

## THE COMPLEXITY OF ADHERENCE ISSUE: A REVIEW OF ITS SCOPE AND DETERMINANTS

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Adherence is tremendously important for efficiency and safety of pharmacotherapy and has a significant influence on its clinical, economic and humanistic outcomes, which can be observed both on the individual level of the patient as well as on the overall healthcare system. The inadequate degree of adherence is a long-lasting and widely present problem which can have immense and long-term consequences. Therefore, the issue of adherence is a big challenge for medical professionals in clinical practice.

The concept of adherence is based on cooperation between patients and medical team members in the process of therapy management. It is focused on patients and implies a two-way transfer of information, agreement and shared responsibility for success in realization of adequate therapy regime and defined goals.

Although there are numerous methods for adherence assessment, the evaluation of this parameter is still considered problematic. The complexity of adherence can be seen in its multidimensionality since numerous factors which individually and in mutual interaction affect medicine-taking behavior and thus create a framework that determines the achieved level of adherence have been identified and analyzed.

Considering the fact that poor adherence is one of the main preventable causes of unsatisfactory therapy results and excessive costs of medical care, it is evidently necessary to ensure a high quality base in the form of knowledge, skills and motivation at the healthcare system level for adherence evaluation and improvement, as well as a multidisciplinary approach based on coordinated activities of healthcare policy creators, researchers and medical professionals. *Acta Medica Medianae* 2016;55(1):51-58.

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Adherence is exceptionally important for the efficiency and safety of pharmacotherapy, as well as for the realization of desired therapeutic outcomes. Medicines belong to the most often used medical technologies and the significance of their appropriate use is reflected in clinical, economic and humanistic outcomes of the therapy, both at the individual level of the patient and the overall healthcare system. Inadequate degree of adherence is a long-lasting and widely present problem which can have large and long-term consequences. This is the reason why the issue of adherence is a big challenge for health professionals in clinical practice (1,2). Many terms are used in literature and in practice in relation with the medication-taking behavior. Terms such as compliance, adherence, persistence and concordance are frequently inappropriately used as synonyms, although they imply a different approach in consideration of the

role of patients in adequate use of medications, as well as the relation between patients and members of the healthcare team. Nevertheless, even though there is a rise of interest in this domain, there are still misunderstandings and inconsistencies regarding definitions and terminology of these concepts that seem similar but are rather different (3).

Historical texts indicate that since the time of Hippocrates (460–370 BC) there has existed a fear that patients do not follow instructions and recommendations of their doctors and do not use prescribed medications while at the same time many of them complain that the therapy has been ineffectual. At the end of the 19th century and the beginning of the 20th century the terminology used by physicians to describe in compliant patients has frequently been extremely critical and condemning. There has been a particularly strict attitude towards people that had contagious diseases such as tuberculosis who have not adhered to instructions of their doctors. Such patients were described as "vicious consumptives, careless, irresponsible and/or recalcitrant" (3,4).

From these reflections healthcare professionals and researchers showed an ever-growing interest in the issue of adherence, considering that

awareness has been developed about its significance in the overall success of a therapy. In the early 70's of the 20th century a basis was created for further contemplation and research of compliance, when two symposiums/ workshops were organized at McMaster University Medical Centre in Hamilton (Canada) in 1974 and 1975 (5). The term compliance was introduced in medical practice in the year 1975 as an official Medical Subject Heading (MeSH) in the US National Library of Medicine (6), and a particularly significant advancement in that sphere was achieved in the year 1976 when Sackett and Haynes published a book called *Compliance with Therapeutic Regimens* (7). In that period the interest of professionals was primarily directed to potential consequences of unfulfilled compliance in the sense of clinical outcomes and results of clinical studies, as well as in developing practical methods for quantitative evaluation of coherence between a prescribed and realized therapeutic regimen (5). In that period, the issue was not considered from the perspective of the patient (8). A later body of research addressed the issue of patients' influence on the choice and prescription of therapy and their role in therapy management in everyday life. The term *pharmionics* was introduced in the year 1987 and implies a discipline dealing with research of use, misuse and abuse of prescribed medicines in a population of ambulatory patients (9).

