Charles University in Prague

Faculty of Social Sciences

Institute of Economic Studies

MASTER THESIS

Behavioral Economics and Motivating Patients to Take Care About Their Health

The Case of Hemodialysis Patients

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Declaration of Authorship

The author hereby declares that she compiled this thesis independently, using only the listed resources and literature, and the thesis has not been used to obtain a different or the same degree.

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Prague, July 31, 2014

Signature

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Abstract

Imperfect patient adherence to treatment leads to adverse individual and social outcomes: it has negative effect on patient health and, consequently, it increases health care costs. The adherence is low particularly in chronically ill patients with complex regimen, such as hemodialysis. This thesis provides an in-depth study of the phenomenon and presents a survey targeted at hemodialysis patients in the Czech Republic. The survey assesses prevalence of nonadherence, identifies predictors of nonadherence, and analyzes patients' attitude to a hypothetical incentive program to promote adherence. Then, an optimal design of an intervention to promote adherence is discussed.

Results show that 72% of patients do not adhere to one or more areas of hemodialysis treatment. Prevalence of nonadherence is highest for following fluid restrictions (62.8%) and diet guidelines (55.7%). On the contrary, medication and appointment nonadherence is not frequent. Strongest predictors for nonadherence are: young age, male sex, treatment for depression, number of prescribed pills, and length of dialysis treatment.

Most of patients (83%) indicated that they would change their behavior when involved in an incentive program to promote adherence. With regard to broad prevalence of nonadherence, an intervention targeted at fluid and diet nonadherence is recommended for its potential to improve patients' health and reduce health care costs.

JEL Classification	I10, I18, D01, D81
Keywords	behavioral economics, patient adherence, predictors, hemodialysis, intervention

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Abstrakt

Nesprávná adherence k léčbě ze strany pacientů má negativní vliv jak na zdravotní stav jednotlivců, tak na celkové náklady na léčbu. Adherence je nízká zejména u chronicky nemocných pacientů se složitým léčebným režimem, jako je např. hemodialýza. Tato práce detailně analyzuje tento fenomén a představuje výzkum zaměřený na hemodialyzované pacienty v České republice. Dotazníkové šetření mapuje rozšíření nonadherence, identifikuje prediktory vedoucí k nonadherenci a zkoumá postoje pacientů k hypotetickému programu na podporu adherence. Následně je diskutován optimální návrh takového programu.

Výsledky výzkumu ukazují, že 72 % pacientů nedodržuje jednu nebo více oblastí léčby. Pacienti nejčastěji nedodržují omezení příjmu tekutin (62,8 %) a doporučená dietní opatření (55,7 %). Správné braní léků a docházení na dialýzu naopak nepředstavuje značný problém. Nejvýznamnějšími prediktory nonadherence jsou: mladý věk, mužské pohlaví, léčba deprese, počet předepsaných pilulek a celkové délka léčby.

Výzkum dále ukazuje, že 83 % pacientů by změnilo své chování, pokud by byli za zlepšenou adherenci odměňováni. Zahraniční studie programů na zlepšení adherence prokazují jejich pozitivní vliv jak na zdravotní stav pacientů, tak na snižování léčebných nákladů. S ohledem na vysokou nákladnost samotné hemodialyzační léčby doporučujeme zavést opatření na podporu adherence, a to zejména v oblasti dodržování omezení příjmu tekutin a doporučených dietních opatření.

Klasifikace	I10, I18, D01, D81
Klíčová slova	behaviorální ekonomie, adherence pacientů, prediktory, hemodialýza, intervence

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Abbreviations

CKD	Chronic Kidney Disease
DDFQ	Dialysis Diet and Fluid nonadherence Questionnaire
e-GFR	estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
ERA-EDTA	European Renal Association-European Dialysis and Transplant Association
ERSD-AQ	End-Stage Renal Disease Adherence Questionnaire
IWG	Interdialytic Weight Gain
OR	Odds Ratio
QALY	Quality-Adjusted Year of Life
RRT	Renal Replacement Therapy
WHO	World Health Organization
WTP	Willingness To Pay

Master Thesis Proposal

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Defense Planned: Summer 2014

Proposed Topic:
Behavioral Economics and Motivating Insurees to Take Care About Their Health

Topic Characteristics:
Health economics as well as behavioral economics are rapidly developing fields of economics in past decades. Most of the research of health economists concerns on analyzing specifics of the market, assessing costs of different treatments or finding an optimal design of insurance. Little attendance is given to behavioral aspects of agents, especially of patients or even insurees with no (visible) health problems. However, lifestyle and environment are main determinants of health status and therefore the issue of influencing people's behavior in order to make them act healthfully is worth studying; not only in the view of one's health status but also in the view of reducing overall health costs and stabilizing health finances. By designing optimal framework to motivate insurees to take care about their lifestyle and therefore improve their health (or minimize the risk of sickness), an insurance company (or any other payer) can save costs of potential later treatment which is usually much more expensive than preventive measures or lifestyle adjustments. Therefore it could be beneficial for the insurance company to engage in such program.
In my thesis, I will analyze what are main determinants of people's behavior in context of preventive care and healthy lifestyle and what is the optimal form of incentive in relation to costs for the provider and health outcome for the insuree. According to these results, I will propose a design of a motivating program that should be beneficial for all agents: the insurance company, an insuree and the company that will provide the program.
I will use data collected in an own survey during Autumn 2013.

Hypotheses:
1. A program that motivates insuree to take care about their health is cost-effective.
2. Different forms of incentives have different effect on insurees behavior.
3. Education is the main determinant of high motivation to take care of own health.

4. Cash incentive is the main driver of motivating to act healthfully.

Methodology:

I will analyze insurees behavior based on my own stated preferences survey. The main question of the survey will be how respondents react to different forms of incentives that should motivate them to act healthfully and how these incentives affect their health status and therefore demand for health care. The survey will also focus on socio-economic determinants of healthy lifestyle. I will use the contingent valuation method (ladder approach) to determine the lower bound of the willingness to accept for a behavioral change (making more exercise, undergo preventive checkups; keep a medical treatment for the case of ill people).

Furthermore, I will analyze the possibility of an insurance company to provide a motivational program in the context of Czech health care system.

According to all found results, I will provide a design of effective motivational program.

Outline:

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1 Introduction

Patient adherence, that is the level to which a patient adhere to the recommended treatment, attract enhanced attention recently. The reason is obvious: in health care systems, funds are always scarce due to rapid medical and technical development requiring substantial investments, population aging leading to increased demand, and limited contribution from public insurance or government. Therefore, any possibility to reduce health care costs is welcomed.

It has been proven that inadequate patient adherence have negative impact on clinical outcomes, risk of hospitalization, survival, and, consequently, on health care costs (Hughes, Bagust, Haycox, & Walley, 2001; Osterberg & Blaschke, 2005). It is believed that nonadherence to treatment occurs in about half of patients (McDonald, Garg, & Haynes, 2002); reported nonadherence rates vary widely with respect to methodology (in particular, definition of nonadherence and method of measurement) and disease. Patients with long-lasting, asymptomatic disease are more vulnerable to deviate from recommended treatment than those with acute condition. Moreover, high complexity of treatment regimen further hinders adherence (Loghman-Adham, 2003).

In this context, patients with end-stage renal disease (ESRD) treated by hemodialysis call for special attention. They hold all predispositions for being nonadherent: the treatment regimen include not only numerous medication, but patients also have to strictly limit their fluid intake, follow plenty of diet recommendations, and, finally yet importantly, they must attend the dialysis facility three times a week. Nonadherence in any of abovementioned areas may have severe or even fatal consequences. Despite this threat, foreign studies report rates of nonadherence in hemodialysis patients approaching 80% (Denhaerynck et al., 2007; Loghman-Adham, 2003; Schmid, Hartmann, & Schiffl, 2009).

Patient adherence in the Czech Republic is not well examined. Current research targets mainly medication adherence and cover limited number of diseases, such as osteoporosis (Vytrisalova et al., 2008), Crohn’s disease (Červený, Lukáš, Bortlík, Kuběna, & Vlček, 2006), or diabetes mellitus (Hendrychova, Vytrisalova,

Smahelova, Vlcek, & Kubena, 2013). To our knowledge, there is no study that analyzes health behavior of hemodialysis patients in the Czech Republic.

With respect to high financial costs of hemodialysis treatment (approximately 1 million CZK per patient every year, Kříž, 2011) and high nonadherence rates reported abroad, there is a need for comprehensive assessment of patient adherence in the Czech Republic. Results can serve as groundwork for an intervention to promote adherence. Behavioral economics proposes several techniques to influence individuals' behavior and motivate them to preserve the change. Incentive programs proved well for preventive screening, smoking cessation, or weight loss (Giles, Robalino, McColl, Sniehotta, & Adams, 2014; Giuffrida & Torgerson, 1997; Kessler & Zhang, 2014). Similar intervention may be implemented for hemodialysis patients to promote their adherence to treatment regimen. However, optimal design of the intervention is unknown: the research in the area is fragmented and gives no clear conclusion.

This study serves several purposes. First, it provides an in-depth study of patient adherence from its forms of measurement to interventions that aim to increase adherence. It presents several theoretical concepts that explain patients' motivation and ways to improve their health behavior. Second, it assesses adherence in hemodialysis patients in the Czech Republic and identifies areas of concern. Third, it determines demographic and treatment characteristics of nonadherent patients. Finally, it synthetizes all available information and proposes an interventional program to promote adherence in hemodialysis patients.

The thesis is organized as follows: Chapter 2 analyzes the phenomenon of patient adherence, methods of its measurement, and strategies to improve nonadherence. Chapter End-Stage Renal Disease in the Context of Patient Adherence3 describes adherence in the context of end-stage renal disease. In briefly introduces the disease and its treatment and discusses specific areas of nonadherence and their clinical consequences. Further, it summarizes current research of characteristics of nonadherent patients and interventions to promote adherence. Next chapter provides description of survey among hemodialysis patients in the Czech Republic. Then, results are presented in Chapter 5. Nonadherence rates, predictors of nonadherence and patients' attitudes to an incentive program are discussed. Finally, Chapter 6 proposes design of an intervention targeted at hemodialysis patients and discusses its implementation. Last chapter concludes.

2 Patient Adherence

Growing research in health economics has indicated proper adherence to treatment as one of potential sources of financial savings for health care funds (Berg, Dischler, Wagner, Raia, & Palmer-Shelvin, 1993; Hughes et al., 2001). Even though roots of the research in this field originated in 1970s (Haynes & Sackett, 1979), the research is highly disorganized and there are no uniform standards for terminology or methodology (Cramer et al., 2008). No general model for adherence or incentive mechanisms has been developed so far and patient behavior has not been fully understood.

Patient adherence refers to the amount to which patients adhere to prescribed treatment. They may have incentives not to adhere to the treatment perfectly, or they may fail to adhere unintentionally. Consequently, their behavior may lead to suboptimal effect of the treatment, and, at the worst, it may have negative effect on mortality.

This chapter summarizes current research concerning patient adherence. Firstly, theoretical background is briefly discussed. Then, several different aspects of adherence are studied, including types of adherence, methods of its measurement, barriers to adherence and consequences of poor adherence. Finally, interventions that promote adherence are presented as well their theoretical foundations.

2.1 Moral Hazard

Supply and demand for health care creates unique market that suffers from many market imperfections. Since every human body is unique and reacts to the treatment differently, the product is far from being homogeneous. There are significant externalities from a treatment of infectious diseases; information is not perfect – both on the side of provider and purchaser. Entry to the market is restricted by licensing, and the demand itself is very specific: since agents seek for health care when they are ill, the demand for acute diseases is unpredictable. Moreover, the demand for health care is derived from demand for health; however, the outcome of a treatment on one’s health is uncertain.

Many of above-mentioned imperfections arise from uncertainty. Uncertainty about the incidence of a disease, the outcome of a medical treatment and its costs leads agents – potential patients – to insure themselves against potential harm in the future. Once they are insured, they feel secure, and they adapt their behavior to it. This problem is called moral hazard. The ultimate consequence of this behavior is that an agent does not care about her health in the extent as if she will not be insured, and she tends not to avoid risky behavior or not to undertake preventive measures in the extent she would take if not insured. Therefore, there are potential costs for health care provider that can be eliminated.

Moral hazard can be distinguished regarding the event of its occurrence to two types (Zweifel & Manning, 2000):

- *ex ante moral hazard*, which describes the situation prior to illness, for example when the agent, due to insurance, does not undertake preventive measures,
- *ex post moral hazard*, which, on the other hand, refers to change in behavior while being sick; due to insurance, the net money price of health care is lower and agent may consume more health care than reasonable.

Ex ante moral hazard depends, as Zweifel & Manning (2000) show in their model, on two factors: opportunity costs of the effort to undertake preventive care, which is usually proportional to wage, and risk aversion. On the other hand, utilization of health care while being sick (and potential ex post moral hazard) is affected by the size of out-of-pocket costs as well as coinsurance rate.

Zweifel & Manning (2000) further conclude that the size and composition of health care expenses is significantly affected by health, sick leave and disability insurance. As many other studies, including clinical trials testing the effect of new drugs, they assume ideal patient adherence to the treatment. Nevertheless, patients are not perfect rational agents as economic theory usually assumes, and their behavior is driven by many subjective factors and different personal characteristics. Consequently, they may have incentives not to take the treatment as recommended or fail to adhere to treatment regimen unintentionally.

2.2 Terminology: Adherence vs. Compliance

Research of adherence and interventions to improve it lack of standards and proper terminology (Cramer et al., 2008). Vague definitions, misuse of terms and different methodological approaches hinder the assessment of results of different studies. Substantial effort has been made to review all the studies concerning adherence to treatment and summarize their outcome; however, due to above mentioned deficiencies, broad meta-analysis cannot be done. Even in a review, all the studies need detailed analysis and only a few are found comparable: for instance, (Haynes et al., 2008) reviewed studies concerning adherence to treatment and interventions to promote it. They found 1020 full articles concerning patient adherence, but only 82 of them fulfil their criteria of unconfounded randomized control trial with full description of design of the research. Similar situation was found in others reviews (see e.g. Desroches et al., 2013, or Hughes et al., 2001).

World Health Organization (WHO) defines adherence to long-term therapy as "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" (Sabaté, 2003, p. 3). Disease duration or length of treatment are not the essential parts of the definition; the emphasis is given on the agreement between the physician and the patient over the treatment.

Nonadherence, on the other hand, refers to the extent to which patient do not adhere to the treatment.

Nature of physician-patient relationship distinguishes adherence from compliance: the latter term assumes paternalistic role of physicians, as it was usual some decades ago. The word compliance implies patient's passive acceptance of physician's recommendations with no consultation with her (Osterberg & Blaschke, 2005). Modern health care systems in developed world, on the contrary, underline equal position of both agents and treats patient as active partner to the physician. Therefore, the term compliance is being abandoned throughout the literature recently.

Some authors confuse concordance with adherence (McDonald et al., 2002); however, this term relates to the nature of physician-patient relationship and proposes equal responsibility of both sides (Bell, Airaksinen, Lyles, & Chen, 2007). Concordance does not refer to patient treatment-related behavior and should not be used as a synonym for adherence (Horne, Weinman, Barber, & Elliott, 2005).

Another term, which is sometimes mistaken for adherence, is persistence. Persistence should be used for measuring length of therapy, as the time of continuous therapy: from its initiation to its discontinuation (Cramer et al., 2008). Together with adherence, it affects the outcome of the treatment; however, persistence does not refer to patient behavior as such and should not be confused with adherence.

2.3 Types and Forms of Adherence

Although adherence is generally defined as the extent to which patient fulfil physician's recommendations, studies measuring adherence often deal with narrow sense of the term: they measure medication adherence, i.e. the extent to which patient adhere to prescribed medication. Other physician's recommendations, such as a diet, more exercise or adjustment of life-style, are not covered. Therefore, terms medication adherence and treatment adherence should be distinguished.

Adherence, or better nonadherence to treatment can be intentional or unintentional. Some patients disagree with their diagnosis and refuse to undertake the treatment, or discontinue the treatment once their symptoms have vanished. Others simply forget to take their medication or do not remember physician's instructions correctly.

Medication adherence can be further distinguished regarding the concrete event which patient fails to adhere (Berg et al., 1993):

- prescription not filled or refilled (sometimes called as primary and secondary nonadherence, respectively, Hughes et al., 2001),
- taking an incorrect dose,
- taking the medication at wrong time,
- omitting one or more doses,
- discontinuing the treatment too soon.

Vermeire et al. (2001) add other, mostly treatment-related problems:

- delay in seeking health care,
- non-participation in health care programs, such as screening or preventive check-up,
- missing doctor's appointment for follow-up care.

All of the above-mentioned forms of nonadherence may have significant consequences for the outcome of the treatment. For antibiotic therapy, it is important to take the medication within certain period and finish the dosing even after symptoms have ceased. Premature discontinuation with the treatment is also significant problem for chronic and asymptomatic diseases, such as hypertension. Omitting one dose in long-term treatment might not be fatal, however, so called drug holidays, that is omitting doses for 3 or more days, can be dangerous and can bias the effect of the treatment significantly (Hughes et al., 2001). Missing doctor's appointment might be an indicator for low medication adherence and can result in giving up the treatment (Haynes et al., 2002).

2.4 Measuring Adherence

As there is no uniform terminology for patient adherence, there is no gold standard for measurement of adherence or any uniform definition of adherence rate. Moreover, methodology for measuring adherence is often poorly documented (Haynes et al., 2002). Typically, medication adherence rate is measured as proportion of doses taken and prescribed. Therefore, it can range from 0% to more than 100% (the case when patient takes more pill than she should). Adherence rate varies according to disease: Berg et al. (1993) report nonadherence rate between 8 and 71%, Hughes et al. (2001) found compliance rate between 45 and 95 per cent. Due to variable methodology among studies, it is not possible to make an estimate for overall adherence rate. Nevertheless, typical adherence rate is believed to be around 50% (McDonald et al., 2002).

There are two ways how to measure adherence: direct and indirect (Osterberg & Blaschke, 2005). None of them is perfect and without drawbacks. The most accurate method is direct observation of the patient taking her medication or meeting her treatment recommendations; however, this method is applicable only for hospitalized patients and even in this case, there is risk that they hide the pill in their mouth and discard it later. Analysis of body fluids (blood, urine) is also fairly accurate method to assess adherence. Nevertheless, biochemical markers are not available for all medications and treatments, and it can be invasive. It also carries significant financial burden, and some medication levels may vary in time. "White-coat adherence", i.e. the case when patient adheres to the treatment only shortly before doctor's appointment, can occur and provide misleading results.

Indirect methods cover questioning the patient, use patient self-reports and diaries, pill count, rates of refilled prescriptions and electronic medication monitors. Interviews or structured questionnaires are prone to overestimate the adherence rate as patients are willing to please the physician, do not want to reveal that they have failed or simply do not remember details about taken medication. The language and form of posing the questions is essential and may improve the outcome. Pill count is fairly precise method of measuring dosing behavior; however, it does not include information about the time of taking the medicine, which might be essential for some treatments. It is also susceptible to patient distortion: they may throw some pills out.

