Adherence to antihypertensive drug treatment and Morinsky test

Around the word, the level of control of hypertension is low. Lack of adherence is an important obstacle to hypertension control within the community. Evaluating the adherence of an individual patient could be a challenge for a physician. In this revision, we analyze the utility of self-reference questionnaires to accomplish this task.

The WHO estimates that the prevalence of non-adherence to antihypertensive medication is between 30 and 50%. Between indirect methods, the 8-item Morisky Medication Adherence Scale (MMAS-8) is a simple test, is a low-cost, easy and that has been widely validated for different chronic diseases and can be used to evaluate the adherence to antihypertensive drugs in real-world settings. The 8-item scale was originally studied on hypertensive patients and the results revealed it to be a reliable tool that showed significant correlation with BP control.

The prevalence of adherence differs depending on countries and regions; it may also be due to cultural, socio-economical and ethnic differences. Thus, in order to know the epidemiology of each country it is necessary to design local strategies aimed at improving the level of adherence on patients in the "real world" setting. The MMAS-8 test reliable approach that can help practitioners to estimate the level of adherence within their patients. It could also provide some clues regarding the mechanism that generates lack of adherence, improving the possibility to select a specific strategy for each patient.

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Introduction

The main cause of mortality in the world is cardiovascular disease and hypertension is the leading risk factor for its development [1]. Thus, an appropriate and opportune diagnosis and control of hypertensive individuals is a cornerstone to decrease cardiovascular morbidity and mortality.

Around the word, the level of control of hypertension is low [2]. Lack of adherence is an important obstacle to hypertension control within the community and it becomes an important barrier against the effective management of hypertensive individuals [3,4]. However, evaluating the adherence of an individual patient could be a challenge for a physician. In this revision, we analyze the utility of self-reference questionnaires to accomplish this task.

Definition and Evaluation

Medication adherence is defined by the World Health Organization (WHO) as "the degree to which a person's behavior corresponds with the agreed recommendations from a health care provider". The WHO estimates that the prevalence of non-adherence to antihypertensive medication is between 30 and 50%, depending on drug-class, type of prevention and adherence measurement methods [2].

The methods to assess adherence can be direct or indirect. Although direct methods have greater accuracy, the high costs and lack of availability of this method have limited their utility. Conversely, indirect methods are easy to use in daily medical practice [5].

Between indirect methods, the 8-item Morisky Medication Adherence Scale (MMAS-8) is a simple test that has been widely validated for different chronic diseases and can be used to evaluate the adherence to antihypertensive drugs in real-world settings. In 1986, a 4-item scale was introduced and this 4-item scale was then revised and updated in 2008 to

additionally encompass the adherence behavior of the respondents. The 8-item scale was originally studied on hypertensive patients and the results revealed it to be a reliable tool that showed significant correlation with BP control.

Table 1. The 8-items Morisky Medication Adherence Scale (MMAS-8).

Characteristics	Response
1. Do you sometimes forget to take your medication?	Yes/No
2. People sometimes miss taking their medications for reasons other than forgetting. Over the past 2 weeks, where there any days when you did not take your medication?	Yes/No
3. Have you ever cut back or stopped taking your medication without telling your doctor because you felt worse when you took it?	Yes/No
4. When you travel or leave home, do you sometimes forget to bring your medication?	Yes/No
5. Did you take all your medication yesterday?	Yes/No
6. When you fell like your symptoms are under control, do you sometimes stop taking your medication?	Yes/No
7. Taking medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	Yes/No
8. How often do you have difficulty remembering to take all your medication?	Never/Rarely
	Once in a while
	Sometimes
	Usually
	All the time
The MMAS-8can range from 0 to 8, with scores of <6, 6 to <8 and 8 reflecting low, medium and high adherence, respectively.	

The questions are shown in Table 1. To rate each answer, response choices are yes/no for items 1 to7 and a 5‑point Likert response scale for the last item. Each "no" response is rated as "1," and each "yes" response is rated as "0" except for item 5, in which each "yes" response is rated as "1" and each "no" response is rated as "0." For item 8, if a patient chooses the response "Never/Rarely," the score is "1" and if they choose the response "All the time," the score is "0." Responses "Once in a while," "Sometimes," and "Usually" are rated "0.75, 0.75, and 0.25," respectively. In this manner, MMAS-8 allows to differentiate two types of behavior for the individual which does not consume the indicated medication. While questions 1, 2, 4 and 5 are related to involuntary forgetfulness, questions 3, 6, and 7 are related to a voluntary decision to interrupt the treatment [5,6].

