Drug adherence in hypertension: from methodological issues to cardiovascular outcomes

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Adherence to treatment is now well recognized as a crucial key in the effectiveness of antihypertensive drugs; however, it is often overlooked in the management of hypertension because methodology to assess it is partly unreliable and limits its use in clinical practice. The available evidence suggests that nonadherence is highly prevalent in a chronic asymptomatic condition such as hypertension. It may undermine benefits expected from antihypertensive agents and therefore, may negatively impact cardiovascular, cerebrovascular and renal outcomes. In this review, we discuss the methodological issues related to the measurement of drug adherence in a research setting and clinical practice, the prevalence and the impact of drug nonadherence on blood pressure control and thus in apparent resistant hypertension, and on cardiovascular, cerebrovascular and renal outcomes.

Keywords: antihypertensive drugs, cardiovascular outcomes, drug adherence, hypertension

Abbreviations: 24-h ABPM, 24-h ambulatory blood pressure monitoring; ACEi, angiotensin I converting enzymes inhibitors; AHT, antihypertensive; ARBs, AT1 blockers; BP, blood pressure; CV, cardiovascular; DENERHTN, Renal Denervation for Hypertension study; LC–MS/MS, liquid chromatography coupled to tandem mass spectrometry; LOQ, limit of quantification; MMAS-4, four-item Morisky Medication Adherence Scale; MMAS-8, eight-item Morisky Medication Adherence Scale; MPR, medication possession ratio; RND, renal nerve denervation

INTRODUCTION

Hypertension is the most common risk factor for morbidity and mortality in the world [1]. A large number of controlled clinical trials have shown that antihypertensive (AHT) drugs are effective in preventing cardiovascular, cerebrovascular and renal complications and death [2]. Although new AHT agents have shown promising results in early clinical trials [3], most of AHT treatment relies on drugs developed decades ago, which are well known to the physicians and have good efficacy/tolerance ratio. AHT drugs from different pharmacological classes can be combined especially in fixed dose combinations in a single pill for a synergistic action on the various mechanisms leading to hypertension [4]. Despite this favorable aspect, blood pressure (BP) control remains poor in all industrialized and emerging countries [5], and drug nonadherence is one of the major causes of insufficient control of BP. A number of different factors, including the frequent necessity to combine AHT drugs, increasing the risk of side effects either specific or nonspecific for a given class of AHT, including mainly fatigue, headache, peripheral edema, cough, allergy, erectile dysfunction and metabolic changes, can favor nonadherence to AHT [6].

Drug nonadherence may prove to be the greatest barrier to the effectiveness of AHT and negatively impacts the prevention of cardiovascular and renal complications [7]. However, it is often overlooked in the management of hypertension because the methods used to detect it are complex, partly unreliable and are of limited use in routine clinical practice [8]. Concerns are raised about the cost of nonadherence, waste of medications and resources and lack of effective prevention of cardiovascular disease [9]. As the number of patients with inadequate BP control despite high cardiovascular risk is increasing [10,11], drug nonadherence is becoming a rising issue in the management of hypertension, as well as in other chronic conditions including diabetes and dyslipidemia.

We summarize here the recent findings about drug adherence in hypertension, including both methodological issues and impact on clinical outcomes, with a final aim to help clinicians and researchers to address the problem more efficiently. To highlight this challenging issue, we focus on apparent resistant hypertension, in which drug nonadherence is commonly implicated in the treatment failure.

MEASURING DRUG ADHERENCE IN RESEARCH SETTING AND CLINICAL PRACTICE

Drug adherence, generally defined as the extent to which patients take their medications as prescribed by their healthcare providers [8], is a complex trait with multiple

Journal of Hypertension 2017, 35:1133–1144

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Received 30 September 2016 **Revised** 13 January 2017 **Accepted** 20 January 2017

DOI:10.1097/HJH.0000000000001299

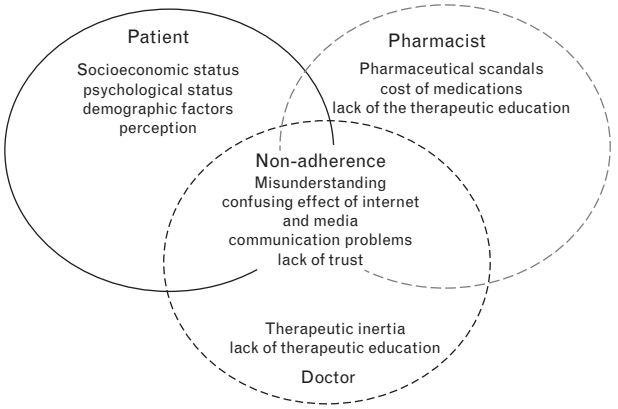

FIGURE 1 Interaction of multidimensional determinants of nonadherence.

determinants: patient behavior, therapeutic inertia, patient–physician relationship, type of medication, external forces like media, Internet and so on (Fig. 1). Because of its multidimensional nature and the strong behavioral component, it is not surprising that after more than four decades of research about drug adherence, concerns regarding its measurement persist. There are several methods to measure drug adherence, each of them having their advantages and weaknesses; so far, none of them can be considered as gold standard [12]. In addition, the measurement itself is often biased by the effect of sensitizing patients that their behavior is monitored (the so-called Hawthorne effect); therefore, the results of drug adherence may greatly be affected, particularly in a research setting. We briefly discuss below the various indirect and direct methods to assess drug adherence.