Rate of refilled prescription is other indirect method for measuring adherence. It is a fairly accurate method for small closed pharmacy system with appropriate informational system. However, refilling prescription itself does not guarantee that the medication is used and there is no information about dosing behavior of the patient. Moreover, pharmacy data are not always available. On the other hand, electronic monitors provide precise information about the time of using medication. However, they record only the time of opening bottles, therefore they do not document the exact dose and whether the medication was taken or not. Moreover, patient can improve adherence when she knows that she her medication taking is controlled. Despite of these drawbacks, it is one of the most accurate methods of analyzing patient behavior. The main barrier of common use of electronic devices is their high cost.

Sabaté (2003) suggests biochemical measurement as a third approach for assessing patient behavior. It is based on supplementing biological markers to medications; their levels in body fluids then provide information about medication taken. However, there are doubts about ethics of this method as it is invasive, and quantitative assay, that is required to obtain the information about patient behavior, is fairly expensive.

Even though research on adherence has received more attention recently, as Kadambi, Leipold, Kansal, Sorensen, & Getsios (2012) document in their analysis of articles published in 2005-2012, there is no precise measure of patient adherence and all above mentioned methods has to be taken as mere estimate of patient behavior.

2.4.1 Optimal Level of Adherence Rate

As the definition of adherence as such varies, level of good adherence is also questionable. It is usually set arbitrary with no link to evidence of substantial change

in treatment outcome. As Steiner & Earnest (2000) point out, treatment recommendations develop over time with increasing evidence about optimal dosing and duration of particular treatment. Even though this problem has been diminished owing to improved validity of advanced randomized controlled trials used for testing new medication and setting the optimal dosing, one concern still remains: adherence rate in RCTs is usually higher than it is in practice since patients in the trial are selected artificially and the nature of the trail itself motivates patients to behave properly. Moreover, many clinical trials do not control for adherence rate and do not consider it at all.

There is little research about the outcome of a partial therapy or minimum participation rate to reach the desired outcome. Nevertheless, some studies indicate that taking 80% of prescribed medication is acceptable, for example for antihypertensive drugs. Therefore, threshold of 20% of missed doses is commonly used to indicate poor medication adherence (Curtin, Svarstad, & Keller, 1999; Tomasello, Dhupar, & Sherman, 2004; Wetzels, Nelemans, Schouten, & Prins, 2004).

2.5 Indicators of Poor Adherence

Adherence to medication or treatment regimen is complex problem that can root in many different factors. There is no socio-economic profile of fully adherent patient, or nonadherent one. Furthermore, socio-economic status, sex or race did not prove to have any significant effect on the level of adherence (Osterberg & Blaschke, 2005). Nevertheless, there are some predictors that can indicate patients with higher probability of nonadherent behavior. Psychological problems or cognitive impairment of the patient indicate potential presence of reduced adherence. Character of the disease and its treatment is significant determinant of poor adherence as well: lower levels of adherence are evidenced for long-term, chronic asymptomatic disease with complex treatment regimen. Potential side effects of a treatment and increased physical disability caused by the disease may also predict poor adherence (Osterberg & Blaschke, 2005). Attention should be given to patients who missed their appointment with physician; it can be first signal of refusing the treatment (Haynes et al., 2002).

Based on studies analyzing patient adherence by electronic monitor devices, six different patterns of patient behavior have been recognized among chronically ill patients:

- fully compliant patients,
- patients who have some timing irregularity, but miss very few doses,
- patient who miss some doses, but rarely more than one at a time,
- patients who take occasional drug holidays (3 – 5 per year),
- patient who take monthly holidays,
- patient who take few or no doses (Hughes et al., 2001).

Those patterns proved to be evenly distributed. While missing few doses occasionally may have no effect on the treatment outcome, higher attention should be given to patients who take monthly holidays or refuse treatment regimen.

2.6 Barriers to Adherence

Imperfect adherence can have several different sources and barriers which identification is essential for design of optimal intervention. Barriers on the side of patient relate to her capacity limitations – forgetting to take medication at prescribed time or failing to remember treatment instructions correctly. Resource limitations of the patient occurs there is high copayment for the treatment (Horne et al., 2005). Some patients have other priorities and decide to omit doses, usually because they have doubts about obtained treatment or have incomplete information about the disease. They may underestimate the importance of treatment once symptoms of the disease vanish or they fear of adverse effects. Higher levels of adherence are evidenced for medication with immediate effect; on the other side, inconvenience from taking medication for long-term treatment of asymptomatic disease such as hypertension may outweigh delayed benefits of the treatment and patient may discontinue the treatment prematurely when a minor adverse effect occur (Berg et al., 1993).

Other barriers come from the side of physicians: their poor communication with the patient may lead to misunderstanding their instructions and consequent misuse of the drug by the patient. Moreover, if they prescribed too complex regimen, it is more difficult for the patient to follow their recommendations. Some medication proved to have the same effect with two doses per day and once-a-day dosing.

Physicians should take into account other medication and regimen restrictions which the patient is already taking (Berg et al., 1993).

2.7 Consequences of Poor Adherence

There is no doubt that poor adherence leads to suboptimal outcome of the treatment. However, the extent to which level of adherence affects health is usually unknown: clinical trials that analyze the effect of medication assumes perfect adherence, the effect of medication taken incorrectly is rarely studied. Poor adherence may lead to lower efficiency of the treatment or may cause adverse effects. Consequently, health benefits are lower and the treatment may be evaluated incorrectly as inefficient. There are also considerable costs related to poor adherence: worsening of the disease or adverse drug reaction leads to higher utilization of health care, and therefore higher costs (Hughes et al., 2001; Osterberg & Blaschke, 2005).

2.8 Interventions to Promote Adherence

Interventions to promote adherence are primarily distinguished based on their target: acute care models focus on symptoms and intend to cure the patient, while chronic care models target long-term conditions and aim to control the progression of the disease, enhance quality of life of the patient, and, consequently, increase survival (Sabaté, 2003). Design an intervention that would effectively increase patient adherence with treatment of long-term, asymptomatic condition is clearly more complicated than improve adherence in patients with acute, symptomatic short-term conditions. The very nature of chronic disease exposes another issue in promoting adherence: maintenance of improved outcome. While it is rather easy to motivate patient to adhere to the therapy in the short term, long-term sustained adherence is a challenge.

Despite growing research in the area, there is no single design of an effective intervention. Naturally, interventions vary with respect to the disease of interest; similarly, diverse interventions are proposed for different groups of patients (children, elderly, patient with cognitive impairment, etc.). Numerous theories have arisen in the field; several of them, with emphasis on chronic conditions, are introduces in this chapter. Types of interventions are also presented.

2.8.1 Theoretical Concepts

In standard economic theory, individual's behavior is driven by monetary value of an action: for instance, people go to work to earn money, and it is assumed that they work harder when there is more money at stake. Therefore, it is expected that incentives in a form of reward (in particular, monetary rewards) motivate people to engage in behaviors they would otherwise avoid. Incentive in the form of financial and non-financial rewards proved to be effective in health-related behaviors such as smoking cessation, weight loss, medical donation, or screening programs (Giles et al., 2014; Kessler & Zhang, 2014).

Behavioral theory explains people's motivation for their actions with more profundity. It proposes several interesting principles. First, it suggests that individuals are averse to losses: they value positive rewards more than equal losses (Kahneman & Tversky, 1979). Second, people often overweight gains with small probability; therefore, lottery game with substantial winning prize is more effective than allocating the same amount of money among the group. In addition, people do not like to regret their actions; consequently, regret lotteries, in which people are eligible for the prize only upon completing specific action, proved to be effective in weight loss or medication taking (study among users of warfarin) (Volpp, John, et al., 2008; Volpp, Loewenstein, et al., 2008). Finally, commitment contracts proved to be effective in promoting healthy behaviors. In this strategy, participants put their own money in a contract; if they fail to achieve the established goal (e.g. weight loss), they lose the money. This method combines self-promoted incentives with loss aversion (Kessler & Zhang, 2014).

Abovementioned theories and strategies were primarily created to explain and improve health-related behaviors such as smoking cessation or weight loss. In the field of patient adherence, several specific theoretical concepts have arisen. All of them aim to change patient behavior; however, the process of change and the motivation varies among different frameworks.

Health Belief Model (Rosenstock, 1974) is probably the most well-known concept in health behavioral theory. It was originally formulated in 1950s to explain patient preventive behavior, in particular, screening for asymptomatic diseases. Afterwards, the framework was extended and applied to acute and chronic diseases, adherence to medical treatment, and life-style behaviors (Janz & Becker, 1984).

The model is rooted in established psychological and behavioral theories that state that individuals make their decisions based in the value they place to an action and its perceived effectiveness. Translated to health-related behavior, it is the desire to avoid an illness and a belief about the effectiveness of a preventive behavior that influence people's decisions. According to the model, five dimensions affect the decision-making process:

- perceived severity of the illness and its potential clinical, medical, and social consequences,
- perceived susceptibility, which include individual vulnerability to a condition and the likelihood of occurrence of a condition,
- perceived benefits of an action,
- perceived barriers such as expensiveness, riskiness, inconvenience, or time-demand of an action, and
- self-efficacy.

The very last component was added to the model later, in an attempt to better explain individual differences in health behaviors. Self-efficacy refers to a person's confidence in being able to successfully perform a behavior to achieve the desired outcome. Self-efficacy is particularly important in explaining long-term behavior such as diet modification or smoking cessation.

According to health belief model, individual's perceptions are influenced by variety of demographic, psychosocial, and structural characteristics. Furthermore, health-related behavior needs a stimulus to trigger the decision-making process: cues to an action are essential part of promoting a behavioral change. They can be either internal, such as pain or symptoms, or external, such as mass media information, interpersonal interactions, or reminders from physicians.

The concept of *self-efficacy* was further extended by Albert Bandura (1977). According to his theory, the level and strength of self-efficacy determines one's engagement in subjectively threatening, but in fact safe actions: unless people believe they can attain desired effects via change in their behavior, they have little incentive to undertake the action or to persist when difficulties occur. Mastery of that behavior then enhances self-efficacy. In the context of patient adherence, it is hypothesized that promotion of self-efficacy via training of specific self-care skills leads to improved adherence to treatment regimen.

Learning from experience is a feature also of *Self-Regulation Theory* proposed by Kanfer & Gaelick-Buy (1991). They state that medical treatment can be successful only when patients are interested in their own health. Only patients with appropriate self-regulation adhere to the treatment. To achieve desired behavior, patients have to complete three stages of self-regulation: self-monitoring, self-evaluation, and self-reinforcement. Self-Regulation Theory was further extended by Leventhal et al. (1997) and applied specifically to patient adherence (Horne, 1997). They suggest that patients who do not understand the medical problem and the process of its treatment have doubts about the need of medication and therefore, do not adhere to the therapy adequately.

Biopsychosocial Model of health and illness, proposed by Engel (1977), emphasizes the role of psychological factor in considering and managing chronic illnesses. Apart from biological and social factors, which are considered in traditional biomedical models, Engel's model perceives psychological factor as a third component: it is consider as a factor contributing to the cause of a disease and its maintenance rather than only a consequence of the disease. Moreover, the role of patients changes: they are no longer passive receivers of prescribed treatment. Conversely, they are active mediators of a change.

Another approach is proposed by *Transtheoretical Model*, also called Stages of change theory (Prochaska, DiClemente, & Norcross, 1992; Prochaska & DiClemente, 1982). The behavior change is perceived as a process rather than a one-time event. It comprises five stages:

- precontemplation (not thinking about a change),
- contemplation (thinking about a change in the future),
- preparation (planning to change),
- action (changing the behavior), and
- maintenance (continuing behavior change).

Ideally, an individual proceeds linearly through the stages; however, in reality, relapses are common. Intervention based on this theory identifies patient's stage of change and afterwards, provide information individually tailored to the stage. It has been proven that such intervention are capable of a behavioral change, for instance for improving dietary habits (Campbell et al., 1994).

Recently, a comprehensive model for care of chronically ill patients was developed: the *Chronic Care Model* (Bodenheimer, Wagner, & Grumbach, 2002). It

reacts to increasing financial burden of chronic care and fragmentization of care: in present health care systems, chronically ill patients are often assigned to several physicians without any coordination of procedures or sharing information. Improved design of care leads not only to better quality of care, but also to financial savings.

The model targets not only patients, but it deals with the entire health care system and defines roles of all agents involved: from patients and their family, to health care providers, and even the system as a whole. Chronic Care Model comprises six elements:

- Self-management support: promote knowledge and skills that help chronically ill control their condition.
- Community resources: apply all possible resources, for instance for patient education, exercises, smoking cessation programs, and so forth.
- Delivery system design: translate workload from professionals to non-professionals when feasible to reduce physicians' administrative workload.
- Decision support: provide clinical guidelines for health care providers; they proved to improve quality of care and, consequently, increase patient satisfaction.
- Organization of health care: provide appropriate reimbursement mechanism that reflects the priority of chronic care; financial incentives motivate providers to improve the quality of care, which translates in future savings.

Chronic Care Model represents a new approach to treatment of chronically ill. In accord with modern requirements, patients act in the treatment process as partners to health care providers; nevertheless, no one but patients is ultimately responsible for their health. For that reason, patient adherence and promotion of self-management are one of keystones of the model.

2.8.2 Types of Interventions

Following van Dulmen and colleagues (2007), interventions to promote patient adherence can be classified into three categories based on their type:

- technical interventions,
- educational interventions, and
- behavioral interventions.

Technical interventions target mainly medication adherence and attempt to simplify the medication regimen for patients. Adjusting dosage frequency and appropriate packaging of medication proved to be effective in promoting adherence (van Dulmen et al., 2007). Review of studies using electronic devices to measure adherence proves that simplified medication regimen result in higher adherence rates: while for once-a-day dose the mean adherence rate was 79% and for twice-a-day dose 69%, for 4 doses a day it declined rapidly to 51% (Claxton, Cramer, & Pierce, 2001). Technical interventions are effective among broad variety of diseases, from antibiotic regimens for peptic ulcers (Buring, Winner, Hatton, & Doering, 1999) to chronic conditions such as diabetes or hypertension (see, *inter alia*, Iskedjian et al., 2002). For the last mentioned group, pill organizers and calendar packaging were also found to be effective (Morrison, Wertheimer, & Berger, 2000). Even though the evidence for positive effect of technical interventions is quite robust, little attention is given to their long-lasting effect, which is crucial for chronic diseases.

Educational interventions cover cognitive didactic techniques (providing information and knowledge). They can be provided in different ways: individually or in groups, face-to-face vs. via Internet or telephone, in writing, etc. Such interventions are effective for diabetes, hypertension or asthma (van Dulmen et al., 2007). However, as in the case of technical intervention, there are doubts about long-lasting effect of patient education. A meta-analysis of educational interventions revealed that the positive effect of education diminishes over time significantly: the effect size after 4 weeks was half the size of the effect after two weeks (Devine & Reifschneider, 1995). Nevertheless, properly designed patient education has indispensable role in management of a disease, chronic one in particular. Effective educational interventions include both cognitive and behavioral aspects, such as promotion of self-management skills (i.e. management of the disease in everyday life, self-care, problem solving, knowledge of the health care system, and enhancing adherence) (Curtin, Mapes, Schattel, & Burrows-Hudson, 2005; Mullen, Mains, & Velez, 1992).

Behavioral interventions target not only medication adherence but also other areas of treatment, such as adherence to recommended diet, doing exercises or attending scheduled appointments. Therefore, there are several different forms of behavioral interventions. Reminders are useful for reducing the number of missed appointments; memory aids in a form of calendars and diaries improve medication adherence; feedback on results of the treatment and incentives to adhere to the therapy target treatment regimen as such. Promotion of self-management skills and

enhancing self-efficacy are tightly linked to educational interventions and attempt to improve patient overall treatment adherence. Some interventions include reinforcements when desired behavior is reached; these incentives may have form of monetary reward, lottery ticket, tokens, consumables, and so forth.

Other interventions not categorized above include social support, interventions targeted at health care system as such and complex or multi-faceted interventions.

Despite relative abundance of studies, reviews and meta-analyses focusing on the effect of different forms of interventions that promote adherence, there is no clear-cut framework for an effective intervention neither a thorough theoretical model. The main reason for not having a unified theory and interventions used lies in the nature of health care: owing to diversified health care systems around world, transmission of an intervention that is effective in one country (or a health care system) to another country may not be successful. Moreover, the theory lacks unified definitions of both adherence and interventions which further hinders comparison among studies. Nevertheless, complex interventions combining more components seem to be the most effective (Roter et al., 1998).

3 End-Stage Renal Disease in the Context of Patient Adherence

This thesis focuses on one particular group of patients: patients with end-stage renal disease treated with hemodialysis. This chronic condition greatly influences patients' quality of life and, at the same time, it poses significant financial burden on health care system.

The aim of this chapter is to briefly present the disease and its treatment, and to investigate current research in the area of adherence of patients treated with hemodialysis and intervention used to promote adherence. It serves as a background for survey on patient adherence in the Czech Republic that is presented in the next chapter.

3.1 End-Stage Renal Disease

End-stage renal disease (ERSD), also referred to as end-stage kidney disease or chronic kidney (renal) failure, is the final stage of chronic kidney disease (CKD). It is characterized by reduced kidney function, measured by estimated glomerular filtration rate (e-GFR), and presence of kidney damage for more than 3 months (Levey & Coresh, 2012). International guidelines for classification of kidney diseases define ERSD by e-GFR lower than 15 mL/min per 1.73 m^2, while normal level of e-GFR is more than 90 mL/min per 1.73 m^2 (National Kidney Foundation, 2002). Being at final stage, the only possible treatment is renal replacement therapy (RRT) – dialysis or transplantation. ERSD is a chronic disease, thus it cannot be cured and the care is palliative – its aim is to alleviate symptoms and to improve quality of patient's life.

The incidence and prevalence rate of the disease in Europe has increased in between 1997 and 2006. While incidence rate grew slowly from 109.9 per million population in 1997 to 125.4 per million population in 2006, the prevalence rate increased significantly from 641.6 in 1997 to 815.6 in 2006 per million population, representing average increase of 2.7% per year (all figures are adjusted to age and gender; Kramer et al., 2009). The main reason for an increase in the two indicators is

ageing of population: since ERSD affects mostly older population – the mean age at the start of renal replacement therapy was between 60 and 64 years in 2011 (Noordzij et al., 2014), improved life expectancy increases the number of newly diagnosed patients. Highest rise in incidence is observed among age groups 75-84 years and 85 years and older (Figure 1). Latest figures from 2011 suggest slowdown of both indicators: prevalence rate in Europe was reported 692 per million population and incidence rate was 117 per million population (Noordzij et al., 2014). However, these figures presented by European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) are not adjusted to age and gender as the figures from 1997 to 2006 stated above, and the registry the data are gathered from is different. Therefore, simple comparison may lead to incorrect conclusions.

