COMPARISON OF TWO DIFFERENT METHODS (PATIENT QUESTIONNAIRE AND MEDICATION POSSESSION RATIO - MPR) FOR MEASURING THE CHRONIC PATIENT'S BEHAVIOR

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SUMMARY

Background: Medication adherence is the extent to which patients take medications as prescribed by their health care providers. There are a number of approaches to study medication-taking behavior. The aim was to compare two most common methods for measuring adherence: Patient Adherence Questionnaire and Medication Possession Ratio (MPR). They belong to the indirect methods.

Methods: In this article four adherence studies were analysed and the results were compared, two wherein the patient questionnaire was applied and other two with medication possession ratio applied.

Results: The obtained results reveal that more than half of respondents (58.9%) experienced constant nonadherence behavior according to the prescribed therapy. The main reason of nonadherence is oblivion, suggesting that it is necessary to pay more attention to this problem.

Conclusions: Nonadherence with therapy has negative consequences on the health of the individual, and an adverse impact on the community health and wealth. Patients should be informed of the importance of regularly taking prescribed therapy. The main problem of long-term therapy is significantly decreased of adherence to medication in a very short time. It is important to stress that almost all the interventions effective for improving patient adherence in long-term care are complex and should be repeated after a while.

Key words: *adherence - medication prescribing – patient's adherence questionnaire - medication possession ratio - pharmacy claims data*

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INTRODUCTION

Medication adherence is generally defined as the extent to which patients take medications as prescribed by their health care providers (Dobbels et al. 2005). Therapy is the act of taking drugs on schedule or taking medication as prescribed. There are a number of approaches to study patient's medication-taking behavior. The most precise methods are directly observed therapeutic outcome, biological methods: measuring the level of medicine or metabolite (blood or urine drug concentrations). Other methods are clinician reports, pill counts, rates of prescription refills, electronic medication monitors, patient diaries, patient self-report scales. Questionnaires have the benefits of being cheap, easy to administer, non-intrusive, and able to provide information on attitudes and beliefs about medication.

There are a number of reasons why patients do not adhere or comply with their medication regimen (Jakovljevic 2014b). The common factors that interfere with medication adherence are social/economic-related factors (age, race, economic status, medication cost), survivor-related factors (forgetfulness, treatment anxiety, mis-understood instructions, fear of becoming dependent on medication), medication-related factors (length of treatment, complexity of treatment, unwanted side effects) and the condition-related factors (level of disability, severity of the condition).

Nonadherence greatly increases the nation's health care bill. The emphasis must be on the interventions on different levels (physician, pharmacist, newspapers, television and so on) with the aim to decrease nonadherenceand improve the therapeutic outcomes. Paradoxically, as cost-driven nonadherence pushes total health care costs higher, these same insurance companies may find themselves less profitable over the long run as they face the high cost of complications caused by medication nonadherence (Hofmann 2013).

The aim is to compare two most common methods for measuring adherence: Patient Adherence Questionnaire and Medication Possession Ratio (MPR) which belong to the indirect methods. Analyses of prescription refills can provide crucial insights into patient willingness to comply. This can be a valuable adjunct to medication management of the individual patient (Roth & Caron 1978, Goldberg et al. 1998, Dezii 2001).

Table 1. Description of four adherence studies

Study	Pharmacy	No. of patients	Method for adherence measurement	Published
Study 1	City pharmacy Zagreb (Gradska ljekarna Zagreb)	635	Self-report questionnaire	Culig J, Leppée M, Boskovic J. Eric M. Determining the difference in medication adherence between the general patient population and patients receiving antihypertensive therapy: A case study. Arch Pharm Res 2011; 34:1143-52. doi 10.1007/s12272-011-0712-0
Study 2	Pharmacies in Varazdin County	56	Self-report questionnaire	Fuckar S. Adherence to medication according to long-term therapy. Thesis. School of Medicine, Josip Juraj Strossmayer University Osijek, 2011.
Study 3	Private pharmacy in Zagreb	150	MPR	Leppée M, Boskovic J, Culig J, Eric M. Pharmacy claims data as a tool to measure adherence. Curr Med Res Opin 2012; 28:1389-93. Posted online on June 22, 2012. doi 10.1185/03007995.2012.705781)
Study 4	Pharmacy Atlantic Zagreb	142	MPR	Mandic-Zovko N. Measuring of adherence to therapy by Medication Possession Ratio (MPR). Thesis. School of Pharmacy and Biochemistry, University of Zagreb, 2014.

