



Review

Drug adherence in hypertension



M. Burnier

Service of Nephrology and Hypertension, Department of Medicine, Centre Hospitalier Universitaire Vaudois, Rue du Bugnon 17, 1011, Lausanne, Switzerland

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ABSTRACT

Blood pressure control remains unsatisfactory in all countries of the world with at best 60% of treated hypertensive patients reaching recommended therapeutic goals. Several factors have been identified which may explain why the rate of blood pressure control remains low. Among them, one can cite medical inertia and a poor adherence to drug therapies. In the absence of new drugs to control blood pressure, drug adherence has become a major issue in the management of hypertensive patients. Numerous studies have demonstrated that the major problem is the lack of persistence followed by a poor day to day execution of the prescribed regimens. Although there are multiple ways of assessing drug adherence, only very few of them are accurate and the most accurate ones are either difficult to implement in clinical practice or too expensive and hence not available outside reference centers. Therefore, physicians have no real capacity to establish a correct diagnosis of non persistence or poor adherence even in high risk patients such as those with resistant hypertension. Today a new approach is becoming increasingly used which consists in measuring urinary drug levels. Nevertheless, there is still an important need for simple and cheap techniques or devices helping physicians in their ability to tackle poor adherence to therapy and thereby improve blood pressure control in the population.

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1. Introduction

Lowering blood pressure (BP) below the targets recommended by most international guidelines for the management of hypertension is recognized as the most effective way to prevent target organ damages and to reduce the cardiovascular mortality of patients with arterial hypertension [1–3]. Yet, assessments of BP control around the world regularly show that less than 50% of treated hypertensive patients actually reach their BP goals and therefore these patients are still at high risk of suffering from

hypertension-induced complications [4]. Indeed, the survival of a treated hypertensive patient not at goal is similar to that of an untreated hypertensive patient suggesting that a lot of efforts are made for little benefits [5]. In clinical trials however, the rate of BP control that is achieved is often much higher reaching percentages of 80% or more. In these studies, the treatment protocol is rigorous, clinical visits are regular and frequent and both physicians and patients are motivated to reach the protocol's objectives. Thus, in a post-hoc analysis of the INVEST (International Verapamil SR-Trandolapril) trial, Mancía et al. have reported that the higher the number of clinical visits with a normal BP, the lower the incidence of clinical outcomes [6]. These observations clearly indicate that there is a major gap between the success rate obtained in clinical trials and the real life data reported in national surveys [7]. Of

E-mail address: michel.burnier@chuv.ch

course many reasons are evoked to explain this gap; among them, factors associated to treating physicians such as medical inertia and factors linked to the patients' behavior, such as poor adherence to the prescribed therapy are probably two important factors contributing to the insufficient control of BP around the world. Indeed, drugs that are not prescribed adequately by physicians and not taken correctly by patients cannot be effective and will certainly not provide the expected clinical benefits. At last, factors associated with the health care systems such as drug costs, drug availability and co-payments, certainly play a role in the poor control rate of hypertension worldwide.

In the last 20 years, no new drug class has been developed for the specific treatment of arterial hypertension. However, pharmacological advances in hypertension therapy have been characterized by the development of multiple single pill drug combinations with the aim to improve efficacy but also to simplify the treatment regimens and hence to improve drug adherence. This shows that even the pharmaceutical industries have integrated in their development plans the fact that adherence is a key issue that deserve improvements. Of note, the problems of adherence to therapy are clearly not specific to the management of hypertension and concern almost all chronic diseases. This is confirmed by the work of Naderi et al. who analyzed drug adherence in a very large group of patients treated for the primary and secondary prevention of cardiovascular diseases and found a low adherence to therapy not only with anti-hypertensive agents but also with lipid lowering treatments and aspirin [8].

In the present article we shall review the role of drug adherence in the management of hypertensive patients. First, we shall revise the definitions and the methods available to measure drug adherence in clinical practice and in studies. We shall also discuss the impact of drug adherence on BP control in the general hypertensive population and in patients with resistant hypertension. Strategies to improve drug adherence will also be evoked.