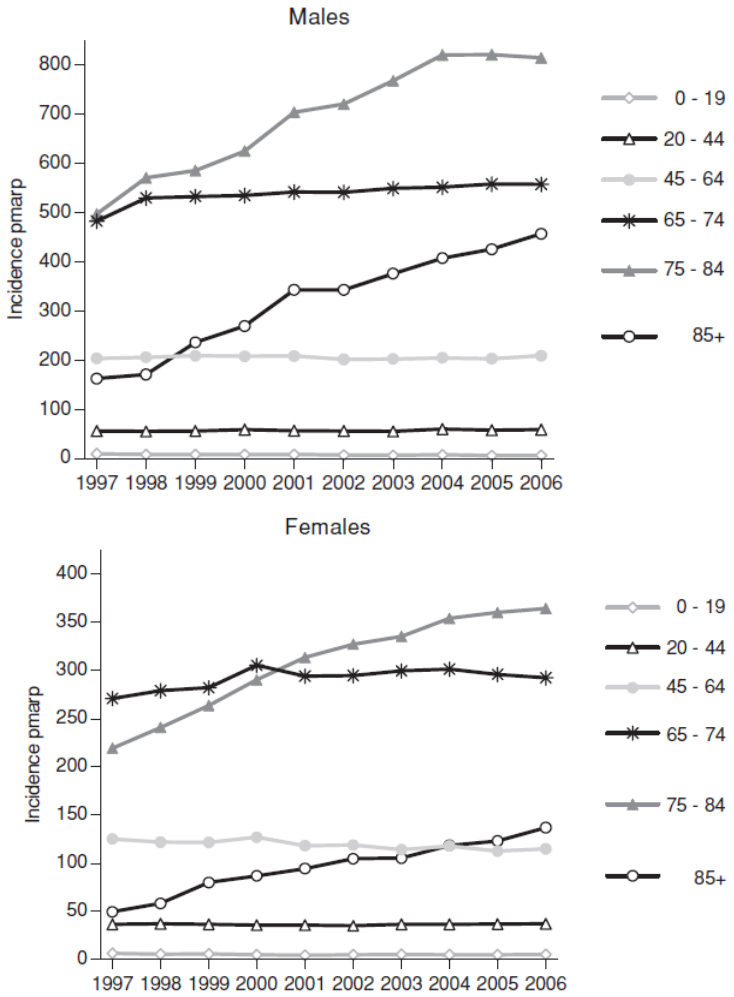

Figure 1. Trends in incidence of RRT per million population during 1997-2006 by gender and age groups

Note: unadjusted incidence; pmarp – per million age-related population
Source: Kramer et al., 2009, p. 3560

The most common treatment of ERSD – hemodialysis – poses significant burden on health care systems around the world: while end stage of chronic kidney disease affects around 0.1% of population, the costs represent 4-6% of health budgets (Bommer, 2002; Ondřichová, 2012). Annual costs for hemodialysis in the Czech Republic account for approximately 800,000 CZK per patient, overall health expenses of a patient treated by hemodialysis (including treatment of comorbid conditions) exceed one million CZK (Kříž, 2011; Ondřichová, 2012). Annual costs for hemodialysis are frequently used as a threshold for willingness to pay (WTP) for additional quality-adjusted year of life (QALY) in medical cost-effectiveness analyses (Kříž, 2011).

3.1.1 Renal Replacement Therapy: International Comparison

There are three methods how to treat end-stage renal disease: hemodialysis, peritoneal dialysis and kidney transplantation. Naturally, transplantation is the most prefereable way for many patient; however, the number of kidney donors is deficient and only small portion of patient with renal insufficiency undergo transplantation. In 2012, there were 460 patients who got a new kidney in the Czech Republic, representing 7.0% of patients treated with hemodialysis or peritoneal dialysis. Overall, 38.4% of patients treated with renal replacement therapy in 2012 underwent transplantation (Rychlík & Lopot, 2013). In international comparison, the proportion of patients with kidney transplant falls behind countries in Western Europe (see Table 1).

Table 1. Patients on RRT by treatment modality in selected countries in 2011

Country	HD (%)	PD (%)	Transplantation (%)
Austria	45.8	4.2	50.0
Czech Republic[a]	55.6	5.0	38.4
Denmark	42.2	10.5	46.9
France	52.0	3.7	44.3
Poland	62.0	3.9	34.0
Spain	44.6	5.3	49.9
Sweden	34.8	9.4	55.9
UK	43.8	7.3	48.9
The Netherlands	35.6	6.7	57.8

Note: HD – hemodialysis, PD – peritoneal dialysis, [a] data for 2013
Source: author's computation based on Noordzij et al. (2014) and Rychlík & Lopot (2013)

Similar conclusion can be made for peritoneal dialysis, a treatment during which patient do not need to visit the medical facility as frequently as in case of

hemodialysis, and therefore it significantly increases patient's quality of life. Despite increasing trend in recent years in the Czech Republic (see Figure 2), the proportion of patients on RRT treated with peritoneal dialysis is smaller than most of the countries in Western Europe. Consequently, the proportion of patient treated with hemodialysis (55.7%) is larger than in other countries such as The Netherlands (35.6%), Sweden (34.8%) or the United Kingdom (43.8%) (Noordzij et al., 2014).

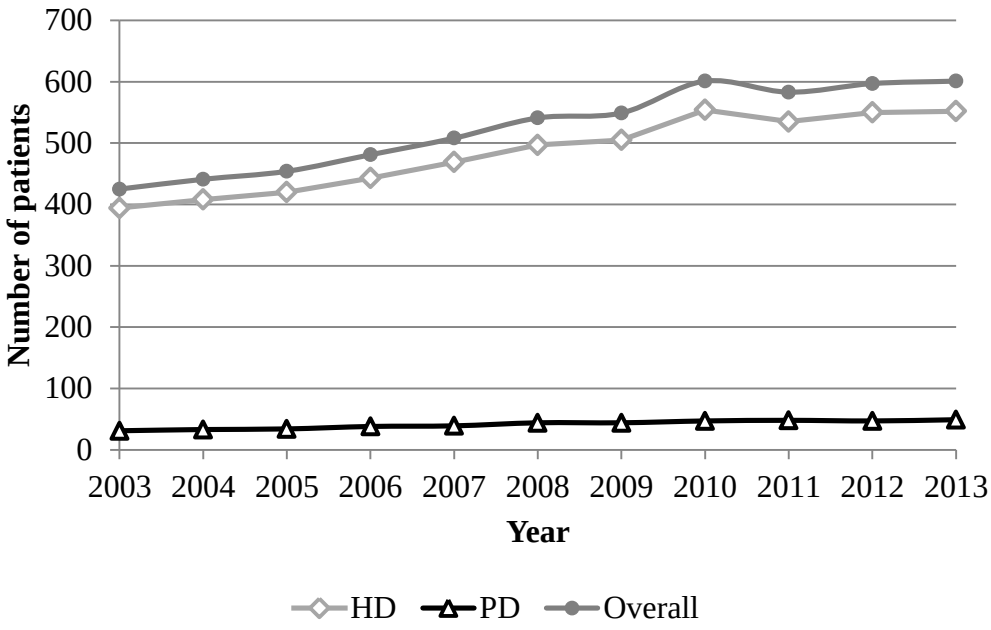

Figure 2. Patients with renal replacement therapy by treatment modality in the Czech Republic in 2003-2012

Note: HD – hemodialysis, PD – peritoneal dialysis
Source: author's computation based on Rychlík & Lopot (2013)

3.1.2 Hemodialysis: Characteristics of the Treatment

As mentioned above, hemodialysis comprises the most prevalent method of treating renal insufficiency in the Czech Republic. During hemodialysis, free water from blood and waste products accumulated in patient's body due to insufficient function of kidneys are removed outside the patient's body by a special machine, the dialyzer. For patients with ERSD, it is necessary to undergo the procedure every other day; therefore, the treatment poses significant burden on patients' life, and life of their family.

Treatment regimen of a patient on hemodialysis requires regular attendance at health care center to undergo the hemodialysis itself – average patient attend three

4-5hours sessions every week. Moreover, patient must obey strict limitations concerning fluid intake: depending on their residual renal function, the day limit for fluid intake ranges from 0.5 to 1 liter. Diet recommendations associated with the therapy include strict control of mineral intake (mainly phosphorus, potassium, and sodium), and increased protein and calcium intake.

Besides the hemodialysis treatment as such, patients are often treated for comorbidities associated with renal insufficiency: 40% of patients on dialysis in the Czech Republic suffer from diabetes, 65% of patients are treated for hypertension (Rychlík & Lopot, 2012). In consequence, patient take many medication to control these conditions: typically 6-12 tablets per day (Schmid et al., 2009), though patients taking more than 20 pills a day are documented (Holley & DeVore, 2006).

3.2 Adherence in Hemodialysis Patients

Generally, adherence rates are higher for patients with acute conditions than for those with chronic diseases. For chronically ill, the adherence to treatment, medication taking and other aspects of the therapy is “disappointingly low” (van Dulmen et al., 2007, p. 56) and decreases with the prolonged duration of the disease: highest drop is observed after first six months of a therapy (Osterberg & Blaschke, 2005). Surprisingly, high degree of severity of the disease does not imply improved adherence: poor adherence is found in patients with life-threatening condition such as HIV patients or patients undergoing oral chemotherapy (Loghman-Adham, 2003). For hemodialysis patients, the nonadherence is enhanced by high complexity of the treatment and long-term effect of many drugs: most of patient medication have no immediate effect (Curtin et al., 1999).

This part is devoted to adherence in patients treated with hemodialysis, which determines the success of the treatment. Documented rates of nonadherence vary due to different definitions and methods of measurement of nonadherence. Schmid et al. (2009) reviewed 19 studies concerning hemodialysis and found rates of nonadherence to oral medication varying between 3 and 80% with mean rate of 67%. It is believed that half of patients on hemodialysis do not adhere to the treatment adequately (Clark, Farrington, & Chilcot, 2013).

Firstly, different areas of nonadherence in hemodialysis patients are presented. Then, these areas are analyzed in detail; methods of measurement and prevalence figures are presented.

3.2.1 Areas of Nonadherence

With regard to specifics of hemodialysis treatment discussed above (see part 3.1), adherence of hemodialysis patients can be classified into four areas (Kim, Evangelista, Phillips, Pavlish, & Kopple, 2010):

- appointment adherence or hemodialysis adherence,
- medication adherence,
- fluid adherence, and
- diet adherence.

Appointment adherence, also referred to as hemodialysis adherence, covers attendance to regular hemodialysis sessions and finishing the full session. Medication adherence analyses patient behavior concerning medication taking, fluid and diet adherence concerns limitation of fluid intake and adherence to recommended diet, respectively.

Several studies suggest that there is a relation among areas of nonadherence. In a small study, Morduchowicz, Sulkes, & Aizic (1993) found correlation between fluid and medication compliance. On the other hand, dietary nonadherence was independent from the others. Leggat et al. (1998) found strong correlation between different aspects of appointment nonadherence: those who skipped at least one hemodialysis session in one month were 3.74 more likely to shorten a session for more than 10 minutes. There were also correlation between appointment and fluid nonadherence. Similar results are presented by Saran et al. (2003), Block, Hulbert-Shearon, Levin, & Port (1998) and (Unruh, Evans, Fink, Powe, & Meyer, 2005)

3.2.2 Appointment Adherence

Appointment adherence, that is skipping and shortening of hemodialysis sessions, is one of forms of documented nonadherence among hemodialysis patients. Unlike other areas of adherence, there is a clear threshold for nonadherence in the literature: yet one skipping of hemodialysis session is considered as nonadherent. For shortening the sessions, the threshold used is 10 or more minutes per session. Adherence is usually measured over one month, with some exceptions (e.g. Ifudu, Paul, & Friedman, 1987).

Skipping hemodialysis sessions seems to be specific for the USA: an international study reveals significant number of skipped hemodialysis sessions among US patients (669 sessions for 415 patients over 6 months, representing 2.3%

of all treatments), while finding no missed treatment within 3-month period in Japan and Sweden (Bleyer et al., 1999). Appointment nonadherence occurred in 35.4% of US patients. Increased rate of skipped sessions in the USA is ascribed to differences in prescription of hemodialysis sessions in the US, where patients get shorter hemodialysis sessions with higher blood flow that may lead to increased adverse reactions, and therefore it may discourage patients from regular attendance to sessions. Another factor may be increased autonomy of the patient.

Outcomes from Dialysis Outcomes and Practice Patterns Study (DOPPS) confirm the results of Bleyer et al. (1999): among five European countries (France, Italy, Germany, Spain and the United Kingdom), 0.6% patients skipped one or more hemodialysis session in a month, the same result was for Japan. On the other hand, for the USA, the proportion of nonadherent patients was much higher: 7.9%. Similarly, shortening a hemodialysis session was more frequent in the USA (19.6%) than in Europe (9.8%) and Japan (5.7%) (Saran et al., 2003).

In a large study of 6,251 US patients Leggat and colleagues (1998) found that 8.5% patients skipped one or more hemodialysis sessions (57.3% of these skipped two or more sessions) and 20.3% shortened one or more sessions by 10 or more minutes. According to a survival analysis provided in the study, skipping one or more hemodialysis session was associated with 25% increase in the risk of death in the next two years. Skipping two sessions increased the risk by more than 50%. Similarly, shortening hemodialysis sessions was also associated with increased risk of death; however, the negative effect was proven only for shortening three or more sessions in a month (an increase of the risk of 20%).

Other studies concerning appointment adherence find the adherence rate for skipped treatments give similar results. In Europe, appointment nonadherence is very rare (below 1%; Hecking et al., 2004), while US figures are higher and more diverse. Ifudu et al. (1987) report that 10% of patients missed at least one hemodialysis session over 10-week study period; Block, Hulbert-Shearon, Levin, & Port (1998) report appointment nonadherence rate 8.8% per month; Sherman, Cody, Matera, Rogers, & Solanchick (1994) report the rate from 5.1 to 7.6% over 4-week period; Kutner, Zhang, McClellan, & Cole (2002) found nonadherence in 19% of hemodialysis patients in 4-week reference period. Shortening of hemodialysis sessions appears in around 30% of US patients (Kutner et al., 2002; Sherman et al., 1994) and in 6.6-12.6% patients in Europe countries (Hecking et al., 2004).

3.2.3 Medication Adherence

Medication adherence analyzes the proportion of prescribed drugs that are really taken. In hemodialysis therapy, this issue is of a high concern since the drug burden on the patients is high: patients take in average 6-12 pills a day (Schmid et al., 2009).

Medication adherence may be evaluated by several methods. Electronic devices, the most accurate form of measurement, are used occasionally due to their high costs. For measuring adherence to phosphate binders, biochemical marker (serum phosphate) is commonly used; however, the threshold for dichotomization of adherence is not unified in the literature and ranges from 4.5 to 7.5 mg/dL (Schmid et al., 2009). For other medication, such as antihypertensive drugs or oral calcium supplementation, no biochemical markers that would indicate the level of adherence are available, and therefore, many studies rely on patient self-reports or structured interviews.

Reported nonadherence rate varies according to definition of nonadherence and used measurement method: in a review of medication adherence studies, Schmid and colleaguew (2009) report nonadherence rate from 3 to 80%, with mean rate 51.5%. Variation in size of the study is also high: from 19 to 6251 patients. Majority of studies analyzes behavior of patients in the USA, as are those reported in other review done by Loghman-Adham (2003).

Detailed study among 135 US hemodialysis patients revealed medication nonadherence up to 98% (Curtin et al., 1999). They investigated nonadherence to two different drugs commonly used by hemodialysis patients, antihypertensives and phosphate binders, and compared results from electronic monitoring devices, pill counts and self-reports. Interestingly, patients highly overestimate their adherence in self-reports: almost 80% of patients indicated that they have taken all prescribed doses of antihypertensive drugs (54% for phosphate binders). According to electronic monitoring, there were only 4.3% perfectly adherent patients for antihypertensives, 2.7% for phosphate binders. Moreover, patients not only missed doses, but also took more doses than prescribed. Results of pill counts were similar to results from electronic monitoring.

Curtin et al. (1999) further distinguishes between minor, sporadic nonadherence and major, repeated nonadherence. Clinical evidence of the effectiveness of antihypertensive drugs indicates that taking at least 80% of the prescribed doses is necessary to reach the desired outcome of the medication.

Therefore, the threshold for sporadic and repeated nonadherence was set to 20%: those who omit less than 20% of prescribed doses were marked as sporadically nonadherent, those who exceed the threshold were called repeatedly nonadherent. Repeated nonadherence was much higher for phosphate binders (72.8%), however, for antihypertensive drugs was also considerably high (46.9%). They conclude that "any and all possible strategies to increase the potential for compliance should be initiated" (Curtin et al., 1999, p. 314).

Large international study analyzing behavior of almost 15,000 patients in 7 countries, provided by Saran et al. (2003), found similar results of medication nonadherence across continents: there were 12.8, 12.1 and 15.4% of patients with serum phosphate higher than 7.5 mg/dL in Europe countries, Japan and the USA, respectively. Relatively low levels of medication nonadherence, compared to other studies, can be partly explained by the threshold set for dichotomizing nonadherence. Hecking and colleagues (2004) analyzed data from the same database (DOPSS) and found medication nonadherence to phosphate binders defined by the level of serum phosphate higher than 7.5 mg/dL in 11.7% patients and in 23.8% of patients when the threshold was lowered to 6.5 mg/dL. Nonadherence was highest in Germany (38.5% for threshold 6.5 mg/dL), lowest in Italy (15.5%). In other studied countries (France, Spain, and the UK), the rate was slightly higher than 20%.

Overall, different definitions of nonadherence and methods used to its measurement hinder the comparison among studies. Nevertheless, we can make two conclusions:

1. Medication nonadherence calls for increased attention since the data suggest that there is significant part of hemodialysis patients who do not adhere to the treatment adequately.
2. Medication nonadherence seems to be higher in the USA than in other countries in Europe or Japan.

3.2.4 Fluid Adherence

Fluid and diet adherences are, in comparison with medication and appointment adherence, more difficult to measure. Although there are biochemical markers that may indicate the level of nonadherence, studies more often rely on self-reported adherence. The drawback of biochemical markers is absence of clear cut-off for dichotomizing nonadherence. Moreover, biochemical markers are influenced not only

by adherence, but also by other individual characteristics and therefore, they may provide misleading results.

For fluid nonadherence, interdialytic weight gain (IDWG or IWG) is commonly used for measuring nonadherence. It indicates the difference in weight between two consecutive hemodialysis sessions – to be more precise, it measures the difference between the weight after one dialysis session and the weight before the next one. Many studies use the absolute level of weight gain as a threshold for nonadherence; interdialytic gain of 2.5 kg or 2 kg, or daily weight of 0.9-1 kg are used (Bame, Petersen, & Wray, 1993; Christensen, Benotsch, Wiebe, & Lawton, 1995; O'Connor, Jardine, & Millar, 2008; Pang, Ip, & Chang, 2001). However, weight gain is associated with total weight and clinical consequences are different for different weight categories. Therefore, IWG as a percentage of dry body weight is used to account for individual specifics. Due to the absence of relevant clinical data assessing the impact of IWG on the effect of hemodialysis, the threshold is artificially set: many authors use the level of 5.7% as a threshold (Hecking et al., 2004; Leggat et al., 1998; Saran et al., 2003). On the other hand, Durose, Holdsworth, Watson, & Przygrodzka (2004) use the threshold of 4% and Khalil & Darawad (2014) apply 5% limit. Lindberg, Wikström, & Lindberg (2007) suggest adjusting the cut-off point to the sample; in their case, the threshold representing weight gain of an absolute value of 2.5 kg is 3.5% of dry weight. Similarly, Chilcot, Wellsted, & Farrington (2010) define nonadherence based on the sample characteristics: patients are considered as nonadherent if their IWG is in the upper quartile of percent weight distribution, i.e. IWG more than 3.21% of dry weight in their case. For better comparison, some studies present results for several cutoff points (e.g. Arenas et al., 2010; Lindberg, Prütz, Lindberg, & Wikström, 2009).

