Compendium on the Pathophysiology and Treatment of Hypertension

Adherence in Hypertension

A Review of Prevalence, Risk Factors, Impact, and Management

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Abstract: **The global epidemic of hypertension is largely uncontrolled and hypertension remains the leading cause of noncommunicable disease deaths worldwide. Suboptimal adherence, which includes failure to initiate pharmacotherapy, to take medications as often as prescribed, and to persist on therapy long-term, is a well-recognized factor contributing to the poor control of blood pressure in hypertension. Several categories of factors including demographic, socioeconomic, concomitant medical-behavioral conditions, therapy-related, healthcare team and system-related factors, and patient factors are associated with nonadherence. Understanding the categories of factors contributing to nonadherence is useful in managing nonadherence. In patients at high risk for major adverse cardiovascular outcomes, electronic and biochemical monitoring are useful for detecting nonadherence and for improving adherence. Increasing the availability and affordability of these more precise measures of adherence represent a future opportunity to realize more of the proven benefits of evidence-based medications. In the absence of new antihypertensive drugs, it is important that healthcare providers focus their attention on how to do better with the drugs they have. This is the reason why recent guidelines have emphasize the important need to address drug adherence as a major issue in hypertension management. (*Circ Res*. 2019;124:1124-1140. DOI: 10.1161/CIRCRESAHA.118.313220.)**

Key Words: blood pressure ■ cardiovascular diseases ■ drug monitoring ■ hypertension ■ prevalence ■ resistant hypertension

The global burden of hypertension, defined as blood pressure (BP, mm Hg) ≥140 systolic or ≥90 diastolic or antihypertensive treatment, was projected to rise from 918 million adults in calendar year 2000 to 1.56 billion in 2025.[1] The projected increase in the burden of hypertension reflected an expected rise in both prevalent hypertension from 26.4% to 29.2% and the worldwide population. By 2010, these projections appeared conservative as the worldwide prevalence of hypertension was estimated at 31.1%, affecting 1.39 billion people.[2] The large increase in prevalent hypertension globally was explained largely by rapidly rising prevalence in low-middle–income countries. In 2010, ≈349 million hypertensive adults lived in high-income countries and 1.04 billion in low-middle–income countries. Prevalent hypertension was lower in high- than low-middle–income countries, whereas awareness, treatment, and control were substantially lower in the latter (Table 1). Among treated hypertensive adults, roughly one-half were controlled in high-income countries compared with one-fourth in low-middle–income countries.

Assuming clinically valid BP values, 2 major factors contribute to hypertension control in treated patients; namely, prescription of an adequate number and dose of prescribed BP medications and adherence with therapy. This review focuses on patient adherence as a critical variable in BP control. Insightful statements with timeless truth include "Drugs don't work in patients who don't take them"[3]; and "the full benefits of medications cannot be realized at currently achievable levels of adherence."[4]

Adherence with pharmacotherapy for hypertension 1-year after initiation is typically reported at <50%.[5,6] The proportion of treated patients controlled, historically ranging from 20% to 50% (Table 1),[2,7] reflects both effectiveness of pharmacotherapy prescribed and adherence with treatment. Using the proportion of treated patients controlled as a proxy for adherence, data that are more recent suggest that adherence has been improving, at least in some countries. For example, in the United States, ≈70% of treated patients have been controlled to <140/<90 since 2007 to 2008,[8] a level achieved in Germany during 2008 to 2011.[9] In Canada, an extraordinary 85% of treated patients were controlled in 2013.[10]

Hypertension control in Canada rivals many clinical trials, which typically exclude patients with comorbidities such as drug or alcohol abuse or dementia, factors that adversely impact adherence and control.[11] In clinical trials, the treatment protocol is rigorous, clinical visits are relatively frequent and physicians and patients are motivated to reach protocol objectives. Thus, in a review of 192 studies in which pill count was used to assess adherence, drug adherence was found to be 93%.[12] But more recent data suggest that even in clinical trials nonadherence can affect a substantial percentage of the participants.[13] Consistent adherence is a key to sustained BP control,

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Nonstandard Abbreviations and Acronyms

BP	blood pressure
HIC	high income countries
INVEST	International Verapamil SR-Trandolapril trial
LMIC	low-middle–income countries
LVH	left ventricular hypertrophy
MEMS	Medication Event Monitoring System
PCSK9	proprotein convertase subtilisin/kexin type 9
WHO	World Health Organization

which, in turn, influences clinical outcomes. For example, in the INVEST (International Verapamil SR-Trandolapril trial), the greater the number of clinical visits with a nonhypertensive BP, the lower the incidence of clinical outcomes.[14]

In the United States, the large improvement in hypertension control over time coincides with a greater number of antihypertensive medications prescribed per patient.[15] Over time, the proportion of uncontrolled hypertensives in the United States with Stage 2 disease (BP ≥160 systolic or ≥100 diastolic) has declined,[16] which suggests adherence improved in some patients not at goal BP, although one cannot exclude an impact of better BP measurement methods. The observations cited suggest that adherence is improving with time and that prior studies on adherence may be less valid currently. Yet, a substantial proportion of adults remains uncontrolled, even in countries with the highest control rates. Of greater concern are the large numbers of adults in low-middle–income countries, with uncontrolled hypertension, who continue to have a relatively low proportion of treated adults at goal BP levels (Table 1).[2] 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.[17]

The impact of suboptimal adherence, a key contributor to uncontrolled hypertension, will be addressed in greater detail subsequently. In brief and from a global perspective, there were ≈56.4 million deaths in 2015. Approximately 70% of deaths worldwide were attributed to noncommunicable diseases including hypertension with 75% of those deaths occurring in low-middle–income countries (noncommunicable disease mortality and morbidity). Global Health Observatory data: http://www.who.int/gho/ncd/mortality_morbidity/en/ (accessed August 16, 2018). Cardiovascular diseases accounted for 45% of deaths because of noncommunicable diseases with uncontrolled hypertension the major risk factor.

In the present review focused on adults with hypertension, we shall (1) define suboptimal adherence and persistence, (2) examine the methods for detecting suboptimal adherence and its prevalence in treated hypertensive patients including those with treatment resistant hypertension, (3) identify contributing and associated factors, (4) describe the health and economic impact of suboptimal adherence, and (5) provide practical guidance for improving adherence.

Definitions of Suboptimal Adherence

Many definitions of compliance or adherence can be found in the literature before the World Health Organization (WHO) published the first official definition of adherence in 2003.[7,18] In contrast to previous ones, it was not restricted to drug therapy and included all aspects of disease management such as diet and lifestyle changes. Thus, adherence was defined as the extent to which a person's behavior-taking medication, following a diet, and executing lifestyle changes, corresponds with agreed recommendations from a health care provider. In 2009, a consensus meeting on adherence was held that gathered together >80 persons of various professional horizons but all involved in patients' care with medications. This consensus meeting resulted in a new taxonomy published in 2012.[19] In this publication, the authors differentiate the processes, such as adherence to medications and the management of adherence, from the discipline studying these processes, that is, the adherence-related sciences. According to this consensus, adherence to medications is a process characterized by 3 major components: the initiation, the implementation, and the discontinuation. Initiation is the time from prescription until the first dose of the medication is taken. In clinical studies, 4% to 5% of patients never start their treatment, despite the fact that they accepted to be enrolled in a study.[5] In clinical practice, noninitiation seems to be much more frequent with figures >20% in patients treated for hypertension but also in those treated for diabetes mellitus or dyslipidemia.[20] However, this phenomenon may vary considerably depending on the countries and the access to medications.

