Patient Preference and Adherence

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REVIEW

A Critical Review of Medication Adherence in Hypertension: Barriers and Facilitators Clinicians Should Consider

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Abstract: Hypertension is a global public health problem, and its prevalence is increasing worldwide. Impacting all human societies and socioeconomic strata, it remains the major modifiable risk factor for global burden of cardiovascular disease all-cause mortality and the leading cause of loss of disability-adjusted life years. Despite increased awareness, the rate of blood pressure control remains unsatisfactory, particularly in low- to middle-income countries. Apparent treatment-resistant hypertension is associated with worse adverse health outcomes. It includes both true resistant and pseudo-resistant hypertension, which requires out-of-office blood pressure monitoring to exclude white-coat effect and confirmation of adherence to the agreed recommended antihypertensive therapy. The depth of medication non-adherence remains poorly recognized among medical practitioners, thus presenting an underestimated modifiable risk factor. Medication non-adherence is a complex and multidimensional variable with three quantifiable phases: initiation, implementation, and discontinuation, collectively called persistence. Non-adherence can be both intentional and non-intentional and usually involves several interconnected factors. Persistence declines over time in the treatment of chronic diseases like hypertension. The risk is higher in patients with new diagnosis, poor insurance status, polypharmacy, and multiple comorbidities, particularly psychiatric disorders. The World Health Organization divides the contributing factors impacting adherence into five categories. Screening and detection for medication non-adherence are challenging due to its dynamic nature and potential white-coat effect. Easy-to-conduct screening methods have low reliability and validity, whereas more reliable and valid methods are costly and difficult to perform. Medication non-adherence is associated with poor clinical outcome and potential negative impact on health-care costs. Evaluation of adherence should become an integral part of assessment of patients treated for hypertension. Medication adherence can significantly improve with a patient-centered approach, non-judgmental communication skills, and collaborative multidisciplinary management, including engagement of the patients in their care by self-blood pressure monitoring.

Keywords: blood pressure control, cardiovascular disease, hypertension, medication adherence, persistence, resistant hypertension

Introduction

Hypertension, as a silent asymptomatic condition, is the most important modifiable risk factor for cardiovascular diseases (CVD) and the number one cause of disability-adjusted life years.[1] It is a global public health problem, affecting both genders, with the prevalence and burden of the disease increasing globally.[2] By the year 2025, an estimated 1.6 billion of the world adult population will have hypertension. This is an increase of about 60% compared to the year 2000.[3] More concerning is that this increase in prevalence is associated with significant disparities between high-income countries and low- to middle-income countries (LMICs). In contrast to high-income countries where awareness, treatment and control rates are increasing, these factors remain significantly lower in LMICs.[4] This is in part due to the aging population, urbanization, and changes in social and environmental risk factors.[5] In the United States, the prevalence is higher overall, and controlled rates are lower among minority populations, particularly in non-Hispanic blacks.[6] Respectively, in a given hypertensive population, there is a group of patients that is unaware of the

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diagnosis. And within the aware and diagnosed group, there is a pool of patients who have uncontrolled or resistant hypertension despite intake of maximally tolerated doses of three different classes of antihypertensive medications, including a diuretic.[7,8] In reality, uncontrolled hypertension could be due to non-persistence with intake of antihypertensive medication. Respectively, patients with resistant hypertension are to be referred to as having apparent treatment-resistant hypertension (aTRH) because they include both true resistant and pseudo-resistant hypertensive individuals.[9] The term aTRH is used to identify "apparent" lack of blood pressure (BP) control on 3 or more medications at maximally tolerated doses, including a diuretic.[10] The pseudo-resistant hypertension can be due to either inaccurate measurement of BP in the clinic with no out-of-clinic confirmation to exclude white-coat effect, or it could be due to non-adherence to the antihypertensive therapy.[11,12] It is important to differentiate true resistant from pseudo-resistant hypertension, because effective BP-lowering treatment with antihypertensives reduces BP-related morbidity and mortality.[13] Further, population-based studies show an increased risk of cardiovascular events, poor renal outcomes, and all-cause mortality in patients with true resistant hypertension.[14,15]

Medication Adherence

Well-recognized but underestimated major barriers to BP control to manage hypertension and aTRH include under-treatment or therapeutic inertia, meaning no treatment changes are made in a patient's antihypertensive regimen by the health-care provider despite clear indication, as well as non-adherence to antihypertensive therapy.[16,17] Therefore, it is important to incorporate the evaluation of medication adherence as part of routine assessment of patients with uncontrolled hypertension or aTRH.[18] Respectively, it is important to be familiar with the following:

1. How do we define medication non-adherence?
2. What are the barriers and contributing factors to medication adherence?
3. How do we screen for and detect medication non-adherence?
4. What is the impact of suboptimal adherence on health and health-care costs?
5. What is the practical approach to improve medication adherence?