Indirect methods

Clinician estimation and patient questionnaires

Since the 1970s, concern about identification of nonadherence and control of hypertension has emerged [13]. Traditionally, the most frequently used method in clinical practice is the estimation of drug adherence by physicians [14–17]. This method is unreliable. Indeed, physicians often fail to detect drug nonadherence [16], and their prediction about their patients' adherence is notoriously poor [17]. Another approach to measure drug adherence has been self-reporting. More than 600 reported studies used questionnaires for assessing adherence in hypertension. Seventy-four of them used the four-item Medication Adherence Scale (MMAS-4) developed by Morisky, which has been validated in a wide range of diseases including hypertension [18,19]. In its first evaluation for hypertensive population [18], MMAS-4 has shown that it suffers from its weak specificity and, as result, a new eight-item Morisky Medication Adherence Scale, derived from MMAS-4, was subsequently designed [20]. These questionnaires are relatively simple to use; however, they are frequently inaccurate and biased by a patients' behavior. Overall, subjective approaches have been criticized for overestimating drug adherence when compared with direct measures [8,21]. At least they have the merit to exist and to stress on the importance of assessing adherence. They may have an educative value and help at building an open dialog with the patient about adherence to treatment.

Pill counting

Pill counting is another way to measure drug adherence commonly used in both clinical trials and clinical practice [22]. This method showed an acceptable estimate of drug adherence when compared with subjective methods, such as patient questionnaires [23,24]. However, it is subject to various informational drawbacks including the reasons for not taking drugs, the timing and the reality of ingestion of pills removed from containers. Moreover, this method may also overestimate drug adherence [25].

Prescription refill

Pharmacy and insurance records may assess, over an extended period, the overall drug adherence in large populations [26,27]. This method may be ideal for assessing overall drug adherence in large hypertensive populations [28,29] including patients with apparent resistant hypertension [30–32]. It is the reference for evaluating drug persistence that essentially refers to the act of complying with a recommendation of continuing treatment for a prescribed length of time [33]. However, although this approach assumes that the patient was in possession of the medication, it does not ultimately translate to drug intake by the patient [8].

Refill adherence is commonly determined by medication possession ratio (MPR), which is essentially defined as the sum of the days' supply for all fills of a given drug in a time period divided by the number of days in the time period [34]. Because MPR tends to overestimate drug adherence, the proportion of days covered (PDC) method may be more adapted to hypertension [35]. The calculation of PDC is similar to MPR, but instead of simply adding the days' supplied in a given period, the PDC considers the days that are really 'covered' by the treatment [36]. Indeed, a patient who refills a medication before running out of it will have overlapping days' supplied, which would elevate MPR. Conversely, PDC makes an adjustment by avoiding double counting when refills overlap with each other or when there is an oversupply of medications. In addition, for regimen including multiple medications, MPR would be calculated as the average of the MPRs for each drug for a given patient [37]. The weakness of this method is that drugs with high MPR can compensate drugs with low MPR, thus leading, and lead, to an overall acceptable MPR for the entire regimen. By contrast, PDC method considers only the days within a particular period when a patient is covered for 'all medications' in a regimen. Finally, the choice of the method depends in part on the condition being studied [37]. For hypertension, it makes more sense to use PDC rather than MPR because patients often use multiple drugs at the same time and may change their therapies to maintain BP control.

Electronic monitoring

The electronic monitoring approach uses an electronic pillbox that records each time the cap is opened. Electronic monitoring can provide a timing of pillbox opening [38]. However, it is unable to certify the ingestion of the correct drug or the correct dose, and the act of opening a pillbox does not necessarily mean that the pill was ingested [39]. In addition, patients must consent to participate in studies

using this approach; therefore, their awareness of being part of a study may influence adherence behavior [40]. Finally, this method is often used in clinical trials but seldom in clinical practice because it is time consuming and costly. Despite above disadvantages, the electronic monitoring provides interesting information on drug adherence, particularly the timing of box opening, and its use has been reported in several studies [41,42] including apparent resistant hypertension (defined essentially as BP remaining above goal despite the use of at least three AHT at maximally tolerated doses including a diuretic).

Direct methods

All the above indirect methods, except the electronic monitoring approach, can be easily implemented in clinical practice, but their accuracy remains limited. Conversely, direct methods, including direct observation of drug intake and measurement of biomarkers or drug assay, give more reliable information on drug adherence. However, because they are costly, their implementation in clinical practice is rather limited.

Direct observation of therapy

The method consists of supervising directly if the patient swallows his/her medication. Although this method remains the most reliable, sometimes patients can hide pills in the mouth and then discard them. This approach is highly accurate and has been tested recently in a research setting for patients with apparent resistant hypertension [43,44]; however, it is not a relevant approach for outpatients in routine clinical practice [8]. This method may also be ethically questionable.

Plasma and urine biomarkers

Measurement of pharmacodynamic biomarkers of AHT drug therapy can also be considered as another direct way to accurately assess drug adherence. For example, to monitor patients' adherence to angiotensin I converting enzymes inhibitors (ACEi), an endogenous biomarker, *N*-acetyl-Ser-Asp-Lys-Pro a substrate of ACE can be measured by an ELISA method in urine or plasma where it accumulates massively when patients are given ACEi [45]. This method is very specific and sensitive; however, the costs of such tests may be prohibitive for a routine use. Other biomarkers include increased plasma renin concentration [ACEi, AT1 blockers (ARBs) and diuretics], uric acid (diuretics), decreased heart rate (β-blockers, verapamil) and so on.

Urine drug detection with ultra high or HPLC coupled to tandem mass spectrometry

Serum drug assay is reliable in detecting drug nonadherence [46,47], but this method has failed to find a place in routine clinical use because of the necessity to draw blood samples, except for some drugs with narrow therapeutic indexes necessitating close therapeutic drug monitoring (e.g. digoxin). Urine drug detection has been recently applied to hypertension using ultra high or HPLC coupled to tandem mass spectrometry (HPLC–MS/MS), a highly sensitive and specific method to detect and measure drug levels in biological samples. This approach relies on both a simple task (urine sampling) and a sophisticated method (HPLC–MS/MS). The latter is increasingly implemented in pharmacology or biochemistry departments of university hospitals. The presence of the unchanged drug or its appropriate metabolite in urine certifies that the drug has been taken by the patient, within a time frame depending on the dose and half-life of the drug. Thus, this approach can give relevant information on adherence to treatment and offer a useful tool for clinicians to check for drug adherence [48,49].

