Medication adherence – the way to understand patients

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The aims of this review are to explore the critical issue of medication adherence, which is essential for effective healthcare outcomes but remains a significant challenge. The review delves into the diverse aspects of non-adherence, including patient perceptions, economic challenges, and complex treatment regimens. It emphasizes the importance of accurate adherence assessments, particularly through self-report questionnaires and retrospective database analyses. The review also explores the historical evolution of adherence concepts and highlights the critical role of pharmacists in educating patients and managing medication regimens. The importance of recognizing and addressing medication non-adherence as a significant health policy issue is underscored, advocating for improved measurement methods and interventions such as multidrug punch cards and medication charts. The review advocates for a patient-centered approach and multidisciplinary collaboration in healthcare, aiming to enhance healthcare outcomes and medication adherence through systemic changes. It also underscores the need for empowering pharmacists with expanded roles and appropriate tools within healthcare systems to further improve patient outcomes.

Key words: medication adherence, adherence barriers, patient adherence, survey and questionnaires, self-report.

Adherencia k liečbe – cesta k pochopeniu pacienta

Cieľom tohto prehľadového článku je problematika adherencie k liečbe, ktorá je kľúčová pre dosiahnutie výsledkov v oblasti zdravotnej starostlivosti. Článok skúma rôzne aspekty non-adherencie, ako napr. postoj pacienta k liečbe, ekonomické prekážky a zložitosť liečebných režimov.
Súčasne je kladený dôraz na hodnotenie adherencie, predovšetkým pomocou sebahodnotiacich dotazníkov a retrospektívnych analýz údajov z databáz. Identifikácia non-adherencie predstavuje prehliadanú oblasť zdravotnej politiky. Využívanie nových možností merania a intervencii, ako sú viacdávkové perforačné karty a liekové karty, môžu prispieť k zlepšeniu adherencie. Nevyhnutnosť systémových zmien, potreba multidisciplinárnej spolupráce zdravotníckych pracovníkov a orientácia na individuálne potreby pacienta predstavujú cestu k lepšej adherencii.

Kľúčové slová: adherencia k liečbe, bariéry adherencie, adherencia pacientov, prieskumy a dotazníky, sebahodnotiace dotazníky.

Introduction

Medication adherence is a crucial factor for achieving optimal treatment outcomes, as it directly impacts patient health (1). However, it is a persistent challenge in healthcare, since many patients struggle to follow their

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The authors attest that their study was approved by the local Ethical Committee and is in compliance with human studies and animal welfare regulations of the authors' institutions as well as with the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly in Helsinki, Finland, in June 1964, with subsequent amendments, as well as with the ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, updated in December 2018, including patient consent where appropriate.

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prescribed medication regimens (2, 3). The consequences of medication non-adherence extend beyond individual patients and affect various participants, including healthcare providers, caregivers, and healthcare systems as a whole (1, 4). Research has revealed that nearly half of individuals who use chronic prescription medications exhibit some form of non-adherence, leading to poor health-related outcomes, increased disease progression, greater healthcare service utilization, escalating care costs, and elevated mortality rates (5, 6). In Europe, poor medication adherence is linked to approximately 200,000 premature deaths annually. The financial impact of non-adherence is significant, with the annual costs being estimated at EUR 125 billion in Europe and USD 105 billion in the United States due to preventable hospitalizations, emergency care, and outpatient visits (7). According to a systematic review of economic impact, the cost of non-adherence for various diseases ranged from $949 to $44,190 per patient per year (in 2015 US$) (8).

Patients with chronic conditions, such as hypertension, diabetes, asthma, and chronic obstructive pulmonary disease (COPD), face a heightened risk of non-adherence, with estimated rates of 50% for hypertension, 50–60% for asthma, and 70% for COPD (9). In general, around 4% of patients fail to start treatment, 30% show non-adherence by day 100, and 40% discontinue their medications within a year (10). In a recent cross-over study, Dietrich et al. highlighted the critical importance of medication adherence for stroke patients with atrial fibrillation, particularly in relation to direct oral anticoagulants (DOACs) to prevent thromboembolic events (11). The adherence rates to DOACs show significant variability, ranging from 38,0% to 99,7% (12). Often, suboptimal adherence is associated with patient perceptions of limited benefits and the challenges of adhering to the strict dosing schedule of DOACs, which is crucial due to their short half-lives of 8 to 17 hours (11). Kim et al. found in their study that the risk for cardiovascular events was lowest in patients who took at least 90% of their prescribed DOAC doses (13). This observation aligns with findings by Solla-Ruiz et al. who reported increased thromboembolic events in patients with less than 95% adherence to DOAC doses compared to those with perfect adherence (14). These findings stress the importance of optimizing DOAC adherence for effective treatment (11).