The implementation of the dosing regimen is the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen. This component of adherence is best assessed using methods providing a complete dosing history, and hence, tackling the day-to-day variations in drug intake.[19] A poor implementation is the typical consequence of occasional forgetfulness or negligence resulting in more or less prolonged periods of treatment interruptions. These latter may

Table 1. Prevalence, Awareness, Treatment, and Control of Hypertension in LMIC Versus HIC in 2000 and 2010[2]

	LMIC			HIC		
Variable	2000	2010	Δ2010–2000	2000	2010	Δ2010–2000
Prevalence	23.80%	31.50%	7.70%	31.10%	28.50%	–2.60%
Aware	32.30%	37.90%	5.60%	58.20%	67.00%	8.80%
Treated	24.90%	29.00%	4.10%	44.50%	55.60%	11.10%
Controlled	8.40%	7.70%	–0.70%	17.90%	28.40%	10.50%
Control/Rx	33.70%	26.60%	–7.10%	40.20%	51.10%	10.90%

HIC indicates high-income countries; and LMIC, low-middle–income countries.

be intentional or nonintentional, but in the majority of cases, there is no clear intention of patients to omit their medications. When the dosing history is available, additional parameters of implementation can be defined and quantified. This includes the proportion of prescribed drug taken, the proportion of days with a correct number of doses taken (taking adherence), the proportion of doses taken on time respecting the dosing intervals (timing adherence) and the number of drug holidays as intervals of time when a patient temporarily stops taking the medications. Yet, it is not possible to define drug adherence quantitatively with a given threshold below which a patient can be considered as poorly adherent. Indeed, although an arbitrary cutoff of 80% is frequently used in the literature to define a good adherence, there is little evidence, if any, that this cutoff is relevant.[21] Indeed, 80% adherence is obtained in many ways as illustrated in Figure 1 and these different profiles may have different consequences in terms of clinical impact. In this context, the pharmacological profile of the prescribed drugs, in particular the duration of action, is a major determinant of the impact of missed doses on BP control.[22] In addition, the clinical consequences of missed doses may differ in patients with mild hypertension and those with severe resistant hypertension, for example.

At last, discontinuation marks the end of therapy, when the next dose to be taken is omitted and the treatment is interrupted thereafter. This parameter enables the definition of persistence, which is the length of time between initiation and the last dose immediately preceding discontinuation. Nonpersistence is one of the most common cause of poor adherence in hypertension with 50% of patients having stopped their treatment at 1 year.[5] It is particularly prevalent among newly treated hypertensive patients,[23,24] and the risk of discontinuation seems to be higher among patients aged <40 years.[25] The choice of drug classes prescribed for the treatment of hypertension also has an impact on adherence and persistence due essentially to the side effect profile,[23,26,27] although the dosing frequency may play as much a role as the drug class itself.[28] Obviously, a lack of persistence has a major influence on BP control as patients remain off medication for long periods.

In recent years, the use of large computerized administrative health databases containing pharmacy or medical data are becoming increasingly common and represent new sources of medical evidence.[29,30] These databases enable assessment of drug prescriptions as well as the utilization patterns and drug persistence in large groups of patients. Although they do not provide a precise dosing history, these databases give information on medication prescription, initiation, and refills during a defined period enabling calculation of drug persistence.[25,31] Sometimes, these data can also be correlated to the occurrence of events such as death or cardiovascular events. Using this approach, the main parameters that are generally calculated are the percentage of days covered by the prescriptions[32] or the medication possession ratio, defined as the ratio of total days of medication supplied to total days in a defined time-period. It is also possible to calculate the new prescription medication gap, a metric that starts with the date of prescription and includes the time until initiation, which is not the case with the medication possession ratio.[33]

Suboptimal Adherence: Contributing and Associated Factors

In the WHO 2003 Report, Adherence to long-term therapies: Evidence for action,[18] it was noted that "The ability of patients to follow treatments is frequently compromised by more than one barrier… Interventions to promote adherence require several components to target these barriers, and health professionals must follow a systematic process to assess all the potential barriers." While the literature on adherence has advanced during the past 15 years, the 5 dimensions of adherence in the 2003 Report remain useful (Table 2). A conceptual understanding of these 5 dimensions can inform a more comprehensive assessment of factors contributing to suboptimal adherence as a prelude to the design, implementation, and refinement of effective, multicomponent interventions to realize more health benefits of antihypertensive therapy.

Sociodemographic, Economic, and Environmental Factors

Several factors in this group, many of which are listed in Table 2, are associated with suboptimal adherence.[6,7,11,34] However, not all of these factors, such as age, income, and race-ethnicity, are consistently related with adherence across all studies. Attempts have been made to derive clinically useful predictors of adherence by combining several sociodemographic and clinical variables, which are significantly different between adherent and nonadherent patient groups. However, a composite score developed from a basket of these variables may not provide clinically useful discrimination even for individuals from which the predictive model was developed.[35] A more effective strategy may be to use reliable methods to detect suboptimal adherence in specific patients and then to identify the specific factors in this dimension rather than designing systems that provide solutions for all patients with barriers in this category, when many are adherent. This statement is not intended to minimize the very real challenges to adherence presented by individuals experiencing various sociodemographic, economic, and environmental barriers but rather to indicate that many individuals are adherent, despite the barriers.

Hypertension control in uninsured and privately insured adults over time is one indirect example of the limited prediction of outcomes from 3 generally recognized predictors of adherence. Publicly and private insured adults in the United States had virtually identical BP control from 1988 to 2010,[36] which included a roughly 22% absolute improvement in control over that time period. However, the publicly insured group had a larger proportion of racial-ethnic minorities with lower incomes and less education than the privately insured, 3 factors often cited as predictors of suboptimal adherence.