METHODS

Four adherence studies are analyzed (Table 1). The study 1 and 2 was designed as a cross-sectional survey by use of a self-administered questionnaire and in the studies 3 and 4 pharmacy claims data were used. The study 1 (Culig et al. 2011, Culig & Leppée 2014) included 635 individuals collecting or buying drugs for the treatment of chronic diseases, with special reference to subjects taking antihypertensive agents (n=361). A total of 1500 questionnaires were distributed of whom 635 (42.3%) questionnaires can be utilized in the statistical analysis. The survey was conducted at Zagreb pharmacies and the 33-item questionnaire was filled out by study subjects with instructions and help provided by the pharmacist as questionnaire administrator. The questionnaire was anonymous and study subjects could ask the pharmacist about any possible vagueness.

According to medication adherence behavior, study subjects were divided into two groups of adherent and nonadherent, as declared by them. The subjects answering the respective question that they had never failed to take their medication on time were considered as adherent, and all others as nonadherent. The questionnaire listed 16 common reasons for nonadherence and study subjects had to answer questions on each of these reasons as the possible cause of his/her nonadherence. These answers were used to analyze the impact of each of these reasons for nonadherence.

The study 2 was conducted in pharmacies in Varazdin County (Fuckar 2011). The survey was conducted in three pharmacies in the wider area of the city of Varazdin and two pharmacies in the town of Varazdin. A total of 100 questionnaires were distributed of whom 56 (56%) questionnaires can be utilized in the statistical analysis. Patients have occasion to raise drug prescribed prescription for a chronic condition in public pharmacies, voluntarily and anonymously completed the questionnaire with the help and guidance pharmacist. Adherence Scale Čulig (Appendix) is attached to the end of the work. All the respondents in terms of persistence to therapy were divided into the adherent and non adherent. The survey indicated 16 very frequent reasons of nonadherence. Based on the responses we analyzed the impact of individual reasons of nonadherence.

In the other two studies (3 and 4) pharmacy claims data were used. In study 3 data of 150 patients were analysed in one Zagreb's public pharmacy to find out the rate of adherence to chronic disease medication (Leppée et al. 2012). Three consecutive dates of filling/ refilling medications for each of 150 patients were analyzed; first at the beginning of the analysis period, followed by the second and third date when the patient is refilled medication. A first pharmacy record dating from the 5th October 2010 and last from 29th September 2011, which implies that the our small study involved pharmacy data in a period of about one year. MPR is used as a measure of adherence to chronic disease medication. The MPR is often defined as the sum of the days' supply of medication divided by the number of days between the first fill and the last refill plus the days' supply of the last refill. This calculation usually results in a ratio less than 1.0 if there are lapses in prescription refilling. Early refilling would lead to an MPR of more than 1.0; the MPR in such a case is often truncated at the maximum value of 1.0, indicating the potential for perfect adherence.

We used the premise that pharmacy claims data and refilling the prescribed medication can be used to determine MPR, and that MPR can be used as a marker of patient adherence to prescribed medication; however, whether the patient consumed it as directed is not certain.

While the analysis of this information does not reveal whether a pill is actually being ingested, it can be reasonably assumed that patients would not continue to

refill a prescription without the intention to adhere. The inclusion criteria were having at least one prescription for chronic disease (long-term medication) in the beginning of the analysis period and during the analysis period (second and third refill). Adherence was measured as a function of the gaps between refills to provide timely information on the dynamics of patient medication adherence. We believe that identification of gaps in medication supply is clinically important. Creating a mechanism whereby clinicians are informed of these refill gaps might help stimulate early intervention, or improve the quality of otherwise scheduled clinical encounters (Hansen et al. 2010). Following past MPR-related studies (Bramley et al. 2006, Fung et al. 2007, Andrade et al. 2006) we take a patient as adherent to therapy only when his/her MPR for each medication is at least ≥80% (Mabotuwana et al. 2008).

In the study 4, that was the administrative claims study, the data on adult patients with multiple chronic disease treated with more than one medication on their first contact with the medication were used (Mandic-Zovko 2014). Authors used pharmacy claims data for 142 patients in one Zagreb's public pharmacy to find out the rate of adherence to chronic disease medication. Patients in this pharmacy receive supplies for various numbers of days (usually for 30 days) depending of kind of medication. Our study involved pharmacy data in a period of about half a year. We used the premise that pharmacy claims data and refilling the prescribed medication can be used to determine Medication Possession Ratio (MPR), and that MPR can be used as a marker of patient adherence to prescribed medication; however, whether the patient consumed it as directed is unknown. Following past MPR-related studies, we take a patient as adherent to therapy only when his/her MPR for each medication is at least ≥80%. The inclusion criteria were having at least one prescription for chronic disease (long-term medication) in the beginning of the analysis period and during the analysis period.

