

## PHARMACIST COMPETENCES AND IMPACT OF PHARMACIST INTERVENTION ON MEDICATION ADHERENCE: AN OBSERVATIONAL STUDY

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### SUMMARY

**Background:** The aim of this study is to determine the results of pharmacist interventions on patient's adherence to drugs in community settings.

**Subjects and methods:** The study was designed using a standard EQ-SDQ questionnaire and a Culig questionnaire about the adherence to drug. General Level Framework (GLF) was used as a tool for competence assessment among community pharmacists. Participants were pharmacists that issued the medication on repeat prescription in the pharmacy. They interviewed the patient at the first visit to the pharmacy and the next time when the patient came to refill the prescription. The survey was conducted during a two-month period in the Atlantic Pharma pharmacy chain. A total of 152 patients were included at the first visit and 87 patients at the second visit.

**Results:** About two thirds of patients (65.5%) identified themselves as adherent during the first survey, and this number increased slightly during the second interview (by 3.5%), but not statistically significant ( $p=0.75$ ). A total number of drugs prescribed during the first and second survey was 252 and 253 respectively. The percentage of the advices given to the patients increased during the second survey, but not statistically significant ( $p=0.62$ ).

**Conclusion:** It is definitely important to check that a patient understands current disease and what are doubts and difficulties in taking a therapy. The reasons for possible nonadherence are different: fears, worsening of the clinical state or other negative treatment outcomes. Enough time should always be left to clarify anything that is unclear and to listen. Application of GLF program for improving pharmacist competences resulted in slightly increased patient adherence to medication. For further development of competences, pharmacist intervention should include some other contents, i.e. tailoring the dosage scheme, counselling about drug-drug and drug-food interactions. The pharmacist counseling should be reimbursed by the Croatian Health Insurance Fund.

**Key words:** pharmacist competences - pharmacist intervention - medication adherence - patient behavior

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### INTRODUCTION

Adherence to medication regimen is generally defined as the extent to which patients take medications as prescribed by their health care providers (Osterberg & Blaschke 2005). Sub-optimal adherence to prescribed medicines is frequently the principal obstacle to successful pharmacotherapy in ambulatory patients, especially when it is unrecognized clinically, as often occurs. It is highly prevalent, associated with increased morbidity and mortality, costly to manage and, until recently, a very much neglected aspect of therapeutics (Vrijens et al. 2012). Improving medication adherence across the health care system is a component that is vital to improving patient outcomes and reducing downstream health care costs (Pringle et al. 2014). Effective strategies for improving medication adherence are viewed as essential to improve patient care (Cutler & Everett 2010) and patient outcomes (Balkrishnan 2005, Ho et al. 2009). The community pharmacy is an untapped resource as a stand-alone strategy for improving

medication adherence at the population level (Agres 2013). A community pharmacy dispenses medication and provides professional counseling and other pharmacy services to people in the local area (Pringle et al. 2014).

According to the definition by Whiddett and Hollyforde, competence is an ability based on work or job outputs (Whiddett & Hollyforde 1999). A significant relationship between individual competence and safe patient care exist: one is a necessary part of the other. Safety is facilitated by universal rules: individual competence is fostered by an understanding of universal rules, but it is brought to fruition only by a deepening of individual values. Safe systems are designed to function without human intervention when possible; competence depends deeply on human engagement (Leach 2004). Development of competences in pharmacy is one of the basic prerequisites for providing pharmacy care and taking responsibility for patient's treatment outcome, especially when it is the combination of task orientated competence and behaviourally related competences that are required to deliver quality care (McRobbie et al.

2001). The public health role of pharmacists, using evidence-based practice to ensure patient safety and the best use of medicines, including individual patient and population outcomes, has been endorsed by The World Health Organization (WHO) (WHO and International Pharmaceutical Federation 2006). Evident differences exist in pharmacy practice among different countries (IMS Health 2007). Discrepancies, omissions and inconsistencies in providing pharmaceutical care are present at the national level in many countries (Nickerson et al. 2005, Husabo 2008, Canadian Pharmacist Association 2008). Medicines are getting more complex and more accessible to patients. Patient safety issues and accountability for the outcomes of therapy have become a primary focus of attention. Quality assurance and higher standards in professional performance are being sought by health professionals, patients and regulators.