The International Society for Pharmacoeconomics and Outcomes Research - ISPOR Medication Compliance and Persistence Work Group defines compliance as the extent to which a patient conforms for the recommendations made by the provider with respect to timing, dosage, and frequency of medication taking (10). Such a definition implies a passive role of the patient as the subject who does not participate actively in the treatment decision making process, since he is only given information and instructions regarding the use itself (11). The patient is expected to comply with received instructions and to be subordinated to the authority of a healthcare professional (2). Furthermore, in such a relation the patient is not encouraged to ask questions, clarify doubts concerning the therapy, or to inform the healthcare professional about the reasons that may negatively influence the therapy management. In that case the patient is only an acceptant but not a contributor of useful information, and there is only a one-way communication. Frequently, in such a model of interaction, the patient does not inform the physician or the pharmacist about dietary supplements or traditional medicinal products which he potentially uses, nor about possible previous experiences with the prescribed medicaments. All this can have serious consequences to the safety and efficiency of the therapy. In case the desired efficiency of the therapy is not achieved as the result of inadequate use, it is deemed that the patient has to bear the entire guilt, since he disobeyed received instructions.

Although the term compliance has been in use for the longest period of time, nowadays it is considered that it is not entirely adequate and that changes in the relation between patients and

healthcare professionals must be taken into consideration. Patients' status is no longer submissive and passive and their role in accomplishing therapeutic objectives does not only imply compliance with medical instructions but active cooperation and agreement with a doctor and a pharmacist. Due to these reasons the term adherence has become more desirable in practice since the 90's of the 20th century (5,11).

Adherence is defined as the extent to which a person's behavior - taking medication, following a diet and/or executing lifestyle changes corresponds with agreed recommendations from a healthcare provider (12). It is also explained in literature as active, voluntary and collaborative involvement of the patient in a mutually acceptable course of behavior to produce a therapeutic result (13,14). Such a definition suggests that the patient has the right and possibility to decide about the therapy plan and to cooperate with the healthcare provider in defining therapy goals and regimens. The context of adherence does not only include the phase in which the patient takes prescribed medicine(s) on his own, but also the phase which precedes it, i.e. agreement and collaboration between the patient and healthcare providers. This concept indicates mutual responsibility for successful realization of adequate therapeutic regimen and defined goals. In such conditions there is more likelihood that patients would provide information, opinions and experiences to a healthcare professional, which might influence the implementation and/or efficiency and safety of the therapy, as well as the probability of possible timely application of necessary modifications. Differences between compliance and adherence are thus not only in the semantic sense but of essential nature. While in compliance the focus is on the healthcare provider who has a dominant status in relation to the patient, the concept of adherence is oriented to the patient and cooperation. In relation to this, the flow of information is one-way and the objective is to achieve obedience of the patient, while adherence implies a two-way information transfer and engagement of both subjects.

A new approach in interpreting adherence started in the year 1997, when the environment in which the patient lives was taken into account, as well as the influence of that environment, the healthcare system and available practices on adherence as a behavioral process (15, 16, 17). Accordingly, a low degree of adherence started to be treated as a complex problem that should be approached from different perspectives with carefully developed strategies and interventions directed to specific factors. Taxonomy proposed by Vrijens *et al.* in the year 2012 relies on three components of adherence: initiation, implementation, and discontinuation (5). According to that division, non-adherence may be in the form of late or missing initiation, suboptimal implementation, early discontinuation or combination of these cases. The term persistence is defined as the time period between therapy initiation and the last dose which immediately precedes therapy discontinuation (5,10).

World Health Organization gave its own definition of adherence in the year 2003 (12), while in

2009 the term medication adherence became a MeSH term (5).

The concept of concordance was introduced by the joint working group assembled by the Royal Pharmaceutical Society of Great Britain in the year 1995 (18,19,20). Introduction of this term emphasizes that, regardless of different perspectives of clinicians and patients, correct and adequate administration of medicine(s) depends on their agreement and cooperation, in which desires and convictions of patients concerning the therapy must be taken into consideration. Concordance as a term includes a consultation process, in which a doctor and a patient agree on therapeutic decisions that incorporate their respective views and support to the patient in further implementation of the therapeutic plan. This term does not refer to mere actions of the patient in the process of medicine-taking, but rather a relation, interaction and partnership of the patient and healthcare providers.