At each patient's visit to the pharmacy, a pharmacist recorded the type and quantity of prescribed and dispensed medication (according to the Anatomical Therapeutic Chemical (ATC) Classification for each medication), diagnosis, a total of up to ten drugs per patient, and some demographic data (name, age, gender). MPR with variable (start to end of therapy) as a measure of adherence to therapy were calculated. MPR was calculated by summing days supply from the first to the last prescription (inclusive) divided by the time between the last prescription date plus days' supply and the first prescription date. Variable MPR was evaluated for all patients and the continuously eligible cohort. Acceptable adherence was defined as an MPR of ≥80%. MPR for each medication is calculated for each patient. If the patient had more than one medication, calculated is average MPR per patient (for all medications). This study was conducted under the supervision of the Department of Pharmacoepidemiology, Andrija Stampar Institute of Public Health, Zagreb, Croatia.

Statistic analysis

Descriptive statistics were used to summarize patient demographics, adherence characteristics, medication variables, and the occurrence of discontinuation. Because the purpose of using refill records is to improve intervention efficiency and identify high risk patients, we focused on minimizing the false positive rate. Student's t-test, a Mann-Whitney Rank Sum test, Chi-square test and multiple linear regressions were used. The Mann-Whitney Rank Sum test was used to examine differences in adherence among patient subgroups. A significance level of $P<0.05$ was used when appropriate for the evaluation of the results. The analysis had enough statistical power to detect the significant difference that would have been evident if the statistical power had been greater. A priori, we set 20% as a threshold for the false positive rate that would be acceptable for clinical application of this method. All analysis was performed with SigmaStat 3.0 for Windows (SPSS Science software products, Chicago, IL, US).

RESULTS

Study 1

In study 1 more than half (n=361; 56.9%) of 635 study subjects were on therapy for arterial hypertension and also for some other diseases. A total 1,357 diagnoses were reported by survey respondents (i.e., an average of 2.1 diagnoses per respondent). The most common diagnoses were diseases of the circulatory system (n=500, 36.8%) and the group of endocrine, nutritional and metabolic diseases (n=285; 21.0%). The number of subjects increased with age, with almost two thirds (64.7%) of subjects older than 55, which is consistent with the known drug utilization increase with age. This relation was even more pronounced in the group of subjects treated for arterial hypertension. In the total study population (n=635), nonadherent subjects prevailed over adherent subjects (n=370; 58.3% vs. n=265; 41.7%). The rate of medication adherence was lower in the group of subjects treated for arterial hypertension as compared with total study population, however, the difference was not statistically significant (p=0.501). The rate of adherent and nonadherent subjects is shown in Table 2. The level of adherence was found to slightly increase with age, so the subjects older than 65 showed a higher level of medication adherence as compared with other age groups. A similar pattern was observed in the group of subjects with arterial hypertension; however, the difference did not reach statistical significance. There was no statistically significant difference in age distribution between total study population and subjects treated for arterial hypertension reporting medication adherence (P=0.298) and medication nonadherence (p=0.273). The great majority of study subjects stated forgetfulness as the main reason for skipping drug dose (n=381; 60.0%),

Table 2. Comparison of the adherence in the Studies 1-4

Study	Adherent		Nonadherent		Total		p
	n	%	n	%	n	%	
Study 1	265	41.7	370	58.3	635	100.0	p>0.5
Study 2	23	41.1	33	58.9	56	100.0	p>0.5
Study 3	54	36.0	96	64.0	150	100.0	p>0.5
Study 4	132	93.0	10	7.0	142	100.0	p<0.05

Table 3. Reasons for medication nonadherence in Studies 1 and 2

Reason for skipping drug doses	Study 1		Study 2	
	n	%	n	%
I just forgot	381	60.0	20	35.7
I was not at home	288	45.4	4	7.1
I fell short of the drug (I had consumed all of it)	282	44.4		
I had problems with the timing of the medication	260	40.9	4	7.1
I take a number of drugs several times a day	251	39.5	8	14.3
The drug was not available due to shortage of supply	228	35.9		
I was feeling well	228	35.9	8	14.3
I wanted to avoid side effects	188	29.6		
My doctor has frequently changed my therapy	165	26.0		
I felt the drug could be toxic/harmful	150	23.6		
I was feeling sleepy at the time of taking the medication	145	22.8		
I felt depressed or broken hearted	145	22.8		
I was afraid of developing drug dependency	143	22.5		
I had cold	133	20.9		
The drug was too expensive	132	20.8		
I did not want other people to see me while taking the drug	79	12.4		
Other			12	21.4

