együttműködése, statin-perzisztencia]. Metabolism [Metabolizmus] 2013. July XI. 3. p. 168-173.

- Marmot MG, Poulter NR. (2002): Primary prevention of stroke. *Lancet* (339) p. 344-347.
- Marrs JC. [2010]: Pharmacy Perspectives in Dyslipidemia Management. Strategies for Improving Patient Outcomes. U.S. Pharmacist December 2010, Jobson Medical Information LLC. p. 1-20.
- McDonnell et al [2003]: The Long-Term Effect of Doxazosin, Finasteride, and Combination Therapy on the Clinical Progression of Benign Prostatic Hyperplasia. *N Engl J Med* 2003; 349:2387-98.
- McMullena CK., Saffordb MM., Bosworthc HB., Phansalkard S., Leongf A., Fagang MB., Trontellh A., Rumptza M., Vandermeera ML., The Centers for Education and Research on Therapeutics (CERTs) Patient-Centered Medication Management (PCMM) Workshop Working Group, Brinkmani WB., Burkholderj R., Frankk L., Hommeli K., Mathewsr R., Hornbrookp MC., Seidi M., Fordisl M., Lambertm B., McElween N., Singhq JA. [2015]: Patient-centered priorities for improving medication management and adherence. *Patient Education and Counseling* Volume 98, Issue 1, January 2015, p. 102–110. doi:10.1016/j.pec.2014.09.015
- Molnár MP. – Dankó D. (2009): The importance and challenges of competition between off patented drugs [A lejárt szabadalmú gyógyszerek közötti verseny jelentősége és kihívásai]. *Pharmacology [Gyógyszerészet]*, 2009. November, p. 652-660.
- Molnár MP. [2010]: Adherence Cyclopaedia [Adherencia Tudástár] 2. How can we measure patient adherence? [Hogyan mérhetjük a beteg-együttműködést?] *Medical tribune*. 8/21. p. 7.
- Molnár MP. [2011]: Adherence Cyclopaedia [Adherencia Tudástár] 6. How can we improve patient adherence? [Hogyan javítható a beteg-együttműködés?] *Medical tribune*. 9/4. p. 5.
- Molnár MP., Dankó D. [2010]: Patient adherence: The key to therapeutic success [A beteg-együttműködés a terápiás siker záloga]. *Orvostovábbképző Szemle* XVII/4, 2010. April p. 13-19.
- Molnár MP., Dankó D. [2011]: Adherence (persistence) in fosinopril therapy [Terápiahűség (perzisztencia) fosinopril-terápiában]. Research report [Kutatási jelentés]. Budapesti Corvinus Egyetem. 2nd April 2011
- Nayeri ND., Mohammadi S., Razi SP., Kazemnejad A. [2014]: Investigating the effects of a family-centered care program on stroke patients' adherence to their therapeutic regimens. *Contemp Nurse*. 2014;47(1-2) p. 88-96. doi: 10.5172/conu.2014.47.1-2.88.
- Nichola MB., Knighta TK., Wua J., Barronc R., Penson DF. [2009]: Evaluating Use Patterns of and Adherence to Medications for Benign Prostatic Hyperplasia. *The Journal of Urology* Volume 181, Issue 5, May 2009, p. 2214–2222. doi:10.1016/j.juro.2009.01.033
- Patel AA., Reardon G., Nelson WW., Philpot T., Neidecker MV. [2013]: Persistence of Warfarin Therapy for Residents in Long-term Care Who Have Atrial Fibrillation.

Clinical Therapeutics Volume 35, Issue 11, November 2013, p. 1794–1804.
doi:10.1016/j.clinthera.2013.09.010

Pharmaceutical Group of the European Union (PGEU) [2008]: Policy statement. Targeting Adherence. Improving patient outcomes in Europe through Community Pharmacists' Intervention. Brussels May 2008. p. 1-36.

Pladevall M., Brotons C., Gabriel R., Arnau A., Suarez C., de la Figuera M., Marquez E., Coca A., Sobrino J., Divine G., Heisler M., Williams LK. [2010]: Multicenter cluster-randomized trial of a multifactorial intervention to improve antihypertensive medication adherence and blood pressure control among patients at high cardiovascular risk (the COM99 study) *Circulation*, 122 (2010), p. 1183–1191.

Medical College of Rheumatologists and Physiotherapists and Hungarian Association on Osteoporosis and Osteoarthritis [Reumatológiai és Fizioterápiás Szakmai Kollégium és Magyar Osteoporosis és Osteoarthritis Társaság] [2005]: Medical guideline of Ministry of Health on osteoporosis and other metabolic bone diseases [Az Egészségügyi Minisztérium szakmai irányelve az osteoporosis és más metabolikus csontbetegségek diagnosztikájára]. 2005. EÜK 12.

Simonyi G. [2013a]: Importance of patient adherence in antihypertensive therapy [A beteg-adherencia jelentősége az antihipertenzív terápiában]. *Háziorvos Továbbképző Szemle*. - ISSN 1219-8641. - 2013. 18/5. p. 283-287.

Simonyi G. [2013b]: Importance of patient adherence in lipid lowering therapy – advantages of fix combinations [A beteg-együttműködés jelentősége a lipidcsökkentő terápiában – A fix kombináció előnyei]. *Metabolism [Metabolizmus]*. - ISSN 1589-7311. – Vol. 11. Supplementum G, p. 6-10.