Compliance, adherence and persistence are parameters which can be quantified in contrast to terms like concordance and therapeutic alliance which do not possess measurable attributes, since they are based on the concept of cooperation, agreement and consultation between the patient and a healthcare provider considering therapeutic plan and shared responsibility for its success (3).

Although adherence is discussed as categorical, dichotomous variable in some studies, it is considered that such a presentation is not adequate for addressing the complexity of the adherence issue (21). It is therefore better to talk about a specific level of adherence than about arbitrary categories such as realized or unrealized, good or bad adherence. Adherence as a continuous variable is most frequently expressed as an amount in percentage and/or with descriptive terms (a low/high, unsatisfactory/satisfactory degree of adherence). The same applies for the term compliance, while quantification refers to determining the extent in which a patient acts in accordance with instructions regarding the dosages and dosage intervals of prescribed medications during a defined period of time (10). It is important to note that concepts of adherence and compliance must be analyzed in the sense of their modifications in the function of time, i.e. as measurements of dynamic character (22). When the taxonomy proposed by (5) Vrijens et al. is taken into consideration parameters of initiation and therapy discontinuation are dichotomous, while the implementation is a continuous variable (23). Persistence is expressed as a time period, i.e. as a continuous variable and it is deemed recommendable to define in advance maximal allowed interval between doses in the form of the so-called permissible gap (5,10). That factor is determined further to pharmacological properties of the medicine and the condition of the patient thus representing the longest allowed period which may pass without administration of the prescribed dose of medicine or without inducing suboptimal outcomes of the therapy (10,24,25).

Although there are numerous methods for the assessment of the realized adherence level,

evaluation of this parameter that significantly influences therapy outcomes is still qualified as problematic, nor has a gold standard been established in this field (12,26,27). The main problem in adherence evaluation as a behavioral process is related to the fact that the measurement procedure, i.e. quantification itself influences the behavior of the patient. It is considered that if patients are conscious that their behavior regarding therapy implementation is monitored, they tend to modify a medicine-taking attitude and activities in order to demonstrate a (false) high level of adherence. Researches have also shown that patients during adherence monitoring tend to fulfill expectations of their doctors, avoid misunderstandings, disappointments and condemnations, and temporarily take the role of the so-called good patients who have achieved a satisfactory high level of adherence (28). All currently available methods for adherence assessment have certain deficiencies regarding accuracy, ethicality, reliability, cost-effectiveness or simplicity of application and interpretation. When selecting the right method it is therefore necessary to make adequate compromise in relation to method limitations, available resources, the aim and goal of the research conducted. Methods for adherence evaluation are classified in two main groups: direct and indirect (27). The group of direct methods includes: directly observed therapy, measurement of the level of a drug or its metabolite in biological material of the patient and detection or determination of a biological marker added to the drug formulation. The other group of indirect methods includes: counting the remaining individual doses of the medicine (so-called pill counts), application of devices for electronic monitoring of medication package frequency opening (so-called electronic monitoring devices), reviewing pharmacy prescription refills records and patients' reports (diaries, questionnaires, interviews) analysis (27,28,29). It should be taken into consideration that none of the existing methods is universally applicable and that the most reliable information is obtained in conditions when it is possible to combine more approaches parallel. Even though it is frequently very hard to accomplish this, it is the best way to significantly minimize limitations of methods when drawing final conclusions.

### Determinants of adherence level

Numerous factors influence successful realization of adherence, considering the fact that adherence is a multidimensional phenomenon. It is tremendously important to identify and analyze factors which individually and in mutual interaction create a framework that determines the adherence level so as to efficiently confront this growing problem. The World Health Organization has singled out five dimensions of adherence: patient-related factors, social- and economic-related factors, health system/health care team-related factors, condition-related factors, and therapy-related factors (12).

