

ORIGINAL ARTICLE

Validity of four indirect methods to measure adherence in primary care hypertensives

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High blood pressure (HBP) is one of the most important risk factors for morbidity and mortality in the world. Non-adherence to medication is associated with the lack of control of HBP. The objective of this study was to assess the validity of four indirect methods for measuring adherence to medication to control HBP in primary health care. A random sample of 120 hypertensive patients who were undergoing treatment for at least 2 months in a primary care unit in Florianópolis (Brazil) were included in the study. The independent variables were four indirect methods to measure adherence to medication: knowledge regarding the HBP medication, the blood pressure level, attitude regarding the medication intake (Morisky–Green test) and self-reported adherence. The classification of HBP was based on criteria established by the Brazilian Ministry of Health.

The gold standard used for measuring adherence was the pill count. Logistic regression was used to estimate sensitivity (highest value of 88.2% for self-report), specificity (highest value of 70.7% for HBP control), positive predictive value (highest value of 46.4% for HBP control) and negative predictive value (highest value of 79.1% for Morisky–Green test) for each of the indirect methods. No indirect method of measuring adherence had a good positive predictive value for adherence, which was best predicted by patients' age and whether they managed to control HBP. The results also revealed low treatment adherence (31.2%) and low control of HBP (37.6%). Non-adherence was mainly associated with side effects of the treatment.

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Introduction

Non-adherence to medication for systemic high blood pressure (HBP) is a significant public health problem that is complex because it encompasses various factors.¹ It is one of the leading current causes of the lack of control of HBP and has implications on morbidity and mortality.¹ According to the 'Law of the Halves', half of the patients have knowledge of their HBP, half of these use medication and half of the latter have their HBP under control.²

Although numerous methods for measuring medication adherence in research settings have been published,^{3–6,8} reliable, inexpensive and easy-to-apply approaches for its measuring in primary health care are not readily available,⁵ and its

assessment in clinical practice is not routinely performed.² Direct methods of measuring adherence such as directly observed therapy (DOT) or biological assays have been found impractical even in clinical trial settings⁴ due to patient's difficulty in observing the monitoring procedures which considerably interfere with daily activities. In addition, large variability between subjects was noticed in clearance of some candidate biological markers in direct methods.² An electronic system that records the date and time of opening the hypertension medication container was also found to be impractical from the patients' point of view.⁴ In a community-care setting, these difficulties in measuring adherence by direct methods are likely to be even greater.

On the other hand, indirect methods for measuring adherence to hypertension treatment include pill counts, therapeutic outcome (e.g. controlling the HBP), self-report, appointment keeping, physician or family (collateral) report, electronic monitoring and physiologic parameters. A rare study comparing

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several indirect methods found low-to-moderate correlations and great variation in adherence between them.⁴

The study conducted by Strelec *et al.*⁷ in Brazil aimed at assessing the relation between blood pressure (BP) control and the following: (a) patient's self-report on medication intake as defined in the Morisky–Green test; (b) patient's knowledge about his/her disease and its treatment; (c) patient's attitude towards side effects of medication intake; (d) patient's attendance at medical consultations; and (e) the physician's opinion. However, this study presented a possible bias in selection by neither specifying whether the population studied was of hospital or primary care origin nor whether all patients accompanied in the public or private health-care system had the same chance of being selected for the study.⁷

Despite being widely used in both clinical trial and community-care settings, the evidence of diagnostic performance of indirect methods of adherence to hypertension medication has been very scarce. The main goal of this study was to determine the sensitivity, specificity and predictive value of four indirect methods to measure adherence to medications in patients with HBP at a primary care centre. The meaning of 'adherence' here is essentially the same as 'patient compliance' used in much of the medical literature.

Methods

A transversal study was conducted with a 1-month interval between its two stages. The aim was to compare diagnostic methods of adherence to medication in a population with HBP at a primary care centre in the municipality of Florianópolis, in the federal state of Santa Catarina, Brazil. There were 342 315 inhabitants distributed in 48 primary health centres in Florianópolis. The study was conducted in the second major primary care centre in the northeast of the city. A simple random sampling was conducted with patients with mild or moderate stage of HBP (diastolic BP between 90 and 109 mm Hg, or systolic BP between 140 and 179 mm Hg, or both)^{8,10} who had been undergoing pharmaceutical treatment for at least 2 months and agreed to take part in the study by signing a written informed consent. These patients were identified from the records kept by health visitors and from the records of HBP patients at the local health centre.