However, it has some limitations. First, because nonadherent patients may take their drugs just before visits (the so-called toothbrush effect or white coat adherence), satisfactory drug levels may therefore falsely indicate a good adherence. Second, the method being very sensitive, traces of AHT drugs can be detected in the urine even long after stopping the medication [50]. Third, some drugs are not excreted in urine. Fourth, this approach gives a snapshot view of drug adherence at the time of the urine sampling and thus fails to provide continuous and long-term information about level of drug adherence that can vary with time. Finally, even if this method can provide quantitative information, fluctuations in drug's pharmacokinetics due to intrinsic (obesity, disease-induced poor absorption, genetic polymorphism in cytochromes P450, drug transporters etc.) and external factors (drug–drug interactions, inhibition/activation of cytochromes P450 and drug transporters) may be observed; therefore, such levels may vary widely between-individual and within-individual patients.

Despite these limitations, the use of urine drug assay in clinical laboratories is increasing as evidenced by the increasing number of publications recently reported especially in hypertension [48,49,51]. The technological improvement in LC–MS/MS allows identifying a large number of molecules with a single procedure (up to 26 in our laboratory) on a spot urine sample. Figure 1a shows the chromatographic profile of a fully adherent patient in one urine sample. The three molecules of his treatment (hydrochlorothiazide, amlodipine and irbesartan) were well detected. Figure 2b shows the chromatographic profile of a fully nonadherent patient. None of the four prescribed molecules (irbesartan, nebivolol, spironolactone and hydrochlorothiazide) were detected. Monitoring of adherence by using urine drug analysis is useful not only for research purposes, but also in routine clinical care at least in some specialized centers where the technology of LC–MS/MS is available. Indeed such approach is very useful to differentiate nonresponsiveness from nonadherence to prescribed AHT therapy and offers to the physician a possibility to take more rational therapeutic decisions and to open a new dialog with the patient about her/his difficulties to adhere to treatment and how to cope with this problem.

Influence of analytical and pharmacokinetics parameters on urine drug monitoring

Although urinalysis of AHT drugs is an important tool for monitoring drug adherence, at least in apparent resistant hypertension, interpretation of results still remains challenging. All published studies reported qualitative but not quantitative results to date. Therefore, the purpose of these studies was to detect the presence or absence of the AHT