As to the factors which relate to the characteristics of the patient, the correlation between age, gender, ethnical background, race, religious beliefs,

marriage status and the realization of desired level of cooperation with healthcare professionals has not been definitely determined (12,27). In conducted studies there is no consistency in evaluating the significance of those demographic parameters. On the other hand, it is considered that psychological and behavioral characteristics are important predictors of adherence (29, 30). Perception of own health condition, seriousness of illness and possible consequences, conviction of necessity of treatment all affect motivation and behavior of an individual regarding therapy administration (31). A frequent reason for insufficient dedication to adequate therapy regimen implementation is attitudes that patients have in regard to medicines. Those include fear from experiencing harmful/unpleasant adverse effects of prescribed medicines, apprehension of unnatural origin of industrially produced medicines and concerns of possible development of addiction/dependence. Furthermore, patients are influenced by worry of potential difficult adaptation to lifestyle and habits' alterations that are necessary in some conditions and therapies (12, 29). All those low levels of adherence risk factors can, however, be considered as preventable since they can be successfully avoided or at least alleviated through communication with healthcare providers and processes of consultation, counseling, support and motivation. Physical/somatic factors such as eyesight and hearing deteriorations, problems with swallowing or decline of cognitive function can, on the other hand, significantly limit the ability of the patient to achieve a high level of adherence. Bearing this in mind a particular dedication is necessary and engagement of healthcare providers in interaction and creation of tailor-made solutions for successful fulfillment of the therapeutic treatment plan.

Health literacy is considered as the most important predictor of health condition and it is very important to reflect upon its influence on adherence. The World Health Organization (WHO) defines health literacy as the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand and use information in ways which promote and maintain good health (32). Health literacy, as a concept, includes political, economic and environmental factors which influence health, and because of this, it is here classified in the social- and economic-related factors category rather than in patient-related determinants of adherence. Moreover, the responsibility for health literacy is not individual but shared among different sectors of the society and the goal is to ensure approach to and functional management of information which are significant for health, their critical analysis and exchange, as well as development of the awareness about health determinants and stimulation of their improvement through individual and collective activities.

When it comes to pharmacotherapy it is essential to ensure that patients can effectively manage available understandable information related to their health condition and therapy in order to achieve desired treatment outcomes. In that process one of the main assumptions of safe and effective therapy is the ability of patients to name and

recognize prescribed medicines, as well as to understand why they need to use them and how to do it adequately. Factors that might have negative effects on this are frequent changes of therapy and complex therapeutic plans, which include numerous medications with specific individual regimens (33). Researches indicate a worrying fact that up to 75% of patients cannot precisely name and explain their therapeutic regimen, while 46% patients wrongly interpret information about the dose and/or frequency of administration of prescribed medication(s). Additionally, in a number of studies it has been determined that patients with a low level of health literacy have particular difficulties in understanding and application of instructions and advices related to medication usage (34). It is important for patients to have the knowledge of potential undesirable side effects, contraindications, warnings and precautions so as to minimize risks regarding endangerment of therapy safety. Patients should be empowered to recognize symptoms of possible adverse effects, take adequate measures on time, as well as to understand the significance of reporting to healthcare professionals about all the problems associated with therapy management. Results of conducted researches, however, direct attention to unsatisfactory comprehension of this information, since it is estimated that up to 54% of patients have difficulties to understand ordinary warnings, while less than 10% of patients adheres to them routinely. Patients with low level of health literacy are exceptionally endangered, since studies have shown that patients in that category are 3.4 times less likely to interpret prescription medication warning labels correctly (35).

Other social factors such as the family situation, residence conditions, employment and incomes may also influence adherence. Researches have suggested that low level of adherence risk is 1.74 times higher in patients which do not come from stable, cohesive families, while conflictive family situation lowers the level of adherence 1.53 times (36). Patients diagnosed with epilepsy, depression, schizophrenia, HIV infection and other socially stigmatized diseases often do not achieve a high level of adherence and consequently the full potential of the therapy (28).