The level of fluid nonadherence measured by IWG ranges between 3.1 to 70% according to the threshold used (see Table 2). Studies with reference weight gain of 5.7% of dry weight, that is 4 kg for 70kg patient, report nonadherence rates between 3.1 to 34.5%, while analyses with stricter threshold (weight gain of 2-2.5 kg or 4% of dry weight) report nonadherence between 16.9 and 70%. Unlike appointment or medication adherence, there is no evidence for disparity between the USA and Europe or other countries; the level of nonadherence depends mainly on the definition of nonadherence.

Table 2. Reports on fluid nonadherence among hemodialysis patients using IWG

Reference	Country	Sample size	Prevalence of nonadherence (%)	Definition of nonadherence (IWG threshold)
Bame et al. (1993)	USA	1,230	49.5	mean daily weight gain ≥ 1 kg
Christensen et al. (1995)	USA	57	42	≥ 2.5 kg
Leggat et al. (1998)	USA	6,251	9.7	≥ 5.7% of dry weight
Saran et al. (2003)	Europe[a]	2,337	11	≥ 5.7% of dry weight
	Japan	1,980	34.5	
	USA	3,359	16.8	
Durose et al. (2004)	UK	82	22.5	≥ 4% of dry weight
Hecking et al. (2004)	France	672	14.3	≥ 5.7% of dry weight
	Germany	571	5.6	
	Italy	600	17.7	
	Spain	576	7.5	
	UK	620	3.4	
Barnett et al. (2008)	Australia	26	69	≥ 2.5 kg
O'Connor et al. (2008)	UK	73	70	≥ 2 kg
Lindberg et al. (2009)	Sweden	4,498	30	≥ 4% of dry weight
			5	≥ 5.7% of dry weight
Arenas et al. (2010)	Spain	165	16.9	≥ 4% of dry weight
			3.1	≥ 5.7% of dry weight
Khalil & Darawad (2014)	Jordan	190	50	≥ 5% of dry weight

Note: [a] analysis include five European countries: France, Germany, Italy, Spain, and the UK
Source: author's search

Despite its broad use, intedialytic weight gain is sensitive to patient's individual characteristic. It is affected not only by fluid intake, but also by other factors like residual kidney function, dry weight and nutrition (Clark et al., 2013; Chilcot et al., 2010). Therefore, questionnaires are used to assess patient adherence to fluid restrictions.

For measuring fluid nonadherence, two standardized questionnaires have been developed: End-Stage Renal Disease Adherence Questionnaire (ERSD-AQ)

introduced by Kim et al. (2010) and Dialysis Diet and Fluid Nonadherence Questionnaire (DDFQ) created by Vlaminck, Maes, Jacobs, Reyntjens, & Evers (2001). The first one assesses all four areas of adherence among hemodialysis patients and analyzes patients' knowledge and perceptions about the treatment, while the latter comprises four simple questions to assess frequency and degree of fluid and diet nonadherence.

ERSD-Adherence Questionnaire is a composite questionnaire assessing not only nonadherence as such, but also focuses on reasons for nonadherent behavior, counselling received by the patient, and patient knowledge about the treatment. It comprises 46 questions using multiple choices, Likert scale and yes/no answers. Reference period for measuring adherence is one week. Fluid nonadherence is found in 10.3-20.5 US patients (Kim et al., 2010)

Even though it gives the researchers fairly detail information about patients' behavior, it has not been widely used so far. To our knowledge, the only published study that uses ERSD-AQ is the one by Kim et al. (2010). In their survey among 58 US patients, they found fluid nonadherence in 6 patients, i.e. 10.3%. Complexity of both completion and evaluation may most likely limit wider application of this questionnaire.

On the other hand, Dialysis Diet and Fluid Adherence Questionnaire (DDFQ) have been frequently used since its introduction in 2001 in Europe, Asia and the USA. The questionnaire in a simple, yet reliable way assesses frequency and degree of both fluid and diet nonadherence. To date, DDFQ was used in Belgium, Germany, Italy, the USA, Turkey, Iran and Jordan (see Table 3). In these studies, perfect adherence (100%) is assumed: nonadherence is defined as not following fluid guidelines for one or more days in the last two weeks. Nonadherence ranges from 68.1% in the USA and Turkey to 79.3% in Germany (Kara, Caglar, & Kilic, 2007; Kugler, Maeding, & Russell, 2011) with one outlier, Iran, with nonadherence rate of 91.8% (Khalil & Darawad, 2014).Half of the patients reported that they did not follow fluid guidelines for 3-5 days (8 days in the case of Iran) in the last 14 days. Having in mind that common threshold for medication nonadherence is not taking 20% or more of prescribed doses, using 20% as a threshold, fluid nonadherence is prevalent in more than half of the patients.

Overall, self-reported nonadherence measured by DDFQ is much higher than nonadherence measured by interdialytic weight gain. Fluid adherence is a keystone of

renal replacement therapy; excessive fluid intake have notable consequences both in short term – edema, particularly around ankles, and breathlessness, and long term – negative effect on mortality (Durose et al., 2004; Leggat et al., 1998). Therefore, high attention should be given to nonadherent patients.

Table 3. Self-reports on fluid nonadherence among hemodialysis patients

Reference	Country	Sample size	Prevalence of nonadherence (%)	Median days of nonadherence
Vlaminck et al. (2001)	Belgium	564	72	5
Kugler et al. (2005)	Germany, Belgium	916	74.6	4
Kara et al. (2007)	Turkey	160	68.1	na.
Kugler et al. (2011)	USA	113	68.1	3[a]
	Germany	343	79.3	3[a]
Ahrari, Moshki, & Bahrami (2014)	Iran	273	91.8	8
Khalil & Darawad (2014)	Jordan	190	76.8	5

Note: [a] median for the whole sample (Germany and the USA altogether); na. – not available
*Source:*author's search

3.2.5 Diet Adherence

Nonadherence to diet recommendation is the trickiest area of nonadherence evaluation in hemodialysis patients. Despite established clinical importance in hemodialysis therapy, dietary recommendations are hard to follow for many patients; in many cases, deep changes in life-style are required since for hemodialysis patients, eating out is at least complicated, if not impossible.

Diet adherence can be assessed by levels of biochemical markers, such as serum phosphorus or serum potassium, or by self-reports. There is no single biochemical marker that would indicate the level of nonadherence; all abovementioned indicators are influenced, apart from nutrition, by other factors, such as medication taking. Moreover, as in the case of interdialytic weight gain, there is no consensus about their optimal levels.

Serum phosphate is commonly used as a proxy for dietary adherence (Denhaerynck et al., 2007). However, the level of phosphate is highly dependent on correct taking of special medication that reduces the level of phosphate in the body, phosphate binders. Therefore, it is also used to measure medication adherence.

Adherence to recommended serum phosphate levels varies between 5.5 to 55% (O'Connor et al., 2008; Unruh et al., 2005). Again, rates are influenced by definition of nonadherence. Despite clear evidence that patients with serum phosphate higher than 6.6 mg/dL confront higher risk of death, the threshold for dichotomizing nonadherence ranges from 5.5 mg/dL to 7.5 mg/dL.

For serum potassium, nonadherence varies from 0.6 to 40.6% (Arenas et al., 2010; Hecking et al., 2004; Unruh et al., 2005). Level for dichotomizing nonadherence is quite narrow: it ranges from 5.5 to 6.5 mmol/L.

According to biochemical markers, prevalence of diet nonadherence seems to be markedly lower than prevalence of fluid or medication nonadherence. However, self-reports suggest that there is not such a huge difference: studies using Dialysis Diet and Fluid Adherence Questionnaire report nonadherence from 72.6 to 82.6% with one outlier – in Turkey, reported nonadherence is only 58.1% (see Table 4). Moreover, Kugler et al. (2011) and Kim & Evangelista (2010) found higher rates for diet nonadherence than for fluid nonadherence.

Table 4. Self-reports on diet nonadherence among hemodialysis patients

Reference	Country	Sample size	Prevalence of nonadherence (%)	Median days of nonadherence
Vlaminck et al. (2001)	Belgium	564	81.4	4
Kugler et al. (2005)	Germany, Belgium	916	81.4	4
Kara et al. (2007)	Turkey	160	58.1	na.
Kugler et al. (2011)	USA	113	77.0	3[a]
	Germany	343	81.9	3[a]
Ahrari, Moshki, & Bahrami (2014)	Iran	273	82.6	4
Khalil & Darawad (2014)	Jordan	190	72.6	4

Note: [a] median for the whole sample (Germany and the USA altogether); na. – not available
Source: author's search

Median number of days of nonadherence is 3 or 4, meaning that half of the patients did not follow their diet guidelines for 3-4 days in the last 14 days (see Table 4). Following diet recommendation, together with fluid adherence, largely affects the success of hemodialysis treatment. According to self-reported data, the prevalence of diet nonadherence is frequent and should be given appropriate attention.

3.3 Clinical Consequences of Nonadherence

There is increasing evidence of adverse effect of nonadherence on hemodialysis treatment. Besides short-term, acute symptoms of deviating from treatment recommendations, such as tremors or feeling unwell in case of elevated potassium level, itching and bone pain for high phosphorus, or hypotensive symptoms (muscle cramps, nausea, headache) for excessive fluid intake, studies suggest that there is causal relation between poor adherence and increased cardiovascular risk and, consequently, mortality.

Association between high blood pressure and nonadherence to hemodialysis regimen has been examined in several studies. Spanish study that monitor hemodialysis patients for 5 years suggests that high interdialytic weight gain (more than 3.9% of dry weight) is directly associated with elevated levels of blood pressure, higher cardiovascular risk (in particular, risk of left ventricle hypertrophy), and, consequently, lower survival rate (López-Gómez, Villaverde, Jofre, Rodriguez-Benítez, & Pérez-García, 2005). Similarly, large US study prove that appointment nonadherence (skipping or shortening dialysis sessions) have negative effect on diastolic blood pressure (Rahman, Fu, Sehgal, & Smith, 2000).

Several studies has proven that skipping of hemodialysis sessions is associated with increased mortality. According to Leggat et al. (1998), skipping one or more dialysis sessions increases the probability of death in the next 2 years by 25%. For skipping two or more sessions, the risk doubles: it is 51% higher than the risk for patients who attend all sessions. Saran et al. (2003) confirm these figures: according to their results, skipping behavior is associated with 30% rise in relative risk of death. Unruh et al. (2005) found hazard of death for patients who skipped a treatment to be 69% higher than for adherers. Moreover, Saran et al. (2003) quantify the effect of skipping on probability of hospitalization: for nonadherers, it increases by 13%.

Impact of shortening dialysis sessions on mortality is not that clear as for the case of skipping of sessions. Leggat et al. (1998) found 20% higher risk for patients who had shortened three or more dialysis sessions. On the other hand, Saran et al. (2003) did not found significant effect on mortality, nor on hospitalization.

Elevated interdialytic weight gain most likely leads to higher mortality. However, the causal relationship is more complex since high IWG is often associated

with better nutrition and, conversely, with elevated levels of unwanted minerals in body, which can contribute to increased mortality. Patients with IWG higher than 5.7% of dry weight bear 12-35% higher risk of death than other patients (Leggat et al., 1998; Saran et al., 2003). Having in mind that 5.7% threshold for elevated IWG is rather benevolent, the risk for lower cutoffs is likely to be higher. On the other hand, Kimmel et al. (2000) and Szczech et al. (2003) did not find higher mortality among hemodialysis patients with increased IWG; they found increased mortality risk only for subsample of patients with diabetes, who bear increased risk in general.

Adequate nutrition is believed to be keystone of hemodialysis treatment. Elevated level of serum phosphate stands for higher mortality: Leggat et al. (1998) and Saran et al. (2003) report 13% and 17% increase in mortality, respectively, for patients with serum phosphate higher than 7.5 mg/dL. According to Block et al. (1998), patients with serum phosphate at the level of 7.9-16.9 mg/dL bear 34% higher risk of death than those with serum phosphate of 6.6 mg/dL. Finally, the increase of mortality risk for patients with serum phosphate above 5.5 mg/dL is 59% (Unruh et al., 2005). Nonadherence to recommendations concerning phosphorus is also associated with higher probability of hospitalization.

The effect of elevated serum potassium on mortality has not been carefully assessed. While Unruh et al. (2005) report increase of risk of death of 50% for patients with serum potassium higher than 5 mmol/L, Saran et al. (2003) did not find significant effect on mortality for patients with serum potassium above 7.5 mmol/L. Further studies are needed to fully understand its importance.

To our knowledge, effect of medication adherence on mortality risk specifically for hemodialysis patients has not been studied. Nevertheless, there is no doubt that imperfect adherence to medication taking leads to suboptimal outcome, including hemodialysis patients.

As was stated earlier (see part 3.2.1), nonadherence in one area of hemodialysis treatment is frequently associated with nonadherence in other area. Consequently, mortality risk of those patients further increases: Leggat et al. (1998) state that the relative risk for patients nonadherent in two or more areas increases by 36% compared with fully adherent patients.

3.4 Predictors of Nonadherence

Several studies measuring adherence in hemodialysis patients also analyzes which characteristics of patients predicts nonadherence. Even though substantial progress has been done in recent years in the area, there is no clear outcome: while many studies analyze associations between nonadherence and patient characteristics (in terms of correlation), only a few of them explore the causal relationship using regression analysis. Moreover, these analyzes provide miscellaneous, sometimes even conflicting results. For instance, it is not clear how gender affects nonadherence: in some studies, men are more likely to be nonadherent (Kugler et al., 2011, 2005; Vlaminck et al., 2001), while in others, female gender is recognized as a predictor of nonadherence (Block et al., 1998; Chilcot et al., 2010; Saran et al., 2003). Therefore, no clear conclusion about demographic profile of nonadherent patient can be made.

Age, sex, race and smoking status are attributes that are most often linked to nonadherence. It is not surprising that smokers are more likely to be nonadherent since smoking is perceived as a marker for lower priority on health (Leggat et al., 1998). On the other hand, inverse relationship between age and adherence, documented in several studies (see, *inter alia*, Kutner et al., 2002; Leggat et al., 1998; Saran et al., 2003; Unruh et al., 2005), might be surprising at first sight. One may think that older people would be more likely to fail to adhere to the treatment due to their impaired cognitive functions. Nevertheless, research suggests that older people are more conscientious than younger ones who do not want the disease to interfere to their life and have more problems reconcile with the disease (Christensen et al., 1995; Kutner et al., 2002). Moreover, older patients usually have lower appetite and therefore they do not have so many problems with following diet and fluid guidelines (López-Gómez et al., 2005). Consequently, patients in age group from 20 to 39 years are twice more likely to have excessive interdialytic weight gain than patients 40-59 years old. Patients older than 60 years are even less likely to be nonadherent (Leggat et al., 1998).

The results concerning the relationship between gender and nonadherence are ambiguous: while several studies found strong correlation between male sex and fluid and diet nonadherence (Kugler et al., 2011, 2005; Vlaminck et al., 2001), other studies, with more elaborate analysis, indicate that females are more likely to be nonadherent (Block et al., 1998; Chilcot et al., 2010; Saran et al., 2003). Similarly, race affects adherence heterogeneously: while black race predicts appointment nonadherence (blacks are more than twice more likely to skip dialysis session), it has

the opposite effect on diet nonadherence (Leggat et al., 1998; Saran et al., 2003; Unruh et al., 2005).

Several other characteristics proved to predict nonadherence, among others depression, education, marital status, diabetes, employment status, length of the treatment or living status. There seem to be inverse relationship between medication adherence and number of prescribed doses and frequency of dosing (Loghman-Adham, 2003). However, it has to be mentioned that many studies did not find significant relationship between all abovementioned features and further research is needed to gather robust evidence. Analysis of predictors of nonadherence in hemodialysis patients in the Czech Republic is aim of this thesis.

3.5 Interventions to Promote Adherence in Hemodialysis Patients

First interventions to promote adherence in hemodialysis patients are dated yet in 1970s (Magrab & Papadopoulou, 1977; Rae Barnes, 1976). Despite long history of research in the field, there is lack of high-quality studies; randomized trials were conducted only in past decade. Previous studies bear serious methodological issues: their sample sizes are very small (frequently not exceeding 10 participants) and they lack randomization and control group (see Sharp, Wild, & Gumley, 2005, and Welch & Thomas-Hawkins, 2005, for reviews). Therefore, the power of their results is questionable and conclusions are not generalizable. Recent studies mostly overcome these issues. However, general applicability of results is hindered by the nature of health care provision: intervention that proved to be effective may have distinct or even opposite effect in a different health care system.

Systematic review of randomized controlled trials that analyzes effect of an intervention on adherence of hemodialysis patients, performed by Matteson and Russell in 2010, indicates that cognitive interventions (patient education) or combination of cognitive and behavioral intervention have positive effect on promoting patient adherence: 75% of analyzed studies documented significant improvement in medication, treatment, diet or fluid adherence of patients. The proportion of effective interventions is significantly higher than what is documented in other chronic conditions: the positive effect in other diseases is found in 33 to 54.1% of studies (Matteson & Russell, 2010). Therefore, it is obvious that there is substantial space for interventions to promote adherence in hemodialysis patients.

Interventions for patients with renal dysfunction target mainly fluid and diet nonadherence. Patient education is a keystone of any intervention; however, patient knowledge about the disease is necessary, but not sufficient factor for improvement in adherence (Matteson & Russell, 2010; Morgan, 2000; Sharp et al., 2005). Studies have shown that increased knowledge is not always associated with increased adherence. Apart from adequate information about the disease and its treatment, patients must possess the ability and skills to adhere to the therapy and, last but not least, the motivation to follow the guidelines (Morgan, 2000). The process is illustrated in Figure 3. Hence, the most successful are behavioral intervention that target at specific change in patient behavior: once a behavioral change is achieved, it is more likely to persist.

Figure 3. Process and technique for improving patient adherence

Source: own graphics based on Morgan (2000)

Interventions usually include individual educational lessons provided by a nurse or a dietician. One-to-one sessions allow for close relationship with the patient and enable to solve individual problems; however, social psychology evidence suggests that group sessions might be more beneficial. Within a small group, participants are more prone to change their beliefs and behaviors (Idier, Untas, Koleck, Chauveau, & Rascle, 2011). Content of lessons varies across studies; some cover only information about kidney disease and its treatment, others target not only patient knowledge but also their skills, self-efficacy and self-confidence. Interventions further include psychological or psychotherapeutical sessions, problem solving and training.

Published interventions in hemodialysis patients are usually quite short: they typically range from one-time event to 12-week programs (Welch & Thomas-Hawkins, 2005). However, single educational session is not sufficient to provide all necessary information and training to acquire appropriate skills. Promotion of adherence is a continuous process; therefore, it may be beneficial not to limit time horizon or number of sessions with the patient, but adjust the schedule to patient's needs and preferences (Idier et al., 2011).

