Optimizing drug adherence in hypertension: More than a mind game

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ABSTRACT

Poor drug adherence to prescribed drug treatments and lifestyle recommendations is a major determinant of poor blood pressure control reported around the World. Prevalence rates of antihypertensive medication nonadherence are highly variable depending on the studied population and may reach up to 40%. Remarkably, the phenomenon stays often undiagnosed and unaddressed mainly because physicians have limited tools to perform a reliable diagnosis. In this review oriented toward practicality, 5 principal aspects of nonadherence will be addressed with a special emphasis on psychological factors influencing adherence patterns, both from a patient's and physician's perspectives.

Key words: adherence, arterial hypertension, psychological determinants, physician-related factors

INTRODUCTION

Over the past decades, great progress has been made to improve outcomes for subjects with arterial hypertension. Nevertheless, high blood pressure (BP) remains the leading modifiable risk factor for attributable deaths according to the Global Burden of Disease data (2019) [1]. Despite technological and pharmacological innovations, BP control is still suboptimal, with only about 40% of hypertensive subjects reaching recommended BP targets in high-income Western countries [2]. In low-income countries, results are even worse [2]. Several factors are responsible for these disappointing results. Among them, poor drug adherence is a major contributor. Still, in daily clinical practice, the problem often remains underdiagnosed and unaddressed, mainly because physicians have limited abilities to make a reliable diagnosis of nonadherence.

In this review, we attempt to offer deeper insights into the phenomenon of nonadherence, by answering 5 main questions.

Is poor drug adherence truly relevant? Impact of adherence on outcomes

Poor drug adherence is a widespread phenomenon in the whole spectrum of chronic diseases, not only limited to the field of cardiovascular diseases. This is particularly true for arterial hypertension, a generally asymptomatic disease requiring long-term, usually lifelong, treatment. Lee et al. [3] have reported a global prevalence of antihypertensive medication nonadherence of 27% to 40% in hypertensive patients, with varying percentages according to different detection methods or types of drugs used [4]. Poor drug adherence leads to poor BP control: patients adherent to treatment are more likely to achieve BP goals [5], while low drug adherence is linked with