Health Care Team/Health Care System

The quality of the relationship between the patient and clinician, the communication style of the clinician, and the patient-centeredness of treatment decisions all impact adherence.[6,7,11,34,37,38] Trust is the critical currency in most human interactions and this applies especially to healthcare. The patient must have confidence that their clinician is competent and has their best interests foremost in management

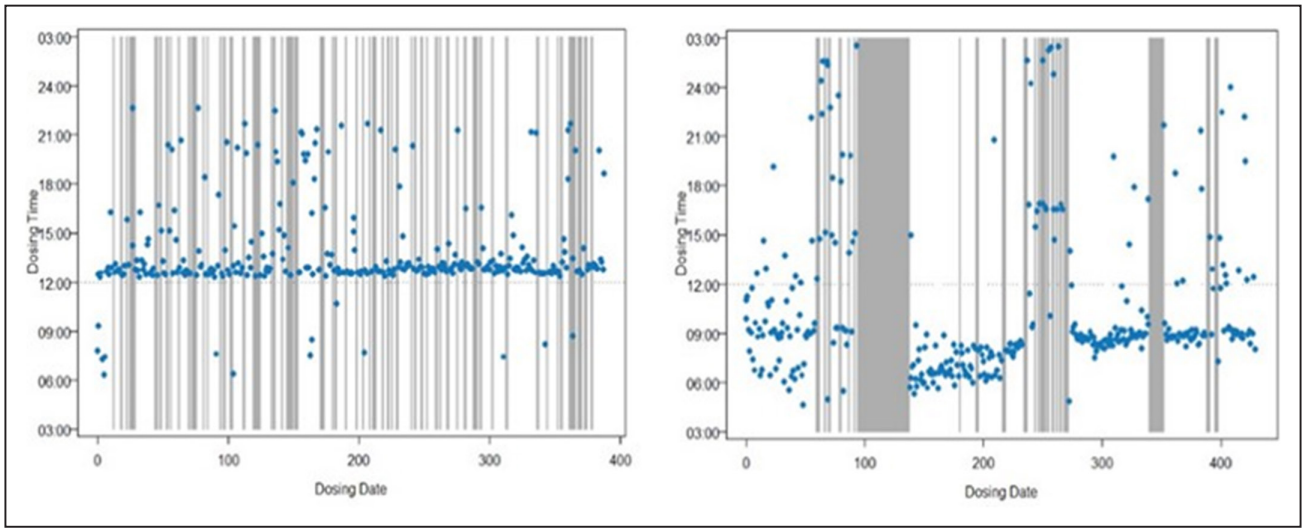

Figure 1. Dosing history of 2 patients with 80% adherence to their medications prescribed once a day. Each vertical bar represents a missed dose. Each blue point represents one opening of the Medication Event Monitoring System (MEMS) pillbox. Note the variability of the timing with doses taken in the morning but also in the evening. Patient on the left has no drug taken for more than a week (gray zone). This illustrates the dynamic process of drug adherence.

decisions. A collaborative communication style and communication that includes circular and reflexive questions are more effective than a lineal and strategic inquisition style akin to a witness being cross-examined by an attorney. Thus, 'did you take your medication(s)?' or 'why don't you follow a low-salt diet?' is less effective that 'are you having any problems with your medications such as they're too costly or cause unpleasant adverse effects?' or 'how does a low-salt diet affect you?' or 'what are some of the difficulties you have with a low-salt diet'?

Patients that participate in decisions on what medications to take are more adherent than patients who are not engaged in the decision.[39] Racial-ethnic minorities are less often engaged in decision on their treatment than white adults, which may be a contributing factor to lower adherence in the former.[40] Team-based care and well-functioning patient-centered medical homes are associated with better adherence and risk factor control than when these factors are not present.[41,42] In addition to suboptimal communication, overworked and burned out clinicians can adversely impact the adherence of their patients. Clinicians and staff are generally happier and more productive in an effective team-based care arrangement, and, clinician burnout is reduced.[42] Often times, clinicians and staff fail to recognize key clues linked to suboptimal adherence such as missed appointments or prescription refills or poor therapeutic response to medications or combinations of medications that are almost always effective.[43]

Practice settings without adaptive reserve in which clinicians, staff, and administration expend all their time and energy working to get through the day and complete all documentation and billing requirements are not positioned to implement constructive changes to improving patient care, adherence, and outcomes.[44] Practice settings with adaptive reserve in which high-quality care is valued and time, resources

Table 2. Adherence: Five Categories of Factors Impacting Adherence to Prescription Medications*

Sociodemographic	Health Care Team/Health Care System	Therapy-Related	Condition-Related	Patient-Related
Young and very old adults	Patient-clinician relationship	Complex regimens	Multiple chronic conditions	Deny diagnosis
Minority race-ethnicity	Communication style	Treatment changes	Depression, psychoses	Perception of illness severity/future impact
Low income, poverty	Patient-centeredness	Treatment failure	Drug/alcohol abuse	Perception of treatment efficacy
Homeless, unstable home	Lack of team-based care	Time to benefit	Dementia	Fear dependence or adverse effects
Social support	Clinician burn out	Adverse effects	Major disability	Lack knowledge/misunderstanding
Copayments	Fail to detect clues	Treatment duration	Symptom severity	Forget
(Health) literacy	Lack knowledge/QI support	Refill frequency	Quality of life	Limited follow-up
Transportation, rural residents	Access to and cost of care	Refill consolidation		Low self-efficacy/discount future
War, disasters	Pay for volume			Alternative therapy

QI indicates quality improvement; and QOL, quality of life.
*Data derived from World Health Organization. Adherence to Long Term Therapies: Evidence for Action; 2003.[18]

and reports are available to support quality improvement are positioned to enhance patient engagement, adherence, and outcomes.

Access to and cost of care and medications are clearly important in clinical outcomes and adherence.[6,7,11,18,34,45] Uninsured adults in the United States experienced no significant improvement in hypertension control between 1988 and 2010, whereas a demographically similar group with public (government)-sponsored health insurance had virtually identical control to a more affluent and better educated group with private health insurance.[36] As noted both insured groups had a roughly 22% absolute improvement in hypertension control during this time-period in sharp contrast to no improvement in uninsured adults. Moreover, healthcare payment directed mainly to volume of care and clinical documentation, which was the standard in the United States is a barrier to supporting patient adherence and key clinical outcomes. For example, a study in the 1970s showed that reallocating some time spent in documenting variables toward patient education and support improved adherence to antihypertensive medications and BP control.[45]

Therapy-Related Factors/Interventions

Complex regimens with multiple medications, especially when paired with multiple daily doses, are long-recognized as barriers to adherence.[6,7,11,18] Alternatively, fewer medications, and especially fewer pills, which can be implemented using once daily single-pill combinations are consistently associated with better adherence and hypertension control.[45,46] Patients who reach therapeutic targets more rapidly, who require fewer adjustments in their medication regimen, and who experience no or limited adverse effects are more likely to adhere than patients with a longer period to control, who often undergo multiple changes to their medication regimens, and experience adverse effects, are less likely to adhere to treatment.[6,7,11,18] Long-term chronic diseases, such as hypertension, are often associated with progressive declines in persistence on treatment with the passage of months and years.[47,48]

In addition to single-pill combinations, clinicians can further improve adherence by prescribing a larger number of pills with each prescription to reduce refill frequency.[49,50] Moreover, patients with hypertension often require multiple medications to control their hypertension, and they frequently have other chronic diseases requiring additional medications. Refill consolidation so that multiple medications are obtained at the same time can improve adherence.[51]

Condition-Related Factors/Interventions

Adults with hypertension, especially with aging, often have multiple chronic conditions and polypharmacy, which may adversely affects medication adherence. Major depression and other psychoses can adversely influence adherence as can drug or alcohol abuse and dementia.[52,53] Interestingly, alterations of memory in elderly patients can results in a poor adherence as well as in an overadherence, with a higher drug consumption than what has been prescribed, which may induce drug toxicity.[54] Not surprisingly, major disabilities and poor quality of life are documented to adversely affect medication adherence,[55] especially when the medication(s) do not attenuate the disability or enhance quality of life. On a related note, severe chronic symptomatology, similar to chronic asymptomatic disease,[56] can adversely impact medication adherence.