Analyses of intervention lacks of long-term follow-up period: it is rarely longer than few months and, despite the urge for a long-lasting improvement in adherence, long-term effects are not investigated. Not infrequently, studies report short-term improvement in adherence during the intervention period; once the intervention terminates, the adherence gets back to its pre-intervention, low rates. Persistence of improved outcomes is clearly one of the greatest challenges of an intervention.

3.5.1 Examples of Interventions

As was stated earlier, interventions using behavioral approach are the most successful. Yet in 1981, a study using behavioral contracting was conducted (Cummings, Becker, Kirscht, & Levin, 1981). In the study, patients in cooperation with their nurse identified behavior to be changed and agreed on a concrete target. Afterwards, concrete timetable, point evaluation of accomplishment as well as form and time of reward was negotiated in the contract. Reward schedule was designed so that it promotes both short- and long-term goals; patient accumulated points that were afterwards exchanged for the rewards – state lottery tickets. The contract was written and signed by both the patient and the nurse. If the patient has great difficulties in achieving the target, the contract was revised.

The intervention lasted 6 weeks; the effect on adherence was examined at the end of the intervention and 3 months after the end of the intervention. There was significant improvement for both diet and fluid adherence after the completion of the intervention, however, in the follow-up period, the effect diminished: the intervention group reduced serum potassium level by 3.4% and IWG by 11%, but the difference was not significant.

Cummings et al. (1981) also tested the hypothesis of Health Belief Model that change in beliefs translates to change in adherence. They used weekly telephone contacts to provide information to patients as well as verbal support. At the end of the intervention, improvement in adherence was found. However, patient' beliefs did not change; therefore, there was some other mechanism that changed patient behavior. Authors suggested that increased contact with the nurse via telephone might have stimulated patients.

Christensen, Moran, Wiebe, Ehlers, & Lawton (2002) provide a study of group administered intervention targeted at fluid nonadherence. The intervention was based on Kanfer's Self-Regulation Theory (Kanfer & Gaelick-Buys, 1991): it

comprises weekly 1-hour sessions focused on self-monitoring, self-evaluation and self-reinforcement. The sessions were led by clinical psychologist with experience in behavior therapy; they were administered in a group of 4-6 patients and lasted one hour for 7 weeks. Sessions include information about adverse effect of nonadherence, instruction in self-monitoring skills, goal setting for fluid intake, self-reinforcements, and so forth. Patients were further instructed to record their fluid intake into a dairy.

Significant improvement in adherence trend was observed eight weeks after the last intervention session: interdialytic weight gain improved by 10 percentage points in the intervention group, while it has worsened in the control group. Despite short follow-up period, the intervention proved to be effective even after its completion.

Bandura's Self-Efficacy Theory (Bandura, 1977) was the base for training program in Taiwan examined by Tsay (2003). Appropriate patient self-efficacy is cardinal part of patient adherence to treatment; for patients with renal dysfunction, the importance of self-efficacy is further increased by strict guidelines for hemodialysis treatment.

The intervention included one-hour individual sessions with nurse specialized in nephrology. They were performed during the dialysis, thus three times a week, and lasted for 4 weeks. Sessions included information about the disease and its medical therapy (pathophysiology, medication, complications), and fluid and diet restrictions. Furthermore, nurse consulted patients' nutritional habits, review their fluid and diet record and agree on attainable goals. Moreover, the nurse teaches the patient how to control thirst, relax muscles or manage stress.

As a result of the intervention, significant reduction of interdialytic weight was observed: patients in the intervention group reduce their IWG in average by 22% while there was no change observed in the control group within six months. This intervention provides good promise of the effect of self-efficacy based program. However, distinct cultural and socioeconomical background of patients may hinder the application abroad, and further research is needed.

3.5.2 Economic Impact

Economic effect of poor adherence to either medication, fluid or diet regimen in hemodialysis patients is not well documented. Several studies assess provider adherence to recommended guidelines that cover also several biological targets such

as levels of serum albumin and phosphorus. Other targets are focused on provider's performance and quality of care: they measure the adequacy of dialysis dose or the use of arteriovenous fistula for vascular access. Unfortunately, most of studies that analyze the effect of attainment of these targets report the data aggregately: they examine the total effect of attainment of a group of targets. Therefore, the effect of specific goal cannot be evaluated (Rocco, Frankenfield, Hopson, & McCellan, 2006). Nevertheless, few studies provide at least partial information about the effect of adherence-related interventions.

Plantinga et al. (2007) provide longitudinal observational study (1995-2003) of 668 hemodialysis patients during their entire hemodialysis treatment in the USA (mean follow-up period is 2.8 years). They investigate the effect of attaining five clinical and quality targets on mortality and hospitalizations. The targets include adequacy and quality of hemodialysis treatment (dialysis dose and vascular access type) and three clinical outcomes: level of albumin, hemoglobin, and Ca-P product. Even though all of these clinical outcomes depend on nutrition, level of hemoglobin is primarily determined by the use of special treatment (administration of human erythropoietin), and therefore it cannot be used as a marker of patient adherence.

Not surprisingly, authors found significant relationship between goal attainment and survival. Target attainment also translates into reduction of hospitalization and number of days in hospital, by approximately 20 and 24%, respectively, for each additional target attained. Consequently, every target attained lowers health care costs by approximately $762 per patient per year. Annual savings are most significant for adherence to the level of albumin: they account for $3.282 per patient. Other targets showed savings from $37 to $3,987; however, the differences between attaining and not attaining the goal were not significant. Nevertheless, there were significant trend toward lower hospitalization rate, fewer days in hospital, and reduced costs with more clinical targets attained.

Nonadherent patients (i.e. attainment of no or one target) have 72% higher probability of being hospitalized compared to adherent patients (4 or 5 goals attained). Authors conclude that "there is tremendous potential value in patients attaining multiple targets (…) in reduced hospitalization, length of stay, and associated costs" (Plantinga et al., 2007, p. 5).

Lacson, Ikizler, Lazarus, Teng, & Hakim (2007) provide cost analysis of a hypothetical intervention targeted at patients with low level of albumin (below

3.5 g/dL). To quantify potential effect, they use large US database of hemodialysis patients. Apart from significant impact on survival, they found substantial effect on hospitalization and associated costs: relatively small, achievable improvement in albumin level by 0.2 g/dL is associated with reduction of 823 to 2,468 hospitalizations and avoidance of 2,624 to 7,871 hospital days, depending on the response to the intervention (they used plausible response range from 25% to 75% of malnourished patients). Translated into costs, the intervention can potentially save $18 to $54 million of US health care costs, again, with regard to the intervention response. Even smaller improvement by 0.1 g/dL can save approximately $29 million.

Other study of the same research team aimed to determine the most significant variables associated with mortality and hospitalization (Lacson, Wang, Hakim, Teng, & Lazarus, 2009). They analyzed data of 78,420 US hemodialysis patient and identified five variables; three of them were clinical outcomes (albumin, phosphorus, and hemoglobin levels). Low level of albumin was associated with 60% higher risk of hospitalization; elevated phosphorus level increases the risk of hospitalization by 55%.

In their further analysis, Lacson, Wang, Lazarus, & Hakim (2009) analyzed patient outcomes on the facility level based on eight quality goals: three of them target quality of care (dose adequacy and type of vascular access – catheter or fistula), four represent clinical outcomes (hemoglobin, albumin, bicarbonate, and phosphorus level), and one targets appointment adherence (missed treatments). Attainment of every single goal was associated with lower mortality within the facility. Moreover, most of the targets were associated with less hospital days per patient per year. With regard to clinical outcomes, patients who adhere to albumin and hemoglobin targets spent on average 2.1 and 3.9 days less in the hospital, respectively. Appointment adherence also significantly reduced the length of hospital stay (reduction of 0.8 days). Overall, attaining more than five outcomes was associated with 3.6 days reduction of hospital days compared to the average (10.2 vs. 13.8 days per patient per year). The difference between adherent facilities (which attained more than 5 goals) and nonadherent facilities (less than two goals attained) was more than 6 days per patient per year.

4 Survey Among Hemodialysis Patients

This chapter describes the survey that was conducted for the purpose of this thesis in May 2014.

4.1 Aim of the Survey

The object of the survey can be divided into three domains:

- to assess patient adherence and their perception of problematic areas of hemodialysis treatment,
- to analyze predictors of nonadherence, and
- to analyze patients' attitude to an incentive program that would reward them for proper adherence.

To our knowledge, there was not conducted any study concerning adherence in hemodialysis patients in the Czech Republic so far. The aim of the current survey is to analyze patient adherence in all four areas as defined in the previous chapter, that is appointment, medication, fluid and diet adherence. Moreover, we aimed to determine predictors of nonadherence and find out similarity and difference to international studies. Third goal of the research was to analyze patients' attitude to a hypothetical incentive program that would reward them for good behavior. This part serves as groundwork for a framework of an intervention proposed in the last chapter.

4.2 Survey Design

The survey was administered in cooperation with four hemodialysis centers across the Czech Republic. Head nurse of respective center was requested to distribute questionnaires to their patients during hemodialysis.

For collection of the data, self-reported questionnaire was chosen for three reasons. Firstly, there is no consensus about relevant clinical data that would reliably evaluate adherence, in particular diet adherence, and since there is no electronic clinical data system in the Czech Republic, the data are hardly available. Secondly,

self-report proved to be reliable and valid in measuring patient fluid and diet adherence (Vlaminck et al., 2001). Finally, questionnaire provides an opportunity for assessing patients' attitude to a hypothetical incentive program.

4.2.1 Study Sample

The survey took part in 4 hemodialysis centers in the Czech Republic; three in Prague and one in Most. Patients treated with hemodialysis were eligible to the study; there were no exclusion criteria apart from physical or mental inability to complete the questionnaire. A total of 260 patients were asked to participate in the study. From the whole sample, 118 patients were unable to complete the questionnaire or refused to participate in the survey. Response rate varied in regard with the dialysis center (see Table 5); diverse results are influenced not only by willingness of the patients to take part in the survey, but also by severity of their disease. Finally, 142 questionnaires were collected.

Table 5. Patients participating in the study by dialysis center

Dialysis center	Total number of HD patients	Participating patients	Response rate (%)
Prague #1	28	8	28.6
Prague #2	99	79	80.0
Prague #3	56	29	51.8
Most	77	26	33.8

Patients were asked to complete the questionnaire during their visit to hemodialysis center or at home, as they preferred. It take approximately 15 minutes to complete the questionnaire. Patients were convinced that their answers will be used only for the purpose of the research and will not have any consequences regarding their treatment.

4.2.2 Instrument

Questionnaire used in the study was prepared in accord to existing research in the field. The questionnaire was compiled with cooperation with a nurse specialized in hemodialysis and a sociologist. It has seven parts:

1. medication taking,
2. diet and fluid adherence,
3. hemodialysis adherence,

4. overall assessment of adherence,
5. reward program,
6. life-style information, and
7. demographics.

For measuring fluid and diet adherence, questions from Dialysis Diet and Fluid Adherence Questionnaire translated to Czech were used. Moreover, patients were asked about their perception of problematic areas of hemodialysis treatment. In the part concerning reward program, a hypothetical scenario of an incentive program is presented and respondents should indicate what type of reward would they choose if they were involve in such program. Demographics and life-style information cover features that proved to be associated with nonadherence (for further details, see Chapter 3.4): age, gender, length of hemodialysis treatment, education, family support, smoking status, and depression treatment. Full questionnaire as it was presented to the respondents is provided in Appendix 1 (in Czech).

Following the literature and after counseling with nurse with specialization in hemodialysis treatment, reference period for medication, diet and fluid adherence was set to last 14 days (Vlaminck et al., 2001), contrary to Kim et al. (2010) who use 7 days (one week). We believe that patients are capable of remembering their behavior in the past two weeks and a fortnight data give us better evidence about patient adherence. For appointment adherence, reference period was set to past six month. It was supposed that appointment nonadherence, in particular skipping sessions, is not much prevalent among Czech patients and that patients would keep such misconduct in their mind.

Since self-reporting of medication adherence is subject to frequent overestimation, control questions were incorporated to the questionnaire. They allow for assessing internal consistency of patients' answers.

Patient were further asked how difficult they perceive various areas of hemodialysis treatment: in the questionnaire, they should indicate how much difficult is, according to their experience, to adhere to different aspects of hemodialysis treatment.

In the part dedicated to reward program, patients were presented to a hypothetical scenario of a program in which they would be rewarded for good adherence to medication taking and fluid and diet recommendations. Subsequently, they were asked to indicate the most attractive reward from a list of various rewards

such as coupons to medical and non-medical services and goods, or direct financial payment.

Before the start of the research, four pilot interviews were performed. The questionnaire proved well, patients did not have problems understanding the questions and answering them. However, after discussion with the four respondents, hypothetical scenario of an *incentive program* was changed to *reward program* since patients did not want to take advantage of public resources: hemodialysis treatment in the Czech Republic is fully covered by health insurance and patients were aware of its expensiveness, and did not want to further exploit public resources. Moreover, it was further stated in the questionnaire that such reward program would be financed exclusively from savings earned by their increased adherence and, consequently, less expensive treatment due to fewer complications.

5 Data Analysis

Data collected in the survey, described in the previous chapter, were used for analysis of patient adherence, determination of predictors of nonadherence and, finally, as a groundwork for design of an incentive program. In this chapter, the analysis and its results are presented. Furthermore, a brief discussion is provided.

5.1 Questionnaire Consistency

Firstly, internal consistency is assessed to evaluate validity of the questionnaire. Questions concerning medication adherence, that is questions number 2-4 of the questionnaire (see Appendix 1), are of concern. The validity of questions regarding fluid and diet adherence have been confirmed elsewhere (see Kugler et al., 2005; Vlaminck et al., 2001).

Internal consistency is calculated by Kuder-Richardson Formula 20 ($KR20$). The method evaluates intercorrelation between dichotomous answers that measure the same construct (in our case, medication adherence). For the purpose of this analysis, question regarding regular medication taking (question #2) was coded as 1 if the answer was ”yes”, and zero otherwise. Following question, “do you encounter problems take the medication as prescribed?”, was coded 1 if the answer was “yes”, zero if the answer was “no”. The last question of concern was coded zero if patient indicated no omitted doses and one otherwise.

Kuder-Richardson Formula 20 is defined as follows (Kline, 2013):

$$KR20 = \frac{k}{k-1}\left(1 - \frac{\sum_{i=1}^{k} p_i q_i}{\sigma_y^2}\right)$$

where k represents the number of question of concern, p_i stands for the proportion of answering 1 on i-th question, q_i equals $1 - p_i$, and σ_X^2 represents variance of all relevant answers. The coefficient ranges between 0 and 1; higher values indicate higher intercorrelation among answers, and therefore higher internal consistency. In psychological testing, values below 0.7 are not acceptable; desirable values are higher than 0.9 (Kline, 2013).

Number of items is 3 in our case; p_i ranges from 0.78 to 0.88. Variance of all answers (σ_X^2) is 0.84. Consequently, Kuder-Richardson Formula 20 has the value of 0.72. Although the value is close to the acceptable threshold stated above, the internal consistency is good enough to prove the validity of the questionnaire.

5.2 Descriptive Statistics

5.2.1 Sample Characteristics

Total of 142 patients took part in the study, which represents approximately 2.14% of all patients treated with hemodialysis in the Czech Republic[1]. There were more men than women (58.1% of men); however, the gender distribution almost perfectly corresponds to the distribution of hemodialysis patients in the Czech Republic (see Table 6). Patients in the study were younger than hemodialysis population: median age in the study sample was 68 years while it is between 70 and 79 years in the Czech Republic (exact figure is not available). Distribution of patients in the study sample compared with all hemodialysis patients in the Czech Republic differs mostly for age group 60-69 years (see Table 6).

[1] All data concerning patients in the Czech Republic was gathered from Registry of patients on dialysis administered by Czech Society of Nephrology, available at http://www.nefro.cz/. The data used here are from 2013 (latest data available) and may slightly differ from actual data due to high morbidity among hemodialysis patients.

Table 6. Characteristics of patients in the study sample compared with hemodialysis patients in the Czech Republic

Characteristic	Czech Republic (*n* = 5888)	Study sample (*n* = 142)
Gender		
Male (%)	58.0	58.1
Female (%)	42.0	41.9
Age		
Mean ± SD (years)	na.	67.7 ± 12.712
Median (years)	70-79	68
Age groups		
50-59 years	11.7	11.1
60-69 years	26.5	11.1
70-79 years	28.0	35.6
80-89 years	20.4	26.7
Remaining (< 50 or > 90 years)	13.4	15.6

Note: na – not available; age groups were set with regard to available data
Source: Czech Society of Nephrology (2014), author's computations

In the study sample, 40.9% of patients were high school graduates; 6.6% had university degree. Sexteen per cent of patients currently smoke and almost half of patients had a history of smoking (see Table 7). Only 8.2% of patients admitted treatment for depression: the proportion is singificantly lower than in other European countries (mean 22.8%) or in the USA (25.6%) (Saran et al., 2003). On the other hand, 87.5% of patients stated that their family supports them in their treatment.

Table 7. Psychosocial and treatment characteristics of patient cohort (*n* = 142)

Characteristic	Prevalence (%)
Smokers	16.2
Depression treatment	8.2
Family support	87.5
Length of treatment (mean ± SD)	2.96 ± 4.975

5.2.2 Nonadherence Rates

The four areas of nonadherence, as described in Chapter 3.2 and following subchapters, were investigated in the survey. It has to be noted that self-reports might not give us precise results: according to Curtin et al. (1999), patients highly overestimate their level of adherence to medication taking. On the other hand,

Vlaminck et al. (2001) proved that self-report is reliable instrument concerning diet and fluid nonadherence.

As was stated several times, there is no uniform definition of nonadherence. To make results of this study comparable, definitions that are published most often in the literature were used; summary of definitions of nonadherence in respective areas is provided in Table 8.

Table 8. Definition of nonadherence used in the study

Area of nonadherence	Definition	Reference period
Appointment	skipping or shortening 1 or more dialysis sessions	6 months
Medication	omitting 20% or more of prescribed doses	14 days
Fluid	deviating from fluid guidelines for 1 or more days	14 days
Diet	deviating from fluid guidelines for 1 or more days	14 days

For the purpose of this study, appointment nonadherence was defined as skipping or shortening one or more sessions in past six months. Not surprisingly, skipping and shortening of hemodialysis sessions were not very prevalent: only five patients (3.5%) admitted they skipped one or more sessions and 17 patients (12.1%) shortened their hemodialysis in past six months. Moreover, only 3 patients shortened their sessions repeatedly, which is considered to be risky. Overall, appointment nonadherence occurred in 14.2% patients. With regard to the long reference period, the prevalence is moderately low: in the USA, appointment nonadherence over six months occurs in 35.4% of patients (Bleyer et al., 1999).