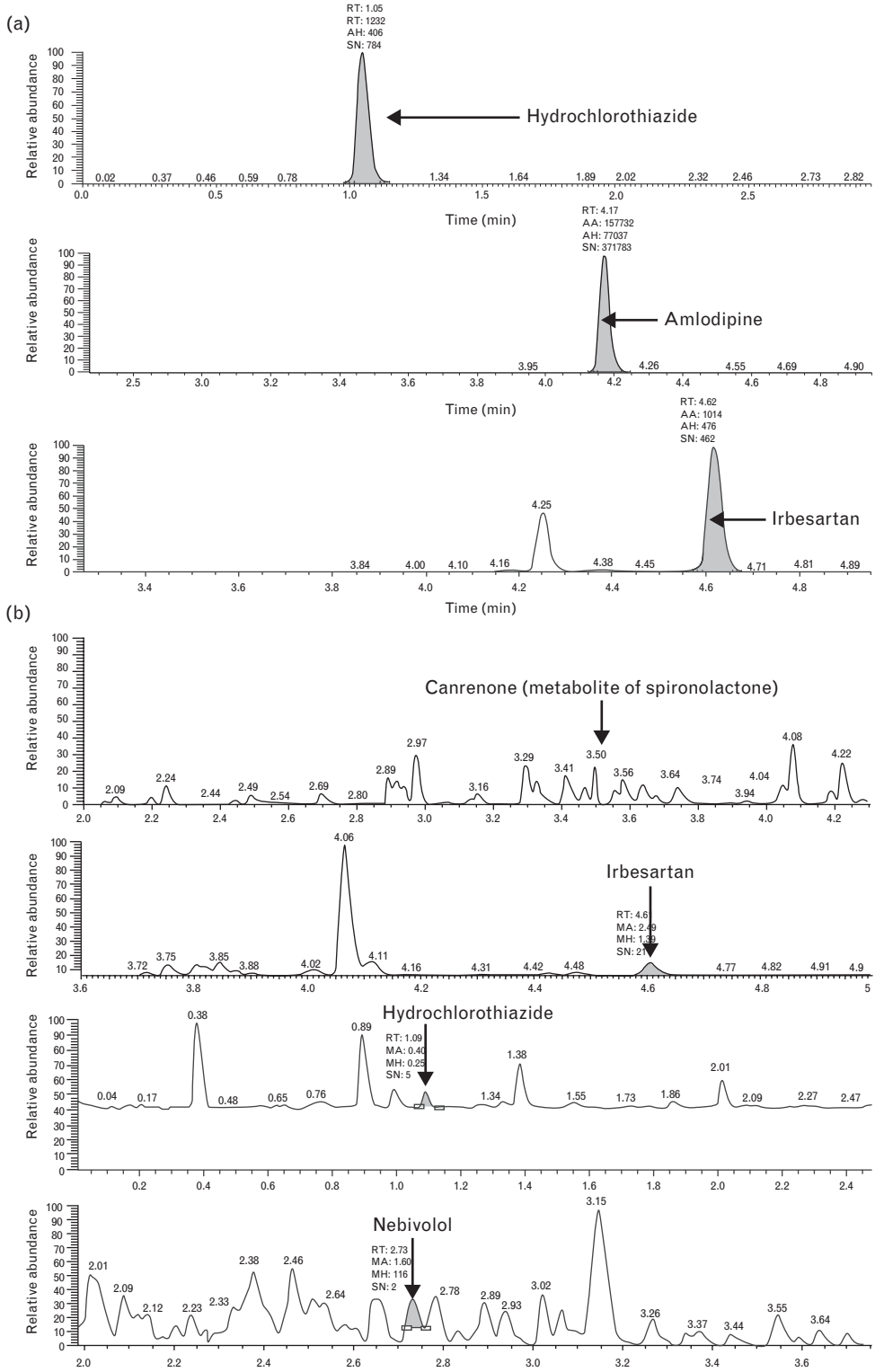

FIGURE 2 (a) Chromatographic profile of a fully adherent patient in one urine sample. The three prescribed antihypertensive drugs of his treatment (hydrochlorothiazide, amlodipine and irbesartan) were well detected. (b) Chromatographic profile of a fully nonadherent patient. None of the four prescribed antihypertensive drugs [irbesartan, nebivolol, spironolactone (canrenone) and hydrochlorothiazide] were detected.

drug in a urine sample using the limit of quantification (LOQ) of the assay for each given drug or metabolite to define patients' adherence profile: patient is classified as adherent to treatment when the drug or a metabolite is present at a concentration at least its LOQ and conversely is classified as nonadherent to treatment when the drug or a metabolite is less than its LOQ. Limits of quantification are defined for each molecule, as the lowest concentration that can be measured with variability and bias less than 20%. LOQ is an analytic parameter that depends on the sensitivity

TABLE 1. Expected urine concentration of several antihypertensive drugs at steady state

Molecule (metabolite)	$T_{1/2}$ (h)	Dose (mg)	Fu (%)	Fully adherent (ng/ml)	1/2 day (ng/ml)	Since 24 h (ng/ml)	Time to <LOQ (days)
Furosemide	1	20	90	12 000	0–12 000	12 000	<1
Hydrochlorothiazide	12	25	95	15 833	3167–12 667	11 875	9
Spironolactone (canrenone)	24	20.4	30	4080	1360–2720	2040	16
Indapamide	18	1.5	6	60	17–43	36	8
Irbesartan	12	300	0.9	1800	360–1440	1350	8
Valsartan	6	80	13	6933	408–6525	6500	4
Amlodipine	48	10	10	667	276–391	195	27
Clonidine	13	0.15	50	50	11–39	36	5
Bisoprolol	12	10	50	3333	667–2667	2500	8
Metoprolol	3.5	200	5	6667	57–6610	6609	2
Rilmenidine	8	1	65	433	48–385	379	4

In a fully adherent patient (Column 5), a patient taking every other day (Column 6), and a patient who takes his/her treatment 24 h before the medical visit (Column 7). Column 8 describes the duration of drug cessation required to reach drug level below LOQ (limit of quantification). Pharmacokinetic simulations are further described in the supplemental data, http://links.lww.com/HJH/A742. $T_{1/2}$ (h), half-life; Fu (%), fraction of drug excreted unchanged in the urine.

of the LC–MS/MS technology and not on the exposure to the drug. Therefore, LOQ-based definition of adherence can be misleading and wrongly classify a patient as adherent or not, depending only on the sensitivity of the LC/MS–MS method.

Based on pharmacokinetic simulations data (Table 1), the qualitative information provided by such approach appears to underestimate drug nonadherence. First, if good adherence is based on urine concentration at least the LOQ, and assuming that LOQ is 0.05 ng/ml (the most often value reported in the analytical methods), a patient can be misclassified as adherent to treatment even if she/he does not take her/his drugs every day. Indeed, when the AHT is taken irregularly (e.g. every 2 or 3 days), the expected urine concentrations remain above the predefined LOQ under these conditions especially for drugs with long pharmacokinetic half-life (Table 1, column 6). Second, such method cannot identify patients who will take their AHT only on the day preceding the medical visit (i.e. white coat adherence) and will also misclassify erroneously as having a good adherence to treatment. Indeed, in that case, the expected AHT urine concentrations will also be above the predefined LOQ (Table 1, column 7). Third, AHT drugs (or their metabolites) can be detected in the urine several days after treatment cessation especially for long-acting drugs. For example, amlodipine takes 27 days to be totally eliminated in urine. Therefore, the risk to falsely conclude to good adherence during the days following treatment cessation is high. This risk is variable among AHT drugs, depending on various variables including prescribed dose, plasma half-life, conversion of a prodrug into its active metabolite and fraction of the molecule excreted unchanged in the urine (Table 1, column 8).

However, in some cases, due to many inherent properties of AHT molecules such as half-life, such approach can overestimate drug nonadherence. If the AHT molecule has a very short half-life ($T_{1/2}$), which is the case, for example of furosemide ($T_{1/2} < 1$ h), the totality of the ingested dose is almost eliminated via urine within 24 h after drug intake. The risk to measure a urine concentration of furosemide below its LOQ after 24 h cannot be excluded, and thus to falsely conclude to nonadherence in truly adherent patient.

Overall, approaches based on LOQ to interpret urine drug concentration reflects predominantly the most recently ingested dose before a urine collection and does not provide a reliable information on long-term adherence to AHT. Thus, such approach can detect only obvious nonadherence to AHT and therefore, more subtle, erratic or irregular nonadherence to AHT may not be detected. To anticipate these critical limitations, drug adherence monitoring requires more rigorous quantitative assessment of drug excreted in urine. The quantitative analysis should integrate pharmacokinetics parameters (within-individual and between-individual patient variability), genetic differences or drug–drug interaction to better understand the relation 'urine concentration/nonadherence'. Such an integrated approach of adherence could then provide valuable information on adherence to AHT treatment on a long-term basis that may be of considerable benefit in clinical practice.