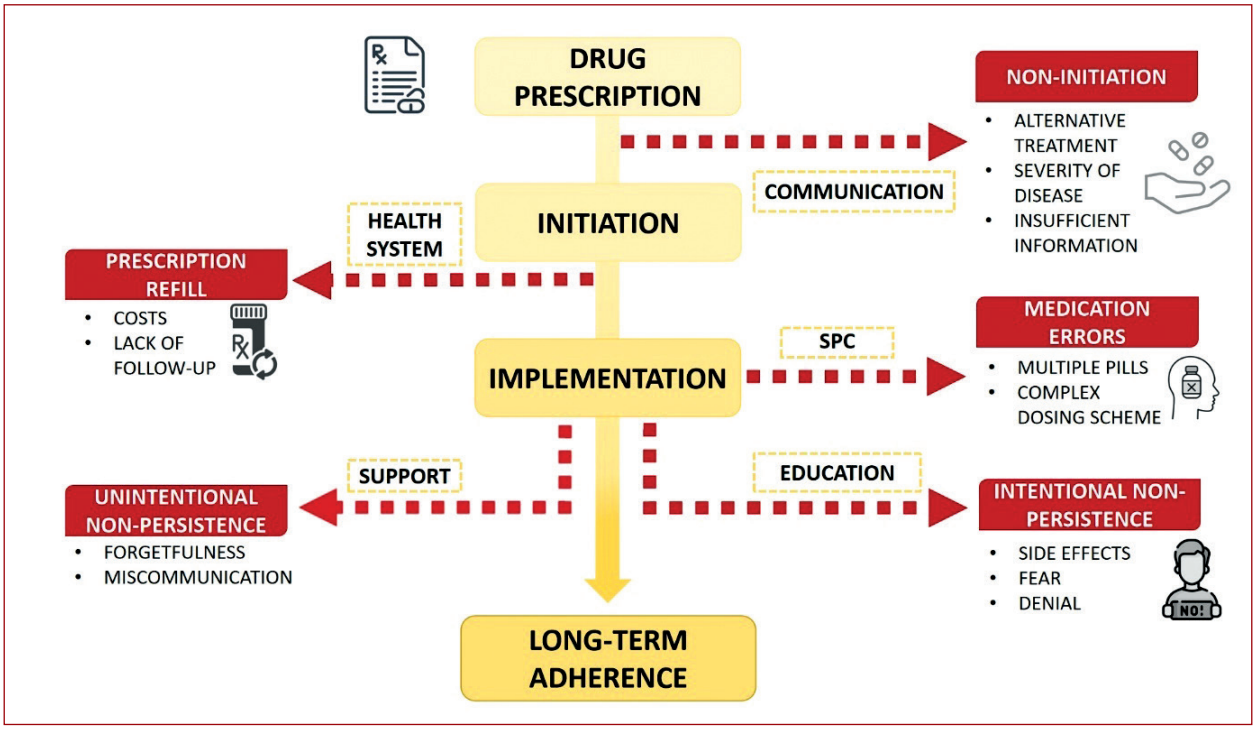

Figure 1. Overview of the different steps involved in the process of adherence

Reasons for nonadherence are shown in the red boxes, with potential remedies shown in the dashed-line boxes
Abbreviations: SPC, single-pill combination

a higher incidence of hypertensive crises [6]. More importantly, poor drug adherence is associated with higher risk of organ damage, such as increased arterial stiffness [7], and a higher incidence of cardiovascular events including acute myocardial infarction, stroke, and heart failure [8–12], as well as kidney failure [13]. At the same time, poor adherence has a substantial socioeconomic impact, with a higher risk of work impairment [14] and greater healthcare costs. In a model developed by Mennini et al. [15], including healthcare system data from Italy, Germany, France, Spain, and England, increasing adherence to antihypertensive drugs to 70% (meaning at least 70% of the population would achieve good drug adherence), would prevent 82 235 cardiovascular events and save € 332 millions of healthcare costs over 10 years. Thus, improving drug adherence might not only improve outcomes for individual patients; it can also improve socioeconomic parameters at the population level.

How to define (non)adherence? Towards a uniform definition of adherence

In the past, many definitions have been used. A first attempt to standardize definitions was undertaken in 2003 by the World Health Organization (WHO). According to the WHO definition, adherence is "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" [16].

In 2012, a new taxonomy was proposed by Vrijens et al. [17]. According to this consensus, adherence refers to the process by which patients take their medications as prescribed. In the process, there are 3 major components: initiation, implementation, and discontinuation of treatment (Figure 1).

Initiation is the first step in which a patient has to start taking the first dose of a prescribed medication. For physicians, it seems obvious that patients will directly start the prescribed drug. However, non-initiation of treatment occurs more often than one would think. Pooled data from a 2018 review report a non-initiation rate of 12.4% for antihypertensive drugs — over 1 in 10 patients never starts a prescribed drug [18]. Rates vary according to geographical regions, with non-initiation almost twice as high in North America compared to Europe. Differences in health care coverage and cost of health care might at least partly explain these differences.

Implementation of the dosing regimen reflects the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken.

Poor implementation of treatment can show many patterns: from day-to-day variations related to forgetfulness, up to longer periods of treatment interruption — intentional or not. Given these variations in adherence patterns, quantification of adherence remains a challenge. Globally, there is no uniform threshold above or below which a patient can be considered as adherent/nonadherent. In literature, an arbitrary cut-off of 80% is often used to define good adherence. However, the relevance of this cut-off remains controversial [19].

Table 1. Strengths and limitations of different methods to assess drug adherence

Method	Accuracy	Resistance to manipulation	Cost and/or workload	Clinical use
Assessment by clinician	■■	■■	■■■■■■	■■■■■■
Questionnaire	■■	■■	■■■■■■	■■■■■■
Pill count	■■■■	■■■■	■■■■	■■■■
Refill data	■■■■	■■■■	■■■■	■■■■
Witnessed drug intake	■■■■■■	■■■■	■■	■■
Electronic monitoring	■■■■■■	■■■■■■	■■	■■■■
Drug assay	■■■■■■	■■■■	■■	■■■■

"Resistance to manipulation" reflects the robustness to manipulation by the patient, with poor robustness resulting in misleading information on true adherence. Scores on characteristics are shown as follows: red bars – weak score; orange bars – average score; green bars – excellent score.