Patients in the study sample took in average 9.5 pills (SD 4.865) per day. Mean frequency of medication taking was 2.7 times a day (SD 0.845). Median for number of pills taken in one day and frequency of medication taking is 8 and 3, respectively. Medication nonadherence, defined as omitting 20 or more percent of prescribed doses in past 14 days, appeared in 18 patients (13%). Furthermore, 30 patients (21.6%) missed at least one dose. It seems that correct taking of medication is not a problem for most of the patients: only sixteen patients (11.3%) admitted they have problems taking medication as prescribed, and 30 patients (21.1%) indicated they do not take medication as prescribed – they either forgot to take a dose or failed to take it regularly.

Fluid and diet nonadherence was defined in accordance to other studies using Dialysis Diet and Fluid Nonadherence Questionnaire as deviating from patients'

guidelines for one or more days in past two weeks. In parallel to published studies, fluid nonadherence was more prevalent than diet nonadherence: 86 patients (62.8%) deviated from their fluid guidelines and 78 patients (55.7%) from diet guidelines. Even though these figures are lower than in other countries (for details see Chapters 3.2.4 and 3.2.5), the prevalence remains high, notably in the context of high importance of fluid and diet restrictions in hemodialysis treatment.

Distribution of frequency of fluid and diet nonadherence is displayed in Figure 1. More than half of patients deviated from both fluid and diet guidelines for less than five days in previous 14 days. The distribution corresponds to the distribution of nonadherence published elsewhere (Kugler et al., 2005). Most of nonadherent patients indicated that their deviation was mild or moderate (94.1% for fluid and 94.8% for diet nonadherence); only 7 patients indicated that their deviation was severe, no one marked her deviation as very severe.

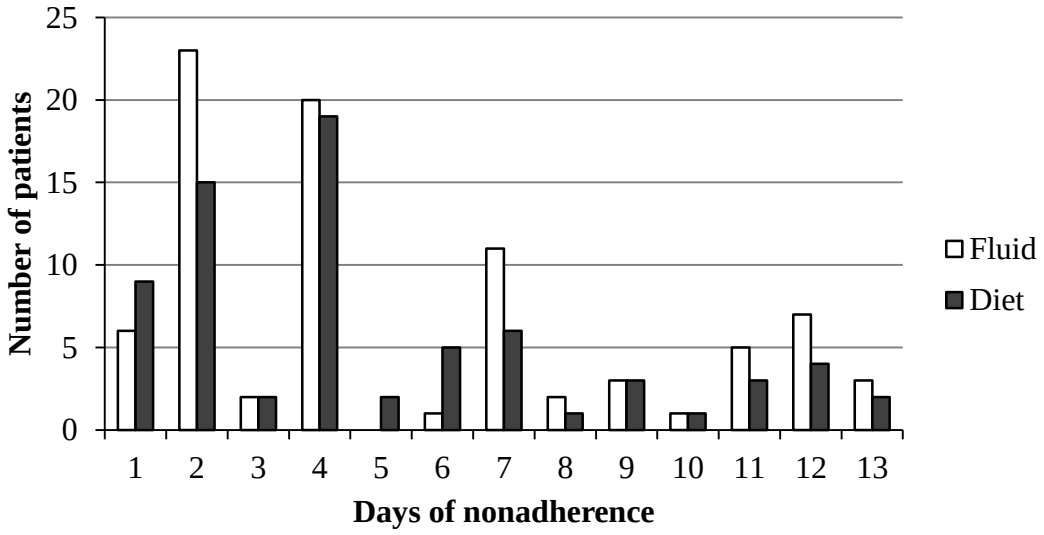

Figure 4. Distribution of frequency of fluid and diet nonadherence in the study sample

Overall, almost three quarters (72.3%) of patients was nonadherent in at least one of the four areas of hemodialysis treatment. Moreover, half of patients were nonadherent in two or more areas. Summary of nonadherence rates obtained from the survey is provided in Table 9.

Table 9. Patient nonadherence rates by area of nonadherence

	Number of patients (n = 142)	Proportion (%)
Appointment nonadherence		
Skipped session	5	3.5
Shortened session	17	12.1
Medication nonadherence		
Missed > 20% of doses	18	13.0
Missed at least 1 dose	30	21.6
Fluid nonadherence		
NA for 1 or more days	86	62.8
Diet nonadherence		
NA for 1 or more days	78	55.7
NA in at least 1 area	102	72.3
NA in 2 or more areas	71	50.4

Note: NA – nonadherence

Patients were also asked to indicate how difficult they find to adhere to various aspects of their treatment. Distribution of answers is displayed in Figure 5. Almost half of patients (49.6%) found it difficult to follow fluid guidelines; moreover, 16.5% of patients indicate it as very difficult. Diet adherence was problematic for 14.1% patients, but only 32.6% indicated they have no problems with it. Medication and appoinment adherence was obstacle for only 4.5% and 7.4% patients, respectively; more than three quarters have no problems adhering to medication taking and attending hemodialysis sessions (76.7% and 79.2%, respectively).

Furthermore, patients should indicate the most problematic area of adherence. Following strict fluid restrictions was by a long way most difficult aspect of hemodialysis treatment: almost 80% of patients marked this option. Diet adherence was the most difficult aspect for 17.6% of patients, medication taking was indicated by only four patients (2.9%).

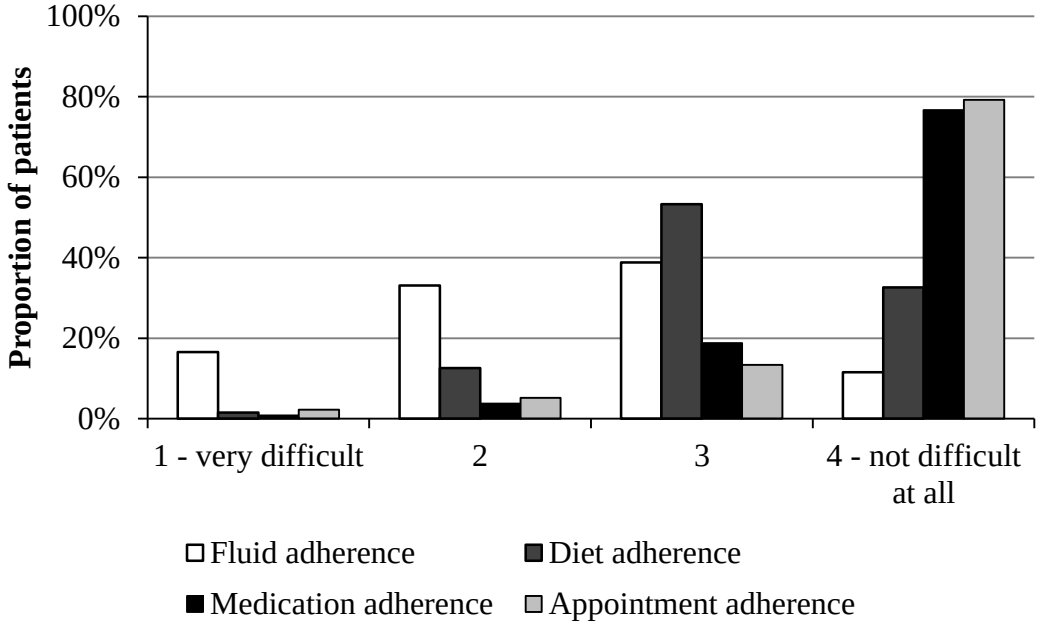

Figure 5. Perceive difficulty in adherence areas

5.2.3 Correlation Between Areas of Nonadherence

Correlation between areas of nonadherence was investigated using Pearson's χ^2 test of independence and Fisher's Exact test. Both analyze independence of categorical variables; moreover, Fisher's Exact test is suitable for small sample sizes.

Null hypothesis for both tests is independence of variables. Resulting p-values are displayed in Table 10; cross-tabulation showing frequency counts are provided in Appendix 1.

Highest correlation was found between fluid and diet nonadherence (p-value < 0.001 for both tests). There is also strong correlation between medication and diet nonadherence (p-value < 0.002 for both tests) and most likely between diet and appointment nonadherence (p-value 0.061 for Pearson's χ^2 test, 0.877 for Fisher's Exact test). On the other hand, association between medication and fluid nonadherence, and fluid and appointment nonadherence was not proven. For correlation between medication and appointment nonadherence, Pearson's χ^2 test was not valid due to low expected frequencies of cells (lower than 5). Nevertheless, the null hypothesis of independence was not accepted even by Fisher's Exact test (p-value 0.285).

Table 10. Correlation between areas of nonadherence

	Medication	Fluid	Diet	Appointment
Medication		0.158; 0.197	0.002; 0.002	0.288[a]; 0.285
Fluid			0.000; 0.000	0.469; 0.618
Diet				0.061; 0.877

Note: First figure represents p-value for Pearson's χ^2 test, second figure represents p-value for Fisher's Exact test; [a] low validity of the test statistic (low expected frequency)

5.3 Predictors of Nonadherence

This section presents analysis of predictors of nonadherence. First, the logit model is introduces. Then, several hypotheses are set. Afterwards, associations between indicators and the four areas of nonadherence are investigated using univariate analysis. Based on results obtained, variables with significant power are then used in logistic regression that analyzes the effect of predictors on the probability of being nonadherent.

5.3.1 Estimation Method: The Logit Model

In accordance to current literature, logit model (also called logistic regression) was chosen for analyzing predictors of nonadherence. The logit model represents one of binary response models, that are models where the dependent variable has only two values. These values are conventionally marked as 1 when the variable possess the characteristic of interest, and 0 when it does not. The model allows us to assess the change in odds of the response variable for a unit change in an explanatory variable, *ceteris paribus*.

Logit model predicts the response probability defined as follows (Wooldridge, 2009):

$$\mathrm{P}(y = 1|\mathbf{x}) = \mathrm{P}(y = 1|\mathrm{x}_1, \mathrm{x}_2 \dots, \mathrm{x}_k),$$

where **x** represents the full set of explanatory variables. The general logit model has the following:

$$\mathrm{P}(y = 1|\mathbf{x}) = G(\beta_0 + \mathbf{x}\boldsymbol{\beta}),$$

where G is a function for which $0 < G(z) < 1\ \forall z \in \mathbb{R}$, and $\mathbf{x}\boldsymbol{\beta}$ is a matrix of all explanatory variables $\mathrm{x}\beta = \beta_1\mathrm{x}_1 + \cdots + \beta_k\mathrm{x}_k$. G in the logit regression model is the logistic function that is defined as follows:

$$G(z) = \frac{\exp(z)}{1 + \exp(z)}$$

The logistic function ensures that $G(\beta_0 + \mathbf{x}\boldsymbol{\beta})$ is strictly between zero and one for all values of parameters and x_j.

Regression coefficients for logit model are estimated by maximum likelihood method that overcomes the problem of nonlinear nature of $\mathrm{E}(y|\mathbf{x})$ and heteroskedasticity in $\mathrm{var}(y|\mathbf{x})$. Interpretation of coefficients is different from linear regression: they no longer quantify the expected change in dependent variable for a unit change in respective explanatory variable. Coefficients of logit model represent natural logarithm of the odds of the dependent variable equaling a case ($y = 1$); consequently, the probability of the dependent variable equaling a case is derived from the logistic function:

$$\widehat{\mathrm{P}}(\mathrm{y} = 1) = \frac{\exp(\hat{\beta})}{1 + \exp(\hat{\beta})}$$

Nevertheless, in medical literature and research related to health care, it have become commonplace to report results as odds ratio (OR) rather than as a probability

Since residual sum of squares and coefficient of determination in logit model does not provide information about predictive power of the model as for linear regression, other measures are used to evaluate goodness of fit of the model. The most straightforward measure is percent correctly predicted. For the purpose of this measure, predictor of y_i is defined as follows:

$$\tilde{y}_i = \begin{cases} 1 \text{ for } G\left(\hat{\beta}_0 + \mathbf{x}\widehat{\boldsymbol{\beta}}\right) \geq 0.5 \\ 0 \text{ for } G\left(\hat{\beta}_0 + \mathbf{x}\widehat{\boldsymbol{\beta}}\right) < 0.5 \end{cases}$$

The percentage of correctly predicted is calculated as the percentage of times when $\tilde{y}_i = y_i$. However, this measure may give satisfactory results even when the least likely outcome is very poorly predicted.

Other method for evaluation of model fit, likelihood ratio test, emerges from the method used to estimate the model: maximum likelihood estimation. The test statistic for likelihood ratio test is twice the difference in log-likelihoods of unrestricted and restricted model:

$$LR = 2(\mathcal{L}_{ur} - \mathcal{L}_r)$$

and has an approximate chi-square distribution with q degrees of freedom, where q is the number of exclusion restrictions. The null hypothesis is that all regressor coefficients are zero: $H_0: \beta_1 = \cdots = \beta_k = 0$. The test is also used for evaluation of adequacy of a single regressor in the model.

Various pseudo-R^2 were suggested specifically for binary response models. Frequently used is McFadden's R^2 (McFadden, 1974) with the measure

$$R^2 = 1 - \frac{\mathcal{L}_{ur}}{\mathcal{L}_0}$$

where $\mathcal{L}_{ur}$ is the log-likelihood function for the estimated (unrestricted) model and $\mathcal{L}_0$ is the log-likelihood for model with only intercept. Naturally, higher McFadden's R^2 represents better model fit; however, the threshold for acceptable model is not clear. It is believed that level above 0.6 shows excellent model fit (similar to R^2 equal to 0.9 in traditional OLS), level of 0.2 equals to classic R^2 of 0.4, which is still acceptable in social research (Domencich & McFadden, 1975).

5.3.2 Variables

Dependent variables used in the models were, in turn, medication, diet, fluid, and appointment nonadherence as defined in Chapter 5.2.2 (for summary, see Table 8).

Explanatory variables include patient personal characteristics (age, sex, education level, smoking status, treatment for depression, and family support) and treatment characteristics (number of pills prescribed, frequency of medication taking, and length of hemodialysis treatment).

5.3.3 Hypotheses

The aim of the survey is to analyze which characteristics determine patient nonadherence. Based on results of existing literature, we stated several hypotheses: first, we assume that age is inversely related to nonadherence, meaning that younger patients are more likely to be nonadherent. Second, smoking is assumed to be strong predictor of nonadherence in all four areas. Third, we assume that adherence will decline in time, meaning that longer history of hemodialysis treatment is assumed to be associated with higher probability of nonadherence. Finally, with respect to medication nonadherence, higher pill burden, that is the total number of pills taken in one day and frequency of dosing, is associated with higher probability of being nonadherent

5.3.4 Results

Predictive power of patient personal and treatment characteristics on various areas of nonadherence was investigated. Predictors varied across nonadherence areas; only the number of prescribed pills per day was significantly associated with all areas of nonadherence except appointment nonadherence. Surprisingly, the direction of the relationship is opposite than we expected: patients with higher number of pills per day are more likely to adhere to the therapy. Nevertheless, the significance for medication and fluid nonadherence was gained only for 10% significance level.

As was hypothesized, age was inversely related to nonadherence; however, the relation was significant only for medication nonadherence (p-value = 0.0365). Increase in age by one year decreases the odds of being nonadherent by 5%. When dichotomized by mean age (67.7 years), being younger is associated with 5-fold increase of risk of nonadherence (OR = 5.03, p-value = 0.0202).

Surprisingly, smoking behavior was not a significant predictor of nonadherence for most of examined areas. Moreover, p-value in case of medication nonadherence approached 1. Also history of smoking (that is current or prior smoking) did not significantly predict any area of nonadherence. Nevertheless, current smoking was a strong predictor of appointment nonadherence with odds ratio equal to 6.32 and p-value 0.0080.

Length of dialysis was found to be related to nonadherence in an opposite direction than we expected. However, the relationship was significant only for one area, diet nonadherence, where one-year longer dialysis treatment was associated with 9% decrease of the likelihood of being nonadherent. When dichotomized by mean value (2.96 years), patients with shorter history of hemodialysis treatment were 3 times more likely to deviate from diet guidelines (OR = 3.24, p-value 0.0095).

There is probably some association between number of prescriber pills per day and medication adherence; however, direction of the relationship is opposite than we assumed (i.e. higher number of pills per day is associated with lower odds of nonadherence) and the relationship is significant only on 10% level of significance (p-value = 0.0559). Surprisingly, there is no relationship between frequency of medication taking and medication nonadherence (p-value = 0.2525).

Apart from abovementioned results, some interesting association arose. First, men were 3 times more likely to deviate from diet guidelines (OR = 3.14, p-value

0.0115). Second, depression was significant and very strong predictor for medication and diet nonadherence, with odds ratio 9.21 and 27.72, respectively. Finally, higher number of pills prescribed per day is associated with adherence to diet guidelines.

On the other hand, education level, family support, and frequency of medication taking was not significantly associated with any of the four areas of nonadherence. Summary of results is provided in Table 11; details can be found in Appendix 4.

Table 11. Predictors of nonadherence from logit regression models (odds ratios), by area of nonadherence

	Medication	Fluid	Diet	Appointment
Personal characteristics				
Age (years)	0.95**	0.98	0.98	0.98
Sex (ref.: male)	1.47	1.92	3.14**	2.05
Education	1.33	1.02	1.22	0.96
Smoking	0.00	1.53	2.14	6.32***
Depression	9.21**	1.37	27.72***	1.74
Family support	0.75	0.63	0.59	1.53
Treatment characteristics				
Pills per day	0.83*	0.91*	0.86***	0.94
Pill frequency	1.57	1.74*	0.98	1.71
Length of dialysis (years)	0.97	0.98	0.91**	0.95

Note: ref. – reference, * p-value < 0.1, ** p-value < 0.05, *** p-value < 0.0.1

Goodness of fit of models was examined using there criteria as described in part 5.3.1: percentage of correctly predicted outcomes, likelihood ratio test and McFadden's R^2. Results are displayed in Table 12. Model analyzing medication nonadherence provide good results: the model correctly predicts almost 90% of cases. Moreover, both likelihood ratio test and McFadden's R^2 give convenient results. Similar results are obtained for models with diet and appointment nonadherence as dependent variables. Test statistics are somewhat poorer than the previous case, but still acceptable. On the other hand, the model explaining fluid nonadherence is very poor: all test statistics give dissatisfactory results.

Table 12. Results of goodness-of-fit tests

	Medication	Fluid	Diet	Appointment
% correctly predicted	89.4	62.2	69.7	89.4
LR test	0.0215	0.1961	0.0009	0.0883
McFadden 's R^2	0.2134	0.0776	0.1673	0.1732

In the literature, several authors use different approach to identify the effect of patient characteristics on the likelihood of being adherent (Ahrari et al., 2014; Kara et al., 2007; Unruh et al., 2005). First, they perform univariate analyses for all variables, that is a set of logistic regressions with only one variable used as explanatory variables. Then, they select variables with significant predictive power: the threshold for significance is set to p-value of respective regression coefficient lower than 0.2. These variables are then used for the final model.

Using this approach in our sample does not improve models substantially (see Table 13 for details of goodness-of-fit tests). For medication nonadherence model, all test statistics are worse. Model for diet nonadherence shows lower McFadden's R^2 and model for appointment nonadherence have worse LR-test statistic. The model explaining fluid nonadherence shows some improvement: likelihood ratio test have p-value lower than 0.05, but McFaddden's R^2 deteriorates. Therefore, the results of these restricted models are debatable.

