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Patients' Adherence to Prescribed Medication

[1] Josip Čulig

[1] University of Applied Sciences Velika Gorica, Croatia

Summary

Background/aim

Adherence is the extent to which a patient´s behaviour towards medication corresponds with the agreed recommendations from a health care provider. Non-adherence to long-term therapy for chronic diseases in developed countries is on average 50%. Poor adherence is the primary reason for poor outcomes, and is potentially a waste of health care resources.

The objective of the Zagreb study was to assess the extent of adherence among the outpatients with long-term medication.

Methods

Patients with chronic diseases were interviewed during their visit to a public pharmacy. Their anonymity was guaranteed. The questionnaire was standardized and approved by the Ethical Committee. 635 questionnaires were collected in total (2000 were distributed). The study design was cross-sectional. The evaluation of pharmacist-patient relationships was also included in the study. 84 pharmacists volunteered to participate in the study.

Results

The average adherence to long-term medication was 41.7%. It was even lower in case of hypertensive patients (39%). The most frequent reasons for non-adherence were forgetfulness (60%), being away from home (45.4%), running out of pills (44.4%), inconvenient time schedule (40.9%), polypharmacy (39.5%), lack of the prescribed brand in the pharmacy (35.9%), feeling well (35.9%), and fear of side effects (29.6%).The pharmacist-patient relationships were seen differently on each side ($p<0.05$ in 5 of 8 questions). Only 14.3% of interviewed pharmacists asked patients to repeat the advice out loud, i.e. how to take the prescribed medicine.

Conclusion

Patients' adherence to long-term medication is low in Zagreb. The strategy for interventions to change patients' behaviour towards prescribed medication should be widely established. The role of pharmacists could be explored more.

Keywords: adherence, compliance, persistence, questionnaire, long-term medication, pharmacist-patient relationship, Zagreb.

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Author for correspondence:
Full Prof. Josip Čulig, PhD
University of Applied Sciences Velika Gorica, Croatia
Veleučilište Velika Gorica
Zagrebačka 5, 10410 Velika Gorica
Josip.culig@vvg.hr

INTRODUCTION

Pharmacotherapy is a part of basic medical discipline. It has particularly developed in the second half of the 20th century following a discovery of new drugs. It is important to prescribe the right dosage in the right dosing intervals to a certain patient. The understanding of pharmacodynamics and pharmacokinetics of a prescribed medicine is a crucial doctor's skill. If the prescribed medicine is ineffective after a certain period of treatment, it should be considered as wrongly selected. The doctor will then change the medication and try with a new therapeutic regimen.

Is it likely that the patient has not taken the medicine at all, or has taken a wrong dose or failed to comply with the dosing intervals? According to some research, 4% of patients do not take their medicine at all, and 50% of patients, especially the ones suffering from chronic diseases, take prescribed medicine improperly: skip the dose very often, forget to take the medicine, or change the therapeutic schemes, for example, they introduce the so-called weekend break[1]. Studies show that such behaviour towards the prescribed therapy is deteriorating further over time[2]. It has been shown that 20% of patients do not adhere to prescribed therapies after 60 days and 50% after 300 days, despite their beliefs that they are taking an effective drug that, for example, controls their blood cholesterol level[3]. Thus, the success of pharmacotherapy depends not only on the choice of the right medicine, the prescribing of the right dosage and choosing the right drug administration scheme, but also on patient adherence to the prescribed therapy, which is an important factor.

Adherence Definition

Adherence is a term that was first used at the beginning of the 21st century and is defined as the level in which the patient's behaviour towards the prescribed medication corresponds with the doctor's prescribed dosage schedule[1]. Thus, it involves a relationship between the doctor and the patient, during which they discussed potential therapies as partners, agreed and jointly adopted a medical plan for the next treatment period. Although the problem of non-adherence to the doctor's instructions was noticed as early as in the seventies of the last century, the approach to dealing with it has gone through various stages of evaluation and intervention. According to the available literature, there are various synonyms that describe the patient's relationship towards medication. The term "compliance" has been used very often in describing the patient following a doctor's advice[4]. Modern researchers emphasize that the notion of adherence also includes the patient's compulsion with future medical treatments, not just mere use of doctors' advice. We often use the term "persistence", which describes the character of the patient in relation to the agreement reached with the doctor on medication[5].