Patient-Related Factors/Interventions

As noted in the 2003 WHO Report on adherence, patient-related factors are often the principal focus of efforts to understand and improve adherence, which can lessen attention to the important role played by the other dimensions of adherence.[18] While most interventions center on patient-related factors can improve adherence, failure to account for other dimensions of adherence typically leads to suboptimal improvements in adherence and associated clinical outcomes. To highlight the importance of these other dimensions, patient-related factors, which are important, were presented last in the 2003 WHO Report and the current review.

Some patients do not accept the diagnosis, which is obviously a major impediment to adherence. While not denying the diagnosis, other patients may fail to perceive the potentially severe impact of a currently asymptomatic disease on future health risk, including symptomatic and life-threatening conditions, such as coronary heart disease, chronic heart failure, stroke, or dementia. If patients perceive that prescription medications are ineffective in controlling hypertension or are likely to have major adverse effects, then adherence is likely to be adversely impacted. A lack of knowledge about hypertension and its consequences are logically linked to suboptimal adherence. Yet, adherence interventions based only on education often lead to suboptimal results,[6,7,11,18,34,57] although education is often a component of successful multimethod interventions. One example of a common misunderstanding that adversely affects adherence is the term hypertension, which connotes too many patients that stress or behavioral issues are the root cause of the elevated BP.[58] In fact, patients with this perception of hypertension are less likely to take antihypertensive medications.

Forgetfulness is a common contributor to suboptimal adherence, a conclusion supported by evidence that multimethod interventions, which improve adherence often address this barrier.[1–5] Low self-efficacy, or lacking confidence in one's ability to self-manage effectively a condition or disease, is another frequently documented barrier to adherence.[6,7,11,18,34,59]

Patients who use alternatives to traditional or Western medicine are less likely to adhere with prescription medications.[60,61] Preference for alternative therapies appears to be more common among black than white adults in the United States and may contribute to lower adherence in the former.[62]

Less well appreciated and investigated is the issue of future discounting. Individuals who discount the future at higher rates appear less likely to engage in preventive health behaviors including taking medications for chronic conditions, although additional research is needed.[62–64] In other words, understanding that hypertension is a serious condition and that treatment is effective may be insufficient to foster adherence if the patient believes that the consequences will occur at a future date, for example, 5 years or more, that does not have value today.

Brief Section Summary

Multiple lines of evidence indicate that adherence is a complex, multidimensional variable. The WHO 2003 Report provides a useful conceptual model (Table 2) for grouping the multiple variables that impact adherence.[18] This conceptual model can serve to inform effective approaches for identifying nonadherence as well as designing, evaluating, and revising interventions to enhance adherence.

Detection of Suboptimal Adherence and Prevalence With Special Reference to Resistant Hypertension

In chronic diseases where medication primarily serves as a preventive measure, and not to suppress symptoms, maintaining long-term adherence is particularly difficult, and the risk of treatment discontinuation is very high. Thus, among various cardiovascular medication classes, prescriptions of antihypertensive and lipid lowering drugs have the highest rates of noninitiation.[65] In addition, in these clinical conditions, only about half of the patients remained on therapy after 2 years.[23,66] Of interest, Naderi et al[67] have found similar low figures in the 50% range in primary as well as in secondary cardiovascular prevention. Thus, in real life, prolonged discontinuation of antihypertensive therapies is extremely common as shown by Corrao et al[23] who analyzed the Lombardy database.

Though poor adherence is recognized as a major contributor of uncontrolled hypertension in surveys, meta-analyses and clinical practice guidelines, detection of suboptimal adherence remains a major challenge for all physicians and healthcare partners. Indeed, as of today, there is no simple, cheap, reliable methods to assess medication adherence in clinical practice. As illustrated in Table 3, simple methods tend to be relatively unreliable, and methods providing the best information tend to be more expensive and demanding in terms of infrastructures. The ideal method to assess drug adherence 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.[21] As of today, none of the available systems fulfills all these criteria.

Patient's Interview

The patient's interview is definitively the simplest approach but studies have reported that interviewing the patients is no better than tossing a coin.[68] There are many reasons to explain this observation. The first is the quality of the interview, which will depend on the communication skills of physicians and on the ability to conduct a nonjudgmental discussion. The second is that patients tend to overestimate their adherence either because they do not recall the missing doses or because they want to please their physicians and avoid embarrassing discussions. The third is the intrinsic nature of adherence, which is highly variable and dynamic process.[21] Hence, it is difficult to characterize precisely a patient who may be adherent during some periods and poorly adherent during others.

Questionnaires

Questionnaires have been developed to improve and structure self-reports. They are rarely used in everyday clinical practice mainly because they are time consuming. Nonetheless, questionnaires represent a good choice in clinical research, a context in which forms can be filled in by the patients themselves or by trained nurses or other healthcare professionals. Today, Nguyen et al[69] have identified >40 English-written adherence questionnaires, the most well-known being undoubtedly the Morisky questionnaire.[70] In general, questionnaires tend to overestimate true adherence and when compared with methods providing a complete dosing history, the correlation is rather low (well below 0.5) even for the Morisky questionnaire, although adherence determined by questionnaires tend to correlate with BP control. Yet, questionnaires are useful as a complement to more objective measures as they may provide additional information on the reasons why patients do not adhere or on the barriers encountered by patients during their medication-taking process.[69]

Pill Count

Pill count is the most frequent method of assessing drug adherence in clinical trials.[71] It provides a relatively good overview of what has been taken by the patient during the study. However, pill count is not devoid of limitations. Indeed, studies have demonstrated a trend towards overestimation of adherence with this approach. This has been evidenced providing

Table 3. Characteristics of Methods Available for the Detection of Poor Adherence in Hypertension

Methods	Interview	Questionnaire	Pill Count	Refill Data	DOT	Electronic Monitoring	Drug Assay	Digital Medicine*
Type of data	Qualitative	Qualitative	Quantitative	Quantitative	Quantitative	Quantitative	Qualitative	Quantitative
Reliability	–	–	+	+	+++	+++	+++	+++
Validity	+	+	+	+	+++	+++	+++	+++
Objectivity	–	–	–	+	+++	++	++	+++
Simplicity	+++	+++	++	–	+	+	±	±
Cost	––	–	+	+	+++	++	+++	–?
Availability	+++	+++	++	–	+	+	+	–
Clinical use	+++	+	+	+	++	+	+	–

DOT indicates directly observed treatment.

*Proteus system newly available in some countries.

pillboxes containing more pills than actually needed. Despite the excess of pills, patients often returned an empty box leading to a calculated adherence rate >100%.