Which method to select for assessing adherence to treatment?

An ideal method for monitoring adherence should be reliable, practical, simple and relatively inexpensive. However, there is no method that meets all these criteria. Table 2 gives a summary of advantages and weaknesses of each type of measurement of drug adherence. The selection of the method to assess drug adherence is conditioned by the goals and the setting of the study. In clinical practice, although patient self-report is known to be less accurate compared with direct measures, its use in a busy, resource-limited clinical setting in large population with low-to-moderate cardiovascular risk, may have an educative value. Regular patient interviews and use of questionnaires may engage a relationship between a patient and his/her physician. They may also help clinicians to identify patients who require some further counseling to improve their AHT medication adherence. In some cases, among patients with apparently uncontrolled hypertension and high cardiovascular risk despite an optimum therapy, direct methods such as urine drug assay would be of great interest for measuring adherence. In clinical trials evaluating the efficacy of new therapeutic strategies, an accurate monitoring of drug adherence is mandatory and is extremely valuable. Under these conditions, drug assay is one of the best tools to check for adherence to treatment. Electronic monitoring devices may also be of valuable help. However, such device may introduce some behavioral biases, for example increased

TABLE 2. Advantages and weaknesses of drug adherence measurements

Methods	Indirect				Direct		
	Clinician estimation	Questionnaires	Pill count	Prescription refill	DOT	Electronic monitoring	Drug assay
Type of data	Qualitative	Qualitative	Quantitative	Quantitative	Quantitative	Quantitative	Qualitative
Device mostly used	Interview	MMAS-4, 8	–	MPR/PDC	–	MEMS	LC–MS/MS
Reliability	–	–	+	+	+++	++	+++
Validity	+	+	+	+	+++	++	++
Objectivity	–	–	–	–	+++	+	++
Simplicity	+++	+++	++	–	–	+	+/–
Cost	–	–	–	+	+	+++	++
Availability	+++	+++	++	–	–	–	+/–
Clinical use	+++	+++	+	–	–	–	+

Reliability is defined as the extent to which a measurement test shows the same result on repeated trials; validity refers to whether or not a test measures what it intends to measure; objectivity is defined in terms of agreement of competent judges about the value of a measurement. DOT, directly observed of therapy; LC/MS, liquid chromatography coupled to mass spectrometry; MEMS, medication event monitoring system; MMAS-4, 8, four-item and eight-item Morisky Medication Adherence Scales; MPR, medication possession ratio; PDC, proportion of days covered.

adherence, and, as such, their results may not be applicable to the general practice. If assessment of drug adherence is considered for epidemiologic studies, pharmacy records can provide a good estimate of drug nonadherence. Finally, a combination of methods is likely the most effective approach because it can identify different components of nonadherence and is therefore recommended.

PREVALENCE OF DRUG NONADHERENCE IN APPARENT RESISTANT HYPERTENSION

Precise estimate of the prevalence of drug nonadherence in apparent resistant hypertension is difficult to determine as evidenced by the wide range (7–86%) reported in both observational studies and clinical trials. This heterogeneity in prevalence could be related to differences in methodology used and setting of the studies, which therefore make comparisons across studies difficult.

Some observational studies, using direct methods, revealed that drug nonadherence was common among patients with apparent resistant hypertension [21,46–49, 51–54]. In the first study published by Ceral *et al.* [46] using measurement of serum AHT drug levels as an indicator of drug adherence among 84 outpatients with resistant hypertension under three AHT drugs, 65.5% of patients were labeled to be partially or fully nonadherent. Some other observational studies [47,48,53] using the same methodology were subsequently published and reported also more than 50% of drug nonadherence. Recently, when using directly observed drug intake, the most accurate measure of drug adherence, Hameed *et al.* [44] reported similar rate of drug nonadherence.

When evaluated in clinical trial setting, often assessed by pill counts and patient self-reporting, or drug assay when available, the prevalence of drug nonadherence to AHT agents is also high [55,56] and may impact the pharmacodynamic effects of the tested drug(s), increasing the variability in BP response and thus impede the correct interpretation of the study results [56]. We used UPLC–MS/MS to assess drug adherence in the Renal Denervation for Hypertension randomized controlled in which renal denervation added to a standardized and optimized AHT was compared with the same standardized and optimized AHT alone in patients with ambulatory confirmed resistant hypertension. Despite patients being tightly monitored by providing monthly visits with the same dedicated healthcare team, signed a consent form for drug assay and no cost to the patient, the rate of nonadherence was alarming [57]. Almost ≈52% of patients were nonadherent to the prescribed AHT therapy, with 13% of them taking none of the seven prescribed AHT after 6 months of follow-up.

The prevalence of drug nonadherence from various populations of patients with uncontrolled hypertension was shown to be relatively low, often no more than 15% [30–32]. Using pharmacy records, Daugherty *et al.* [32] showed that among ≈3500 patients with uncontrolled hypertension assigned to receive three or more AHT drugs, 12.4% of them were classified as nonadherent.

As Table 3 illustrates, observational or clinical studies using direct methods generally reported higher nonadherence rates compared with indirect methods. Thus, direct methods appear to be more sensitive, specific and accurate to detect nonadherence. Ideally, such methods, when available, should be preferentially used for assessing adherence to AHT in clinical practice. Further, these findings are an illustration of the relevance of gathering rigorous information on drug adherence while assessing the results of therapeutic strategies in clinical trials.