followed by not being at home (n=288; 45.4%) and being short of the drug (having used it all) (n=282; 44.4%) (Table 3). Like total study population, the majority of subjects treated for arterial hypertension reported forgetfulness as the main reason for medication nonadherence (n=220; 60.9%). The second most common reason was a drug shortage (n=169; 46.8%) and being away from home (n=163; 45.2%). Comparison of reasons for medication nonadherence in the total study population versus subjects on antihypertensive therapy showed no statistically significant difference in any of the reasons (P=0.895), indicating that subjects treated for arterial hypertension did not differ from the total study population according to the reasons for medication nonadherence. Analysis of reasons for medication nonadherence according to age groups in the total study population pointed to forgetfulness as the leading reason (61.0%) in the oldest and largest age group (66+; n=249) as well as in all other age groups. In the 66+ age group, the second leading reason for medication nonadherence was a drug shortage (41.4%), followed by taking a number of drugs several times a day (41.0%). The latter reason was not among the first three reasons in any other age group. Absence from home was the second leading reason in most age groups; however, in the 66+ age group it ranked only fifth reason for medication nonadherence. In the 56-65 age group, away from home and drug shortage were the

second and third leading reasons for medication nonadherence (51.2% both).

There was no statistically significant difference among particular age groups according to the four leading and major reasons for medication nonadherence, indicating that age had no effect on these reasons. Analysis of reasons for medication nonadherence according to age groups in the group of subjects treated for arterial hypertension indicated forgetfulness as the leading reason (60.8%) in the oldest and largest age group (66+; n=166) as well as in all other age groups. In the 66+ age group, the second leading reason for medication nonadherence was taking a number of drugs several times a day (42.2%), and it ranked so high only in this age group. It was followed by a drug shortage (42.2%) and having problems with medication timing (37.3%). Absence from home ranked second in other age groups, while sharing only the sixth to seventh place in the 66+ age group. In the 56-65 age groups, absence from home ranked second (52.9%) and shortage of drug third (51.0%), the same pattern being recorded in the 46-55 age groups. There was no statistically significant difference among particular age groups according to the four leading reasons for medication nonadherence (P=0.171), suggesting that age had no impact on the reasons for medication nonadherence in subjects treated for arterial hypertension either. In the latter, age had no effect on the reasons for nonadherence, i.e. the same

pattern was recorded across all age groups, although forgetfulness was expected to be more common in older age groups.

Study 2

In the study 2, there were 56 patients of all ages included. Most of the respondents were in the middle age groups, i.e. 40-69 years of age (n=44, 78.6%). In particular, in the range of 40-49 years in the survey were attended by 15 participants, or 26.8% of all respondents. At the age of 50-59 years participated in 16 respondents, or 28.6 % of all respondents, as this age group makes the most members. Also a large number of respondents (n=13) were in the age group of 60-69 years in the percentage of 23.2% of all respondents. Of the total number of subjects (n=56), there were more nonadherent (n=33, 58.9%) than adherent (n=23, 41.1%).

Considering the relatively small number of subjects in the study (n=56), only the respondents in the middle age groups (40-69 years) were analyzed and it was found again that adherence increases with age. In the age group 40-49 were 33.3% adherent subjects, in the next age group (50-59 years) adherent subjects increased to 43.8%, and in the next age group (60-69 years) participation of adherent subjects were 46.2%. Women were significantly more adherent than men (60.9%:39.1%). Of the listed reasons, the most of the respondents indicated oblivion (n=20, 35.7%) as the main reason of nonadherence. As the second and third reason follows the taking multiple medications several times a day and good sense (n=8, 14.3%). On the fourth and fifth place were the fact that he/she was not at home and that he/she had problems with taking the drug at a specific time (n=4, 7.1%).

Respondents were the most frequently treated from diseases of the heart and blood vessels (n=44, 45.4%), accounting for almost half of all diagnoses (n=97).

Study 3

The study 3 was a pilot study which includes 150 patients with chronic disease medications prescribed. According Medication Possession Ratio (MPR) the most patient were nonadherent (n=96; 64.0%). Most patients (n=130, 86.7%) were with one or more ATC group C (cardiovascular) medication prescribed. There was not a significant difference between adherence for all patients with prescribed chronic disease medication, patients with prescribed ATC group C medication and patients with medication other than group C (p=0.333).

It needs to be noted that herein we present an analysis using overall MPR and C medication MPR, but the same analysis can be carried out on a drug class specific basis as well (using the drug class specific MPRs) if required. Medication nonadherence due to cost issues among study patients was evaluated. We analyzed patients with and without co-payment for medication. Adherence was surprisingly slightly higher in those

without co-payment, but there is no difference among these two groups of patients (p=1.000).

We analyzed up to five medications per patient. The most patients used a combination of two (n=44, 29.3%) and three (n=34; 22.7%) medications. There was no difference between patients with different number of medications (from one to five) according to adherence rate (p=0.071).