Finally, after initiating and correctly implementing the prescribed drug scheme, the last hurdle must be overcome: continuation of the so-called long-term drug compliance. Unfortunately, early discontinuation of treatment contributes largely to nonadherence. A trial studying adherence by electronic monitoring has reported that about half of the patients stopped their antihypertensive drug within one year [20]. Prescription refill data in the Lombardy region cohort show similar results (discontinuation rate of 33% at 6 months and 41% at 1 year) [21]. However, late discontinuation due to adverse side effects or multidrug therapies is also common. Choice of therapy might impact discontinuation rates, with a lower hazard ratio observed for angiotensin receptor blockers and a higher likelihood of discontinuation for b-blockers and diuretics.

(Non)adherence is a complex and elusive concept, varying over time and according to different prescribed medications, with different patterns of drug implementation.

Non-initiation or delayed initiation of prescribed treatment, sub-optimal implementation of the prescribed dosing regimen, or early discontinuation of the treatment represent different forms of nonadherence. Limiting evaluation of adherence to a mere percentage would oversimplify its meaning and neglect the dynamic nature of the phenomenon.

How to detect nonadherence? The ABC of adherence screening

Before addressing the question of how to detect nonadherence, one should know when to search for it. The current European Society of Hypertension (ESH) guidelines recommend screening for nonadherence to antihypertensive treatment at every clinical appointment, as part of routine assessment [22]. Particular attention to adherence must be paid before treatment escalation, before screening for secondary hypertension, or when resistant hypertension is suspected. Nonadherence should also be considered in patients who are taking two or more antihypertensive drugs, with inadequate BP response [22]. Generally, a <10 mm Hg drop in systolic BP despite the prescription of 2 antihypertensive drugs can be considered a threshold for adherence screening [23].

Assessment of nonadherence in daily clinical practice is often limited to an interview by the physician. Yet, physicians tend to overestimate the value of this approach, which in fact has been shown to be unreliable [24]. Indeed, patients tend to under-report nonadherence due to different reasons (e.g. recall bias, desirability bias, fear of being blamed). In a recent European survey, 50% of patients do not inform their physician when they interrupt their treatment [25].

Drug adherence can be assessed by indirect methods, such as questionnaires, pill count, and evaluation of prescription refills. These methods imply reasonable cost and workload, explaining why they are more often used in clinical practice. Nevertheless, the sensitivity of these methods is poor, and results are subject to recall errors and manipulation by patients. Direct methods, such as witnessed drug intake and drug dosage in blood or urine samples, offer more certainty about medication, at least at that specific time, but they also have some limitations [26]. For example, drug measurement in blood or urine is exposed to a marked Hawthorne effect. The strengths and limitations of different methods are shown in Table 1.

According to a recent meta-analysis addressing the problem of nonadherence in resistant hypertension, indirect methods clearly underestimate the prevalence of nonadherence. Only 20% of subjects were considered to be nonadherent by indirect methods, compared to 46% with direct methods [27, 28].

One way to monitor drug adherence is by using electronic monitoring systems or so-called MEMS (Medication Event Monitoring System) [29]. Pill dispensers record every box opening, with non-openings reflecting missing doses. The system can be used for longer periods (months to even years), thereby providing a long-term dosing history. It is the only system enabling a better understanding of adherence patterns and detection of dynamic changes in adherence over time. Moreover, this information offers an extra educational value about patients, by unraveling individual adherence habits. Improving insight into the patient's specific adherence pattern can help improve drug adherence.

Admittedly, the system can be intentionally manipulated since it only reflects box opening and not ingestion of the pill. Thus, it is not possible to ascertain drug intake with each opening. However, the most important information collected by electronic systems comes from non-opening since any non-opening is associated with lack of adherence.

Pill ingestion can be confirmed by drug assays. The majority of antihypertensive drugs used nowadays can be detected in blood or urine samples with liquid chromatography-tandem mass spectrometry (LC-MS/MS). A screening panel including the most used antihypertensives (i.e., the top 95% of locally prescribed antihypertensives) can be used [23]. Ideally, at least oral informed consent should be obtained before testing. To avoid the Hawthorne effect — also called white coat/toothbrush adherence: in patients knowing they will be tested, consent can be obtained on the day of sampling. Thus, as observed with electronic monitoring, the most important information comes from the total absence of drugs in analyzed fluids. A global strategy on how to apply chemical adherence testing has been proposed by Lane et al. [23].