2. Definitions and taxonomy of drug adherence

Since the mid 1970s when the modern area of drug adherence started with the organization of a scientific event focused on patient compliance by the Mac Masters University Medical Center, several terminologies have been used to describe drug adherence such as adherence, compliance, concordance or persistence. Some of these terms are sometimes used as synonyms and what they actually represent is not always well understood. According to the World Health Organization, 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". Recently, a particular effort has been done to clarify the terms and their exact definitions in order to help standardizing the medical literature and facilitating health politicians in their decisions regarding improvement of medication adherence. To this purpose, a consensus conference was held in the context of a large EU project leading to an important publication of a new 2012 taxonomy [9]. According to this latest consensus, *adherence to medication* is the process by which patients take their medications as prescribed: it has three components: *initiation*, *implementation*, and *discontinuation*. *Initiation* is the time from prents: *initiation*, *implementation*, and *discontinuation*. *Initiation* is the time from prescription until first dose of the medication is taken. The *implementation* of the dosing regimen is defined as the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken. It reflects the day to day execution. *Discontinuation* marks the end of therapy, when the next dose to be taken is omitted and the treatment is interrupted thereafter. *Persistence*

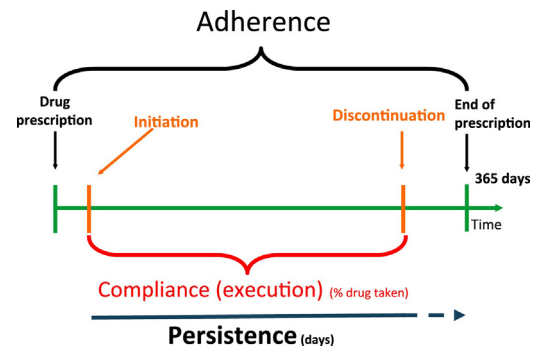


Fig. 1. Illustration of the different components of drug adherence.

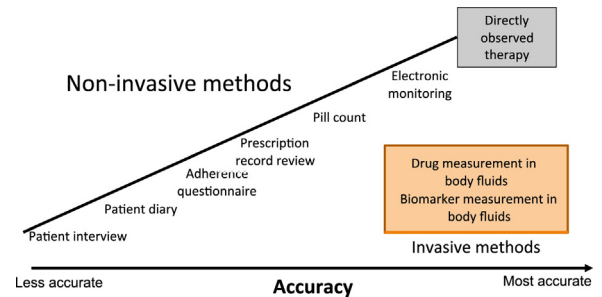


Fig. 2. Methods of assessment of drug adherence according to their accuracy.

is the length of time between initiation and the last dose, which immediately precedes the discontinuation [9]. The clinical consequence of these definitions is that 3 major types of deviations from given instructions can occur and are particularly common i.e. non-initiation, short persistence and poor execution [10]. In clinical studies, about 4–5% of patients never starts their treatment despite being in a study and represents the non-initiation process. However, in clinical practice Non-initiation is much more frequent with figures as high as 24% and this, whatever the disease [11]. Besides non-initiation, non-persistence is definitively the most common cause of poor adherence in hypertension with 50% of patients having stopped their treatment at one year [12]. At last, the poor execution which is the typical consequence of occasional forgetfulness or negligence results in more or less prolonged periods of treatment interruptions. Each of these aspects of adherence to medication have a direct and major influence on the quality of BP control in hypertension, the most critical ones being of course a non-initiation and a lack of persistence. The different processes are illustrated in Fig. 1.

3. Drug adherence in hypertension: methodological issues and developments

As mentioned in a recent review the ideal method to assess drug adherence in clinical practice should "provide a reliable capture, storage, analysis, and communication of dosing history data in ways that make it difficult or impossible for patients or trial staff to censor or otherwise manipulate the data" [13]. Though many techniques enabling to estimate and to detect non-adherence have been published in the literature, detecting non-adherence reliably remains a real challenge for practicing physicians (Fig. 2). Indeed, most physicians have limited time to perform complex investigations or to use adherence questionnaires unless they participate in a study. For example, a careful interview of the patient leading to a physician's impression on what the patient is actually doing with his/her medications appears to be simple and easy to do. Physicians tend to think that they obtain more pertinent information with the interview

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