Particularly significant group of factors which determines adherence refers to healthcare providers and healthcare system. The relation between healthcare providers and patients will have a positive influence on adherence if it features mutual respect, trust and shared dedication to creating and following an individualized treatment plan. Considering the fact that healthcare providers define diagnoses, prescribe therapy, monitor clinical outcomes and provide feedback information to patients, variables which reflect interaction and communication manner between them represent key determinants of a realized adherence level and health outcomes (12). Communication which stimulates the patient to actively participate in the treatment process, indicate potential problems and demand necessary explanations and advices, with adjusted terminology and understandable expressions has a positive effect on adherence. There is a higher probability

that the patient will respect an agreement related to the therapy if he is satisfied with the work of healthcare providers and if the reasons for therapy administration, as well as the significance of consistency in following the prescribed regimen has been clearly explained to him. Healthcare continuity and higher frequency of appointments are considered as predictors of better therapy management and higher level of adherence. Communication which emphasizes collaboration, expresses empathy, support and motivation, allows open discussion of benefits, risks, and barriers to adherence enhances the quality of this relation and increases satisfaction of the patient as the user of the healthcare system in regard to rendered services. Patients' discontent concerning interactions with members of the healthcare team, the type and scope of obtained information, explanations and advice can represent an obstacle in achieving high level of adherence (27,28,37). Neglecting patients' opinions, demands and needs in decision making related to the therapy can result in negative attitude and frustration among patients (12). Terminology used by the members of the healthcare team in their communication with patients should be adapted to the knowledge, age, education, condition and needs of the patient.

Characteristics of the healthcare system with reference to organization and resources availability, work efficiency and success in ensuring justice and financial protection from costs which may arise due to illness and disability all have significant influence on patient adherence (38). Relation between the healthcare system and adherence can be analyzed from a number of perspectives. Lack of financial and geographical accessibility of medical care, shortage of medications, long periods of waiting for scheduled diagnostic, therapy or rehabilitation procedures are considered as predictors of non-adherence (29). A low level of adherence, on the other hand, influences the healthcare system through irrational expenditure of already limited resources, additional unnecessary burden of the healthcare service and an increase of healthcare costs (38, 39). Characteristics of the healthcare system can make a significant impact on the patients' behavior, considering the fact that the healthcare system controls the process of resource allocation, terms of payment and medical care costs refunding, determines availability and possibility of patients' medical history information exchange, as well as the continuity of medical care (12). For example, excessive work load of the healthcare provider with demanding schedule in relation to examinations, follow-ups and/or consultations with patients does not leave sufficient time to be dedicated to adherence in communication. Additionally, lack of financial reimbursement for services of patient counseling has a negative influence on motivation of the healthcare team for development and implementation of adherence-focused interventions. Conversely, well developed healthcare information system facilitates evaluation of adherence and represents a platform for a critical analysis and improvement of work and organization efficacy.

Condition-related factors influence adherence as well. More problems with adherence might be expected in the category of chronic than in the category of acute illnesses, especially considering the dynamic aspect of the adherence phenomenon and modifications which arise in the function of time (7,12,40). Absence of illness symptoms can make adherence quite challenging, regarding the fact that they stimulate medication use by acting as a reminder or by reinforcing perceptions of need. A high level of obstructions of lifestyle patterns and usual daily activities coupled with the life quality decrease due to illness represent a good motivation factor and are associated with a higher adherence rate. A positive correlation between the severity of illness and success in achieving high adherence level has also been reported (2, 29). Conversely, a symptom withdrawal and clinical improvement before the expiration of the planned therapy duration results in the perception that the illness is more benign than it actually is, leading to doubts about the necessity of a continuous treatment. Adherence-related problems might also be expected with patients who have psychiatric disorders and mental retardation (27,41).

Numerous studies have suggested that polypharmacy, higher dosing frequency and a significant impact of therapy on lifestyle and habits have a negative effect on adherence (5, 12, 27, 42, 43). For example, a study conducted in the category of patients with chronic cardiovascular diseases estimated the adjusted weighted mean percentage adherence for medications taken two and three times per day were 6.9% and 13.7% lower, respectively, comparing with once daily dosing. It is important to emphasize that twice-daily dosing was associated with a 22.9% decrease in timing adherence and this was 30.4% lower for medications taken three times per day when compared with medications taken once daily (44). In addition, higher incidence and severity of medication adverse effects have a negative impact on adherence and persistence, as well as inadequate dosage forms of the medicines which do not ensure comfortable therapy administration and/or are not tailored to the age, condition and needs of the patient (27,45,46).