Table 13. Results of goodness-of-fit tests for restricted models

	Medication	Fluid	Diet	Appointment
% correctly predicted	89.3	64.1	70.1	88.6
LR test	0.0647	0.0487	0.0010	0.0012
McFadden R^2	0.0776	0.0465	0.1165	0.1560

All variables, which are significant in restricted models, proved to be significant in the original models with one exception: length of dialysis is no longer significant predictor of diet nonadherence. Even though numerical levels of coefficient differ, the direction of effect does not. Therefore, we conclude that for the purpose of our study, restricted models do not provide any additional information, and we keep working with the original model. Results of restricted models as well as

details of univariate analyses are provided in appendices (Appendix 5 and Appendix 6).

5.4 Incentive Program

One part of the questionnaire focused on hypothetical incentive program. The aim was to analyze potential effect of such intervention and to identify the most attractive reward.

Eighty-three percent of patients indicated that such program would affect their behavior: they will more precisely follow treatment guidelines. Only 11% of patients indicated that they would most likely not change their behavior, and 5% denied any change in behavior in response to the intervention.

In the questionnaire, respondents were introduced with a set of rewards from which they chose three most attractive and sorted them. The list of rewards comprise following items:

- medication discount voucher,
- free transport to dialysis center,
- discount voucher for nutritional supplements and vitamins,
- discount voucher for physiotherapy and exercise,
- sport discount voucher,
- entertainment discount voucher, and
- financial reward (100 CZK per week).

Figure 6 shows distribution of patients' answers: white bars represent proportion of patients who select the particular reward as one of their three most preferable and black bars show the proportion of patients who select the reward as their very first choice. Results identify three most popular rewards: voucher for either medication or nutritional supplements and vitamins, and direct financial reward.

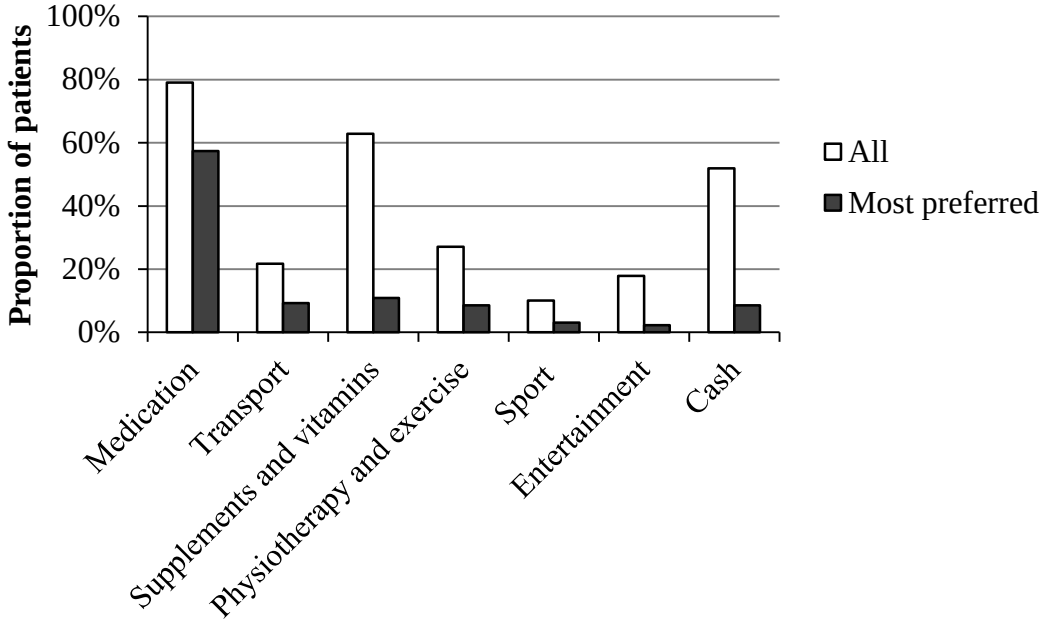

Figure 6. Attractiveness of provided rewards

Discount voucher for medication was the most popular reward: almost 80% of patients included it in their choice, and 57.4% of patients set it as the most attractive reward. Discount toucher for nutritional supplements and vitamins, and monetary reward were chosen by more than a half of patients (62.8% and 51.9%, respectively). On the other hand, free transport to dialysis center, discount voucher for exercise and sport, and entertainment discount voucher were not very attractive.

5.5 Discussion

This study provides an overview of adherence in hemodialysis patients in the Czech Republic. It has three objects: first, to analyze the level of nonadherence in four areas of hemodialysis treatment (medication, fluid, diet, and appointment nonadherence) and to identify the most problematic area as viewed by patients. Second, the survey aimed to identify patient characteristics associated with nonadherence. Finally, it serves as groundwork for potential intervention to promote adherence: it surveys patients' attitude to a hypothetical incentive program and analyzes possible reward.

The survey was conducted among four hemodialysis facilities and includes 142 patients. Response rate of 54.6% is acceptable since it includes not only patients who refused to take part in the survey, but also patients who were not able to complete the questionnaire due to their physical or psychological impairment. Such

limitations can be fairly often among hemodialysis patients: hemodialysis population covers mainly elderly (mean age between 70-79 years) and patients frequently suffer from other medical conditions. Patients in the study were younger than average: mean age was 67.7 years. However, the age distribution differs substantially only for age groups 60-69 and 70-79 years; the remaining allocation was similar to Czech hemodialysis population.

The questionnaire was compiled with respect to existing research. Its content was discussed with a sociologist with experience in applied research and a nurse with specialization in hemodialysis treatment. Special attention was given to wording; moreover, the final version was modified slightly after pilot interviews. Afterwards, internal consistency was validated by Kuder-Richardson Formula 20 ($KR20 = 0.72$). Overall, the questionnaire proved well; no complications during the investigation were reported.

Results of the survey show that 72.3% of patients was nonadherent in at least one area of hemodialysis treatment and more than a half (50.4%) was nonadherent in two or more areas. The most problematic aspects are following fluid and diet guidelines: prevalence of nonadherence is 62.8% and 55.7%, respectively. Moreover, 80% of patients indicated that fluid adherence is the most difficult aspect of hemodialysis treatment. On the other hand, medication and appointment adherence was not frequent: only 13% of patients admitted they omit more than 20% of prescribed doses in past 14 days and 14.2% skipped or shortened their hemodialysis session in past 6 months.

In international comparison, nonadherence rates reported in our study are somewhat lower. With regard to appointment nonadherence, it is not very surprising: skipping and shortening of dialysis sessions is prevalent mainly in the USA. Health care system in the Czech Republic prevents from deviating from the treatment plan: patients are usually aware of expensiveness of the therapy and are grateful that it is provided for free[2]. Moreover, extensive network of dialysis facilities in the Czech Republic (there are 101 dialysis centers) secures proximity to patients. Finally, majority of patients are retired or disabled and they do not perceive time-demand of the therapy as a problem.

[2] In the Czech Republic, health care is provided for free from public health insurance. Copayment for treatment is very limited and includes only fees for visit of a physician and hospitalization.

Medication nonadherence was significantly lower than in other studies (see part 3.2.3 for a review). Two potential explanations for such behavior arise: first, despite our best effort to ascertain patient behavior accurately, patients might have underestimated their nonadherence. This phenomenon is frequent in measuring nonadherence, medication taking in particular (Curtin et al., 1999). Second, such a low prevalence of nonadherence may result from good management of medication regimen. Median frequency of medication taking was 3 times per day; when tied to specific day routines, such as meal, patients might not have problems with proper taking. This hypothesis is supported by another survey results: only 4.5% of patients stated that medication taking is difficult for them and 11.3% indicated that they have problems to take medication as prescribed. Moreover, most of medication is partially covered by public insurance and patients do not face huge financial burden as in other health care systems.

Despite pleasant results of prevalence of medication and appointment nonadherence, following fluid and diet guidelines remains complicated for hemodialysis patients. Given the evidence about negative effects on clinical outcomes, survival, hospitalization, and, consequently, health care costs, interventions to promote adherence in these areas are required.

With regard to predictors of nonadherence, our survey provides several unexpected results. For instance, medication nonadherence is not driven by pill burden, as we hypothesized. To our surprise and in contrast with literature (Loghman-Adham, 2003), the relationship between number of prescribed pill per day and medication nonadherence goes in the opposite direction: increasing number of pills taken in one day decreases the likelihood of being nonadherent. Nevertheless, the association is not very strong (OR = 0.83) and it gains significance only on 10% significance level. Frequency of medication taking did not proved to be significant predictor of medication nonadherence. According to our model, typical patient who do not follow medication regimen is young patient treated for depression: age under 68 years increases the likelihood of being nonadherence 5 times, treatment for depression 9 times.

Depression is even stronger predictor for diet nonadherence: odds ratio equals to 28 with p-value 0.0073. Diet nonadherence is further associated with shorter tenure of hemodialysis treatment, male gender and lower number of prescribed pills. It seems that patients gradually learn what food is appropriate for them. Moreover, men

have more problems following diet guidelines; the reason might be lack of cooking experience or higher appetite.

Appointment nonadherence was strongly associated with smoking (OR = 6.32). This result is not surprising: smoking is perceived as a marker for lower priority for health. Therefore, smokers are more likely not to follow hemodialysis regimen. Moreover, long duration of dialysis (3 or 4 hours) may be difficult to complete for heavy smokers; they may be more prone to shorten their session.

Our model did not predict clear association between any of examined variables and fluid nonadherence. Moreover, quality of the model was very poor; it did not even improve with a different methodological strategy. Therefore, determinants of fluid nonadherence remain unclear and further research is needed.

With regard to a hypothetical incentive program, the survey confirms that patients would be interested in such program and that they would change their adherence behavior if there were rewards in place. As a reward, patients preferred rewards related to their treatment regimen (discount voucher for medication or nutritional supplements and vitamins) or direct financial incentive.

5.6 Limitations of the Survey

It is acknowledge that this study bear some limitations. First, the study sample was not randomized and selection bias may arise. However, random selection is not very frequent in studies assessing patient adherence, probably due to the limited number of hemodialysis patients. Moreover, response rate in our survey was fairly high, notably in the context of social research, and the group of hemodialysis patients is supposed to be quite homogenous unit.

Second, the sample size was limited to 142 participants. However, the confidence interval for this sample size, given the total of 5,888 hemodialysis patients in the Czech Republic and 95% confidence level, is at acceptable level of 8.15. Moreover, when analyzing the effect of incentive program, patients who participated on the survey will be more likely to participate in an incentive program because they are more concerned.

Third, adherence can be significantly overestimated in self-reports and more accurate measure of nonadherence is required. However, there is no clear standard

how to measure nonadherence: even objective measures such as clinical outcome and laboratory data demonstrate considerable shortcomings with regard to the threshold for dichotomization and individual variation. Moreover, patient data are hardly available in the Czech Republic since there is no uniform clinical information system that collects such data. For these reasons, we chose self-report as the best method to assess patient adherence. We performed our best to overcome all concerns connected to social survey; experts in hemodialysis and social research reviewed the questionnaire, and pilot interviews were provided to evaluate the convenience of the instrument.

Despite these limitations, we believe that the aim of the survey, that is to provide an overview of adherence of hemodialysis patients, was accomplished.

6 Proposed Intervention

There is no doubt that inadequate patient adherence leads to suboptimal outcomes. As was discussed in Chapters 3.3 and 3.5.2, nonadherence in hemodialysis patients has significant negative impact on survival, risk of comorbidities, hospitalization, and, consequently, health care costs. Therefore, an intervention that targets problematic areas of hemodialysis treatment may have significant effect on patient health, utilization of health care services, and health care costs. Nevertheless, the design of the intervention is crucial for its effectiveness. This chapter discusses main features of such intervention.

6.1 Status Quo Evaluation

An intervention can be effective only if it is well targeted. Therefore, evaluation of actual state is necessary. In particular, several questions need to be addressed:

1. What areas of hemodialysis treatment cause patients difficulties?
2. What is the prevalence and degree of the problem?
3. Is it possible to resolve these difficulties by changing treatment regimen?
4. What is the level of disease-related knowledge among patients?

Our survey provides an insight into patient adherence and answers the first and second question. Following fluid and diet guidelines is by far most effortful area of hemodialysis treatment. On the other hand, it seems that medication taking is well managed in the Czech Republic and appointment nonadherence is not a great issue: according to the survey, only 5 of 142 patients skipped a session in past six months and 2 patients shortened sessions repeatedly, which can be risky. Therefore, the intervention should target fluid and diet adherence.

Answers to following questions are not so straightforward. Extremely strict restrictions of fluid intake emerge from patient's health status and cannot be easily simplified. The only way to extend fluid limitations is to perform dialysis more often. Several studies assessed the effect of daily dialysis; they found promising effect on patients' clinical outcome as well as quality of their life. However, economic and

organizational concerns such as lack of existing infrastructure to provide this service and financial issues hinder wider use of this method (Locatelli et al., 2005).

Scope for simplification of diet guidelines is broader. Special medication, such as phosphate binders or parenteral nutritional supplements, can be used to avoid undesirable effects of mineral overload. Therefore, therapy of nonadherent patients should be carefully reviewed and adjusted to patients' needs.

The last question focuses on patient knowledge related to the disease and its treatment. It was confirmed that appropriate knowledge about the disease, its treatment as well as about negative effects of inadequate adherence is fundamental for improving patient behavior (Sharp et al., 2005). However, the level of knowledge among patients varies and for the intervention to be successful, it has to be adjusted to individual needs and abilities. Therefore, it is necessary to assess patient knowledge.

6.2 Intervention Design

6.2.1 Content

Basis of every intervention to promote adherence in hemodialysis patients is patient education. Moreover, combination of cognitive interventions, such as educational sessions, and behavioral strategies proved better than to provide education solely (Matteson & Russell, 2010).

Education ought to be individualized to patient's needs to the highest possible level. Therefore, it is necessary to assess patient knowledge at first. Effective educational lessons cover pathophysiology of the disease, its treatment, medication, associated conditions and potential complications, and significance of fluid restrictions and proper nutrition. They should discuss benefits of medication and adherence rather than focus on their negative effects.

To obtain the best possible results, it is suggested to combine individual lessons with group sessions. Within a group, patients can share their concerns, beliefs, and problems that face in daily routine. The advantage of individual session is its intimacy where personal problems can be solved. They are provided usually provided once a week either during hemodialysis or separately; nevertheless, it is suggested that patients are more concentrated if the lessons are provided out of hemodialysis sessions (Prowant et al., 1989). Length of a session ought to be

individualized to patient needs; it usually ranges from 20 to 60 minutes (Sharp et al., 2005)

Behavioral strategies focus on promotion of self-efficacy and self-management. They include training of specific skills related to hemodialysis treatment, stress management, and control of thirst. To reduce nonadherence, it is effective to set specific goals with the patient. Appropriate target setting is vital for patient motivation: goals have to be personally important and attainable within given time horizon. They ought to target both short- and long-term objectives. It is effective to categorize the level of goal attainment (i.e. good, acceptable, or poor control) to enhance patient motivation for improvement (Olivarius, Beck-Nielsen, Andreasen, Hørder, & Pedersen, 2001) and reward well-performing patients to support maintenance of the change (Hart, 1979; Rae Barnes, 1976). It is worth noting that not behavioral change as such, but rather its maintenance in long-term is the ultimate goal of an effective intervention since improved adherence translates into improved outcomes only in the long term. Our survey suggests that discount vouchers for medication, nutritional supplements and vitamins, or direct financial rewards have the greatest potential to influence patients' behavior. Patient may be rewarded directly for attainment of a given target or lottery game may be used, as suggested by behavioral theory to reduce costs (Kessler & Zhang, 2014). However, population of hemodialysis patients is rather old (median age between 70-79 years, Rychlík & Lopot, 2013) and a lottery game may be too complicated for them. Therefore, direct rewarding is suggested.

With a reward system based on goal setting, there arises a question how to measure attainment of particular goal. Objective measures are needed since patients may overestimate their attainment in self-reports. Nevertheless, objective measures are not suitable for all patients and individual characteristics may influence the effect of adherence on selected measures. Therefore, subjective evaluation of patient adherence and their effort to change their behavior should be incorporated in the reward system, for instance using a point evaluation system that incorporates subjective assessment.

For fluid nonadherence, interdialytic weight gain is an easy and inexpensive, yet convenient method to assess patient adherence. The threshold for dichotomizing should be set with regard to patient dry weight; the level of 5.7% of dry weight is the most frequently measure. Assessing diet nonadherence is more difficult since patients have to control the level of several minerals and other nutrients. Laboratory data can

be used; however, patients have to be educated how concrete aliments influence these levels.

6.2.2 Staff

Chronic Care Model proposes that the workload should be translated from physicians and nurses to non-professionals any time feasible. However, in case of interventions in hemodialysis patients, close relationship with the patient is needed. Therefore, the most effective way is to engage a nurse, who are in regular contact with patients, and employ already established relationship. It is suggested that nurses serve better than dieticians do (Morgan, 2000), most likely due to their extensive experience with hemodialysis patients and long-term relationship.

Good communication between the nurse (or other interventionist) and a patient is essential (Kammerer, Garry, Hartigan, Carter, & Erlich, 2007; Morgan, 2000). To reach better outcomes, patients have to agree with the treatment plan and worth it. Nurses should support patients and acknowledge their achievement rather than blame them for their failures. Moreover, enhanced communication itself can lead to improvement (Cummings et al., 1981).

6.2.3 Target Group

Naturally, the effectiveness of an intervention increases if it is targeted only at nonadherent patients. However, health care is supposed to be provided for everybody; therefore, ethical concerns may arise if the intervention is provided only to subpopulation of patients. Moreover, adherent patients may be also interested in an educational program (Idier et al., 2011).

Nevertheless, special attention should be given to patients who are treated for depression: according to our results, they are the most vulnerable group.

6.3 Implementation

6.3.1 Organizer

Administration of an intervention that promotes adherence in hemodialysis patients may be of interest for every level of health care system. First, ministry of health or government is responsible for sustainability of health care funding. Consequently, they are interested in potential future savings since the population of hemodialysis patients and costs for their treatment are growing. Second, health insurance

companies may use an incentive program to attract new insurees and to retain actual ones. Depending on employed reimbursement system, they can make profit from the program since it reduces individual health care costs. Next, health providers may have the same intention: through increased quality of care, they can enhance their popularity among patients and thus benefit from the implementation. Finally, third parties, such as patient organization, can be interested in the intervention: improved health and quality of life of patients leads to increased patient satisfaction.

If government coordinates the program, appropriate reimbursement system has to be introduced to motivate providers to participate. International evidence shows decent effect of public reporting of providers' results and direct financial motivation of providers via pay-for-performance (P4P) scheme (Plantinga et al., 2007).

6.3.2 Benefits

As was stated, benefits of an intervention program arise in several areas. First, improved adherence translates into improved clinical outcomes, meaning better patients' health and improved quality of their life. Second, enhanced patient-provider relationship combined with improved health status have positive effect on quality of care and patient satisfaction with the service. Finally yet importantly, improved outcomes translate to reduced health care costs via fewer hospitalizations and fewer days in hospital. However, the financial effect is hard to quantify: studies of economic impact of patient nonadherence are scarce and more research is needed in the area.