MMAS-8 is the most widely used way to assess adherence level. Score can range from zero to eight and has previously been trichotomized into three levels of adherence in order to facilitate its use in clinical practice: high adherence-MMAS score 8; medium adherence-MMAS scores 6 to <8; and low adherence-MMAS scores <6. Prior research has revealed that this new scale is significantly associated to blood pressure control in patients with hypertension [5,6].

Prevalence Adherence

The prevalence of adherence differs depending on countries and regions. Although this could represent methodological issues, it may also be due to cultural, socio-economical and ethnic differences. Thus, in order to know the epidemiology of each country it is necessary to design local strategies aimed at improving the level of adherence on patients in the "real world" setting.

A meta-analysis performed by Naderi et al. evaluating adherence to antihypertensive drugs in 376,162 patients from 20 studies estimated a global adherence of 57% [7]. However, the adherence varies widely among different regions or countries. In this regard, a recently published meta-analysis, including studies performed in Africa (6 studies; n=1277) and Asia (8 studies; n=5917), America (9 studies; n=4982) and Europe (2 studies; n=452), showed a variable level of adherence for different countries and continents. African individuals presented the lowest adherence 47.5%, while Asia, Europe and America presented an adherence of 56.5%, 62.9% and 63.4% respectively. Recently, we have performed a multicenter cross-sectional study in 13 cities in Argentina, which showed similar values (59%) [8].

Several studies have suggested that ethnic origin could interfere with the level of adherence to antihypertensive

treatment, being the black race less adherent than the white race. However, ethnicity by itself is probably not enough to explain levels of adherence, and psychosocial factors could be of major importance.

There is a discussion regarding relationships between age and medication adherence. Several studies [9-11] have demonstrated that medication adherence on hypertensive patients increases with age, which can be explained by the presence of comorbidities; very ill patients probably have further perception of their disease and they therefore may be prone to pay due attention to the prescribed treatment [12,13]. On the other hand, many factors related to aging can interfere with adherence in elderly patients (such as cognitive impairment or coexistence of frailty).

Reasons for Non-Adherence

A review of 21 clinical studies found that adherence to antihypertensive therapy drops with time from diagnosis, with about half of the patients discontinuing treatment after one year [14].

A systematic review of randomized controlled trials of medication adherence interventions concluded that most strategies have not been successful at improving neither adherence nor clinical outcomes [12,15]. This widens the need to identify risk factors contributing to low medication adherence. Factors contributing to the lack of adherence to antihypertensive drugs could be grouped into 5 categories: patient-related, condition-related, therapy-related, health system–related and socioeconomic factors.

Patients may have a poor understanding or may lack awareness of the long-term consequences of elevated BP or of the importance of BP control, particularly because hypertension is often asymptomatic and life-long [15]. One of the most important aspects related to the patient is the level of education. The importance of this matter is shown in a study of adherence within a cohort of individuals with hypertension performed in Argentina. The study found that in the multivariate regression model, higher education levels (completed high school or higher) had a strong protective effect against lower-medium level of adherence (OR 0.37, 95%CI 0.28-0.49, p<0.001) [8].

Another factor that can alter the level of adherence is the cognitive state and the mental pathologies individuals may present. A recent systematic review of 15 studies concluded that individuals with cognitive impairment had lower rates of medication adherence compared to those without cognitive impairment [16]. Furthermore, the Cohort Study of Medication Adherence among Older Adults (CoSMO), a prospective cohort study of 2,194 older adults with hypertension, examined the barriers against antihypertensive adherence and their clinical outcomes [17]. Participants with low compared with high cognitive functioning were 2.71 times more likely to have low medication adherence. Likewise, the Framingham Heart Study evaluated risk factors for medication adherence and the relationship between adherence and levels of CVD risk

factors among older hypertensive participants [18]. This study showed that depressive symptoms were associated to an increased likelihood of low medication adherence.