How to Determine Patient Adherence?

By reviewing literature, five different basic methods of patient adherence determination could be identified:

- as the doctor's opinion based on the examination and discussion with the patient, i.e. an evaluation of therapeutic outcomes;
- counting of the remaining pills when the patient delivers a drug package for checking and, of course, if the drug form is suitable for that method (for example, it is more difficult for medicines in the form of syrups or ointments);
- controlling of drug concentration or metabolites in the tissue, most commonly plasma;
- interviewing patients with standardized questionnaires,
- using electronic drug packaging devices that record exactly each bottle opening (assuming the pills are consumed!); an electronic medication event monitoring (eMEM), which is mainly used today in clinical therapeutic trials.

Each of these methods has its shortcomings, which the researcher must be aware of, and the results of each research must be cautiously interpreted[6].

METHODS

Patients' adherence behaviour to the prescribed medication was studied by a cross-sectional method using an anonymized questionnaire. The 635 chronic patients participated (of 2000 asked) in a randomly selected sample of a total of 171 public pharmacies in the city of Zagreb. The questionnaire was previously standardized[5,7] and approved by the Ethics Committee of the Faculty of Pharmacy and Biochemistry in Zagreb. A piggyback survey on pharmacist-patient relationship was carried on in 84 pharmacies, which voluntarily agreed to participate.

RESULTS

Data in Table 1 shows the relationship between adherence and demographic data of patients participating in the study. Most of the patients were older than 66 (249). Total adherence rate was 41.7%. Patients were offered the possibility of 16 reasons why they did not take the medication as prescribed (Table 2). "I just forgot" was the reason mentioned by 381 patients (60.0%). "I was not at home" and "I didn't re-fill my supply" were used by 45.4% and 44.4% patients, respectively. Patients and pharmacists were asked 8 questions that describe their relationship when taking medication (Table 3). There are statistically significant differences in patient and pharmacist attitudes in five areas (**bold in Table 3**, $p < 0.05$). When asked "Has the pharmacist asked you about your attitude towards your drug therapy?", 58.3% of the patients and 36.9% of the pharmacists responded positively ("Yes."). Only 46.8% of the patients and 75% of the pharmacists agreed with the statement "The pharmacist informed me why it is important to adhere to the prescribed therapy". "The pharmacist advised in detail how to take the drug" was confirmed by 57.2% of

Table 1. **Adherent /Non-adherent according to age and gender**

AGE GROUP	Adherent		Non-adherent	
	n	%	n	%
26 – 35	16	32.0	34	68.0
36 – 45	22	42.3	30	57.7
46 – 55	50	41.0	72	59.0
56 – 65	62	38.3	100	61.7
66+	115	56.2	134	53,8
Total	**265**	**41.7**	**370**	**58.3**
GENDER	n	%	n	%
Male	109	42.4	148	57.6
Female	156	41.3	222	58.7
Total	**265**	**41.7**	**370**	**58.3**

Table 2. **Reasons for non-adherence to their medication in the study population**

	N	percentage
I just forgot.	381	60.0
I was not at home.	288	45.4
I didn't re-fill my supply.	282	44.4
I didn't take my medication on time.	260	40.9
I take a number of drugs several times a day.	251	39.5
The prescribed drug was not available.	228	35.9
I felt well, I didn't need medication.	228	35.9
I was afraid of side effects.	188	29.6
My doctor changes my therapy.	165	26.0
I was afraid that drug can be toxic.	150	23.6
I fell asleep before the time for my dose.	145	22.8
I was depressed.	145	22.8
I was afraid of developing dependence.	143	22.5
I had a cold / flu.	133	20.9
The prescribed drug was too expensive.	132	20.8

Table 3. **Patients' and pharmacists' answers regarding pharmacists' advice on drug treatment**