Overall, an incentive program targeted on fluid and diet adherence of patients treated with hemodialysis is promising way how to improve patient engagement in the treatment. No treatment can be effective without patient involvement; this fact holds especially for hemodialysis therapy.

7 Conclusion

To our knowledge, this study provides first comprehensive assessment of adherence in hemodialysis patients in the Czech Republic. It measures the prevalence of the phenomenon, identifies problematic areas, and analyzes predictors of nonadherence. Furthermore, it reveals patients' attitude to a hypothetical incentive program to promote adherence and suggests optimal design of an interventional program to promote adherence in hemodialysis patients.

For the purpose of this study, nonadherence in hemodialysis patients is categorized into four areas. Appointment nonadherence is defined as skipping or shortening hemodialysis session one or more times during past six months. Other areas have reference period the last 14 days: medication adherence is defined as omitting 20 or more per cent of prescribed doses, fluid and diet nonadherence are defined as deviating from recommended guidelines for 1 or more days within the period. Nonadherence was assessed based on self-administered questionnaire. Its internal consistency was confirmed using Kuder-Richardson Formula 20.

Survey among 142 hemodialysis patients in the Czech Republic reveals that the most problematic are following fluid and diet guidelines: the prevalence of fluid and diet nonadherence is 62.8% and 55.7%, respectively. Moreover, more than half of patients deviated from fluid or diet guidelines for more than 4 days in past two weeks. Almost half of patients (49.6%) find it difficult to restrict their fluid intake. On the other hand, appointment and medication nonadherence is not frequent (occur in 13% and 14.2% of patients, respectively). Moreover, potentially risky skipping behavior appears only in 5 patients (3.5%). Overall, majority of patients (72.3%) are nonadherent in at least one area of hemodialysis treatment. Moreover, half of patients (50.4%) are nonadherent in two or more areas. The figure is of concern since nonadherence in more areas of hemodialysis treatment increases mortality risk by 36% (Leggat et al., 1998).

Using logistic regression, we examined the relationship between nonadherence and age, sex, level of education, smoking status, treatment for depression, family support, number and frequency of prescribed medication, and length of hemodialysis treatment. Three of the variables, namely educational level,

family support, and frequency of medication taking, did not proved to be significant predictor of nonadherence in any of the four areas. Other predictors of nonadherence vary across the area of interest. Medication nonadherence is associated with young age and depression: being under mean age of 67.7 years increases the odds of being nonadherent 5 times and treatment for depression 9 times. Diet nonadherence is associated with male gender (OR = 3.14) and, again, with treatment for depression; the relationship in this case is even stronger (OR = 27.72). It is further inversely associated with length of dialysis treatment and number of pills taken in a day. Smoking is the only, but strong predictor of appointment nonadherence: it increases odds of being nonadherent more than 6 times. Unfortunately, the model for fluid nonadherence provide no clear outcome: there was no significant predictor and the model fit was not satisfactory even when alternative approach was used.

Finally, optimal design of an interventional program to promote adherence is discussed. Despite growing research in the area, there is no single framework for an effective intervention. Nevertheless, it has been proven that combination of cognitive (educational) and behavioral interventions is the most successful approach. Therefore, we suggest combination of educational lessons with a nurse and an incentive program. In the program, individualized targets are set with each patient and patients are rewarded for attainment of specific goals. Design and evaluation of goal attainment should respect both short-term and long-term objective as well as subjective and objective assessment.

Based on the results of our survey, the program should target fluid and diet nonadherence. The most appropriate forms of rewards are medication vouchers, vouchers for nutritional supplements and vitamins, and cash. Since most of the patient (83%) indicated they would improve their behavior if they would be involved in such program and with regard to broad prevalence of nonadherence and its huge potential to improve patients' health and reduce health care costs, it is recommended to implement such intervention.

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Appendices

List of Appendices

Appendix 1. Questionnaire

Vážená pacientko, vážený paciente,

děkujeme za spolupráci na výzkumu, jehož cílem je zmapovat chování pacientů na dialýze a zjistit, zda je pro pacienty možné vytvořit program, který by je motivoval k lepšímu dodržování léčby.

Vyplnění dotazníku Vám nezabere déle než 15 minut. Vámi poskytnuté informace budou sloužit pouze k uvedenému výzkumu a Vaše jméno nebude figurovat v žádné fázi výzkumu; dotazník je striktně anonymní. ***Vaše odpovědi nebudou poskytnuty žádné třetí osobě*** *(včetně ošetřujícího lékaře a ostatního personálu)* ***a v žádném případě nebudou mít vliv na Vaši léčbu.***

V tomto dotazníku neexistují správné či špatné odpovědi – důležitá je pro nás Vaše zkušenost. Odpovídejte, prosíme, co nejupřímněji.

Děkujeme

Bc. Petra Kučová a kol.

Užívání léků

1. Během Vaší léčby užíváte určité množství léků. Zkuste si vzpomenout na všechny léky, které máte předepsány, a prosím uveďte:

   kolik pilulek celkem denně užíváte: .....

   kolikrát denně léky užíváte: .....
   Př.: Pokud užíváte dvě pilulky ráno před snídaní, tři pilulky ráno po snídani, dvě v poledne a dvě večer, uveďte celkem 9 pilulek, 4x denně (před snídaní, po snídani, v poledne, večer).

2. Berete prášky pravidelně – tedy tak, jak Vám lékař předepsal?
   Pouze jedna odpověď
   a) Ano
   b) Ano, jen několikrát se mi stalo, že jsem zapomněl/a
   c) Ano, ale občas zapomenu
   d) Snažím se brát je pravidelně, ale nedaří se mi to
   e) Léčbu nedodržuji

3. Dělá Vám obtíže brát všechny léky tak, jak Vám je lékař předepsal?
   Pouze jedna odpověď
   a) Ano
   b) Ne

4. Kolikrát jste během posledních 14 dní zapomněl/a užít některý z léků, který Vám lékař předepsal? .....
   (počet opomenutých dávek)

Dietní omezení, pitný režim

S léčbou selhání ledvin je spojeno výrazné omezení příjmu tekutin a mnohá doporučení týkající se stravy, např. snížení příjmu soli, zvýšení příjmu bílkovin a vlákniny, vyvážení hladiny draslíku, fosforu, sodíku či vápníku. Dodržovat veškerá omezení a doporučení vyplývající z Vaší léčby je mnohdy velmi náročné a ne vždy se podaří všechna doporučení lékaře dodržet. Prosím, uveďte:

5. Kolik dní během posledních 14 dní jste opravdu dodržel/a veškerá doporučení lékaře týkající se **dietních** opatření? ..... *(počet dní - zapište číslicí v rozmezí 1 až 14)*
6. Pokud jste nedodržel/a některá dietní doporučení, jak závažné bylo toto odchýlení? *Ohodnoťte na stupnici od 1 do 5 (zakroužkujte číslici)*

   Minimální Mírné Závažné
   1 2 3 4 5
7. Kolik dní během posledních 14 dní jste opravdu dodržel/a veškerá doporučení lékaře týkající se **omezení příjmu tekutin**? ..... *(počet dní - zapište číslicí v rozmezí 1 až 14)*
8. Pokud jste nedodržel/a některá doporučení týkající se omezení příjmu tekutin, jak závažné bylo toto odchýlení? *Ohodnoťte na stupnici od 1 do 5 (zakroužkujte číslici)*

   Minimální Mírné Závažné
   1 2 3 4 5
9. Kolik litrů byl Váš průměrný **denní** příjem tekutin během posledních 3 dní?
   ……. *litrů*

Dialýza

10. Stalo se Vám během posledních 6 měsíců, že jste vynechal/a dialýzu?
    Pouze jedna odpověď
    a) Ano, vícekrát
    b) Ano, stalo se mi to jednou
    c) Ne, byl/a jsem na všech domluvených dialýzách
11. Zkrátil/a jste si někdy dialýzu? (během posledních 6 měsíců)
    Pouze jedna odpověď
    a) Ano, několikrát
    b) Ano, jednou
    c) Ne, nikdy

Celkové hodnocení dodržování léčby

Zamyslete se nyní nad tím, do jaké míry se Vám daří dodržovat léčbu (braní léků a docházení na dialýzu) a opatření s ní související (dietní omezení, omezení příjmu tekutin).

12. Jak byste celkově ohodnotil/a Vaše dodržování léčby a léčebných opatření?
    Vyjádřete v procentech, do jaké míry se Vám daří dodržovat léčbu a léčebná opatření:
    Uveďte v procentech na škále od 0 do 100, kde:
    100% léčbu a léčebná opatření vždy dodržuji
    50% léčbu a léčebná opatření dodržuji zhruba z poloviny
    0% léčbu a léčebná opatření se mi nedaří vůbec dodržovat

    ..... *(číslice 0 – 100%)*

13. Do jaké míry je pro Vás obtížné dodržovat:
    Zakroužkujte číslici odpovědi.

	Velmi obtížné	Spíše obtížné	Spíše mi nedělá problémy	Vůbec mi nedělá problémy
omezení příjmu tekutin	1	2	3	4
dietní opatření	1	2	3	4
správné užívání léků	1	2	3	4
pravidelné docházení na dialýzu	1	2	3	4

14. Které z následujících léčebných opatření je podle Vás nejnáročnější dodržovat, které Vám činí největší problémy?
    Pouze jedna odpověď
    a) Správné braní léků
    b) Omezení příjmu tekutin
    c) Dietní opatření

Program odměn

Představte si, že by byl zaveden program odměn pro pacienty na dialýze. Podobně jako například řidiči, kteří jezdí bez nehod, dostávají různé bonusy či slevy na havarijní pojištění, by v tomto programu byli pacienti odměňováni svou zdravotní pojišťovnou za správné užívání léků, dodržování doporučeného omezení příjmu tekutin a správné stravování. Odměny by byly financovány z úspor, které vzniknou snížením počtu komplikací díky správnému dodržování léčby.

15. Pokud byste byl/a zapojen/a do tohoto programu odměn, které z následujících odměn byste považoval/a za nejlákavější? Vyberte 3 pro Vás nejatraktivnější odměny a seřaďte je podle atraktivity.
    Zakroužkujte odpovídající křížek vybrané odpovědi
    – v každém sloupci zakroužkujte jeden křížek.

Odměna	**Nejlákavější**	**2. nejlákavější**	**3. nejlákavější**
1. Slevové poukázky na léky	x	x	x
2. Zajištění dopravy do dialyzačního střediska (mimo sanitku)	x	x	x
3. Slevové poukázky na doporučené potraviny, vitaminové doplňky	x	x	x
4. Slevové poukázky na rehabilitace či zdravotní cvičení	x	x	x
5. Slevové poukázky na sportovní aktivity	x	x	x
6. Slevové poukázky na kulturu	x	x	x
7. Finanční odměna ve výši 100 Kč/týdně	x	x	x

16. Pokud byste do takového programu byl/a zapojen/a, dbal/a byste více na správné užívání léků, dodržování doporučeného omezení příjmu tekutin a správnou výživu?
    Pouze jedna odpověď
    a) Určitě ano
    b) Spíše ano
    c) Spíše ne
    d) Určitě ne

Životní styl

Předposlední část dotazníku se týká Vašeho životního stylu.

17. Měl/a jste během posledních 14 dní makový koláč?
    Pouze jedna odpověď
    a) Ano
    b) Ne
18. Vztah ke kouření: Kouříte? Kouřil/a jste?
    Pouze jedna odpověď
    a) Ano, kouřím
    b) Ne, ale dříve jsem kouřil/a
    c) Ne, nekouřím a nikdy jsem nekouřil/a
19. Léčíte se s depresí či úzkostí?
    Pouze jedna odpověď
    a) Ano
    b) Ne

Demografické údaje

20. Pohlaví: muž žena

21. Rok narození: ……..

22. Jak dlouho jste léčeni dialýzou?
    Uveďte měsíc a rok započetí léčby: …….. *(např. 10/2013)*
    nebo celkovou délku léčby …….. (*např. 6 let)*

23. Jaké je Vaše nejvyšší ukončené vzdělání?
    a) Základní
    b) Vyučen/a
    c) Středoškolské bez maturity
    d) Středoškolské s maturitou
    e) Vysokoškolské
24. Podporuje Vás rodina v léčbě, pomáhá Vám?
    a) Ano
    b) Ne
    Toto byla poslední otázka dotazníku.
    Mockrát děkujeme za jeho vyplnění.

Appendix 2. Cross-tabulation of areas of nonadherence

	Fluid adherence	Fluid nonadherence
Medication adherence	47	72
Medication nonadherence	4	14

	Diet adherence	Diet nonadherence
Medication adherence	60	62
Medication nonadherence	2	16

	Appointment adherence	Appointment nonadherence
Medication adherence	108	16
Medication nonadherence	14	4

	Diet adherence	Diet nonadherence
Fluid adherence	38	13
Fluid nonadherence	22	64

	Appointment adherence	Appointment nonadherence
Fluid adherence	45	6
Fluid nonadherence	72	14

	Appointment adherence	Appointment nonadherence
Diet adherence	57	5
Diet nonadherence	63	15

Appendix 3. Patient characteristics in relation to nonadherence: details of univariate analysis

Medication nonadherence					
Predictor	Coefficient	p-value	% correctly predicted	Likelihood ratio test (p-value)	McFadden R^2
Personal characteristics					
Age (years)	-0.0280788	0.1547	88.1	0.1611	0.019989
Sex	0.318454	0.5556	87.5	0.5513	0.003464
Education	0.175590	0.4111	88.3	0.4078	0.006936
Smoking	-18.3905	0.9972	88.2	0.0139	0.061352
Depression	1.16375	0.1147	88.1	0.1422	0.021915
Family support	-0.558045	0.4259	88.2	0.4449	0.005924
Treatment characteristics					
Pills per day	-0.980806	0.1103	87.9	0.0720	0.031255
Pill frequency	0.107090	0.7233	87.1	0.7226	0.001176
Length of treatment (years)	0.0420345	0.3689	88.1	0.3885	0.007568

Fluid nonadherence					
Predictor	Coefficient	p-value	% correctly predicted	Likelihood ratio test (p-value)	McFadden R^2
Personal characteristics					
Age (years)	-0.0325645	0.0364	64.9	0.0293	0.027270
Sex	0.754841	0.0405	63.6	0.0394	0.024533
Education	-0.0983853	0.4882	62.4	0.4876	0.002736
Smoking	0.856051	0.1159	62.1	0.0980	0.015629
Depression	0.540517	0.4416	61.8	0.4271	0.003620
Family support	-0.433636	0.4432	62.1	0.4337	0.003499
Treatment characteristics					
Pills per day	-0.0389143	0.2872	63.0	0.2860	0.006395
Pill frequency	0.264809	0.2231	62.7	0.2200	0.008497
Length of treatment (years)	0.0133589	0.7157	61.8	0.7138	0.000772

Diet nonadherence					
Predictor	Coefficient	p-value	% correctly predicted	Likelihood ratio test (p-value)	McFadden R^2
Personal characteristics					
Age (years)	-0.0231224	0.1058	57.5	0.0988	0.014728
Sex	0.771385	0.0299	60.0	0.0286	0.025788
Education	0.0585050	0.6681	54.4	0.6679	0.000982
Smoking	0.709030	0.1520	54.1	0.1417	0.011593
Depression	2.28632	0.0317	53.7	0.0052	0.042204
Family support	-0.470334	0.3838	54.8	0.3767	0.004204
Treatment characteristics					
Pills per day	-0.0532116	0.1414	58.7	0.1347	0.011812
Pill frequency	-0.159349	0.4398	55.5	0.4375	0.003218
Length of treatment (years)	-0.0235268	0.5015	53.7	0.5001	0.002457

Appointment nonadherence					
Predictor	Coefficient	p-value	% correctly predicted	Likelihood ratio test (p-value)	McFadden R^2
Personal characteristics					
Age	-0.0437455	0.0236	87.4	0.0240	0.049855
Sex	1.13316	0.0558	86.0	0.0394	0.038580
Education	-0.109290	0.5872	56.9	0.5862	0.002779
Smoking	2.08901	0.0002	86.8	0.0002	0.127635
Depression	1.50181	0.0291	86.7	0.0411	0.039341
Family support	-0.395896	0.5681	86.8	0.5798	0.002884
Treatment characteristics					
Pills per day	0.0002405	0.9962	86.4	0.9962	0.000000
Pill frequency	0.0403447	0.8909	86.3	0.8908	0.000170
Length of treatment (months)	-0.0218951	0.7007	87.4	0.6923	0. 001532

Appendix 4. Results of logistic regression model

	Medication nonadherence		Fluid nonadherence		Diet nonadherence		Appointment nonadherence	
	Odds ratio	p-value	Odds ratio	p-value	Odds ratio	p-value	Odds ratio	p-value
Personal characteristics								
Age	0.95	0.0365	0.98	0.17701	0.98	0.2425	0.98	0.3947
Sex (ref.: male)	1.47	0.5776	1.92	0.12043	3.14	0.0115	2.05	0.3406
Education	1.33	0.2853	1.02	0.91691	1.22	0.2415	0.96	0.8839
Smoking	0.00	0.9988	1.53	0.49109	2.14	0.2431	6.32	0.0080
Depression	9.21	0.0439	1.37	0.69389	27.72	0.0073	1.74	0.6135
Family support	0.75	0.7561	0.63	0.48006	0.59	0.3911	1.53	0.7183
Treatment characteristics								
Pills per day	0.83	0.0559	0.91	0.05202	0.86	0.0056	0.94	0.4562
Pill frequency	1.57	0.2525	1.74	0.05151	0.98	0.9504	1.71	0.2115
Length of treatment (years)	0.97	0.7283	0.98	0.67212	0.91	0.0307	0.95	0.4562

Note: ref. – reference; all dependent variables are coded as 1 for nonadherent patient and zero for adherent patient.

Appendix 5. Association between patient characteristic and nonadherence: results of univariate analyses (odds ratio)

	Medication nonadherence	Fluid nonadherence	Diet nonadherence	Appointment nonadherence
Personal characteristics				
Age	0.97	0.98	0.99	0.98
Sex (ref.: male)	na.	1.89*	2.83**	na.
Smoking	na.	1.59	1.62	6.73***
Depression	4.09*	na.	16.24**	1.76
Treatment characteristics				
Pills per day	0.89	na.	0.90**	na.

Note: ref. – reference, na. – not applicable, * p-value < 0.1, ** p-value < 0.05, *** p-value < 0.0.1

Appendix 6. Association between patient characteristics and nonadherence: results of univariate analyses

	Medication nonadherence	Fluid nonadherence	Diet nonadherence	Appointment nonadherence
Personal characteristics				
Age	0.1547	0.0364	0.1058	0.0236
Sex	0.5556	0.0405	0.0299	0.0558
Education	0.4111	0.4882	0.6681	0.5872
Smoking	0.9972	0.1159	0.1520	0.0002
Depression	0.1147	0.4416	0.0317	0.0291
Family support	0.4259	0.4432	0.3838	0.5681
Treatment characteristics				
Pills per day	0.1103	0.2872	0.1414	0.9962
Pill frequency	0.7233	0.2231	0.4398	0.8909
Length of treatment (months)	0.3657	0.7203	0.4897	0.7195

Note: figures show p-values of respective regression coefficient in univariate analysis