Tab. 1. *Various factors contributing to non-adherence*

Factor Category	Specific Factors	Impact on Non-Adherence
Patient Beliefs	Perception of medication necessity; concerns about side effects	Influential in shaping adherence behavior
Economic Factors	High medication costs; unemployment; poverty	Significant role in non-adherence, particularly in marginalized groups
Complexity of Regimens	Multiple medications; strict dosing schedules; long-term treatment	Increases the difficulty of adherence; prevalent in chronic diseases
Side Effects	Fear of adverse reactions; impact on quality of life	Leads to intentional non-adherence or discontinuation of therapy

Studies have shown that factors contributing to non-adherence are multifaceted and complex (15–17). Patient perceptions, beliefs, and attitudes toward medication, as well as concerns about side effects, are influential in shaping their adherence behavior (5). Moreover, economic factors, such as unemployment, poverty, and high medication costs, play a significant role in non-adherence (Table 1) (15, 17). These multifaceted factors underline the need for tailored measures and interventions to improve medication adherence and patient outcomes (15, 17–19).

Accurate assessment of medication adherence is essential for designing effective treatment plans and interventions (20, 21). Various methods are available to assess adherence, each with its advantages and limitations (22, 23). The choice of measurement method is crucial, as it can impact the accuracy of the results. For example, patient self-reports may lead to under-reporting or over-reporting, while electronic medication monitoring may not confirm actual consumption (24–26).

The aims of this review were to provide a comprehensive examination of medication adherence and to deepen our understanding of the underlying mechanisms of non-adherence, recognizing it as a significant issue in clinical practice. It acknowledges that medication adherence, while being of vital importance, is also a complex issue influenced by numerous factors (27–31). To address this complexity, a multi-approach strategy may be necessary to gain deeper insights into adherence behavior (32). Furthermore, collaboration among healthcare professionals, including physicians, nurses, and pharmacists, is essential for addressing non-adherence (33, 34). Standardized reporting forms, questionnaires, and improved care coordination can all simplify the evaluation of adherence and ultimately lead to better patient outcomes (35–38). In addressing medication non-adherence, a key challenge is the limited awareness among stakeholders, often resulting in its exclusion from national health policy agendas. This oversight contributes to inadequate monitoring and utilization of adherence metrics, ultimately limiting the enhancement of healthcare outcomes. Healthcare providers frequently underestimate the prevalence of non-adherence, and there is a notable lack of evidence-based, cost-effective strategies to improve adherence at a systemic level (7). In summary, medication adherence is a critical factor for therapeutic success, and this review explores its challenges.

History of medication adherence

The historical perspective on patient adherence in medicine traces its origins to ancient times, with Hippocrates being the first to have highlighted the challenges of relying on patient-reported medication use. This concern persisted through the centuries, notably with the discovery of tuberculosis as a contagious disease in 1882. Monitoring patient adherence, particularly among transient individuals and alcoholics, proved challenging. In the early 20th century, the convergence of urbanization, industrialization, and social disparities shaped views on non-adherence. Efforts to address this issue had been limited until World War II, when it gained renewed attention, particularly among tuberculous veterans. The introduction of antibiotics in the late 1940s offered hope for tuberculosis treatment, but patient non-adherence remained a frustration (39).

The topic was officially incorporated into medical terminology in 1976 when Sackett and Haynes introduced the term 'compliance' (40). Then, in 1993, the discourse shifted from 'compliance' to 'adherence', signifying a more nuanced understanding of patient engagement with their medication regimens (41). The term 'persistence' was introduced in 2001, further expanding the scope of this field. In a significant development in 2003, the World Health Organization (WHO) released a comprehensive report on medication adherence, contributing greatly to the body of knowledge (42). Between 2008 and 2009, the term 'medication adherence' was recognized as a MeSH term, marking its significance in medical research. In 2010, the International Society for Medication Adherence (ESPACOMP) introduced the ABC taxonomy, a framework for categorizing adherence (Fig. 1) (41, 43).