Should we blame the patient? Patient-related factors contributing to poor adherence

The key question in tackling the issue of nonadherence is not only knowing if the patient is adherent but also *why* he or she is not adhering to prescribed treatment. Without understanding the root of the problem, solutions are hard to achieve. Most often, nonadherence is unintentional: a patient is not taking his/her pills due to forgetfulness, organizational limitations, etc. However, some patients do not take medication intentionally, driven by factors such as lack of symptoms, fear of side effects, preferences for alternative treatments, etc.

Side effects can negatively impact treatment adherence. Notably, there seems to be a sex-related difference in occurrence of side effects, with adverse drug reactions more frequently reported by women [30, 31]. Typically, peripheral edema secondary to calcium channel blockers, dry cough secondary to angiotensin-converting enzyme inhibitors, and electrolyte disturbances secondary to diuretics are more frequently observed in women [32]. Factors such as differences in body weight and composition, hepatic metabolism, and hormonal influences could explain these variations since they might contribute to drug overexposure in women [33, 34]. Some studies even suggest a sex-related difference in BP lowering effect (e.g., greater BP reduction by amlodipine in women), raising the question of whether sex-specific guidelines should be developed [35].

However, pooled data on BP lowering effect and cardiovascular outcome showed no difference between men and women for major drug classes [36].

Moreover, sex-specific pharmacokinetics are not well studied for many antihypertensives, and women are typically underrepresented in cardiovascular trials [32]. Therefore, awaiting further data, sex-specific recommendations concerning optimal treatment cannot be made yet.

Table 2. Risk factors for poor adherence (adapted from [37])

Young age
Male sex
Cognitive impairment
Depression
Asymptomatic disease course
Low socioeconomic status
Higher cost of treatment
Higher number of drugs or complex treatment schedule
Drug tolerability/side effects of treatment
Perceived lack of efficacy of treatment
Lack of understanding of treatment benefits

Intentional nonadherence may be observed in patients with difficult experiences and/or altered psychological profiles (see below). It is more frequent in patients with apparent treatment-resistant hypertension (i.e., uncontrolled BP despite prescription of 3 antihypertensive drug classes including a diuretic) and may be detected by direct methods. This type of nonadherence requires a different approach compared to unintentional nonadherence [26].

Nonadherence in general is usually the result of an interplay of many different factors at different levels: socioeconomic, patient-related, therapy-related, condition-related, and healthcare system-related [16]. Multiple risk factors for poor adherence have been identified, as shown in Table 2 [37]. Some factors such as age, sex, or socioeconomic status are not necessarily modifiable but can serve as warning signs. Other factors such as complexity/tolerability and cost of treatment, are not only risk factors but above all modifiable targets for improvement in drug adherence.

Besides demographic and socioeconomic factors, multiple underlying psychological determinants influence adherence patterns. Again, the role of these factors appears to be more important in patients with difficult-to-control and apparently treatment-resistant hypertension, particularly in young patients without established vascular disease, advanced target organ damage, or secondary hypertension [38, 39]. In this subset of patients, the main factors associated with poor drug adherence — but also severity of hypertension irrespective of drug adherence — were low capacity to put things in perspective, altered expression of emotions/ alexithymia, and somatization. In a substantial proportion of cases, this profile was associated with an underlying post-traumatic disorder. It may be hypothesized that emotions so unbearable that they cannot be expressed by words will be expressed by symptoms, which may eventually lead to established diseases. Causative mechanisms may include chronic inflammation, immune response, and activation of the renin-angiotensin and sympathetic nervous systems. On the other side, this constellation of psychological traits is also associated with

poor drug adherence and probably other unhealthy and risky behaviors [38, 39].