Study 4

In study 4 were included 142 patients with chronic disease medications prescribed. The female patients predominated over the male (female: n=75; 53.5%, male. n=67; 46.5%). The patients were mostly older than 70 (n=57; 40.1%) and in the 60-69 age group (n=48, 33.8%). Almost two-thirds of patients were 60+ (n=105; 73.9%). We analyzed up to a maximum ten medications per patient. The most patients (n=92; 64.8%) used two (n=54; 38.0%) and three (n=38; 26.8%) medications. Only 28 patients (19.7%) take only one drug (single medication). All study patients have taken 485 medications, what is the average of 3,42 per patient. Initial MPR in the initial phase was in 132 patients (93.0%), 80%≤MPR, which means that they were adherent to medication. Over time, that rate has decreased (only 15.0% at fifth refill!).

For the duration of drug taking, adherence to therapy continuously was falling and the number of patients with the same MPR was reduced. After three refills 100% ≤MPR patients are reduced for one-third (35.3%). A number of the patients with initial MPR 90% ≤MPR<100% reduced for three-fourth (73.8%) and the patients with 80% ≤MPR<90% halved (for 54.5%) (Table 4).

Table 4. Comparison of Medication Possession Ratio (MPR) among Study 3 and Study 4

MPR Condition	Study 3		Study 4	
	n	%	n	%
100% ≤MPR			68	47.9
90% ≤MPR<100%	54	36.0	42	29.6
80% ≤MPR<90%			22	15.5
60% ≤MPR<80%	78	52.0	7	4.9
40% ≤MPR<60%	15	10.0	2	1.4
MPR<40%	3	2.0	1	0.7
Total	150	100.0	142	100.0

There was some different number of refills among study patients. The most patients had four refills (57; 40.1%), followed by three refills (33; 23.2%). Long-term drug therapy decreased the adherence. As people take a medication a longer time, adherence to this medication more decreases. Difference among first and last MPR is bigger at the high number of refills. This means increasing the drop of adherence to medication according to the number of refills. During the five refills adherence to therapy decreased by 51.2% (from 100.%

to 48.8%) and after only two refills it decreased by 17.7% (from 100.0% to 82.3%). The difference in the median values between all two groups (first and last) in any refill number was a statistically significant (p≤0.001). There was no statistical significant difference between numbers of medications, according to adherence to therapy. There is no statistic significant difference among medications for different diagnosis, according to MPR Average MPR is a 103.4 indicating excellent adherence to medication regardless of type of disease. In the initial phase of testing they probably had a stock of medications and towards the end of the study MPR decreased, so that the average MPR is high.

DISCUSSION

In present article we compared two most common methods for measuring adherence: Patient Adherence Questionnaire and Medication Possession Ratio (MPR) which belong to the group of indirect methods. The common characteristic of both methods is the degree of adherence, but in all other aspects, patient questionnaire has the advantages: someone can get many other data related to patient, such as demographic, social, economic and other characteristics, the relationship between patient, physician and pharmacist, data about patients' diseases and many other data. MPR is simple in regard to the questionnaire, but is cheaper and easier to perform because it uses pharmacy claims data and do not require the work of interviewers. Among the many reasons people give for not adhering to drug treatment, forgetfulness is the most common. The key question is: Why do people forget? Sometimes, the psychological mechanism of denial is at work. Having a disorder causes concern, and having to take a drug as a constant reminder. Or, something about the treatment, such as possible side effects, may greatly concern the person, resulting in a reluctance to follow the plan. By discussing concerns, people can learn that denial of their disorder and misconceptions about their treatment can lead to forgetting to take drugs as prescribed, resulting in unwanted effects and therapeutic failure (The Merck's Manuals 2007).

Research on adherence has typically focused on the barriers patients face in taking their medications. Common barriers to adherence are under the patient's control, the interventions toward them are necessary step in improving adherence behavior. The typical reasons cited by patients for not taking their medications included forgetfulness (30 percent) (Osterberg & Blaschke 2005). The absence from home could also be associated with forgetfulness since the patient should have thought about dosing scheme and bring drug along when going out. The next reason reported by study subjects was shortage of drug, which could also be related to forgetfulness, i.e. failure of drug supply on time. Positive attitude towards own ability to comply with physician's medication instructions predominated

over negative attitude in all age groups. A similar pattern was also recorded in the group of subjects treated for arterial hypertension, although higher motivation for regular therapy administration was expected in older hypertensives. Hypertensive subjects showed a statistically significantly higher rate of positive attitude towards treatment and ability to comply with medication instructions than those that were not sure about it. Self-reported medication taking adherence behavior of 132 high blood pressure patients was analyzed using an expanded version of the health belief model. Bivariate analysis showed that control over health matters, depend on providers, perceived barriers, duration of treatment, and others' nonconforming experience were significantly related to adherence (p<0.05). Log-linear multivariate analysis revealed that three of these five variables-control over health matters, perceived barriers, and duration of treatment-contributed independently to patient adherence. Self-reported medication taking was significantly related to blood pressure control (p<0.02). These data provide the basis for developing interventions for providers to facilitate the medication taking behavior of clinic patients (Hershey et al. 1980).