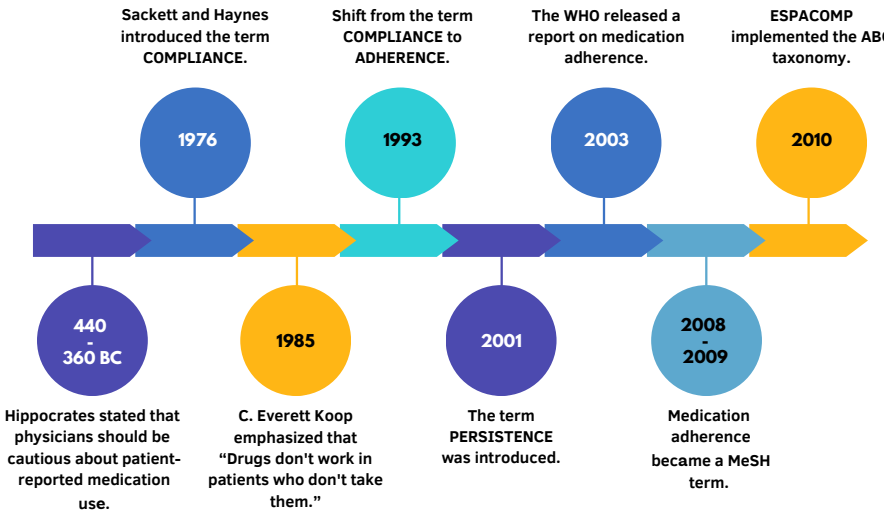
Definition and significance of adherence

In order to properly understand the concept of medication adherence, it is essential to grasp the distinction between adherence and compliance. While these terms are often used interchangeably, they carry nuanced yet significant differences in their meaning. Medication adherence, as defined by the WHO, refers to "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider." Compliance, on the other hand, indicates a more passive and authoritarian approach where patients simply follow prescribed directives without active involvement in decision-making. Recognizing this difference is fundamental in promoting effective healthcare outcomes and patient-centered care (42). According to the 2003 WHO report, adherence is a multidimensional phenomenon influenced by five key dimensions: health system/healthcare team, social/economic, condition-related, therapy-related, and patient-related factors. This challenges the traditional misconception that adherence is solely the patient's responsibility (42, 44). Viewing medication non-adherence as the patient's "fault" is a misinformed and detrimental perspective. As Everett Koop emphasized, "Drugs don't work in patients who don't take them." Therefore, it is crucial for health professionals to acknowledge that inadequate medication adherence leads to suboptimal clinical outcomes. This is supported by the WHO's statement that improving adherence may have a greater impact on health than enhancing specific medical treatments. A continuous, collaborative approach is required to achieve optimal medication adherence and fully utilize the benefits of current therapies (45). The Medication Adherence Reporting Guideline (EMERGE), adopted by the ESPACOMP, employs a three-phase classification known as the ABC taxonomy to categorize medication adherence. The phases include (a) initiation, (b) implementation, and (c) persistence. Persistence is defined as the duration from initiation to the final dose before discontinuation. In each phase, there are distinct methodological challenges related to defining, measuring, and analyzing medication use (43). Non-adherence comes in eight forms, adapted from Arnet et al.'s classification, including primary non-adherence, drug holidays, the toothbrush effect, perfect adherence with the wrong medication, dosage errors (overdose, underdose, erratic dosing), incorrect dosing frequency, early therapy discontinuation, and polypharmacy (Table 2) (46).

Understanding the underlying mechanism of non-adherence

Our comprehension of non-adherence remains partial, with some factors and treatments not fully addressing the underlying causes of this behavior. Therefore, selecting the appropriate treatment should be guided by the reasons behind non-adherent behavior and the patient's level of commitment (47).