Questions	1		2	
	n	%	n	%
Has the pharmacist asked you whether you are taking the drug for the first time?	391	61.6	61	72,6
Has the pharmacist asked you to repeat aloud the instructions on how to take the drug?	145	22.8	12	14,3
Has the pharmacist informed you on the importance of complying with the prescribed therapy?	**297**	**46.8**	**63**	**75.0**
Has the pharmacist advised you in detail on how to take the drug?	**363**	**57.2**	**76**	**90,5**
Has the pharmacist advised you on combining your therapy with OTC drugs?	**344**	**54,2**	**57**	**67.9**
Has the pharmacist advised you on solving the possible drug side effects?	277	43,6	41	48.8
Has the pharmacist asked you about skipping your therapy doses and why?	**265**	**41.7**	**24**	**28.6**
Has the pharmacist asked you about your attitude towards your drug therapy?	**370**	**58.3**	**31**	**36.9**
TOTAL	**635**	**100.0**	**84**	**100.0**

1) The patient stated that the pharmacist always asks him/her the question.
2) The pharmacist stated that he/she always asks the patient the question.

patients and 90.5% of pharmacists. The question "Do you skip the prescribed dose of your medicine" was set up by only 28.6% of pharmacists!

DISCUSSION

The therapeutic success of prescribed medication depends on the patient's adherence. For example, despite the existence of highly effective antihypertensive drugs, some studies show that only 30% of patients in the United States achieve adequate blood pressure control[1]. In Zagreb, according to our research, it is somewhere below 40%[8]. Well-known high-risk complications of unregulated blood pressure are: 3-4 times greater chance of ischemic heart disease, and 3 times greater incidence of stroke[4]. In addition to the positive therapeutic effect, different side effects are associated with drug use. However, in our research it has been shown that persistent patients have statistically significantly fewer overall health problems than the unreliable ones[8]. It is important to warn the patient about any possible side effects, such as, for example, orthostatic hypotension in some antihypertensive agents, so as not to be disappointed with the effect of the drug and give up the prescribed medication. Sometimes patients apply the so-called "weekend breaks" technique, which in some cases may cause adverse effects, such as a feedback phenomenon in interruption of therapy with a beta blocker, which may result in angina due to increased sympathetic activity. It is therefore important that the patient be persistent and does not change the self-initiated dosage regimen. It is very common that patients forget one daily dose, most often at noon or in the evening, which we observed in our research. Otherwise, the occurrence of the change in the dosing interval is known; this can cause a condition in which the patient is underdosed. Less frequent dosing pattern is common in non-adherent patients. It should be noted that skipping one or two doses may in some circumstances mean an absolute therapeutic failure (for example, insulin in diabetes type I). It is, in fact, surprising that considering such a low adherence in chronic patients (an average of about 40%), therapeutic failures are not more frequent. It seems that part of the explanation lies in the fact that dosing of some drugs is too high. Namely, a survey of documentation of newly registered drugs in the United States in the period from 1980 to 2000 has shown that in 22% of cases the recommended doses based on real-world evidence were reduced up to 50% of initial recommendations in the registration files[10]. Thus, clinical trials that precede the registration of a drug are carried out with higher doses of medicine than is usually necessary. This can be interpreted by the desire to achieve a statistically significant advantage of the new therapy before the registration. This results in a better negotiating position of the pharmaceutical industry when determining the price of a drug on the market. However, multiple doses are associated with a higher risk of side effects, so doctors need to keep an eye on it when they