Exclusionary criteria included the coexistence of mental illness, such as serious depression, advanced Alzheimer's disease and grave personality disorders, as well as serious organic diseases that would prohibit participation in the research.

Since the object of the study was not to measure the strength of the association between the risk factors and non-adherence, the required size of the sample was estimated based on adherence

prevalence of 50%,^{4,5} type I error of 5%, maximum acceptable difference of 10% and allowing loss of 20% of subjects. Under these conditions, the final sample size was estimated at 121 patients.

The data collection included the application of a structured questionnaire that considered identifying factors, socio-economic situation and variables related to adherence to medication such as duration of disease, cigarette smoking, alcohol consumption, the number of medications, the cost of medication, side effects of the medication, the search for health services, perception of the disease, family history of HBP, salt intake, physical activity and visits from health visitors.

The dependent variable of the study was adherence to medication quantified by the percentage of pills remaining in a bottle issued to the patient. It was assumed that the missing pills were ingested by the patient. Adherence was considered to be the ingestion of 80–110% of the pills, and non-adherence to be any value above or below these amounts.⁸ The independent variables were the four indirect methods: (a) degree of control of HBP on the second visit; (b) knowledge about BP medication, defined as patient capacity to correctly identify antihypertensive medication among the medications prescribed; (c) self-report on adherence defined by answering 'yes' or 'no' to the question 'You think you took your antihypertensive medication as prescribed by physician in the last month'; and (d) the attitude of the patients in relation to their medication as defined in the Morisky–Green test.⁹ The test comprised four questions to be answered with 'yes' or 'no': (1) Have you ever forgotten to take your medicine? (2) At times are you not careful about taking your medicine? (3) When you feel better, do you sometimes stop taking your medicine? (4) At times, if you feel worse when you take your medicine, do you stop taking them? A person was considered to be non-adherent if he/she responded affirmatively to at least one question.

The first visit was conducted at the local health centre. A structured questionnaire was administered with details on age, sex, race, marital status, educational level, family income, duration of disease, cigarette smoking, alcohol consumption, the number of medications prescribed, knowledge about BP medication, the cost of medication, its side effects, the use of health services, perception of the disease, family history of HBP, salt intake, physical activity and the number of visits from health visitors. BP was taken and anthropometric data were recorded on this occasion. The second visit was conducted in the same local health centre 25 days later. Pills were counted and the Morisky–Green test was applied. BP was also measured on this occasion.

The BP measurement technique followed the recommendations of the current Brazilian Guidelines on Blood Pressure.¹⁰ A pre-calibrated Tycos Lifetime aneroid sphygmomanometer was used to

measure the BP. A patient was considered to have HBP if the systolic–diastolic BP was equal or higher than 140–90 mm Hg. Values below this were considered to indicate good control of BP.

A univariate and multivariate logistic regression was conducted with the Stata 9.0, considering statistically significant a type I error lower than 0.05.

The work was approved by the ethics committee of the Federal University of Santa Catarina and by the Municipal Health Secretary of Florianópolis. All of the patients signed a Free and Informed Consent Agreement.

Results

Of the 120 patients initially selected, 109 completed the study with non-response rate of 8.2%. Ten patients were lost to follow-up and one patient was excluded because of erroneous classification of HBP.

Majority (53.7%) of the patients were over 60 years of age, female (71.6%), Caucasians (85.3%), with less than 4 years of formal education (56%).

The adherence found in this study was 31.2%. Only 37.6% of the patients had good BP control at the time of the study according to the standards used for BP lower than 140/90.⁷

Upon comparing adherence to medication, defined by pill counts, among the risk and comorbidity factors in univariate analysis, the preponderant factor was the presence of side effects of medication that decreased adherence almost seven times when compared with the groups without side effects (Table 1). Another significant result was that the people who initiated the use of medication 2–5 years earlier had more than three times lower chance of adhering to the treatment when compared to the patients who began treatment 10–15 years ago.

Among the indirect methods for the evaluation of adherence to medication, only BP control had a statistically significant association with adherence in univariate logistic regression (Table 2). Patients who did not have good control of their HBP had three times lower chance of adhering to the treatment when compared with those who did ($P=0.008$). The patients who had a negative attitude about HBP (Morisky–Green test) had a lower chance of adherence to treatment in comparison with those who had a positive attitude, but this was only marginally significant ($P=0.06$).