Notably, in patients with difficult-to-treat hypertension, a higher tendency to self-blame or to blame others was associated with the severity of hypertension, irrespective of drug adherence [38]. This further supports the recommendation to avoid confrontational and judgemental approaches when addressing the problem of nonadherence with patients, as it may further enforce negative psychological loops. Therefore, we should never blame the patient — rather create a climate of confidence and open a dialogue to identify and address in a personalized and empathetic way his/her reasons for nonadherence. More generally, patients with unexplained resistant hypertension, particularly young patients without severe organ damage or secondary hypertension, may benefit from both direct assessment of drug adherence and psychological evaluation [26].

Should we blame the doctor? Physician-related factors contributing to poor adherence

When confronted with nonadherent patients in daily practice, physicians might be tempted to leave the responsibility for nonadherence entirely with the patient. It is noteworthy that nonadherence and therapeutic inertia go hand in hand: physicians who assume that the patient will not take the treatment anyhow will be less likely to intensify treatment, thereby leaving the patient exposed to a higher cardiovascular risk [40]. In fact, studies have shown that physicians mention several reasons why they do not intensify or adapt treatment when BP is not well controlled and the phenomenon of medical inertia is rather common [41, 42]. Thus, one should not neglect the impact of the caregiver's behavior on adherence. In the next section, we propose a stepwise approach to improving patient adherence that health professionals can adopt.

Step 1: Be aware! The importance of knowing your patient and yourself

The first step in improving adherence is to recognize the problem. As stated earlier, identifying nonadherence can be challenging and time-consuming. Interestingly, data from a 2021 ESH survey suggest that physicians might overestimate their capabilities to identify and tackle nonadherence [43]. Indeed, only a minority of them acknowledge that identifying nonadherence can be really challenging, while the vast majority solely use detection techniques with poor reliability, such as patient interviews or questionnaires. When assessing the proportion of nonadherent patients, physicians typically report lower rates for their own patients compared to nationwide estimations. Although comparative data are lacking, this probably reflects overestimation of personal performance. A good way to overcome this phenomenon would be to offer each physician at least temporarily access to a more reliable adherence assessment tool (such as MEMS or drug assays). A confrontation with real-life nonadherence data could serve as an eye-opener and trigger increased alertness to nonadherence.

Once aware of limitations to correctly identify nonadherence, they should keep their eyes open for warning signs. Alertness to the previously mentioned patient-related risk factors will help identify patients at risk of nonadherence. In this context, attention should also be paid to the patient's socioeconomic background. Limited financial resources can make patients skip medication doses or medical appointments to lower their medical expenditures. Physicians should provide information on financial aspects of treatment, prescribe low-cost generic drugs, and/or address patients to assistance programs if needed.

Step 2: Educate! Correcting patients' beliefs and disbelief biases

Many caregivers presume that patient nonadherence is partly due to disbeliefs and lack of knowledge of hypertension [43]. Educating patients can help to fill this knowledge gap. However, education is often based on the healthcare provider's personal perspective, thereby it does not address alternative beliefs and disbeliefs, fed by the patient's cultural and socioeconomic background.

Research addressing the lay perspective demonstrated some frequently recurring views on hypertension [44]. The role of stress is one of them. Many patients believe stress is the main cause of their hypertension, thereby assuming that treatment is no longer necessary once stress levels decrease. Another frequently heard opinion is that high BP always produces symptoms. Patients might believe they can identify the moments when their BP is high, driving them to stop treatment when they are asymptomatic. Others believe long-term intake of medication will cause damage or even addiction, which stops them from continuing treatment.

Identifying the patient's beliefs helps inform him/her more adequately and correct wrong assumptions, which is a step towards better adherence. Creating an atmosphere where patients feel allowed or even stimulated to discuss their experiences and opinions, is a crucial step. Physicians themselves can help open up the discussion, by actively questioning side effects or bringing up delicate topics such as sexual dysfunction.

Step 3: Optimize treatment! The era of single-pill combinations

Optimization of drug treatment can improve drug adherence. One way to do so is to maximize the use of single-pill combinations (SPC) [45]. The more pills patients have to take every day, the lower the probability they actually will, especially when administration is spread over different moments throughout the day. Selecting long-acting combinations of pills, administered once a day, will help to overcome this barrier. Compared to both (initial) monotherapy and free-equivalent combinations, SPC use has

turned out beneficial for adherence [46]. In addition, SPC improves BP control [45], with a more rapid achievement of the BP target [47] and a reduction in cardiovascular events and even all-cause mortality [48, 49].