start prescribing newly registered medicines. Fear of side effects of a drug is one of the factors that affects the patient's adherence behaviour. In our study, as many as 29.6% of non-adherent patients cited fear of side effects as a cause[5]. An interesting study of adherence to medication with doxycycline for the treatment of chlamydial infection has emerged in the literature. Doxycycline is prescribed 2 x 100 mg daily for 7 days as a standard dose. It was found that the therapeutic success was the same in patients who took 100% of the prescribed dose and those who took only 25% of the prescribed dose of doxycycline[3]! The second question is whether such patient behaviour in terms of therapy can cause other side effects, such as the development of resistant strains of bacteria during antimicrobial treatment. It is therefore important to know the factors that influence the patient's adherence to medication. Adherence to medication is a multifactorial problem. We can divide reasons that affect adherence into 5 different groups: socioeconomic factors (level of wealth), organization of the health service (primary care doctors, pharmacists in public pharmacies and other health professionals involved in the provision of medical services), the characteristics of the disease for which the patient takes medication (for example , the severity of symptoms, such as pain), the characteristic of the medication itself (for example, multiple medication dosage at once, complicated therapeutic scheme, frequent changes in prescribed drugs), and finally a group of factors that represent the patient's personality (education, age, beliefs, perception of the disease)[11].

Although studies do not show consistent conclusions, a lower socioeconomic status of the patient, unemployment, unhygienic living conditions, and cultural prejudices must be considered as factors which affect adherence. In Europe, the share of the elderly population in the total population is growing. This increases the number of chronic diseases, as well as the consumption of drugs. The risk of poor adherence among the elderly patients lies in the fact that elderly people usually have more than one chronic illness, which usually means that more than one drug is prescribed at the same time. They often suffer from cognitive impairment, which increases the chance of misusing the dosing scheme. In our group of patients, we found that adherence increased with age[8]! This may, however, lead to increased incidence of side effects and drug interactions. The health care organization can play a crucial role in gaining patient's trust and consequently improving their adherence to the prescribed medication. Unfortunately, our research has shown that patients are not entirely satisfied with the existing situation; they complain of too many drug changes, lack of medicines or too little time for discussion with the doctor about the type of medication and the possible consequences of taking the drug. Doctors complain that too much paperwork leaves them with insufficient time for each patient. According to our research, a potential resource that could affect the patient's adherence are pharmacists in public pharmacies. We found that patients received less information from the pharmacist than they expected[11]. The average drug delivery lasts about 5.26 minutes in pharmacies in Zagreb if the patient comes for the first time to get the prescribed drug, and only 2.21 minutes if they have to refill the drug. In Zagreb we started an intervention project in which pharmacists were trained to inform the patient about the importance of adherence to the prescribed medication. Similar programs already exist in the UK and Switzerland[12]. It is assumed that the severity of the disease affects adherence. In our study, we did not find a significant difference between chronic diseases that were analysed (hypertension, hyperlipidaemia, diabetes, asthma, chronic back pain). A complicated dosage schedule, multiple drug interactions, the influence of various supplements that the patient is taking together with the prescribed therapy, including the consumption of alcohol and the free-for-sale preparations (OTC and complementary medicine), significantly affect adherence. It has been shown that one-off daily treatment has better adherence, since patients often forget one dose if they take their medication, for example, in the morning and evening (more often in the evening!). Of course, the one-off dose tendency also has higher risks of therapeutic failure if the patient is unsettled, as we have already mentioned in Table 4. Therefore, it is good to plan the therapy scheme with the patient and help them fit it into their daily routines and duties so that they would not fail to take the dose "because they were not at home", which was the case with 67.5% of our unsightly patients (Table 2). However, it seems that the most important factor for adherence is the patient's personal motivation. The patient's knowledge about the disease, the motivation to be cured, the belief in the agreed treatment process, and the expected therapeutic success certainly have a significant impact on the implementation of the agreement with the doctor. Still, it is not all that easy, especially in long-term treatment with relatively small improvements in the patient's condition, aimed at preventing potential deterioration, which the patient does not quite understand and then dislikes as a motive.