Combination and interaction of factors affecting adherence are specific for each patient and it is remarkably important to comprehend them adequately in order to create individualized, effective and sustainable solutions which promote adherence and desired therapy outcomes.

## Conclusion

Understanding magnitude, a scope and consequences of poor adherence, it is evidently necessary to direct attention towards development and implementation of appropriate interventions. Nevertheless, the complexity and mutual interaction of numerous factors which are considered as detrimental for patients' medicine-taking behavior indicate the complexity of that process. There is no universal strategy which would be efficient for all patients, in all conditions, regardless of the disease

type or the therapy prescribed. Therefore it is necessary to create a general framework of interventions which could be flexibly adapted further to unique individual needs and characteristics of the patient. Additionally, considering that adherence is a dynamic and multidimensional phenomenon the most successful measures are those which address the issue of adherence from different angles and which are revised according to modifications that arise in the function of time.

Healthcare providers have a professional and ethical obligation to perform expert evaluation of the overall patients' therapy, give information and advice, identify potentially existing factors which predispose a low adherence level, apply individually tailored strategies for adherence enhancement and continually monitor patient cooperation and therapy outcomes. In order to empower them to successfully fulfill all those responsibilities it is neces-

sary to insist on the development of adherence-related competences within the educational and programs of continual professional training, as well as to evolve consciousness about the significance of that aspect of the therapy management. In addition, it is essential to create a set of system-level measures so that members of a healthcare team can entirely comprehend the significance of cooperation and shared responsibility, as well as the potential of a high quality collaborative practice.

Since the low level of adherence is one of the main preventable causes of unsatisfactory therapy outcomes and excessive costs of medical care, it is evidently necessary to ensure a high quality base in the form of knowledge, skills and motivation at the level of the healthcare system for adherence evaluation and improvement, as well as a multidisciplinary approach based on coordinated activities of healthcare policy creators, researchers and medical professionals.

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## PITANJE ADHERENCE: SLOŽENOST KONTEKSTA I DETERMINANTE NIVOA ADHERENCE

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Adherenca je izuzetno važna za efikasnost i bezbednost farmakoterapije i značajno utiče na njene kliničke, ekonomske i humanističke ishode, što se može pratiti kako na individualnom nivou bolesnika, tako i na celokupnom zdravstvenom sistemu. Neadekvatan stepen adherence odavno je prisutan i široko rasprostranjen problem koji može imati velike i dugoročne posledice. Zato pitanje adherence predstavlja veliki izazov za zdravstvene profesionalce u kliničkoj praksi.

Koncept adherence je utemeljen na saradnji bolesnika i članova zdravstvenog tima u procesu upravljanja terapijom. U potpunosti je orjentisan ka bolesniku i podrazumeva dvosmerni transfer informacija, dogovor i podeljenu odgovornost za uspešnost u realizaciji adekvatnog terapijskog režima i definisanih ciljeva.

Iako postoji veliki broj metoda za procenu ostvarenog stepena adherence, još uvek se evaluacija ovog parametra smatra problematičnom. Kompleksnost adherence ogleda se u njenoj multidimenzionalnosti, budući da je identifikovan i proučen veliki broj faktora koji pojedinačno i u međusobnoj interakciji utiču na ponašanje bolesnika u vezi sa terapijom i tako kreiraju okvir koji determiniše ostvareni stepen adherence.

Budući da je nizak stepen adherence jedan od glavnih preventabilnih uzroka nezadovoljavajućih terapijskih ishoda i prekomernih troškova zdravstvene zaštite, evidentna je potreba da se obezbedi kvalitetna baza u formi znanja, veština i motivacije na nivou zdravstvenog sistema za evaluaciju i unapređenje adherence, kao i multidisciplinarni pristup, koji je zasnovan na koordinisanim aktivnostima kreatora zdravstvene politike, istraživača i zdravstvenih profesionalaca. *Acta Medica Medianae 2016;55(1):51-58.*

**Ključne reči:** *adherenca, komplikjansa, terminologija, determinante, zdravstveno ponašanje*