Prescription Refills Data

As discussed previously, in large epidemiological surveys, persistence can be assessed using prescription refills data.[25,29,32] With the calculation of the percentage of days covered by the prescriptions, one can obtain a rough estimate of drug adherence and persistence. This approach is particularly useful when an electronic monitoring of drug prescriptions in pharmacies is available. However, this method assumes that patients are taking their drugs adequately every day when the therapy is available and this is certainly not the case. Moreover, it is crucial that the data acquisition system covers all sources of medication delivery as reported, for example, in countries like Sweden.[29]

Today, 2 techniques of measuring drug adherence tend to prevail in clinical practice and in clinical trials, that is, the electronic monitoring of medication adherence and the measurement of antihypertensive drugs in blood or urine using high-performance liquid chromatography-tandem mass spectrometry.

Electronic Monitoring System

The first electronic monitoring system for medication adherence, known as the Medication Event Monitoring System (MEMS), was developed in 1977. Its principle consisted in the incorporation of a microcircuit into medication packages such as any removal of a dose of the drug is detected in real time, time stamped, analyzed, stored, and communicated. Today, >750 articles involving over 1 million trial subjects have been published in peer-reviewed journals with this technique but its implementation in clinical practice remains limited to expert centers. The availability of dosing histories has repeatedly demonstrated that in ambulatory care, drug intake is characterized by a high irregularity with a wide spectrum of deviations from the prescribed regimen leading in general to an underdosing because of missed or delayed doses.[72] Interestingly, these observations were made across all therapeutic areas including chronic diseases, such as hypertension or dyslipidemia, but also life-threatening conditions, such as HIV,[73] organ transplantation,[74] or cancer chemotherapy.[75] Poor adherence or nonadherence was even reported in large clinical trials confounding sometimes the interpretation of the study results.[76–78] One general criticism to the electronic monitoring systems is the possibility that the system is activated while opening the pillbox but the dose is not taken. This is indeed the case, but when analyzing the data, the critical features are the nonopenings rather than the openings. In this respect, the system is analog to the determination of drug levels where the total absence of a compound is more relevant in terms of nonadherence than the actual presence of the drug. Moreover, studies comparing the MEMS data and the drug concentrations have shown that there is 97% accuracy between the 2 methods suggesting that when the pillbox is opened drugs are indeed taken.[79] Yet, in contrast to drug measurements, which are punctual, electronic monitoring systems provide additional information on drug-taking behaviors (taking, timing, frequency of omissions, compensatory intakes) based on the dosing history. Therefore, despite its limitation, electronic monitoring is one the most reliable technique to diagnose poor adherence and to follow and support adherence in chronic treatments. Several investigators have used the MEMS system to investigate the prevalence of poor adherence in hypertension.[80–82] Interestingly, in contrast to the general physicians' perception, drug adherence was often found to be high (>90% adherence) although with a great variability and rather weak correlations between the level of adherence and that of BP.[83,84] The main explanation for this apparent discrepancy between the perceived adherence and the measured adherence may be the measurement bias, as adherence tend to improve as soon as it is measured. The absence of strong correlation may also be because of the fact that high BP values can be found in nonadherent as well as in adherent patients if these latter are insufficiently treated. The measurement bias is particularly strong when the monitoring is of short duration and it tends to disappear over time.

Measurement of Drug Levels

With the development of new interventional techniques for the management of patients with apparent resistance to therapy,[85–89] such as renal denervation, 2 techniques have become increasingly used. The first is ambulatory BP monitoring to ascertain that BP is truly uncontrolled and the second is the measurement of drug levels to ascertain that one is facing a true resistance and not a pseudo-resistance because of poor adherence to therapy.[90] The measurement of drugs in bodily fluids has taken advantage of the development of the high-performance liquid chromatography-tandem mass spectrometry, which has a very high specificity and sensitivity, and hence has been used to detect drugs in forensic laboratories and to screen for doping in sports.[91–94] In the field of hypertension, the preference has been given to urine because of the noninvasive nature of the collection, though some groups are using blood levels. As of today, almost all antihypertensive medications or their metabolites can be detected in the urine. The complete absence of a medication in a sample guaranties that the medication has not been taken for a duration equivalent to several half-lives. Nevertheless, urinary as well as blood levels will depend on the pharmacological profile of the drug and on the patient's ability to metabolize it. At last, as mentioned previously, drug levels provide a punctual assessment of poor adherence and do not reflect long-term persistence with antihypertensive therapy. In addition, the presence of a drug in plasma or urine may be affected by the white coat adherence, that is, the fact that adherence tends to improve during the days preceding and following a clinical term.[95] Other limitations may be the cost, the need of an adequately equipped laboratory and finally the fact that patients may adapt their behavior, knowing that drug concentrations are measured at appointments.

Directly Observed Technique

Other approaches enable screening for poor adherence, one of them being the directly observed technique.[96] With this approach, antihypertensive therapy is given under supervision of a member of the clinical staff every day for a certain period.[97]

This technique is effective but is logistically heavy, expensive and requires the patient to attend the hospital every day. In addition, it is not devoid of potential adverse effects as major episodes of hypotension may occur during the first days when the full prescribed treatment is given.[96,98] Today, directly observed technique clinics have been organized in some countries to detect and support adherence.[98]

Digital Medicines

The latest technique to monitor drug adherence and identify poor adherence in various clinical settings was designed by Proteus Digital Health with the aim to provide feedback on drug adherence and could be called Digital Medicines.[99] The system, which is now accepted by the Food and Drug Administration, consists of tiny (1.0×1.0×0.3 mm) ingestible sensors incorporated in the pill during the manufacturing process, which will be ingested by the patient. Once ingested, an electrochemical reaction will be triggered in the stomach leading to an activation of the sensor and generating a unique message coded for the medication name and dose to a wearable patch worn by the patient on the torso and record the date and time of the sensor ingestion. Thus, this technique combines the dosing history and the proof that the drug was ingested. The information collected by the patch is encrypted and transmitted wireless to a designated device using Bluetooth (Figure 2). Sensors are then eliminated as solid waste within 72 hours. Early clinical studies were conducted in several therapeutic areas including hypertension[100,101] and the system was found to be safe regarding toxicology, mechanical, and electrical safety. In hypertensive patients uncontrolled with at least 2 antihypertensive agents, the use of the Proteus system was associated with significant decreases in BP (−9.7 mm Hg systolic and −5.0 mm Hg diastolic) and 32% of participants achieve BP targets of <140/90 mm Hg.[101] In a larger trial involving patients with uncontrolled hypertension and type 2 diabetes mellitus,[100] the use of the Proteus system for 4 or 12 weeks versus usual care was associated with better control of BP and glycemia but the average adherence rate was 86% during the 4 weeks and 84% in the 12 weeks groups, respectively. This suggest that the Proteus system may help improving drug adherence in some patients. However, whether it will be accepted in the real-world needs to be demonstrated. In addition, the system is not devoid of possible manipulations by patients at the level of the wearable patch, which needs to be replaced weekly. Recently, the Food and Drug Administration has approved use of the Proteus system for the treatment of patients with mental disorders.