Croatia has a population of 4,465,096 inhabitants (Croatian Central Bureau of Statistics 2011). There are 181 pharmacy subjects that are a part of the primary health care system, and various forms of ownership are permitted. Some pharmacies are state-owned (20.4%), others owned by pharmacists like an only one pharmacy (27.6%), while pharmacy chains owned by pharmacist or non-pharmacists are also permitted (50.0%) (Croatian Chamber of Pharmacists 2009).

Although the pharmacists' new roles in the pharmaceutical care have been promoted in Croatia over the past decades, the primarily role of community pharmacists remains the traditional role of drug supply, drug dispensing and compounding medicines (Ministry of health 2006).

Aim of the study is to determine the results of pharmacist interventions in community settings associated with patient's adherence to drugs.

## **SUBJECT AND METHODS**

Participants were pharmacists that dispensed the medication on repeat prescription in the pharmacy. They interviewed the patient at the first visit to the pharmacy and the next time when the patient came to refill the prescription. The survey was conducted during a two-month period: from 01/08/2010 to 30/09/2010 in the Atlantic Pharma pharmacy chain. The patients who came in the pharmacy for the first time with repeat prescription were interviewed. There was no possibility for patients to obtain the drug elsewhere, because back in 2010 repeat prescription was available only in paper form and it was stored till last refill in the pharmacy where patient came for the first time to fill prescription. Patients were individuals suffering from chronic diseases that need to pick up medicine at precisely defined intervals. Although during the first survey 152 patients had been warned that it is in their interest to take medication regularly, large number of patients (65) didn't adhere to these recommendations and did not come to refill prescription at the expected time. This

data shows a high percentage of nonadherence to drug due to the stock of the drug at home, while some alternative ways to obtain the drug are less likely. The study was designed using a questionnaire that is a combination of the standard EQ-SDQ questionnaire that makes a standard set of questions concerning socio-demographic variables for use with the EQ-5D (Euro Quality Dimensions 5) valuation questionnaire and Culig adherence questionnaire (Culig et al. 2011, Boskovic et al. 2014). EQ-5D is a standardised measure of health status in order to provide a simple, generic measure of health for different appraisal (EuroQol Group 1990). The survey was conducted in pharmacies Farmacia, Pharma Division of the Atlantic Group from Zagreb, Croatia. Questionnaire was filled out by the pharmacists working in this pharmacies' chain. The questionnaire was anonymous. General Level Framework (GLF) was used as a tool for competence assessment among community pharmacists in order to evaluate current competences in patient care of community pharmacists and to enable their further development by testing performance.

The relationship between pharmacist and patient was defined by eight questions and advices that were asked or given to patients by the pharmacist. The aim was to determine whether these questions had been asked and advices had been given to patients, or not.

## **Statistical analysis**

Student's t-test and chi-square test with a significance level of  $p < 0.05$  were used when appropriate for the evaluation of the results. All analysis were performed with SigmaStat 3.0 for Windows (SPSS Science software products, Chicago, IL, U.S.).

## **RESULTS**

Patients showed varying degree of adherence to therapy according to age. Women showed a higher degree of adherence than men (72.9% and 56.4%, respectively). Higher degree of adherence is characteristic for persons with educational level above elementary school, as well as persons with professional qualifications (professional qualifications are awarded after a number of years experience, formalised training and/or study and passing examinations). Demographic and social characteristics of study subjects are shown in Table 1.

Patients indicated statements which best describe their own health state (Table 2).

Most patients had no problems with self-care, usual activities and mobility. The most of their problems were related to pain and discomfort, and the majority of patients (71.3%) claimed to have moderate pain or discomfort. Also, half of the patients (49.4%) claimed to be moderate anxious or depressed. There was no statistically significant difference between adherent and nonadherent patients with regards to these questions ( $p$ -values for pain/discomfort and anxiety/depression were 0.38 and 0.11, respectively).

**Table 1.** Demographic and social characteristics of study subjects

Demographic and social characteristic		All study subjects n=87		Adherent %
		n	%	
Age	30-39	4	4.5	50.0
	40-49	8	9.2	75.0
	50-59	25	28.7	68.0
	60-69	25	28.7	56.0
	70+	25	28.7	72.0
Gender	Male	39	44.8	56.4
	Female	48	55.2	72.9
Status	Employed	31	36.9	67.7
	Retired	42	50.0	61.9
	Home	11	13.1	63.6
Education level	Elementary school	9	10.3	55.6
	More than elementary school	78	89.7	66.7
Professional qualifications	Yes	57	65.5	70.2
	No	30	34.5	56.7

During the first survey, about two thirds of patients (65.5%) identified themselves as adherent, and this number increased slightly during the second interview (by 3.5%) as shown in Table 3. Consultation with the pharmacist and his/her advice of the necessity for taking medication regularly didn't yield better results ( $p=0.75$ ).