When selecting the preferred combination of antihypertensives in SPC treatment, multiple aspects can be taken into account. One aspect is treatment tolerance. Historically, higher discontinuation rates have been observed for β-blockers and diuretics when used in initial monotherapy [50]. However, when treatment is started with a combination therapy, adherence is typically better [51]; that is probably due to synergistic effects between different drug classes with lower risk of side effects. In a meta-analysis by Parati et al., SPC use clearly improved overall adherence, with no preferrence for specific combination of anti-hypertensives [38]. Nevertheless, it can be useful to keep common side effects of antihypertensives in mind. Taking foreseeable side effects into account before treatment initiation, particularly for patients with specific susceptibility, might help avoid early treatment discontinuation or modifications. On the other hand, in patients with underlying comorbidities such as heart failure, certain drug classes offer protective effects beyond the BP-lowering effect. Patients should not be deprived of these protective effects due to theoretical concerns regarding treatment tolerability.

In conclusion, the choice of antihypertensives should be tailored to individual characteristics, taking comorbidities into account, as discussed in detail in the latest ESH guidelines [22]. Choosing antihypertensive drugs with a long half-life — ideally longer than the 24-hour dosing interval — is advisable. These so-called "forgiving drugs" may allow for maintaining BP reduction despite occasionally missed doses.

The use of fixed-dose combinations may be expanded beyond antihypertensive drugs. Most hypertensive patients present other cardiovascular risk factors (e.g., dyslipidemia, diabetes) or comorbidities, requiring specific treatment. Using a lipid-lowering combination pill [52] or even a so-called cardiovascular polypill (containing antihypertensives and lipid-lowering treatment with or without low-dose aspirin) has been shown to have a positive impact on both adherence and cardiovascular outcomes [53]. According to the context, the use of generic, low-cost poly-pills may help overcome socioeconomic barriers in cardiovascular prevention [54].

Another simple trick to improve adherence is synchronizing medication refills. By renewing all medication prescriptions at the same time for the same period, the risk of missing prescription refills decreases [55].

Some have put hope in the development of very long-acting (injectable) antihypertensive compounds, such as angiotensinogen RNA-interfering molecules [56]. Indeed, one injection would cover the treatment needs for several months. Unfortunately, technical innovations will not overcome all barriers related to nonadherence. Data on the use of PCSK-9 inhibitors, an injectable long-acting cholesterol-lowering treatment, show a non-compliance with treatment of 33% after only 60 days [57]. One could even consider which option is worse: missing antihypertensive pills now and then, or missing one injection, which results in removing treatment benefits for several months.

Step 4: Monitor! Monitoring drug adherence in daily clinical practice

As recommended by the latest ESH guidelines, one should screen for nonadherence [22]. Practical details are described in the previous section and Table 1.

Since nonadherence is a dynamic phenomenon, it should be monitored over time. Confirmed adherence in the past does not exclude a decrease in adherence over time, and vice-versa. Indeed, trials studying adherence by using electronic monitoring (MEMS) showed a decrease in adherence over time, even when supportive measures to improve adherence were used [58]. Continued vigilance for nonadherence should thus be part of our daily clinical practice.

Screening for nonadherence should be done in a non-judgmental way. As stated previously, the goal is not to blame the patient but to identify barriers interfering with good adherence.

Conversely, monitoring adherence also enables giving positive feedback on the patient's behavior once adherence is improving.

Finally, patients should be encouraged to self-monitor their BP since data suggest it helps to improve adherence and compliance [59].

Step 5: Cooperate! The need for a multidisciplinary approach

Optimizing adherence is complex and time-consuming, probably too complex for a single physician. A wide range of potential interfering factors have to be identified and addressed, implying the need for a multidisciplinary approach. Developing drug adherence programs will allow for fine-tuning essential interactions between the patient, physician, pharmacist, and dedicated healthcare providers such as nurses, social workers, and psychologists.

Adherence programs should be tailored to patient's preferences. Enforcing self-management [60], patient-centered communication, and shared decision-making help improve adherence [61].

Digital progress could improve information exchange between healthcare professionals and help develop easily accessible monitoring systems and patient reminder technologies [62], without diminishing the need for a human approach.

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