Definition

It is important to differentiate between adherence and compliance, with the latter viewed by many to have a negative connotation. Compliance is when the patient obeys the health-care provider's recommendation passively and is subservient to prescriber.[19] In contrast, according to World Health Organization (WHO), adherence is 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.[20] Along the same lines, there is limited evidence in the literature to support the arbitrary cutoff of 80% or more intake of prescribed medication as good adherence. According to the European Society for Patient Adherence, Compliance and Persistence (ESPACOMP), medication adherence starts when the prescription is issued for the patient, but it has three quantifiable phases.[21] The first phase, initiation, starts when the patient takes the first pill. The second phase, implementation, provides information on the actual dosing and can be suboptimal due to forgetfulness or negligence. Interruptions in treatment can be intentional or nonintentional. Patient can have taking non-adherence or timing non-adherence. The final third phase, discontinuation, is when the patient stops taking the medication despite prescription being refilled. These three phases are collectively called persistence. In a perfect world where all patients take their medication regularly, the persistent would be 100%. But longitudinal database study of 21 clinical trials of 4783 participants with hypertension show that the persistence declines over time and by the end of one year, almost half of the patients stop taking their medication.[22] Early discontinuation of treatment and suboptimal daily execution of the prescribed regimen are the most common causes of poor adherence. Additionally, there is usually an initial abrupt small drop in the persistence curve representing the proportion of patients who never engage with the dosing regimen, ie, initiate intake of prescribed medication. This is estimated to be about 5% in clinical trials and up to 20% in real practice. Moreover, on any given day patients with persistence can have up to 10% omission of the scheduled doses. In other words, patients can have poor implementation at any given time.

Contributing Factors of Medication Non-Adherence

Medication non-adherence is a critical problem in management of hypertension. The chronic asymptomatic nature of the disease and the occasional or even frequent omission of recommended dose appear to be without immediate consequences. Medication adherence is highly variable within the course of treatment and generally declines over time. According to the WHO, barriers and factors impacting medication adherence can be divided into the following five categories:[20]

1. Sociodemographic: age, ethnicity, level of income and literacy, social status and support.
2. Health-care system-related: patient–clinician relationship, patient-centeredness, physician's communication style, quality-based payment, therapeutic inertia.
3. Therapy-related: choice of complex regimens, frequent treatment changes, adverse effects, lack of refill frequency and consolidation.
4. Condition-related: multiple comorbidities including depression, psychoses, drug or alcohol abuse, dementia, major disability.
5. Patient-related: patient's misunderstanding or lack of knowledge, poor perception of illness and treatment efficacy, denial of diagnosis, fear of dependence or adverse effects, lost to follow-up.

Understanding these risk factors can help clinicians discern the right approach to identify the barriers early and design an intervention of several components simultaneously to promote better adherence. Medication non-adherence is a complex and multidimensional variable including several interconnected factors that are to be targeted simultaneously.[23] In other words, no one size fits all.

Although certain sociodemographic characteristics are statistically associated with higher risk of medication non-adherence, a combination of these characteristics alone is not sufficient to predict adherence to treatment.[24] Racial-ethnic minorities who have lower income, less education, and are publicly insured have identical BP control compared to affluent, better-educated, privately insured patients.[25] Despite these limitations, data from actual clinical practice show that persistence decreases over time. Barriers to persistence are usually present early in the treatment and the risk is higher in chronic conditions like hypertension. It is more prevalent among newly diagnosed hypertensive patients, and is worse among young males of minority race-ethnicity or very old individuals, possibly due to comorbidities and polypharmacy.[26–29]

Increasing evidence shows that the quality of patient–clinician relationship is important. Patient-centered care, professional and non-judgmental communication skills, and patient's trust and confidence in the clinician's knowledge can effectively enhance medication adherence. Quality-based payment and low clinician burnout rate could lead to improvements in health system-related factors and health outcomes of the individual.[30,31]

Several therapy-related factors can increase risk of medication non-adherence. These include increased number of prescribed antihypertensive medication, the choice of the drug class and its side effect profile, ie, diuretics or diuretic containing fixed-dose combination drugs are associated with higher rate of non-adherence.[32,33] There is even a heterogeneous effect within any given class, possibly due to complex regimens requiring frequent daily dosing.[34] Similarly, frequent treatment changes and adjustments that delay benefit of BP control can affect adherence.[35] Medication adverse effects can be severe enough to affect adherence to antihypertensive medications.[36] The contribution of adverse events to the low level of adherence remains unknown. Symptoms affecting the patient's quality of life and attributed by the patient to adverse effects of antihypertensive medication can change their medication intake behavior without appropriate communication with health-care provider.[37] Respectively, patients should be counseled about potential adverse effects common to the prescribed antihypertensive medications and be directly involved in the treatment decision-making. Patients' adherence can be further improved by consolidating and limiting refill frequency by prescribing 90-day supplies.[38]