Resistant Hypertension

Although poor adherence can occur in all hypertensive patients whatever the number of drugs and the stage of hypertension, medication nonadherence is suspected mainly in clinical conditions where the prescribed treatment does not provide the expected reduction in BP. This is typically the case of apparent resistant hypertension.[102–105] Indeed, when BP does not decrease despite the prescription of at least 3 drugs including a diuretic, physicians are confronted with 2 crucial questions: Is the patient a nonresponder to therapy or is the patient not taking drugs as recommended thus being a nonadherer? In this context, if poor adherence is the issue, adding new drugs will only aggravate the situation. Many recent surveys demonstrated that a high percentage of patients with apparent resistant hypertension are actually pseudo-resistant, the major issue being poor adherence to the prescribed therapy.[88,93,106–109] The precise prevalence of partial or complete nonadherence to antihypertensive treatment in apparent resistant hypertension is difficult to estimate owing to the lack of robust definitions and gold-standard diagnostic methods. Therefore, as reviewed recently, the prevalence of poor adherence in resistant hypertension ranges between 7% and 87% in observational studies and clinical trials depending on the assessment tool.[110] Using the MEMS, the prevalence of nonadherence in difficult to control

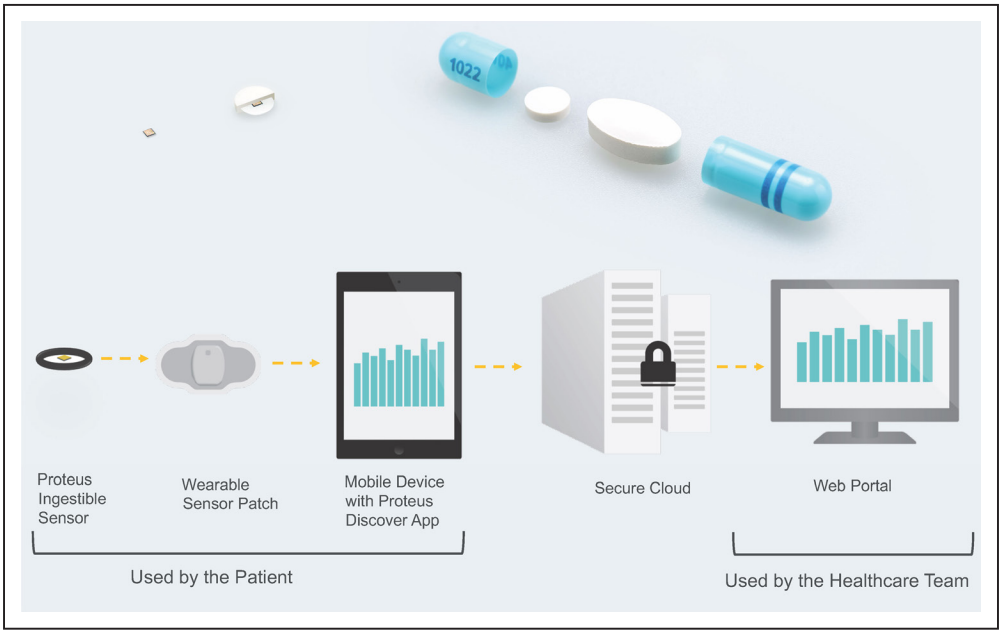

Figure 2. Description of the Proteus system with an ingestible sensor transmitting the information to a mobile. Reprinted from Frias et al.[100] Copyright ©2017 (see: https://creativecommons.org/licenses/by/4.0/).

patients ranges between 30% and 50%[111,112] whereas using drug measurements in urine >50% of patients with apparent resistant hypertension are completely or partially nonadherent to the prescribed medications.[110,113] Interestingly, data have also demonstrated that drug adherence varies over time, for example, before and after renal denervation, leading to unpredictable effects on clinical study results.[114] Therefore, monitoring of drug adherence should be incorporated systematically in any drug or device development.[113,115] Unfortunately, as of today, adherence to therapy remains largely underdiagnosed in clinical studies, despite the availability of adequate noninvasive methods and the situation is even worse in clinical practice where adherence is almost never measured.

Health Consequences and Economic Impact of Suboptimal Adherence to Antihypertensive Medications

The adverse impact of suboptimal adherence to antihypertensive medications is multi-fold (Table 4), and the untoward economic impact potentially large.

While the table may be perceived as splitting categories of adverse outcomes, it is important to recognize the broad impact of inadequately or untreated hypertension that can result from suboptimal adherence to effective prescription medications. Hopefully, the list will serve to raise the value of adherence from the perspective of clinicians and the patients they serve as well as healthcare payers and policy makers as integrative approaches are required to optimize adherence. There is, however, a caveat. Before amplifying items in Table 4, it is important to recognize the potential for overestimating the adverse effects of nonadherence. Evidence suggests that differences beyond BP reduction or hypertension control between more and less adherent patients may account for a substantial proportion of variance in adverse outcomes.[7,144–146] For example, more adherent patients appear to generally have a more positive attitude toward preventive health measures, which could favorably impact multiple outcomes.[7,144]

Table 4. Consequences of Suboptimal Adherence to Antihypertensive Medications

Adverse Outcome	References
1. Uncontrolled hypertension	Abegaz et al,[116] Butler et al,[117] and Breekveldt-Postma et al[118]
2. Progression to hypertensive crisis	Saguner et al[119]
3. Vascular stiffness	Berni et al[120]
4. Left ventricular hypertrophy	Comberg et al[121] and Bruno et al[122]
5. Microalbuminuria	Kim et al[123]
6. Myocardial infarction	Mazzagliaet al,[124] Corrao et al,[125] Chowdhury et al,[126] Herttuaet al,[127] Yang et al,[128] Perreault et al,[129,130] and Breekveldt-Postma et al[131]
7. Stroke	Mazzagliaet al,[124] Corrao et al,[125] Chowdhury et al,[126] Herttuaet al,[127] Yang et al,[128] Perreault et al,[129,130] and Breekveldt-Postma et al[131]
8. Chronic heart failure	Mazzagliaet al,[124] Corrao et al,[125] Chowdhury et al,[126] Herttuaet al,[127] Yang et al,[128] Perreault et al,[129,130] and Breekveldt-Postma et al[131]
9. Chronic kidney and end-stage renal disease	Cedillo-Couvert et al[132] and Roy et al[133]
10. Cognitive dysfunction, dementia	Poon et al[134] and Vik et al[135]
10. Excess emergency department and hospital admissions	Herttuaet al,[127] Heaton et al,[136] and Pittman et al[137]
11. Reduced quality of life	Wiklund et al[138]
12. Impaired work productivity, disability	Mokdad et al[139] and Wagner et al[140]
13. Increased healthcare costs	Pittman et al[137], Iuga et al,[141] Cherry et al,[142] and Roebuck et al[143]
14. Death	Cherry et al[142]

Health Consequences of Suboptimal Adherence

The literature documents the multiple adverse clinical consequences of suboptimal adherence. The adverse effects include uncontrolled hypertension and hypertensive crises. Suboptimal adherence is also associated with various target organ changes linked to a greater risk of cardiovascular events, including vascular stiffness, left ventricular hypertrophy (LVH), and microalbuminuria. Suboptimal adherence is also associated with multiple adverse cardiovascular events including acute coronary syndromes, stroke and transient ischemic attack and chronic heart failure as well as mortality.