Fig. 1. *Illustration of the history of medication adherence with significant events modified according to Vrijens et al. (41)*



Tab. 2. *Eight forms of non-adherence, modified and adapted from Arnet et al.'s classification (46)*

Abbreviation	Form	Description
NON	Primary non-adherence	Medication is not obtained or picked up from the pharmacy.
A	Drug holidays	Patients temporarily stop taking their prescribed medication.
D	Toothbrush effect	Patients start following doctor's recommendations shortly before an appointment but may otherwise ignore them.
H	Perfect adherence but with the wrong medication	Patients take medication as prescribed, but it is the incorrect medication.
E	Dosage errors, overdose	Patients take more medication than prescribed.
R	Dosage errors, underdose	Patients take less medication than prescribed.
E	Dosage errors, erratic dosing	Patients inconsistently follow the prescribed dosing schedule.
N	Incorrect dosing frequency	Patients take medication at the wrong frequency (e.g., twice a day instead of the prescribed three times).
C	Early therapy discontinuation	Patients discontinue therapy prematurely.
E	Medication cocktail, polypharmacy pattern	Patients engage in a pattern of taking multiple medications simultaneously.

Increased knowledge, by itself, does not automatically lead to adherence (48, 49). Improving drug therapy adherence relies on patient education, but one which goes beyond simply repeating instructions or providing printed materials. Indeed, a holistic approach is needed that includes gathering patient-specific information, customizing instructions, providing support, encouragement, monitoring and evaluating the patient's response to treatment to determine its effectiveness in improving patient outcomes (50). Medication non-adherence, including errors in administration such as incorrect use, is a major contributor to adverse drug reactions and hospitalizations. In particular, elderly patients with polypharmacy for chronic diseases are at the highest risk for such adverse drug reactions (51). Medication non-adherence has been documented as a contributing factor in over 20% of preventable adverse drug events (ADEs) in older patients in ambulatory care settings (52). Studies indicate that more than 10% of admissions of older adults to acute care can be attributed to non-adherence to medication regimens (53). Col et al. reported in their study that one-third of older persons admitted to hospital had a history of non-adherence (54).

Medication non-adherence is categorized as either intentional or unintentional. Intentional non-adherence involves a patient's active choice to not follow treatment, considering the pros and cons. In contrast, unintentional non-adherence is passive, often due to factors outside the patient's control. Intentional non-adherence is linked to a patient's beliefs and motivation, while unintentional non-adherence is reportedly more associated with demographic factors such as age (55).

Challenge to measure

Adherence to medications is the basic precondition of successful treatment of chronic diseases that require long-term use of medications (e. g., cardiovascular diseases, asthma, COPD). The recent increase in access to patient-level prescription and dispensing data in administrative records has created new possibilities for objectively measuring medication adherence at the population level (56). Nowadays, robust data extraction from prescription records or insurance databases is a valuable resource for analyzing medication-taking behavior, enabling retrospective analysis. This objective measure approach is particularly relevant in the context of chronic diseases and in cases involving polypharmacy. The advantages include a detailed analysis of adherence and persistence, understanding the impact of various factors on adherence, and simplified data access for population analysis (57). In a register-based retrospective cohort study, Wawruch et al. explored the factors influencing medication adherence in persistent angiotensin-converting enzyme inhibitors (ACEI) users and non-persistent ACEI users (n = 6,578). The most significant predictors of medication non-adherence were the use of mineralocorticoid receptor antagonists, bronchial asthma/COPD, and dementia, highlighting the complex interplay of comorbidities and medication regimens in influencing adherence. These findings emphasize the need for tailored approaches in managing such patients to improve medication adherence. The results of the study can help in determining the cohort of patients who require increased attention (58).

Non-adherence is commonly assessed using two key indexes: the Proportion of Days Covered (PDC) and the Medication Possession Ratio (MPR). The PDC is calculated by dividing the number of days covered by medication treatment by the number of days in the follow-up period, with a common threshold for non-adherence set at PDC < 80 % (57). To standardize and enhance the reporting accuracy for PDC, enabling more reliable comparisons across studies and health systems, Dalli et al. introduced the TEN-SPIDERS tool. This acronym stands for Threshold, Eligibility criteria, Numerator and denominator, Survival, Pre-supply, In-hospital supplies, Dosing information, Early Refills, and Switching. Each component of this tool provides specific guidelines for reporting PDC-related parameters (56). Similarly, the Medication Possession Ratio (MPR) generally indicates the percentage of days' supply received over a specified time. However, discrepancies in the MPR denominator definition can contribute to variations in research findings and complicate cross-study comparisons (59).