Presence of chronic diseases and comorbidities, especially psychiatric disorders, drug or alcohol dependency, age-associated dementia and disability plus polypharmacy can all adversely affect medication adherence, BP control, and clinical outcomes.[39,40]

Finally, patient-related factors are fundamental and a key dimension of medication adherence. These may include patients' misunderstanding of the diagnosis or its cause; lack of knowledge about the disease with an inaccurate perception of the asymptomatic illness severity and treatment efficacy; or fear of adverse effects and drug dependency. These can all result in disease denial, use of alternative therapy, and poor follow-up, increasing the risk of medication non-adherence and threatening an individual's health outcome.[41,42]

It is important to note that medication adherence is a dynamic phenomenon and there is a potential risk for white-coat adherence.[43] Patients tend to improve their adherence before clinic visits. This masks suboptimal adherence by creating a false clinical impression and making the detection of non-adherence in clinical practice extremely difficult.[44]

Screening Methods for Identification of Patients with Medication Non-Adherence

The risk of medication discontinuation increases over time in chronic diseases like hypertension. Due to the dynamic nature of the medication adherence, accurate assessment of this process is a major challenge for clinicians. The ideal assessment method should provide reliable data, but unfortunately there is no single best assessment method, as each method has advantages and disadvantages. It is important to use a valid, reliable, cost effective, simple and readily available objective method. Simple and cheap methods tend to be relatively unreliable. Methods with high validity are more expensive and demanding in terms of infrastructures. As of today, none of the available methods fulfill all these criteria.[45]

The current available methods could be divided into two simple groups of 4Ps and 4Ms.[12]

The 4Ps include:

- Patient questionnaire and self-reporting
- Patient interview
- Pill counting
- Prescription refill data

The 4Ms include:

- Medication intake under observation
- Medication event monitoring system
- Medication level measurement in body fluids
- Digital Medicine

The 4Ps are simple, inexpensive, though time-consuming methods. These methods are unreliable, and do not fully confirm ingestion of antihypertensive medications when compared with more objectively measurable methods providing a complete dosing history.

Patient questionnaires and self-reporting assess patients' behavior, beliefs, and barriers to medication adherence. The eight-item Morisky's questionnaire has high sensitivity with low specificity. These methods tend to overestimate true adherence and correlate poorly with drug levels measured in urine samples.[46,47]

Physicians' perception of medication intake is subjective and generally inaccurate. Patient interview requires physicians' non-judgmental communication skills and can be no better than tossing a coin.[48] Pharmacy database records are not robust if not all pharmacies used by the patient are captured. Furthermore, prescription refill is not equal to actual medication intake.[49] Pill counting, although a useful method, is time consuming and in general does not provide accurate assessment of medication adherence.[50]

These methods are potentially associated with bias or misclassification, have low diagnostic specificity, and can overestimate patient's adherence to medication intake.

In contrast, the 4Ms are reliable but costly assessment methods and difficult to conduct in real clinical practice.

Medication intake under direct observation, as practiced in treatment of infectious diseases like tuberculosis, is rarely done in the management of hypertension. It is logistically very difficult and time consuming to do. Additionally, it requires appropriately skilled staffing and monitoring to avoid complications from unpredictable BP-lowering effect with the intake of medication in patients with aTRH secondary to non-adherence.[51]

Medication event monitoring system (MEMS) using electronic medication packaging devices is an expensive but accurate and commonly used method in clinical practice. Such systems provide excellent information on medication intake behavior. Unfortunately, they are limited to tracking of one single medication for each pill box. Each time the system is activated, it records and stores automatically the exact time of dosing event. Although MEMS has the potential risk of no intake of the medication despite pillbox activation, it is considered a reliable quantitative method and is associated with increased adherence.[52,53]

The gold-standard, robust method that prevails in the clinical practice setting and clinical trials is medication-level measurement in body fluids, urine, or blood, using high performance liquid chromatography–tandem mass spectrometry (HPLC-MS).[54] In this method, one can separate, identify, and quantify 40 most common antihypertensive medication and their metabolites.[55] It has very high specificity and sensitivity. The biochemical analysis of a spot urine sample is non-invasive and provides a qualitative result.[56] In contrast, analysis of blood sample gives more of a quantitative measurement. One drawback of HPLC-MS is it provides punctual information, because it depends on the nature of patients' behavior in taking the medication and on the half-life or pharmacokinetics of the medication. Thus, detailed information on medication dosing, pharmacokinetics, and pharmacodynamics of the drug is needed when interpreting the results.