Uncontrolled Hypertension and Progression to More Severe Hypertension

Evidence supports the notion that patients with controlled hypertension are more likely to adhere to antihypertensive pharmacotherapy than are individuals with uncontrolled BP.[116,117] Conversely, patients staying on therapy are more likely to achieve long-term BP targets.[118]

Hypertensive Crises

Several of the initial randomized, double-blind, placebo-controlled studies in hypertension showed that treating hypertension reduced progression to more severely elevated levels of BP as well as accelerated and malignant hypertension.[147,148] In a similar vein, more recently reports found that poor medication adherence was linked with the occurrence of hypertensive crises.[119]

Vascular Stiffness

Greater vascular stiffness, as measured by arterial pulse wave velocity, was associated with a clinically and statistically significant increase in the first occurrence of a major cardiovascular event (composite myocardial infarction, unstable angina, heart failure, or stroke).[149] Low adherence to antihypertensive medications, in turn, was associated with increased arterial stiffness derived from 24-hour ambulatory BP monitoring.[120]

Left Ventricular Hypertrophy

Incident LVH by electrocardiography did not occur in either black or white adults with hypertension during the 5 years of stepped-care therapy in the Hypertension Detection and Follow-Up Study. However, in the 7 years of follow after completing stepped-care therapy, LVH was a relatively

common occurrence, especially among black adults.[121] The authors noted specifically that adherence to antihypertensive medications declined substantially among black men during the follow-up period and viewed that fact as contributing to incident LVH. In another report, LVH by electrocardiography was significantly associated with poor adherence to antihypertensive medications before stroke among patients that suffered an acute stroke.[122]

Microalbuminuria and Macroalbuminuria

Among 40 473 Korean adults with hypertension, 2657 had urine albumin/creatinine ≥30 µg/mg including 499 with values ≥300 µg/mg. Low adherence to antihypertensive medications was independently associated with the presence of albuminuria.[123]

Cardiovascular Events Including Acute Myocardial Infarction, Stroke, and Chronic Heart Failure

In view of the association of poor adherence with uncontrolled hypertension, hypertensive crises, and several risk factors for cardiovascular disease, the association of suboptimal adherence with major adverse cardiovascular events is expected.[124–130] Some reports included very large numbers of patients such as a meta-analysis with 1 978 919 unique patients and the Italian Lombardy Region with 242 594 newly treated hypertensives.[125,126] Moreover, suboptimal adherence has also been associated with individual components of composite cardiovascular disease, including myocardial infarction, stroke, and chronic heart failure.[127,128,131]

Chronic Kidney Disease

Suboptimal adherence to medications generally is associated with faster progression of chronic kidney disease.[132] Moreover, suboptimal adherence to antihypertensive medications specifically is independently linked to greater risk for incident end-stage renal disease.[133]

Cognitive Function and Dementia

Cognitive dysfunction and dementia are well-recognized causes of poor adherence in elderly patients[53,54] because they impair the abilities in planning, organising, and executing medication management task. Because BP control plays a role in the prevention of cognitive dysfunction and dementia,[134] a good adherence to antihypertensive should be favorable. Studies have demonstrated that it is possible to improve drug adherence in patients with cognitive dysfunction or dementia, but none has really demonstrate a clear impact on the reduction of health outcomes.[135]

Emergency Department and Hospital Admissions

The US National Hospital Ambulatory Medical Care Survey for 2005 to 2007 indicated that ≈13% of emergency department admissions were related to medication nonadherence. The likelihood of emergency department visits for hypertension was strongly related to nonadherence.[136,137] In addition, >20% of emergency department admissions associated with nonadherence led to hospital admission compared with 12.7% unrelated to adherence. Other reports confirm that adults with suboptimal adherence to antihypertensive medication have more hospital admissions for cardiovascular-related events.[127,137]

Reduced Quality of Life

More intensive hypertension control to BP values below <140/<90 was associated with more serious adverse events attributable to more intensive therapy or lower BP levels.[150,151] Yet, other data indicate that better hypertension control and greater adherence to BP medications are associated with a higher quality of life.[138]

Disability and Reduced Work Productivity

Ischemic heart disease was the leading cause of disability-adjusted life-years in the US during 1990 and 2016 with stroke 10th in 1990 and 12th in 2016.[139] Uncontrolled hypertension is a major contributor to both events. Self-reported low adherence to antihypertensive medication was linked to higher levels of work impairment and presenteeism, that is, individual present but less productive.[140]

Greater Healthcare Costs

In the United States, suboptimal adherence is estimated to account for up to 10% of total healthcare costs.[141] With regard to adherence and hypertension, among employees of a large manufacturer and their dependents <65 years old,[142] hypertension-related healthcare costs were lower for individuals with 80% to 100% at $4871/y than the 4 groups with lower adherence (range $4878–$6062/y). Similarly, total healthcare costs for hypertensive adults with high adherence ($8386) were lower than for the other 4 lower adherence groups ($8929–$11 238). In another report,[143] data on 112 757 hypertensive patients were obtained from a large pharmacy benefit manager. Annual medication costs were $429 greater for patients with high than low adherence but were associated with $3908 lower annual medical expenditures.

Analysis of large claims database indicated that mean annual healthcare costs were lower for hypertensive patients with 80% to 100% adherence to BP medications ($7182, n=467 006) than for patients with 60% to 79% adherence ($7560, n=96 226) and <60% adherence ($7995, n=62 338).[137] Patients with moderate and low adherence were more likely to have emergency department and hospital admissions for cardiovascular conditions than those with high adherence.

In a model derived from observational data, both ideal and real-world adherence were linked with survival advantages. There was an estimated incremental cost of real world adherence over no adherence of $30 585 per life-year gained.[137] While several reports suggest that suboptimal adherence generally and cardiovascular and hypertension medications specifically is associated with higher healthcare costs, other evidence indicates incremental cost per life-year gained.

Clinical Management/Mitigation of Suboptimal Adherence

Once poor adherence is detected, efforts should focus on implementing interventions to improve and maintain long-term adherence. This can be achieved using several different approaches, which concern not only patients but also physicians, health care systems and the medical therapy itself as already partly discussed in Suboptimal Adherence: Contributing and Associated Factors of this review and illustrated in Table 5. Despite the multiplicity of possible interventions,

Table 5. Interventions That May Improve Drug Adherence in Hypertension

Level of Intervention	Types of Interventions
Physicians	Provide information on the risks of hypertension and the benefits of treatment, as well as agreeing a treatment strategy to achieve and maintain BP control using lifestyle measures and a single-pill-based treatment strategy when possible. Distribute information material and use programmed learning, and computer-aided counselling. Empowerment of the patient Positive feedback on behavioral and clinical improvements Improvement in communication skills Assessment and resolution of individual barriers to adherence (provide clues) Collaboration with other healthcare providers, especially nurses and pharmacists
Patients	Self-monitoring of BP (including telemonitoring) Instruction combined with motivational strategies Self-management with simple patient-guided systems Use of reminders or week/mo organizers Obtain family, social, or nurse support Provision of drugs at worksite Group sessions
Drug treatment	Simplification of the drug regimen Use single pill combinations Prefer long-acting drugs once a day Avoid high doses of drugs with adverse effects
Health systems	Accessibility of drugs Reimbursement of single pill combinations Supporting the development of monitoring systems (electronic monitors, telephone, follow-up, home visits, and telemonitoring of home BP) Reduce copayments Financial support of the collaboration between healthcare providers (eg, pharmacists and nurses) Development of national databases, including prescription data, available for physicians and pharmacists

BP indicates blood pressure.

meta-analyses and systematic reviews on interventions to ameliorate adherence conducted between 1996 and 2014 tended to conclude that current methods of improving medication adherence for chronic health problems were mostly complex, not very effective and with a minor effect size.[152–155] In addition, it was difficult to demonstrate that one approach is better than another is at increasing adherence and combination of approaches appeared to be best.