Digital databases are also useful in terms of researching primary medication non-adherence (PMN). PMN occurs when a patient fails to pick up a newly prescribed medication. A study by Bruthans et al. underscored the importance of considering age-related factors when addressing medication adherence issues. This research of electronic prescription database in the Czech Republic indicated that PMN varied significantly across age groups, with the highest rates observed in younger patients (18–39 years old) and the lowest in older patients (75 years and older). The study showed a PMN of 4.56 percent which is comparable with other studies on PMN (60–62). The approach and findings of the study contribute to a broader understanding of medication adherence, particularly in the context of electronic health records (60).

In clinical settings, it is vital to use self-report questionnaires for numerous reasons (e. g., for their being inexpensive, widely accepted, uncomplicated to use, non-invasive, and time-efficient). Importantly, the unique capability of self-reporting lies in its ability to both track medication use patterns and identify reasons for non-adherence. This underscores the necessity for an accessible tool that not only detects adherence issues in routine settings but also paves the way for effective adherence-improvement interventions. These interventions should be specifically targeted to the identified issues and personalized for the individual patient (63, 64). Therefore, focusing on patient-adjustable factors is essential in the assessment phase.

The extensive range of adherence measurements available in the existing literature complicates the process for healthcare providers in determining the most appropriate instrument for their clinical practice. In a secondary analysis of data by Kwan et al. (2020), a total of 121 unique instruments for measuring medication adherence were evaluated for their psychometric quality and evidence, following the COSMIN guidelines (65, 66). None of the instruments evaluated met the criteria for all nine key measurement properties. Cross-cultural validity was notably absent despite numerous translations. The study identified inadequately established psychometric properties for medication ad-

herence instruments, with limited evidence supporting their use. This underscores the need for a minimal set of standardized measurement properties (66). It is hence evident that a practical validated tool to measure medication adherence is needed. Arnet et al. developed and validated a novel questionnaire named 15-STARS (Screening Tool for AdheRence to medicineS). The objective was to create a self-report instrument specifically assessing medication non-adherence. This tool is designed to meet several criteria: quick to complete; suitable for ambulatory patients; relevant to the adherence implementation phase; capable of identifying personalized, changeable factors behind non-adherence; and incorporating a numerical assessment of adherence. The 15-STARS questionnaire demonstrated good acceptability, low rates of missing responses, and satisfactory validity and reliability with acceptable psychometric properties (64).

Interventions – the way forward

The effectiveness of interventions in healthcare is greatly enhanced by frequent patient interactions, particularly those focused on adherence. A study by Gregoriano et al. showed significant improvements in adherence among asthma and COPD patients due to patient-tailored support, which included audio reminders and feedback on the intake patterns of inhaled medication, as well as regular support calls for non-adherent patients. This method is more effective than the limited, predefined follow-up appointments often used in other studies. Furthermore, a randomized clinical trial by Sulaiman et al. confirmed these findings, demonstrating that repeated feedback significantly improved inhaler adherence (67). In a systematic review comparing interventions, Torres-Robles et al. highlighted that, over the past decade, diverse interventions demonstrated positive effects on medication adherence and clinical outcomes (68). Effective adherence interventions have been associated with positive results, including achieving viral suppression in HIV patients (69), lowering lipid levels and total cholesterol in individuals taking lipid-lowering medications (70), reducing HbA1c levels, decreasing hospitalizations, and lowering all-cause mortality in patients with diabetes mellitus (71). The incorporation of technical components, involving gadgets, instruments, or systems that facilitate medication intake, can enhance medication adherence. These interventions are helpful for individuals with memory issues or busy social lives that may otherwise limit their ability to adhere to medication routines (68).

One of the valuable interventions in supporting patient adherence in medication management, particularly in primary care settings, is multidrug punch cards. These tools are designed to organize and dispense multiple medications, thereby enhancing adherence and safety. In their study, Boeni et al. demonstrated that multidrug punch cards led to high patient satisfaction and improved adherence. Particularly beneficial for older adults managing polypharmacy, these cards enhanced medication safety and ease of use, with their success being influenced by trust in healthcare professionals and individual patient experiences. The study encourages healthcare professionals to actively recommend these cards to patients with complex medication routines, highlighting their importance in improving patient outcomes in primary care (51). The use of medication charts in daily practice with a focus on 'patients', 'process', and 'terms and conditions' has been recognized by both physicians and pharmacists as beneficial. In a narrative systematic review by Dietrich et al., patients with a medication chart showed an increase in medication adherence from 86 % to 93 %, as measured by pill counting, compared to those without a medication chart. These charts are particularly valuable at transitions of care, such as at hospital discharge or when being moved to a different care facility. Medication charts typically list all of a patient's current medications, including prescription and over-the-counter drugs. They are designed to be handed over to the patient as a hardcopy and serve as an informative tool for both patients and healthcare providers, such as doctors, nurses, and pharmacists. For patients, one of their roles is that of an extra reminder tool. Healthcare providers find medication charts beneficial for enhancing record quality and achieving better interdisciplinary cooperation. It is essential, particularly for patients with polypharmacy, that the data on the chart is accurate and up to date to maximize its benefits (72).