Some studies were designed to compare the rate of drug nonadherence (using indirect methods) among patients with and without apparent resistant hypertension (Table 4) to assess the relevance of drug nonadherence in explaining treatment failure. These studies showed no [58] or only modest [30,31] difference on rate of drug nonadherence between the two groups, thus suggesting that other factors than drug nonadherence may be implicated in the treatment failure. However, these findings should be interpreted with caution because of possible selection and differential measurement bias that may have occurred. Here again, these studies were limited by the method used for assessing adherence: electronic monitoring is likely underpowered, pharmacy records often overestimate drug adherence and MMAS-4 lacks accuracy. The combined results of these studies are inconclusive. Poor adherence to treatment is thus a major issue in resistance to recommended therapy.

TABLE 3. Overview of the prevalence of nonadherence in apparent resistant hypertension

Design	Reference	Study period (year)	Method	No. of patients	Population	% Nonadherence
Observational						
	Yakovlevitch and Black [14]	1991	Interview	91	Resistant hypertension, tertiary care	10
	Garg *et al.* [15]	2005	Interview	141	Uncontrolled BP, tertiary care	16
	de Souza *et al.* [22]	2009	Pill count	44	Resistant hypertension	36
	Ceral *et al.* [46]	2011	Drug assay	84	Difficult-to-control BP	65
	Strauch *et al.* [47]	2013	Drug assay	163	New referral outpatients	47
	Strauch *et al.* [47]	2013	Drug assay	176	Work out for exclusion of a secondary cause	19
	Jung *et al.* [48]	2013	Drug assay	76	Uncontrolled hypertension, primary care	53
	Brinker *et al.* [52]	2014	Drug assay	56	Apparent resistant hypertension	54
	Tomaszewski *et al.* [49]	2014	Drug assay	66	Uncontrolled BP	38
	Tomaszewski *et al.* [49]	2014	Drug assay	125	New referrals patients, primary care	18
	Tomaszewski *et al.* [49]	2014	Drug assay	17	Referred for consideration of RND	24
	Pandey *et al.* [21]	2015	MMAS-8	47	Apparent resistant hypertension	26
	Ewen *et al.* [51]	2015	Drug assay	100	Resistant hypertension undergoing RND	48
	Hameed *et al.* [44]	2015	DOT + 24-h ABPM	50	Uncontrolled BP	50
	Pandey *et al.* [21]	2015	Drug assay	47	Apparent resistant hypertension	51
	Florczak *et al.* [53]	2015	Drug assay	36	Primary resistant hypertension	86
	Schmieder *et al.* [54]	2016	Drug assay	79	Apparent resistant hypertension	44
Clinical trial						
	Fadl Elmula *et al.* [43]	2014	DOT + 24-h ABPM	83	Resistant hypertension, Oslo study	29
	Azizi *et al.* [55]	2015	MMAS-8	106	Resistant hypertension, DENERHTN study	25
	Beaussier *et al.* [56]	2016	Combination methods	168	Resistant hypertension, PHARES study	18
	Azizi *et al.* [57]	2016	Drug assay	85	Resistant hypertension, DENERHTN study	51
Large population						
	Irvin *et al.* [31]	2012	MMAS-4	2654	Apparent resistant hypertension	8
	Daugherty *et al.* [32]	2012	Pharmacy records	~3500	Uncontrolled BP on 3 or more drugs	12
	Sim *et al.* [30]	2013	Pharmacy records	>60 000	Resistant hypertension	7

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; MMAS-4, 8, four-item and eight-item Morisky Medication Adherence Scales.

IMPACT OF DRUG NONADHERENCE ON BLOOD PRESSURE CONTROL AND CARDIOVASCULAR OUTCOMES

Adherence is an important parameter for the effectiveness of AHT therapy. Schematically, drug adherence can be viewed as a continuum from overadherent to completely nonadherent patients, with most patients falling somewhere in between [33,59]. The most common form of drug nonadherence is the underuse of drugs. This form may be conditioned by noninitiation, nonexecution or nonpersistence with therapy. Although the degree of nonadherence that can lead to drawback in outcomes may vary from one condition to another, overall it is assumed that the underuse of AHT drugs affects clinical outcomes negatively [60].

Despite the heterogeneity of methods used to assess drug adherence, some studies conclude that nonadherence to AHT therapy is associated with poor BP control [49,61]. Indeed, high drug adherence defined by MPR more than 80% evaluated by pharmacy refill data was associated with high odds of BP control [odds ratio: 1.45; 95% confidence interval (CI) 1.04–2.02] compared with low drug adherence [61]. Furthermore, when evaluated objectively by drug assay among patients with apparent resistant hypertension, patients who did not or partially adhered showed significantly higher BP compared with patients who adhered correctly [49]. More importantly, Beaussier *et al.* [56] showed by using a scoring from combination of measures of drug adherence (pill count, interview and drug assay) among patients with resistant hypertension that not only good drug adherence contributes to optimal control of BP, but also independently of BP changes, it contributes to the regression of target organ damage, including changes in pulse wave velocity and left ventricular mass.

As far as target organ damage was concerned, drug nonadherence was associated with high risk of cardiovascular events in general hypertensive population. In a survey of 18 806 newly diagnosed hypertensive patients in whom drug adherence was assessed by pharmacy database, it was shown that high drug adherence, during a mean follow-up

TABLE 4. Rate of low adherence in patients with and without apparent resistant hypertension

Study	Method	Population	Rate of low adherence (%)		*P*
			Resistant patients (%)	Nonresistant patients (%)	
Irvin *et al.* [31]	MMAS-4	$n = 2654$	8	5	0.001
Sim *et al.* [30]	Pharmacy record	$n > 60\,000$	7	10	0.001
Nuesch *et al.* [58]	Electronic monitoring	$n = 103$	18	15	0.33

MMAS-4, four-item Morisky Medication Adherence Scale.