Simonyi G. [2012]: Patient adherence in anticoagulant therapy [Betegadherencia az antikoaguláns terápiában]. *Cardiologia Hungarica*. - ISSN 0133-5595. - 2012. Vol. 42. Issue 4. p. 199-201.

Simonyi G., Kollár R. [2013]: Importance of patient adherence in cardiovascular therapy [A beteg-együttműködés jelentősége a cardiovascularis terápiában]. *Orvosi Hetilap*. - ISSN 0030-6002. - 2013. Vol. 154. Issue 23. p. 883-888. doi: 10.1556/OH.2013.29624

Simonyi G., Molnar MP. [2014]: Persistence of vitamin K antagonist therapy in the real world. ESC CONGRESS 2014, Abstract 81747

Simonyi G., Molnár MP., Pálosi M. [2014]: Persistence in fibrate therapy in Hungary [A fibrát terápia perzisztenciája Magyarországon]. *Metabolism [Metabolizmus]*. - ISSN 1589-7311. - 2014. Vol. 12. Issue 2. p. 93-96.

Stock S., Drabik A., Büscher G., Graf C., Ullrich W., Gerber A., Lauterbach KW., Lungen M. [2010]: German Diabetes Management Programs Improve Quality Of Care And Curb Costs. *Health Affairs*, 29, no.12 (2010):2197-2205 doi: 10.1377/hlthaff.2009.0799

Stuurman-Bieze AG., Hiddink EG., van Boven JF., Vegter S. [2013]: Proactive pharmaceutical care interventions improve patients' adherence to lipid-

- lowering medication. *Ann Pharmacother.* 2013 Nov;47(11) p. 1448-1456. doi: 10.1177/1060028013501146
- Stuurman-Bieze AG., Hiddink EG., van Boven JF., Vegter S. [2014]: Proactive pharmaceutical care interventions decrease patients' nonadherence to osteoporosis medication. *Osteoporos Int.* 2014 Jun;25(6) p. 1807-1812. doi: 10.1007/s00198-014-2659-8.
- Taitel M., Jiang J., Rudkin K., Ewing S., Duncan I. [2012]: The impact of pharmacist face-to-face counseling to improve medication adherence among patients initiating statin therapy. *Patient Prefer Adherence*, 6 (2012), p. 323–329. <http://dx.doi.org/10.2147/PPA.S29353>
- Medical College of Urologists [Urológiai Szakmai Kollégium] [2010]: Medical guideline of Ministry of National Resources on benign prostate hyperplasia (BPH) 1. modified version based on EAU Guideline 2009 [Az Egészségügyi Minisztérium szakmai irányelve a Benignus prostata hyperplasiáról (BPH). 1. módosított változat. Készült az „EAU Guideline 2009” alapján]. 2010. EÜK 11.
- Yeung M., O'Connor S.A., Parry D. T., Cochrane G. M. [1994]: Compliance with prescribed drug therapy in asthma. *Respiratory Medicine*, 1994, 88:31–35. DOI: [http://dx.doi.org/10.1016/0954-6111\(94\)90171-6](http://dx.doi.org/10.1016/0954-6111(94)90171-6)
- Vegter S., Oosterhof P., van Boven JF., Stuurman-Bieze AG., Hiddink EG., Postma MJ. [2014]: Improving adherence to lipid-lowering therapy in a community pharmacy intervention program: a cost-effectiveness analysis. *J Manag Care Pharm.* 2014 Jul;20(7) p. 722-732.
- Verhammea KMC., Dielemana JP., Bleuminkb GS., Boschc JLHR., Strickerb BHCh., Sturkenboomc MCJM. [2003]: Treatment Strategies, Patterns of Drug Use and Treatment Discontinuation in Men with LUTS Suggestive of Benign Prostatic Hyperplasia: The Triumph Project. *European Urology* 44 (2003) p. 539–545. doi:10.1016/S0302-2838(03)00376-2
- Vermeire E., Hearnshaw H., Van Royen P., Denekens J. [2001]: Patient adherence to treatment: three decades of research. A comprehensive review. *Journal of Clinical Pharmacy and Therapeutics* *Journal of Clinical Pharmacy and Therapeutics* October 2001, Volume 26, Issue 5, p. 331–342. DOI: 10.1046/j.1365-2710.2001.00363.x
- Waeber B., Burnier M., Brunner H.R. [2000] How to improve adherence with prescribed treatment in hypertensive patients? *Journal of Cardiovascular Pharmacology* 35(Suppl 3) p. 23-26.
- Wilson-Pessano SR., Scamagas P., Arsham GM., Chardon L., Coss S., German DF., Hughes GW. [1987]: An evaluation of approaches to asthma self-management education for adults: the AIR/Kaiser-Permanente Study. *Health Educ Q.* 1987 Fall;14(3):333-43.
- Wogen J, Kreilick CA, Livornese RC, Yokoyama K, Frech F. [2003]: Patient adherence with amlodipine, lisinopril or valsartan therapy in a usual-care setting. *J Manag Care Pharm* 2003;9(5): p. 424–429

World Health Organization [2003]: Adherence to Long-Term Therapies: Evidence for Action. WHO, Genf, 2003.