We have shown that in a multicenter study, forgetfulness was the most frequent cause of no-adherence. Involuntary forgetfulness was more frequent in low-medium adherence than the voluntary decision to interrupt treatment (82.9% vs 30.5%, respectively). Remarkably, despite the high prevalence of involuntary forgetfulness, 67.5% of the non-adherent patients said that they "never forget their medications" (question 8, MMAS-8), thus demonstrating the lack of perception regarding treatment and reinforcing the association between education and adherence [8].

Other factors contributing to poor adherence are therapy-related. Complex medication regimens-multiple drugs and/or multiple doses per day-have shown to decrease adherence in Cochrane Controlled Trials Register [19]. This meta-analysis included 38 studies with 15519 patients with follow-up durations ranged from two to 60 months and showed that simplifying dosing regimens increased adherence from 8% to 19.6%.

Likewise, the initial choice of therapy, either a monotherapy or a combination regimen, can affect adherence [20]. A study performed on patients who were newly diagnosed with hypertension showed that 46.8% of patients with monotherapy vs 23.8% with combination regimen remained on what was initially prescribed within 1 year. Furthermore, treatment with antihypertensive drugs combined on a single pill improves adherence compared to the use of multiple drugs per separate. A study including 81 958 patients compared 1 prescription of a single-pill with a combination of antihypertensive drugs vs2-pill free-dose combinations and showed that the rates of treatment cessation were higher for free-dose combinations [21].

Numerous studies of antihypertensive agents published over nearly a decade have consistently demonstrated higher persistence rates on some classes. Meta-analyses (including 18 studies involving 631,579 patients) found the following rank order of discontinuation of original antihypertensive drug after 1 year: diuretic >b-blocker >CCB >ACE inhibitor >ARB [22]. Moreover, a meta-analysis of 26 studies showed that patients using diuretics were less adherent than those treated with ACEIs, ARBs and CCBs [23]. Similarly, in our study the multivariate analysis showed that diuretics use was independently associated to lower adherence (0.60 0.45-0.80<0.001) [8].

The influence of economic factors on adherence is difficult to estimate. Patients with hypertension treatment on research protocol study (receiving medications free-of-charge) have higher levels of blood pressure compared to those outside of the research setting [24]. Recent surveys show that up to 32% of older adults take less medication than prescribed in order to avoid costs [25]. Patients who reduce medical costs by taking their medications sporadically, splitting pills, or delaying refills do not achieve the full therapeutic benefits of therapy and may be at

increased risk of declining health [26]. A meta-analysis showed that not having prescription drug coverage represents a significant and robust risk factor for non-adherence. Furthermore, having any type of prescription drug coverage consistently reduced the risk of discontinuing treatment. This was confirmed using data of 17,685 Medicare beneficiaries, in which individuals who did not have coverage were less adherent [27].

Strategies to Improve Adherence

Adherence to antihypertensive drugs involves multiple factors; being able to know these, allows multidisciplinary interventions aimed not only at the patient, but at their entire environment. It has been shown that interventions with more than one technique (involving specially trained nurses, combination of home visits, education and special dosing devices) increased adherence from 5% to 41% [28-30].

Physicians should individualize antihypertensive regimens, considering the degree of BP elevation and cardiovascular risk, as well as accompanying diseases and chronically used drugs. On another hand, involving the patient in treatment decisions, as well as ensuring that the patient understands the consequences of hypertension and the importance of their treatment, providing an adequate follow-up and modifying the regimen is necessary to achieve the BP target level.

However, we have shown that (in Argentina at least) the lack of adherence was more frequently due to forgetfulness of the medication intake [8]. In consequence, the use of reminders such as alarms, telemedicine, prescription of fixed combinations and less complex regimens could improve adherence specifically in our population.

Finally, having a high level of education (graduated from high school or higher) seems to be an important factor for achieving good adherence to chronic treatments. Yet, the cost of the drugs negatively influences the level of adherence. Therefore, socio-economic political initiatives must accompany the individual strategies that each doctor should carry out with its patient, in order to improve adherence to treatment and consequently improve BP control, reducing cardiovascular morbidity and mortality.

Conclusion

The MMAS-8 test is a low-cost, easy and reliable approach that can help practitioners to estimate the level of adherence within their patients. It could also provide some clues regarding the mechanism that generates lack of adherence, improving the possibility to select a specific strategy for each patient.

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