Nevertheless, more recently, some systematic reviews have identified interventions that demonstrated both improvements in adherence and clinical outcomes in the management of cardiovascular diseases.[156] These were short message services (65% versus 13% of participants with high adherence in the intervention versus control group) and simplification of treatment regimens using single pill combinations (86% versus 65% adherence, risk ratio of being adherent, 1.33; 95% CI, 1.26–1.41). In this respect, improvement of adherence with the use of single pill combinations has been confirmed in a meta-analysis.[157] In terms of pharmacotherapy, the future may be in the development of chemically synthesized compounds or vaccines able to interfere with an important regulatory system for several months. One example is the recent development of an interfering RNA designed to target the PCSK9 (proprotein convertase subtilisin/kexin type 9) mRNA in hypercholesterolemic patients, which has been shown to lower cholesterol up to 6 months after a single injection.[158]

The integration of community health worker-based interventions in a team-based care system is also improving drug adherence in this review (97% in the team-based care group compared with 92% in the control group; odds ratio=2.62, 95% CI, 1.32–5.19).[156] This latter observation confirm previous experiments indicating that a multidisciplinary approach involving pharmacists and nurses is effective in supporting adherence and improving BP in hypertensive patients.[159–161] Unfortunately, this strategy is often limited by the difficulty to establish a collaboration between physicians and pharmacists and by the reimbursement of pharmacists' activities through the health care system. Thus, the cost-effectiveness of the team-based care has been questioned.[162–164]

Devices integrated into the care delivery system and designed to record dosing events, such as the MEMS, were also found to be more frequently associated with a significantly improved adherence compared with other devices, with differences in mean adherence ranging from a decrease of 2.9% in the control group to an increase of 34.0% in monitored patients.[165]

Among other useful interventions, one can cite that linking drug intake with habits, giving positive feedback to patients on adherence, self-monitoring of BP, using pill boxes and other special packaging, and motivational interviewing leading to patients' empowerment.[21] A greater involvement of pharmacists and nurses increases drug adherence and is now strongly recommended by hypertension guidelines.[166] Recent data suggest that adherence to treatment may also be improved with the use of telemetry for transmission of recorded home values, maintaining contact between patients and physicians[167–169] and with electronic prescription systems, which improve the initiation process.[20]

One common observation, however, is that any technique used to detect poor adherence is also associated with improvement of adherence. This is the case with the electronic monitoring of adherence[112] but also with the measurements of drug levels in plasma or urines.[106,170] Thus, in a retrospective analysis of hypertensive patients attending specialist tertiary care centers in 2 European countries (United Kingdom and Czech Republic), nonadherent hypertensive patients responded to repeated liquid chromatography-tandem mass spectrometry biochemical analyses with an improved adherence and significant BP drops, which were correlated with the improvement in drug adherence.[170]

At last, as discussed previously, one important step to improve patients' adherence would be to reinforce the physicians' communication skills and hence their ability to present

the objectives of the therapy and to discuss the clinical importance of poor adherence in a nonjudgmental way. In 1976 already, Inui et al[45] has demonstrated that adherence-trained physicians spend more time educating their patients, which results in an increased likelihood that their patients take at least 75% of the prescribed BP medications and reach BP targets. The empowerment of the patient is critical. In patients with diabetes mellitus and hypertension, Naik et al[171] found that shared-decision-making style and proactive communication demonstrated significant direct effects on hypertension control. Easier access to healthcare and reduction of treatment costs represent other clues to promote medication adherence and increase BP control.

Taken together, available data show that there are several useful approaches to improve and support adherence to therapy in hypertension. However, one important aspect is that these approaches probably need to be combined to be most effective. A good example is the significant increase in BP control obtained in the Northern California Kaiser Permanente System between 2001 and 2009 (from 43 to almost 85%) with the implementation of a large-scale hypertension program.[172] This latter included a comprehensive hypertension registry, the development and sharing of performance metrics, evidence-based guidelines, medical assistant visits for BP measurement, and the use of single-pill combination pharmacotherapy.[172]

Summary

The global epidemic of hypertension is largely uncontrolled and the predominant risk factor for cardiovascular events, the leading cause of noncommunicable disease deaths worldwide. Treatment and control of hypertension prevent cardiovascular death. While a large proportion of uncontrolled hypertension is untreated, suboptimal adherence among treated adults is a major factor.

Suboptimal adherence includes failure to initiate pharmacotherapy, to take medications as often as prescribed, and to persist on therapy long-term. The healthcare team can take several steps to improve patient adherence through shared-decision making on management, insuring patients understand the severity and consequences of their disease and benefits of treatment and control, facilitating BP self-monitoring with relay and advice, prescription of low-cost, effective medications, especially as single pill combinations, and frequent follow-up of patients with uncontrolled hypertension.

Several categories of factors including demographic, socioeconomic, concomitant medical-behavioral conditions, therapy-related, healthcare team and system-related factors, and patient factors are associated with nonadherence. Understanding the categories of factors contributing to nonadherence is useful in managing nonadherence.

Simple, low-cost screening tests can be useful for identifying nonadherent patients with uncontrolled hypertension and a low to moderate risk for cardiovascular events. Patients who have severe and treatment resistant hypertension, despite prescription of usually effective combination antihypertensive pharmacotherapy, have a higher probability of nonadherence. In these high risk patients, electronic or biochemical monitoring are useful for detecting nonadherence and for improving adherence. Increasing the availability and affordability of these more precise measures of adherence represent a future opportunity to realize more of the proven benefits of evidence-based medications. Despite challenges in overcoming nonadherence globally, in countries, such as Canada, Germany, and the United States, 70% to 85% of treated hypertensive patients have controlled BP, a proxy for adherence. Understanding and translating these successes provide opportunities for improving cardiovascular health worldwide.

Despite the description of many new mechanisms involved in the pathophysiology of hypertension, few new drugs will arrive on the market in next years for improving the treatment of hypertension.[173] The possible approval of device-based therapies for treating hypertension will perhaps reduce the clinical impact of poor-adherence but it will not suppress it, as in most device-based studies drugs were still necessary to control hypertension after the intervention.[174] Therefore, it is important that healthcare providers focus their attention on how to do better with the drugs we have. This is the reason why recent guidelines have emphasize the important need to address drug adherence as a major issue in hypertension management.[166,175]

Disclosures

None.

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