Adherence will be affected by a variety of factors such as forgetfulness, psychosocial stress, anxiety due to potential side effects, disliking attitude towards chemical preparations, fear of addiction, depressive mood, and absence of devotion to the agreement reached with the doctor. In addition, various public affairs concerning the doctors, the pharmaceutical industry and some ethical aspects have recently been mentioned, all of which affect the sensitive issue of adherence to medicine. We have already noted that the patient adherence measuring methods have limited sensitivity and precision. It is surprising that the doctoral evaluation is least reliable in assessing adherence! Patients will rarely admit to their doctor that they did not take the prescribed medication as they previously agreed. They are afraid of cheating, embarrassed to disappoint the doctor, and they do not want the doctor to blame them. Unfortunately, this will lead to a completely wrong doctor's position in the event of absence of a positive treatment outcome. He/she will conclude that the drug is not effective, so the doctor will change or increase the dose or add another cure. A good is example is the published case of the refractory hypertension research. Namely, a group of researchers at the Swiss Hypertension Clinic continued the same treatment with which the patients diagnosed with refractory hypertension were admitted to the department (3). The eMEM adherence measurement method was applied. It was found that even in 50% of cases, the diagnosis of refractory hypertension was wrong! Patients did not take the prescribed therapy. After an agreement with the doctor and an explanation of the importance of adhering to the agreement on prescribed medication, the blood pressure was normalized with initial treatment. The doctor can rely on the counting of the pills if they ask the patient to take the medicine on each check. It has been shown, however, that adherence can be evaluated by this method. In 1989, Pullar et al. published a comparative study of tablet counting and plasma concentration measurements. They concluded that pill counting method should be forgotten[13]. In addition, the so-called "white coat" influence is known. A few days before the check-up and visit to the doctor's office, patients begin taking their prescribed therapy regularly. Measurement of drug or metabolite concentration in blood, urine or saliva is an objective method. The limitation of the interpretation of findings of adherence assessment is in the pharmacokinetic properties of the drug. Modern pharmacotherapy generally uses drugs that are T ½ about 12 hours. Thus, the measured drug concentration in the body is an indicator of a period of 3-4 half-lives of the drug. The survey found that the patient's adherence assessment, if standardized, is susceptible to the subjectivity of the patient and his/her desire to substantiate the answers he/she presumes will appeal to the doctor. However, if the poll is anonymous, that is, if the patient is convinced that he/she cannot be identified on the basis of the response, the data presented can be very useful at the population level. Such findings can be of key importance in the planning of intervention programs to improve patient adherence to premature medical practice[14].

Based on the survey of literature from 1970 to the present day, a list of documented cases may be drawn up in which the missed drug dose or drug intake according to the agreed treatment scheme resulted in significant clinical outcomes[15].

Table 4. **List of drugs for whose efficacy patient adherence is important**

1.	Non-intrinsic sympathomimetic activity (atenolol, betaxolol)
2.	ACE inhibitors (enalapril, trandolapril)
3.	Oral contraception - combined steroid hormones
4.	Calcium channel blockers (amlodipine, diltiazem, nifedipine)
5.	Antidepressants (paroxetine, sertraline, fluoxetine)
6.	Antimicrobial therapy (combined antiretroviral therapy)
7.	Combined antihypertensive therapy
8.	Glycaemic control therapy (insulin)
9.	Hypolipemics
10.	Anticoagulant therapy (warfarin)
11.	Antiepileptics (phenytoin, carbamazepine)
12.	Antiasthmatics (inhaled corticosteroid)
13.	Immunosuppressants (cyclosporine in transplant patients)

Apparently, in real-life practice, there are other examples in which therapeutic failure has led to patient's inadvertence but they have not been adequately explored. Haynes, one of the pioneers in the field of adherence, once stated: "Increased patient's adherence to medication can have far greater significance for better population health than new (innovative) medical therapy[4]." Of course, we do not have to (and will not) agree completely with this statement, but we certainly must not neglect it!