Patients with chronic diseases such as asthma, hypertension and diabetes have difficulty in adherence to prescribed therapy, resulting in unsatisfactory control of the disease.

Problem of adherence can be seen in all the situations when it is necessary that the patient is receiving therapy alone, regardless of the type and severity of the disease and the availability of health care. Low persistence is the main reason for lack of clinical benefit of therapy. It causes medical and psychosocial complications of the disease, reduces the quality of patients' lives, and wasted health resources. It is necessary to maintain a high adherence, because the patients with high levels of adherence have a significantly lower risk of cardiovascular disease. Patients who are within 120 days after the myocardial infarction took a single dose of the prescribed therapy had an increased likelihood of death by 80 % compared to those who took, and those who have taken some medication had a 44 % greater chance of death (Jackevicius et al. 2008). Often, patients discontinue therapy within one year of the first prescription (Kulkarni et al. 2006). The patients who are treated with antihypertensive but lowering therapies perseverance is poor, a third of them are persistent within 6 months (Chapman et al. 2005). Only 26 % of elderly patients who started taking statins to reduce the risk of coronary heart disease are retained high level five years later. The largest decline occurred perseverance during the first 6 months (Benner et al. 2002). We have found that in patients with age slightly increases the degree of persistence and the elderly show a higher degree of persistence than other age groups, corresponding to the data found in the literature (Morris et al. 2006). In

developed countries, people over the age of 60 spend about 50% of all prescribed drugs (about three times more per capita than in the general population) and are responsible for 60 % of all costs related to drugs, even though they're only 12% to 18% of the population in these countries (Eney & Goldstein 1976).

In that study nonadherent subjects prevailed over adherent (64.0%) which was slightly higher rate than in our Croatian studies (adherence has been based on patient self-report (58.3%). The similar difference is found in nonadherence to cardiovascular and antihypertensive therapy in both studies (63.1%/60.7%). We used pharmacy claims data for a small group of chronic patients and sought to identify a medication gap length between refills that may be useful in introduction action to improve patient adherence. The lengths of gaps varied in great range from eight months to lower. Some authors found that gaps between 8 and 19 days were highly predictive of discontinuation without exceeding a 20% false positive rate. Through electronic prescribing records, general practices can identify substantial levels of long-term medication adherence problems (Mabotuwana et al. 2009). There is some vagueness about measurement of adherence to therapy by prescription claims data. Many people obtain drugs regardless of the needs and refill or pharmacy claims data cannot be a true indicator of timely taking medications. After five refills (months), only 48.6% of patients are adherent to therapy. Clinicians tend to overestimate medication adherence, inadequately detect poor adherence, and may therefore miss important opportunities to intervene to improve antiretroviral adherence (Miller et al. 2002). For example, one study addressing differences in adherence between a one-pill combination-drug therapy and a two-pill polytherapy shows an adherence benefit with combination products (Dezii 2000). Many interventions to improve patient adherence are unsuccessful and sound theoretical foundations are lacking.

Comparisons are difficult, due to differences in adherence measures, intervention methods and in study populations (Dodds & Rebair-Brown 2000). The problem of prescription claims data is inability to verify regularity of medication intake, although the patient regularly purchases a medication. For patients in the most countries it is common to fill 90-days supplies of maintenance medication using retail or mail order channels. In Croatia patients refill medications as needed and only by retail. We used pharmacy claims data for a small group of chronic patients and sought to identify a medication gap length between refills that may be useful in introduction action to improve patient adherence. The lengths of gaps varied in a great range among patients and the same patient raises a variety of drugs in different terms.

Poor adherence to medications is associated with worse health outcomes (Ho et al. 2006, Simpson et al. 2006) and increased health care costs (McCombs et al. 1994). Furthermore, many factors associated with poor

adherence have been identified, including but not limited to increase cost-sharing, pill burden and regimen complexity, side-effects, and patient beliefs about whether the drugs actually improve their health. Again, it is noteworthy that these studies almost universally measure the effect of interruptions (secondary nonadherence) or discontinuations (lack of persistence) with chronic medical therapies that have actually been started. Improving adherence to exercise, diet, and medication as well as focusing on addictive disorders such as smoking cessation requires patient, provider, and health care system combined approach (Miller 2011). The placebo and nocebo phenomenon and its psychobiological underpinnings, as well as mastering placebo-nocebo responses in everyday clinical practice must be taken into account (Jakovljevic 2014a). It can change a patient's sense of health and significantly affect the patient's adherence to medication. Further research of this effect is needed.