It was reported that during the first survey 252 drugs were prescribed, which averaged 2.9 drugs per patient (Table 4).

The most prescribed medications were those from C group of medication according to ATC classification, i.e. drugs for cardiovascular disease, (133 or 52.8%) with adherence of 65.8%. They were followed by drugs for diseases of the nervous system that belong to N group of medication according to ATC classification (29 or 11.5%) with adherence of 47.1%, drugs for diseases of the digestive system, A group of medication according to ATC classification, (26 or 10.3%) with adherence of 52.2% and drugs for diseases

**Table 2.** Statements of patients' own health status (according EQ-5D)

Statement of own health status		Total		Adherent		Nonadherent	
		n	%	n	%	n	%
Mobility $p=0.64$	I have no problems in walking about	55	63.2	41	74.6	14	25.4
	I have some problems in walking about	32	36.8	19	59.4	13	40.6
	I am confined to bed	0	0.0	0	0.0	0	100.0
Self-Care $p=0.84$	I have no problems with self-care	72	82.8	48	66.7	24	33.3
	I have some problems washing or dressing myself	15	17.2	12	80.0	3	20.0
	I am unable to wash or dress myself	0	0.0	0	0.0	0	100.0
Usual Activities $p=0.67$	I have no problems with performing my usual activities	60	69.0	45	75.0	15	25.0
	I have some problems with performing my usual activities	23	26.4	12	52.2	11	47.8
	I am unable to perform my usual activities	4	4.6	3	75.0	1	25.0
Pain/ Discomfort $p=0.83$	I have no pain or discomfort	21	24.1	17	81.0	4	19.0
	I have moderate pain or discomfort	62	71.3	40	64.5	22	35.5
	I have extreme pain or discomfort	4	4.6	3	75.0	1	25.0
Anxiety/ Depression $p=0.67$	I am not anxious or depressed	40	46.0	32	80.0	8	20.0
	I am moderately anxious or depressed	43	49.4	26	60.5	17	39.5
	I am extremely anxious or depressed	4	4.6	2	50.0	2	50.0

**Table 3.** The difference in adherence measured with the Culig Scale between first and second survey ( $p=0.75$ )

Patients	First survey		Second survey		Trend %
	n	%	n	%	
Adherent	57	65.5	60	69.0	+3.5
Nonadherent	30	34.5	27	31.0	-3.5
Total	87	100.0	87	100.0	100.0

**Table 4.** Adherence measured with the Culig Scale according to drugs reported to be commonly used in both surveys ( $p=0.89$ )

ATK	Drugs	First survey			Second survey		
		n	%	Adherence (%)	n	%	Adherence (%)
C	Cardiovascular	133	52.8	65.8	128	54.5	71.6
N	Nervous	29	11.5	47.1	24	10.2	60.0
A	Alimentary	26	10.3	52.2	25	10.6	68.2
M	Musculoskeletal	21	8.3	46.7	16	6.8	63.6
Total		252	100.0	62.9	235	100.0	69.0

of the musculoskeletal system, M group of medication according to ATC classification (21 or 8.3%) with adherence of 46.7%, making these four groups of drugs account for over 4/5 of total drug spending. First survey showed overall adherence of 62.9%. During the second interview it was reported that 235 drugs were prescribed, which averaged slightly less than in the first survey (2.7 drugs per subject). Drugs for cardiovascular disease (128 or 54.5%) were prescribed the most, as in the first survey, with adherence in taking medications by 71.6%. They were followed by drugs for diseases of the digestive system (25 or 10.6%) with adherence of 68.2%, followed by drugs for diseases of the nervous system (24 or 10.2%) with adherence of 60.0% and drugs for diseases of the musculoskeletal system (16 or 6.8%) with adherence of 63.6%, making these four groups of drugs account for over 4/5 of total drug spending.