Medication intake using digital medicine is a relatively new and expensive technology that is approved by Food and Drug Administration (FDA) for the treatment of patients with mental disorders only. In this technology, an ingestible sensor is incorporated in the pill during the manufacturing process. Once ingested by the patient, an electrochemical reaction will be triggered in the stomach leading to the activation of the sensor and generation of a unique coded message for the medication name. The encrypted dosing history is captured by a wearable patch worn by the patient on the torso and then transmitted via a mobile device wirelessly to the cloud, which can be accessed by the health-care provider via the web portal. The effectiveness of digital medicine to improve clinical outcomes in patients with uncontrolled hypertension and type 2 diabetes has been shown in a prospective, open label, cluster randomized trial.[57]

Impact of Medication Non-Adherence on Health and Healthcare Costs

Poor medication adherence has significant and multi-fold effects on the management of hypertension, increasing the risk of cardiovascular events, poor renal outcome, including end-stage kidney disease, and all-cause mortality.[58] Population-based prospective studies show significant reduction in cardiovascular risks and events with longer persistence with intake of medication.[59] The hazard ratio reduction is proportional to level of adherence. Similarly, self-reported medication adherence in patients enrolled in a prospective observational chronic renal insufficiency cohort (CRIC) study is associated with slower chronic kidney disease progression and all-cause mortality.[60] In addition to poor health outcomes, medication non-adherence can result in costly and unnecessary investigations or even potentially harmful treatment intensification.[61] These steps carry the risk of increased emergency department visits, leading to unnecessary hospitalizations and further increase in health-care costs.[62,63]

Practical Approach to Improve Medication Adherence

Medication non-adherence is a much more complex problem than simply blaming the patient.[64]

The approach to assess medication adherence should address as much as possible all of the potential detectable barriers listed under the five WHO categories discussed above. Interventions should be tailored and individualized, as the effort can be labor intensive, and long-term positive effect may be difficult to sustain due to the dynamic nature of the process.[65]

Better medication adherence is strongly associated with patients' knowledge and appropriate perception of the disease plus satisfaction with clinic visits. Accordingly, patient-centered care and non-judgmental physician communication skills are the essential components in the management of hypertension.[66] It is important to educate health-care providers on these components, the importance of counseling and education of the patients regarding their care, and correction of

any misunderstandings and incorrect beliefs regarding the long-term treatment.[67] Increased patient self-engagement in their care can foster medication adherence to improve BP control and clinical outcomes.[68] Important considerations in the management of hypertension include effective initial drug choice, healthcare service utilization including appropriate follow-up, avoidance of polypharmacy, and consolidation of adequate number of prescription refills to a single pharmacy.[69] Use of fixed-dose combination pills or drugs with longer half-life may offset non-adherence in some patients compared to single-agent dosing of drugs with shorter half-life.[70] Developing effective anti-hypertensive drugs has come a long way over the last 5 decades, finally reaching a point wherein virtually all phenotypes of hypertension can be successfully addressed with medical therapy, if adherence is achieved.[71] To optimize adherence to antihypertensive medication, a multi-disciplinary, patient-centered approach can be implemented utilizing assistance of other health-care providers, including pharmacists, to provide additional education and behavior counseling.[72,73]

Conclusions

Medication non-adherence is an underestimated, modifiable risk factor in the management of hypertension and aTRH. Evaluation of medication adherence should become an integral part of assessment of patients with hypertension and particularly aTRH. It is true that drugs do not work in patients who do not take them, but medication non-adherence is a much more complex problem than simply blaming the patient. There are patient-related factors as well as healthcare-related ones. It requires a significant effort to identify this problem in a chronic asymptomatic condition like hypertension due to its dynamic nature. While no single perfect method exists to assess medication adherence, a multi-complementary strategy can improve medication adherence by focusing on interventions to address immediate short-term barriers as well as maintaining long-term adherence, because medication adherence is a key preventive measure in the management of chronic diseases like hypertension. The following skills could help providers in their interventions to improve patient's medication adherence:

1. Have non-judgmental communication skills assessing the barriers and patient's fears.
2. Educate and counsel patients on risks of uncontrolled hypertension.
3. Engage and empower patients in a shared decision-making process.
4. Reinforce self-BP monitoring.
5. Provide positive feedback on behavioral and clinical improvements.
6. Avoid complex regimens and polypharmacy and use fixed combination pills with longer half-life if possible.
7. Assess for potential medication adverse effects.
8. Obtain family support and collaborate with other health-care providers including pharmacists.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, execution; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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