Person-centered medicine method for improving adherence can be remembered by the acronym SIMPLE: Select medications respecting the patient's preference and Simplify the regimen; Increase knowledge; Modify negative patient's attitudes and behaviors; Provide person-centered pharmacotherapy and motivational interviewing; Leave paternalism and empower patients to self-manage their medical condition; and Evaluate adherence regularly (Jakovljevic 2014b).

Limitations

The limitations of this report include several factors as: the consideration of a relatively small sample of patients, claims data within single pharmacy in Zagreb, the results may not be generalizable, in case of medication switching adherence is difficult to measure with pharmacy claims data and some patients may have additional drug use not captured within the claims database (e.g., samples, cash purchases). MPR does not provide accurate information on the continuity of medication usage and the precise measurement of each medication adherence, identification eventually drug stockpiles, measurement of gaps in medication supply with special emphasis on the allowable gap to obtain a refill of medications and calculation of a grace period are some attempts to remedy this limitation. The combination of an MPR and an adherence metric could provide timely information on the dynamics of patient medication adherence. MPRs rely on the accuracy of the days' supply figure provided by the pharmacist. In the case of inhalers, injectables and liquids, these figures are notoriously unreliable, so the reporting of an MPR is simply not appropriate for many medications. For oral pills, the problem is less significant but comes into play when different drug dosages have price parity and/or pill-splitting is common (Motheral. 2013). Study limitations included also lack information on reasons for medication initiation and discontinuation, severity of disease symptoms, and use of over-the-counter medications.

CONCLUSIONS

The both methods used reveal that more than half of respondents (cca 58%) experienced constant nonadherence according to the prescribed therapy. However, a difference between these methods in terms of determining the rate of adherence is not statistically significant. Nonadherence with therapy has negative consequences on the health of the individual, and an adverse impact on the community. The main reason of adherence is oblivion, suggesting that it is necessary to pay more attention to this problem. Patients should be informed of the importance of regularly taking prescribed therapy, and in agreement with them to figure out a good way to remind them to take the prescribed therapy. Of great help could be various applications for alerting on mobile devices that are now in mass use. After analyzing the reasons of nonadherence, we conclude that the adherence to the medication increases with age.

The main problem of long-term therapy is significantly decreased of adherence to medication in a very short time after prescribing. It is important to remember that almost all the interventions effective for improving patient adherence in long-term care were complex, including a combination of more convenient care, information, reminders, self-monitoring, manual telephone follow-up, reinforcement, counselling, family therapy, psychological therapy, crisis intervention, and supportive care (Haynes et al. 2008).

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Appendix. Adherence Scale Culig

A. General information

1. Age a) 26-35 b) 36-45 c) 46-55 d) 55-65 e) 65+	4. Education a) university degree b) bachelor degree c) high school d) primary school e) non of stated	7. Marital status a) married b) divorced c) widower/widow d) extra-marital relationship e) never married

2. Gender
 a) male
 b) female
	5. Croatian veteran
	 a) yes
	 b) no
		8. Disability
		 a) yes
		
		   if yes, what
		   percentage?_____
		 b) no

3. Employment a) employed b) unemployed c) retired d) beneficiary of social assistance e) student f) housewife g) farmer h) other	6. Do you live alone a) yes b) no	

B. These questions revealed the subject's attitude towards his ability to comply with the physician's instructions and whether he/she believe his/her therapy to be beneficial for his/her health

	Question	I am not sure at all	I am quite sure	I am very sure	I am absolutely sure
1.	Are you sure you will be able to comply with your physician's medication instructions?	0	1	2	3
2.	Are you sure that treatment will be positive for your health?	0	1	2	3

C. Community (family and friend) support in your health treatment

	Question	I am very unsatisfied	I am mostly unsatisfied	I am mostly satisfied	I am very satisfied
1.	Are you satisfied with the support of your family and friends?	0	1	2	3
2.	Do your family and friends remind you to take medication on time?	0	1	2	3

D. When was the last time when you failed to take your medication

1. last week	☐	4. 1-3 month ago	☐
2. 1-2 week ago	☐	5. more than 3 months ago	☐
3. 3-4 week ago	☐	6. I never fail to take my medication on time	☐

E. People do not take their medication for various reasons. Here is a list of reasons for not taking your medication/drug