Second survey showed overall adherence to medication of 69.0%, representing increase of 6.1% in comparison with first survey, but there was not statistically significant difference in comparison with first survey ( $p=0.89$ ).

The largest number of diagnoses, as reported by patients, were those related to circulatory diseases or according to ICD classification, from I00-I99 blocks: 61 diagnosis in the first and 63 diagnosis in the second survey (Table 5 and 6).

A share of these diagnoses in the total number of reported diagnosis in the first and second survey was 39.1% and 40.4%, respectively. The ratio between adherent and nonadherent patient suffering from circulatory diseases increased in favour of adherent (68.9% vs. 71.4%) by 2.5%, in the period between two surveys.

Endocrine, nutritional and metabolic diseases or, according to ICD classification diagnosis from E00-E99 blocks, were in second place according to their share. During the first and second surveys these diagnosis were represented with 22.4%. Patient adherence to medication increased by 8.6%, i.e. from 60.0% during the first survey to 68.6% in the second survey. Diagnosis related to diseases of the musculoskeletal system and connective tissue were in third place with a share of around 10%. Patient adherence to medication increased by 10%, i.e. from 50.0% during the first survey to 60.0% in the second survey. The meaning of these three groups of diagnosis is the fact that they dominate and cover more than 70% of total diagnoses.

Most pharmacists asked the patient whether the drug was prescribed for the first time or it had been already prescribed (Table 7). Such question was asked during the first survey by 86.2% pharmacists, and during the second survey by 94.3% pharmacists.

In second place was a verbal and written advice on appropriate mode and timing of medication (79.3% and 83.9%, respectively), and in third place was the advice about the importance of adherence (70.1% and 88.5%, respectively). All other questions and advices were asked/given by much smaller number of pharmacists. Question in which patients were asked to repeat out loud how to take medication is very interesting as only 25.3% patients claimed that pharmacists asked this question during the first survey. However, the number of patients claiming that this question was asked almost doubled during the second survey, i.e. increased by 95.5%, which represents the highest increase among all the questions and advices posed/given in communication between the pharmacist and the patient. In the

**Table 5.** Adherence measured with the Culig Scale according to reported diagnosis (as per ICD classification), first survey ( $p=0.13$ )

ICD-10 blocks <sup>a</sup>	n			All diagnosis (%)			Structure of each ICD block (%)		
	Adherent	Non adherent	Total	Adherent	Non adherent	Total	Adherent	Non adherent	Total
I00-I99	42	19	61	42.4	33.3	39.1	68.9	31.1	100.0
E00-E99	21	14	35	21.2	24.6	22.4	60.0	40.0	100.0
M00-M99	8	8	16	8.1	14.0	10.3	50.0	50.0	100.0
G00-G99	2	5	7	2.0	8.8	4.5	28.6	71.4	100.0
Other	26	11	37	26.3	19.3	23.7	70.2	70.2	100.0

Legend: I00-I99 Diseases of the circulatory system; E00-E99 Endocrine, nutritional and metabolic diseases; M00-M99 Diseases of the musculoskeletal system and connective tissue; G00-G99 Diseases of the genitourinary system;

**Table 6.** Adherence according to reported diagnosis (as per ICD classification), second Survey ( $p=0.92$ )

ICD-10 blocks <sup>a</sup>	n			All diagnosis (%)			Structure of each ICD block (%)		
	Adherent	Non adherent	Total	Adherent	Non adherent	Total	Adherent	Non adherent	Total
I00-I99	45	18	63	42.5	36.0	40.4	71.4	28.6	100.0
E00-E99	24	11	35	22.6	22.0	22.4	68.6	31.4	100.0
M00-M99	9	6	15	8.5	12.0	9.6	60.0	40.0	100.0
J00-J99	4	3	7	3.8	6.0	4.5	57.1	42.9	100.0
Other	24	12	36	22.6	24.0	23.1	66.7	33.3	100.0

Legend: I00-I99 Diseases of the circulatory system; E00-E99 Endocrine, nutritional and metabolic diseases; M00-M99 Diseases of the musculoskeletal system and connective tissue; J00-J99 Diseases of the respiratory system;

second survey, the number of patients claiming that the pharmacist asked them about possible skipping the prescribed medication doses and reasons for such behavior was also increased in comparison with the first survey (an increase of 47.6%).

There was no statistically significant difference between answers in the first and second survey ( $p=0.62$ ).