The findings of Marquis et al. reveal that approximately 9 % of polypharmacy patients experience ongoing swallowing difficulties, often leading to intentional non-adherence. These issues, related to specific medications rather than the number of tablets, underscore a lack of awareness among healthcare professionals. The study points out the importance of an intervention which systematically addresses swallowing difficulties in primary care to enhance medication management and patient care (73). Last but not least, healthcare professionals should be aware of the Hawthorne effect. The Hawthorne effect is defined as a phenomenon where individuals modify or improve an aspect of their behavior in response to their awareness of being observed or having their behavior assessed. This change is often influenced by the individual's beliefs about the researcher's expectations, as well as factors such as conformity and social desirability (74).

Healthcare systems and role of pharmacist

Fragmented healthcare systems create obstacles to medication adherence due to compromised healthcare coordination and limiting patient access to care. The limited availability of health information technology restricts a physician's access to patient information across different care settings, potentially compromising patient care. In an overburdened healthcare system, clinicians often have limited time with each patient, which may delay assessments of medication-taking behaviors. Considering the significant impact of medication adherence on patient well-being, healthcare systems need to adapt to prioritize its importance. Systemic changes should be implemented to ensure that adequate time is dedicated to discussing medication adherence. In response to time constraints, there may be a shift towards employing a team-based healthcare framework. This model involves the training of non-physician personnel to undertake tasks conventionally performed by physici-

ans.This delegation provides physicians with time to focus on understanding and addressing patient medication adherence patterns (45). Effective doctor-patient communication leads to a 19 % higher patient adherence rate, as evidenced by 106 studies with compelling statistical significance. Patients with poorly communicating doctors face a 47 % higher risk of non-adherence (75). By extending clinical services and embracing a patient-centered approach, the pharmacy profession holds a key role. It can enhance the coordination of the entire medication process by consulting patients on medication adherence. Hepler and Strand highlight the key term *covenant* which represents the connection between the patient and the pharmacist. This is the bond that cements the therapeutic relationship (76). The role in community pharmacies, particularly through direct patient counseling, has proven crucial for enhancing medication adherence. Such interactions not only educate patients about their treatments and conditions but also improve medication schedules, leading to improved adherence. Boeni et al. underline the observed evidence on the significant impact that targeted counseling by pharmacists has on medication adherence and persistence. However, reports suggest that counseling practices in community pharmacies are limited. Patient counseling in community pharmacies often assumes a minor role, with a tendency towards nonmedical or product-centered communication rather than a patient-centered approach (77). In summary, pharmacists have significant opportunities to overcome conventional obstacles, utilizing their expertise to enhance patient understanding, adherence, and clinical outcomes. It can be accomplished by providing counseling and education while also enhancing their professional growth. The requirements are evident, pharmacists have a well-documented role, and a promising opportunity awaits (76).

Conclusion and perspectives

Therapeutic care is founded on respect for the patient's individuality and stands in clear contrast to paternalistic and authoritarian approaches. It is essential to rethink medication adherence, encouraging a shift from viewing it as a strict enforcement by the practitioner's authority to seeing it as a joint effort involving everyone committed to resolving a specific issue. Non-adherence to medication negatively impacts health and increases healthcare costs. It is crucial for relevant parties to first acknowledge this issue's existence and properly understand its primary causes. Prioritizing medication adherence in policy discussions is crucial to raise awareness and implement effective solutions. Future efforts should focus on improving methods for measuring and screening medication adherence, with validated instruments, to better understand and address the nuances of this issue. Additionally, interventions such as multidrug punch cards and medication charts show their potential in enhancing adherence, particularly in polypharmacy. A collaborative, patient-centered approach in healthcare is vital, empowering pharmacists to play a more integral role. This approach, combined with effective adherence measurement and screening, holds the key to improve patient medication adherence.

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