	Cause of nonadherence	Never	Very rare (1-2 yearly)	Sometimes (3-5 yearly)	Often (more than 5 yearly)
1.	I was not at home	0	1	2	3
2.	The drug was not available due to the short supply	0	1	2	3
3.	I just forgot	0	1	2	3
4.	I take a number of drugs several times a day	0	1	2	3
5.	I wanted to avoid side effects	0	1	2	3
6.	I did not want other people to see me taking drug	0	1	2	3
7.	My doctor frequently changes my therapy	0	1	2	3
8.	I felt the drug to be toxic/harmful	0	1	2	3
9.	I felt sleepy at medication time	0	1	2	3
10.	I had cold	0	1	2	3
11.	I felt depressed or broken	0	1	2	3
12.	I had problems with taking medicine at specific time (eg. with meal, on an ampty stomach)	0	1	2	3
13.	I have ran out of medication	0	1	2	3
14.	I felt well	0	1	2	3
15.	I was afraid of developing drug dependence	0	1	2	3
16.	The drug was too expensive	0	1	2	3

F. How often during the last week you

	Question	Never	Rarely	Sometimes	Often
1.	Felt sad	0	1	2	3
2.	Felt lonely	0	1	2	3
3.	Were down in the mouth	0	1	2	3
4.	Had difficulty with memory	0	1	2	3

G. How often during the last month you

	Question	Never	Rarely	Sometimes	Often
1.	Were upset because something unexpected happened	0	1	2	3
2.	You were confident that you can solve your problem	0	1	2	3
3.	You were nervous or stressed	0	1	2	3
4.	You had a feeling that problems accumulated and you can not solve them	0	1	2	3

H. Health habits

1. How often do you exercise actively (cycling, brisk walking, jogging, etc.)?	2. How often do you drink alcohol?
▪ Never	▪ Every day
▪ Less than once a week	▪ Almost every day
▪ 1-2 times a week	▪ 3-4 times a week
▪ 3-4 times a week	▪ 1-2 times a week
▪ 5 or more times a week	▪ 2-3 times a month
	▪ Once a month
	▪ Never

I. Did you have health problems during the month?

Health problem	I did not have this health problem	It does not matter	I had this health problem Bothers me a little	Bothers me a quite	Bothers me very much
1. Fatigue	0	1	2	3	4
2. Fever or cold	0	1	2	3	4
3. Vertigo	0	1	2	3	4
4. Pain or stiffness	0	1	2	3	4
5. Problem with memory	0	1	2	3	4
6. Nausea or vomiting	0	1	2	3	4
7. Diarrhea	0	1	2	3	4
8. Depression	0	1	2	3	4
9. Nervousness, anxiety	0	1	2	3	4
10. Insomnia sleepiness	0	1	2	3	4
11. Skin changes	0	1	2	3	4
12. Cough	0	1	2	3	4
13. Headache	0	1	2	3	4
14. Loss of appetite	0	1	2	3	4
15. Abdominal bloating	0	1	2	3	4
16. Pain in muscles and joints	0	1	2	3	4
17. Sexual problems	0	1	2	3	4
18. Weight changes	0	1	2	3	4

J. - 1. Claims about relationship with your family physician

Relationship with family practice	Yes	No
1. I can contact my doctor whenever I have personal or emotional problem	0	1
2. I go to the doctor for preventive examinations	0	1
3. My doctor knows if I live healthy (nutrition, smoking, alcochol)	0	1
4. Sometimes my doctor does not listen me	0	1
5. I do not always feel comfortable asking my doctor questions	0	1
6. My doctor monitors my problem solving (either directly or by telephone)	0	1
7. My doctor knows how much my family affects my health	0	1
8. The doctor always explains me the results of laboratory tests, X-rays and other specialist findings	0	1
9. I notice that my doctor advises and collaborates well with other healthcare professionals (eg pharmacists, nurses, etc.)	0	1

J. - 2. Pharmacist's questions and advice offered to the patient

Questions and advices	Always	Sometime	Never
1. Has the pharmacist asked you whether you took the drug for the first time	0	1	2
2. Has the pharmacist asked you to repeat aloud the instructions on how to take the drug	0	1	2
3. Has the pharmacist informed you on the importance of complying to the therapy prescribed	0	1	2
4. Has the pharmacist advised you in detail on how to take the drug	0	1	2
5. Has the pharmacist advised you on combining your therapy with OTC drugs	0	1	2
6. Has the pharmacist advised you on solving the possible drug side effects	0	1	2
7. Has the pharmacist asked you about skipping your therapy doses and why	0	1	2
8. Has the pharmacist asked you about your attitude towards your drug therapy	0	1	2

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