**Table 7.** Questions and advices that the pharmacist asked/gave to the patient - the order in the first and second survey and the difference between two surveys ( $p=0.62$ )

Questions and advices <sup>a</sup>	First survey		Second survey		Difference (3/1) %
	1 n	2 %	3 n	4 %	
1.	75	86.2	82	94.3	+9.3
2.	22	25.3	43	49.4	+95.5
3.	61	70.1	77	88.5	+26.2
4.	69	79.3	73	83.9	+5.8
5.	44	50.6	53	60.9	+20.5
6.	40	46.0	47	54.0	+17.5
7.	42	48.3	62	71.3	+47.6
8.	38	43.7	47	54.0	+23.7

Legend: 1. asking the patient whether the drug was prescribed for the first time; 2. asking the patient to repeat aloud how to take the medication, thus ensuring that the patient understands medication instructions; 3. advice on the importance of adherence to therapy prescribed; 4. verbal and written advice on appropriate mode and timing of medication; 5. advice on the potential consequences of combining therapy prescribed with some other medication or food; 6. advice on solving the possible medication side effects; 7. asking the patient about skipping the prescribed medication doses, how frequently and why; 8. asking the patient about his/her attitude towards medication

## DISCUSSION

The patient can fail to ask questions about his disease or therapy which interests him in direct communication with the pharmacist, while the pharmacist, assuming that the patient knows everything, can fail to provide patient with detailed instruction related to therapy. Using the General Level Framework (GLF) (Competency Development Evaluation Group 2007), as a tool for defining, measuring and developing professional and scientific behavioural competences in delivering pharmaceutical care among a selected group of pharmacists, showed a tendency to slightly increase in adherence to drugs. Attention was particularly focused on the regular use of drugs and the consequences that could arise from non-adherence.

Special attention directed from pharmacists toward the patients using cardiovascular drugs (the most prescribed drugs in both surveys) led to the increased adherence to this group of medication as well.

Similarly, adherence was increased in patients with diagnoses from ICD-10 I00-I99 block (diseases of the circulatory system).

Pharmacists, who participated in this survey, continuously studied and applied GLF, a program to increase the competence and their competences were tested repeatedly. The levels of all 26 tested competences slightly increased, especially in the competences which had the lowest level in the beginning of testing. Pharmacists attended vocational training in areas in which they showed the lowest grade point average, they participated in related workshops and began to record the medical intervention, the observed interactions, side effects, use of guidelines and keeping illegal and incomplete prescriptions. They provided a number of written information for patients and created standards for the conduct of structured interviews in pharmacies through additional services for patients, open channels of communication with patients, their family members, doctors and colleagues, pharmacists, and enhanced information flow and exchange of experience. A research about Croatian community pharmacists' progress in competence development using the General Level Framework (GLF) as an educational tool in a longitudinal study has already been conducted. The patient care competences of 100 community pharmacists were evaluated and this study, confirmed that GLF is a valid educational tool for pharmacist development (Mestrovic et al. 2012).

Feedback in one Singapore study indicated that the GLF process was a positive experience, prompting reflection on practice and culminating in needs-based learning and ultimately improved patient care (Rutter et al. 2012).

Good Pharmacy Practices in some countries already include advising patients with polypharmacy on medication use (Latif & Boardman 2008). In such counseling interventions like dose regimen tailoring, drug-drug and drug-food interactions, which patients cannot find in usual information platform, are included.

Comparing both surveys, in the direct communication between patient and pharmacist some questions and advices were asked/given to higher number of patients, during the second survey. The highest increase was in question about asking the patient to repeat out loud the way how the drug has to be taken, which ensures to check that the patient understands the instructions. During professional education, participation in workshops and training related to conducting structured interviews, pharmacists were instructed to ask the patient to repeat out loud how the drug would be used. Open-ended questions should be asked during conversation in order to help a patient to express him/herself. The great increase is also noticed in the number of patients claiming that they had been asked if they skipped taking a prescription drug, how often and

why as well as the increase in the number of patients who had been advised about the importance of adherence.