of 4.6 years, was associated with the long-term reduction of acute cardiovascular events (hazard ratio: 0.62; 95% CI 0.40–0.96; $P = 0.03$, vs. low drug adherence) [62]. In other retrospective studies [63–65] using the same methodology for assessing drug adherence, it was also shown that compared with patients with low drug adherence (MPR < 80%), patients with high drug adherence (MPR > 80%) showed relative risk (RR) reduction of 11% in chronic heart failure (RR: 0.89; 95% CI 0.80–0.99) [63], 10% in coronary events (RR: 0.90; 95% CI 0.84–0.95) [64] and 22% in cerebrovascular events (RR: 0.78; 95% CI 0.70–0.87) [65]. In the real-life setting, if good drug adherence is maintained on the long term (persistence to treatment), it was shown also to be effective in the primary cardiovascular prevention: after an average follow-up of 6 years, patients who continued treatment had a 37% reduced risk of cardiovascular events (RR: 0.63; 95% CI 0.60–0.66) compared with those who experienced at least one episode of treatment discontinuation [28]. Interestingly, a recent meta-analysis of 44 individual studies, involving nearly 2 million participants, showed that high adherence to AHT treatment was associated with 29% in RR reduction in all-cause mortality (RR: 0.71; 95% CI 0.64–0.78) [66]. Taking together, these results indicate that drug nonadherence leads to worse clinical outcomes in hypertension.

Adherence as a proxy for behavioral particularities

Although drug adherence is assumed to be an important contributor for good BP control and better cardiovascular outcomes, it is difficult to assume that better clinical outcomes are only due to the better drug adherence. Indeed, observational studies evaluating this relationship were, at least in part, biased by the 'healthy adherer effect'. This effect was firstly described in 1980 [67]. It occurs when patients who adhere to medication are more likely to engage in other healthy behavior (e.g. change in lifestyle), which can influence outcomes, than nonadherent patients. Motivated by a paradox arising from previous studies [68,69] that indicated better outcomes in adherent patients to placebo compared with their counterpart nonadherent patients, Simpson *et al.* [70], in a meta-analysis, showed effectively a reduction of risk of mortality in patients with high adherence to the active drug therapy and even to the placebo. This result supports therefore that 'healthy adherer effect' may play an important role in the junction between drug adherence and a tendency to better clinical outcomes in patients with high drug adherence compared with those with low adherence. However, the degree to which adherence as a behavior mediates its protective effect on clinical outcomes in hypertensive population is still unknown.

PREDICTORS OF DRUG NONADHERENCE IN APPARENT RESISTANT HYPERTENSION

Many studies have analyzed the determinants of drug nonadherence in the general hypertensive population [71,72]. Here, we would like to focus on the determinants of nonadherence in patients with apparent resistant hypertension.

Patient-related factors

Sociodemographic factors, such as age, ethnicity and sex, may impact adherence to AHT therapy [31,46,47]. Although the relationship between nonadherence and age has not been formally evaluated in apparent resistant hypertension, some studies measuring drug adherence have shown that young patients were more likely to be nonadherent [46,47]. Although data on the influence of sex on drug adherence are inconsistent in general hypertensive population, women were more likely to exhibit nonadherence than men in apparent resistant hypertension [21,31]. Nonwhite race, elevated depressive symptoms and history of chronic heart disease are also related to low drug adherence [31]. In addition, hospitalization may positively affect adherence process [47]. The reasons may be that patients increase motivation to adhere before hospitalization and the higher expected quality of medical care at hospital compared with usual outpatient care. Finally, socioeconomic factors, including poor health status, low educational level, low income and unemployment may decrease adherence to AHT drugs [31,47]. Such low socioeconomic status may impact negatively the access to medicines, which leads to nonadherence (noninitiation) and therefore increase in cardiovascular risk.

Therapy-related factors

Dosing frequency was inversely related to adherence [73,74]. Indeed, in the study by Bloom [73], the persistence at 1 year after start of treatment was significantly lower with twice-a-day dosing than with once-a-day. Furthermore, Claxton *et al.* [74] showed significantly higher adherence for once-daily vs. three-times-daily, once-daily vs. four-times-daily and twice-daily vs. four-times-daily regimens. Furthermore, complex treatment regimen may also influence drug nonadherence. Indeed, significant decreases in drug adherence 1 year after treatment intensification in previously adherent patients with apparent resistant hypertension were reported [75], suggesting that as regimen become more complex, medication adherence may decline. Patients' adherence may also be influenced by the AHT drug class(es) used to treat them. Kronish *et al.* [76] reported in a meta-analysis greater adherence to ARBs and ACEi and lower adherence to diuretics and β-blockers in general population of patients with hypertension. However, comparable and evenly distributed drug adherence has been observed in several observational studies in outpatients with apparent resistant hypertension between β-blockers and diuretics and ARBs or ACEi [47,48]. These findings suggest that the results of this meta-analysis may not be generalized to patients with apparent resistant hypertension, who are treated with multiple AHT. Medication side effects (severity and nature) may negatively influence adherence in general hypertensive population [77,78]. However, the evidence of the role of this factor, as well as the effect of the cost of therapy on drug adherence, has been little studied in apparent resistant hypertension.

Behavioral-related factors

Behavioral determinants appear to play an important role in the process of drug nonadherence but they remain difficult to evaluate precisely. This includes efficiency of

TABLE 5. Factors associated with drug nonadherence*

Sociodemographic	Younger age; nonwhite, women
	Low educational level; low income; not working
Therapy	Complex treatment regimen
	Side effects, perception of benefits of medication
Health system	Poor communication and relationship with healthcare provider
	Patient dissatisfaction
Condition	Asymptomatic and chronic condition, depression symptoms

*Refs. [8,31,46,47,73,75].

the healthcare setting, communication and relationship with healthcare providers. Perception of benefits or risks of medications may also impact drug adherence, particularly in chronic asymptomatic disease [8]. Indeed, the absence of perceived and immediate benefits from AHT therapy, which is often associated with the possibility of immediate side effects, may discourage drug intake.