CONCLUSION

The adherence of patients to prescribed medication is a widespread problem. It is estimated that adherence in the treatment of chronic diseases is only about 50%. Since the share of chronic diseases in the population is increasing, it is estimated that in 2020 the number will increase to 65% (mental illness, consequences of atherosclerotic changes, human immunodeficiency virus). This problem should not be ignored in terms of population health status, but also economic damage, both direct and indirect, resulting from the cost of prescribed medication. Better adherence will improve the patients' quality of life, but also prevent unwanted events that may occur due to non-adherence with the agreed therapeutic scheme. It is a fact that patients have problems with sticking to the agreed therapeutic scheme either for personal reasons of forgetfulness or convenience, the complicated treatment scheme, or insufficient explanation that the prescribed medication has to be taken regularly. The health care organization needs to be restructured to better serve the patients. It also must adapt to the adequate resources and time available for the development of partner relationships between the doctor and the patient. We are witnessing health reforms aimed at improving administration, rationalizing financial resources, and dealing with the adaptation of the relationship between healthcare professionals and healthcare providers. As patient adherence is multifactorial, intervention needs to be subtle and diverse. It should not be basically criticism, but encouragement and motivation. Therefore, health professionals need to be educated in communication skills, which are not sufficiently taught during their education at the medical and pharmaceutical faculties. It is also necessary to create a new role of the pharmacist, which by only dispensing the prescribed medicines has threatened the foundation of its profession. The pharmacotherapeutic model in the public pharmacy that promotes patient adherence to the prescribed medication is a useful challenge.

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ADHERENCIJA PACIJENATA PREMA PROPISANOJ MEDIKACIJI

Sažetak

Uvod/cilj

Adherencija se definira kao razina pacijentova pridržavanja dogovora s liječnikom o propisanoj medikaciji. Procjenjuje se da je prosječna neadherentnost pacijenta prema dugotrajnoj terapiji kod kroničnih bolesti u razvijenim zemljama oko 50 %. Slaba adherencija glavni je razlog neuspješnoga kliničkog ishoda, ali i potencijalnog trošenja sredstava za liječenje komplikacija bolesti uslijed neuspješnog liječenja. Proveli smo istraživanje u Zagrebu kod bolesnika kojima je propisana dugotrajna medikacija zbog kroničnih bolesti

Metode

Pacijenti su intervjuirani prigodom posjeta javnoj ljekarni koja je sudjelovala u ispitivanju i uzimanja lijeka za kroničnu terapiju na recept. Standardizirani intervju odobrilo je Etičko povjerenstvo i pacijentu se jamčila anonimnost. Ukupno je prikupljeno 635 anketa. Studija je planirana kao presječna. Dio pitanja odnosio se na odnos ljekarnika i pacijenta. Samo 84 ljekarnika pristalo je sudjelovati u istraživanju.

Rezultati

Prosječna adherencija prema dugotrajnoj medikaciji bila je 41,7 %, dok je u kohorti pacijenata s hipertenzijom bila čak i niža (39 %). Kao glavni razlog neadherencije pacijenti su navodili zaboravljivost (60 %), zatim nisu bili kod kuće u vrijeme uzimanja lijeka (45,4 %), ili im je uzmanjkalo lijeka (44,4 %) ili je propisano vrijeme uzimanja lijeka bilo nezgodno (40,9 %) odnosno uzimaju više različitih lijekova (39,5 %). Također se navodi razlog da nije bilo propisanog lijeka u ljekarni, a nisu mogli dobiti zamjenu (35,9 %), neki su se osjećali dobro (35,9 %) ili su htjeli izbjeći neželjene učinke lijeka (29,6 %). Odnos pacijent – ljekarnik sudionici u studiji različito su ocijenili (u čak pet od osam pitanja odgovori su se razlikovali statistički značajno, $p < 0,05$). Na primjer, samo 14,3 % ispitanih ljekarnika traži od pacijenta da glasno ponovi uputu o uzimanju propisane medikacije.

Zaključak

U Zagrebu je razina adherencije pacijenata prema dugoročnoj terapiji niska. Potrebno je strateški planirati i intervenirati kako bi se ponašanje pacijenata promijenilo. Moguće je kreirati novu ulogu farmaceuta u procesu povećanja adherencije prema propisanoj medikaciji.

Ključne riječi: adherencija, pridržavanje uputa liječnika, ustrajnost, upitnik, dugotrajno uzimanje lijekova, odnos ljekarnik – pacijent, Zagreb