It is definitely important to check that a patient understands his/her current situation, what he/she knows about his/her disease, what are his/her doubts and difficulties in receiving a therapy, and what are the reasons for possible nonadherence: fears, worsening of the clinical state or other negative treatment outcomes. Enough time should always be left to clarify anything that is unclear and to listen. 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 taking prescribed therapy regularly, and, in agreement with them, to figure out a good way to remind them to take the prescribed therapy. Various applications for alerting on mobile devices, that are now in mass use, could be of great help. After analyzing the reasons of nonadherence, we conclude that the adherence to the medication increases with age (Boskovic 2014).

Lack of knowledge about the disease and the reasons medication is needed, lack of motivation, low self-efficacy, and substance abuse are associated with poor medication adherence (Krueger et al. 2005, WHO 2003). A person's perception of the danger posed by their disease may affect adherence to treatment. Older adults with chronic diseases that pose no immediate limitations or have few or no symptoms - such as high blood pressure, high cholesterol, or osteoporosis - may dismiss the importance of medication adherence. When medications are slow to produce effect, as with antidepressants, a person may believe the medication is not working and thus become nonadherent. On the other hand, a person's belief that a medication will work or is working is directly related to treatment adherence, as is the ability to manage side effects and a positive attitude (Krueger et al. 2005).

It is well known that a person's knowledge, motivation, and attitudes toward medication therapy can significantly influence medication adherence. The World Health Organization has proposed a foundational model for medication adherence that is based on three factors: information, motivation, and behavioral skills (self-efficacy). Interventions based on this model have been effective in influencing behavioral change.

Adherence and nonadherence are behaviors. Information is a prerequisite for changing behavior, but in itself is insufficient to achieve this change; motivation and behavioral skills are critical determinants. Information and motivation work largely through behavioral skills to affect behavior; however, when the behavioral skills are familiar or uncomplicated, information and motivation can have direct effects on behavior (World Health Organization 2006).

Several different intervention strategies for improving adherence in psychiatric population have been studied: psychoeducation, cognitive-behavioral therapy (CBT) and motivational interviewing (MI) (Ehret & Wang 2013). Psychoeducational interventions without accompanying behavioral components and supportive services are not likely to be effective in improving medication adherence in schizophrenia (Zygmunt et al. 2002). The greatest improvement in adherence in these with schizophrenia was seen with interventions employing combinations of educational, behavioral, and affective strategies with additional secondary gains such as: reduced relapse, decreased hospitalization, decreased psychopathology, improved social function, gains in medication knowledge, and improved insight into the need for treatment (Dolder et al. 2003). CBT may show a potential for improved adherence, better use of coping skills and perhaps, in longer term, reduced length of time in hospital (Turkington 2002). MI adaptations can improve treatment adherence and dual disorder outcomes among psychiatric patients (Chanut et al. 2005).

Developing their competences, the pharmacist has to know that psychopharmacotherapy as a sole form of treatment may carry the wrong message that patients don't have to change their lifestyle and don't have to learn any new skills, they just have to receive their medication on time because the only problem is in brain chemistry. Evidence-based psychopharmacotherapy and person-centred narrative psychopharmacotherapy are not competitors but a complementary duality, as intimately connected as brain and soul (Jakovljevic 2015).

There are a number of possible limitations of this study. One of them is a small number of patients. Average interval between surveys was only 25.4 days. This investigation was conducted for the first time, and so some pharmacists felt uncomfortable, which surely resulted in some deviations from their regular behaviour.

## CONCLUSION

Application of GLF program for improving pharmacist competences result in slightly increased patient adherence to medication. However, pharmacists are the most accessible highly educated health care professionals and bigger importance should be paid to the pharmacist role in patient treatment. Contemporary approach is that medication have to be tailored to the individual patient based on their predicted response or risk of disease. The use of tailoring the treatment to patients has risen in usage in recent years which gives the growth of new therapeutic approaches that provide a clear evidence base on which to stratify related patients.

Medication adherence is a challenging problem across all disease states, but can be particularly hard in those with mental illness. Pharmacists, as the most accessible health care professionals, have the opportunity to involve the patients in the treatment process. (Ehret & Wang 2013).

Non-adherence is a major target for interventions to improve the quality and outcomes of health care (Jakovljevic 2014).

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### **Contribution of individual authors:**

Jelena Bošković: study conception and design, acquisition of data, literature research, writing the manuscript

Arijana Meštrović: acquisition of data

Marcel Leppee: statistical analysis, writing the manuscript

Martina Bago, Zvonimir Sostar: writing the manuscript

Dario Naletilić: literature research

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