Although some factors associated with drug nonadherence might be more important than others, it is recognized that drug nonadherence behavior cannot be understood by taking any of these factors individually. Significantly, factors of drug nonadherence (Table 5) are, at least in part, similar to those of patients with apparent resistant hypertension: more likely younger, nonwhite race, with low income, less educational level, elevated depressive symptoms and under complex regimens. These characteristics make patients with apparent resistant hypertension more vulnerable to the incorrect use of AHT therapy and vice versa. Improving adherence to help maximizing the potential of AHT therapy is therefore an urgent need in this group of patients.

MANAGEMENT AND INTERVENTION STRATEGIES TO IMPROVE DRUG ADHERENCE

Although the aim of every caregiver is to improve adherence, specific interventions may be indicated at least for patients at high risk for drug nonadherence, including patients with apparent resistant hypertension. First, preventing drug nonadherence may appear to be the optimum way to optimize drug adherence in the long term. This can be achieved by using extensive and regularly reinforced therapeutic education. Optimal therapeutic education can be reached by using informational and teaching tools. Reinforcing information about drugs' purpose, explanation about the need for continued drug adherence and address specific patient concerns may be effective for improving drug adherence. It is very important to ensure that patients are well informed and understand the information to better control their own AHT therapy as prescribed. In this context, implementation and enhancement of empowerment can promote self-management skills that serve for the increase in drug adherence, as evidenced in other population with chronic disease [79]. Developing a routine for taking medication, use of electronic reminders and organizational tools are some of the simple educational strategies by which we may improve drug adherence.

Second, because every patient with hypertension is at risk of drug nonadherence, regular assessment of drug adherence is essential during every clinic visit. Assessment of drug adherence by using urine drug detection during an outpatient visit or analyzing the data of the pillbox may reinforce the relationship between care provider and patient. In addition, the act of assessment itself may improve drug adherence behavior [80] and BP control [52,81]. A number of methodological, practical and ethical issues then arise. The cost of these methods has already been discussed, as well as the cost/benefit ratio. The frequency to which these measurements should be repeated is not settled. From a methodological point of view, should patients be aware of the possibility of urine drug detection? If so, 'false positive' results can be due to a 'toothbrush effect'. From an ethical point of view, patients should be informed that a biological analysis will be performed on their urine sample and that it will not be the usual glucose, nitrate or leukocyte detection, but drug detection. How to maintain the patient–doctor trust if repeated controls of drug intake occur and how to explain them to the patient even if they are more and more aware in their working place that 'trust does not exclude control' and 'control does not exclude trust'. What should be the best psychological approach of the patient when urine drug detection is negative for all medication?

Drug nonadherence is a dynamic process, and patients may experience changes in behavior in addition to treatment progress, so medication adherence should be reviewed regularly by either method. If suboptimal drug adherence is detected, it is useful to discuss with the patient which barriers made taking treatment difficult. As far as complexity of treatment affects drug adherence negatively, it is recommended to simplify the drug regimen (e.g. reducing pill burden by the use of single pill combinations of treatments) and the use of treatment options that enhance flexibility for patients, so long as efficacy is not compromised [82,83]. Increasing the frequency of visits [84] and further investigation of the barriers contributing to this nonadherence including side effects, behavioral or psychosocial problems may also be helpful. Behavioral strategies that include reinforcement of the patients' use of strategies to improve drug adherence (e.g. alarms) and discussion about drug adherence issues may reinforce adherence behavior and self-management, particularly on the long term. Because drug nonadherence is recognized as a multifactorial phenomenon, interventions to improve it are likely a combination of the different strategies aforementioned. Further studies remain to be done to determine which combination is the most effective.

What is the efficacy of these strategies on drug adherence? In a recent published systematic review of randomized controlled studies [85] to promote drug adherence in chronic medical conditions, the combination of educational, social and behavioral strategies was effective at improving drug adherence. However, their effect on clinical outcomes showed to be less than expected. Further, implementation of such intervention to routine clinical practice was shown to be difficult [86,87]. Today, little evidence exists that drug adherence can be consistently improved within the resources usually available. More studies of interventions to promote drug adherence should therefore be undertaken.

In conclusion, the current review highlighted several priorities for research and clinical practice on drug adherence to optimize apparent resistant hypertension management. Drug adherence is suboptimal in hypertension, and no unique explanation exists for this complex phenomenon. To achieve the optimal clinical outcome expected from BP reduction in patients with hypertension without having to deal with nonadherence issues, alternative device-based treatments including renal denervation [57], baroreceptor stimulation [88] and arteriovenous shunting with a coupler [89] are being developed. As these approaches are still experimental and tested in clinical trials and long time will be necessary to evaluate the efficacy and safety of these new approaches [3], at present, efforts aiming at measuring and improving drug nonadherence may be much more cost effective.

ACKNOWLEDGEMENTS

Conflicts of interest

There are no conflicts of interest.

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Reviewers' Summary Evaluations

Reviewer 1

This is an exhaustive review on the available approaches to measure adherence to antihypertensive drugs in clinical practice. Unlike other reviews on the same topic, this work also concerns the methodological issues and the difficulties in the decision makers' findings interpretation. Finally, particular attention was focalized on the evaluation of nonadherence impact in the apparent resistant hypertension

Reviewer 2

The strength of the paper is the large amount of information about the methodology, the impact and the role of drug adherence in patients with hypertension. The paper summarizes many years of investigation in this important field by describing the reasons, the methodology and the clinical impact of drug adherence. The limitation is the one of any paper dealing with adherence, we all know the problem very well, but the assessment of adherence is still dependent on methodological limitations that do not allow a complete reliability on their long term impact in the assessment of adherence in clinical practice.