Control of HBP had the lowest sensitivity (55.9%) and the greatest specificity (70.7%) among the four indirect methods, as well as the highest positive predictive value (46.4%) and a reasonable negative predictive value (77.9%) (Table 3). This indicates that once HBP is well controlled, the chance that the patient would truly have good adherence to the medication is 46.4% and if the patient does not have HBP under control, the chance that he/she is not adhering is 77.9%. Self-report has the highest

Table 1 Medication adherence and clinical risk factors

Independent variables	Adherence				Total	
	Yes		No		n	%
	N	%	n	%		
<i>Initiation of HBP</i>						
<5 years	10	23.8	32	76.2	42	38.5
5–10 years	12	34.3	23	65.7	35	32.1
10–15 years	5	50.0	5	50.0	10	9.2
>15 years	7	31.8	15	68.2	22	20.2
<i>Use of medication</i>						
<2 years	12	40.0	18	60.0	30	34.1
2–5 years	4	12.9	27	87.1	31	35.2
5–10 years	9	33.3	18	66.7	27	30.7
>10 years	9	42.9	12	57.1	21	23.9
<i>Medications per day</i>						
1–3	12	30.0	28	70.0	40	36.7
4–6	18	38.3	29	61.7	47	43.1
>6	4	18.2	18	81.8	22	20.2
<i>Paying for medication</i>						
Yes	29	32.2	61	67.8	90	82.6
No	5	26.3	14	73.7	19	17.4
<i>Medication side effects</i>						
Yes	1	5.3	18	94.7	19	17.4
No	33	36.7	57	63.3	90	82.6
<i>Spoons of salt per day</i>						
<1	21	36.2	37	63.8	58	53.2
1–2	7	25.9	20	74.1	27	24.8
≥3	6	25.0	18	75.0	24	22.0
<i>Health visitor last month</i>						
No visits	21	28.0	54	72.0	75	68.8
1–3 visits	13	39.4	20	60.6	33	30.3
4–5 visits	0	0.0	1	100.0	1	0.9

Abbreviation: HBP, high blood pressure.

sensitivity (88.2%) and the lowest specificity (18.7%) among the indirect methods.

The multivariate logistic regression showed that the patients with controlled HBP had nearly five times greater chance of having adhered to the treatment compared with those who did not control HBP, after accounting for age (Table 4). Adherence also increased with age, principally after 60, when it was more than five times that of those from 35 to 60 years of age. Nevertheless, even among patients older than 60 years, 2 in 3 were not adhering to the treatment if their BP was not controlled (Figure 1).

The multivariate logistic model showed a satisfactory fit when checked by Hosmer and Lemeshow test ($\chi^2=4.09$ with three degrees of freedom and associated P -value of 0.25) and by distribution of standardized residuals within normal range (details not shown). The interaction between controlling HBP and age was also tested but was complicated by colinearity between the two, leading to a dubious convergence of the statistical model. The latter was therefore disregarded.

Table 2 Relationship between medication adherence and indirect methods using simple logistic regression, with corresponding 95% CI and P-values

Independent variables	Adherence				Total		OR and 95% CI		P-values
	Yes		No		n	%			
	N	%	n	%					
<i>HBP control</i>									
Controlled	19	46.3	22	53.7	41	37.6	1.00 ^a	0.14–0.76	0.008
Not controlled	15	22.1	53	77.9	68	62.4	0.33		
<i>Knowledge of HBP medication</i>									
Yes	28	30.8	63	69.2	91	83.5	1.00 ^a	0.33–3.70	0.830
No	6	33.3	12	66.7	18	16.5	1.12		
<i>Self-report</i>									
Yes	30	33.0	61	67.0	91	83.5	1.00 ^a	0.18–1.92	0.360
No	4	22.2	14	77.8	18	16.5	0.58		
<i>Morisky–Green test</i>									
Positive attitude	25	37.9	41	62.1	66	60.6	1.00 ^a	0.16–1.14	0.060
Negative attitude	9	20.9	34	79.1	43	39.4	0.43		

Abbreviations: CI, confidence interval; HBP, high blood pressure; OR, unadjusted odds ratio.

^aReference category.**Table 3** Percentage values of sensitivity, specificity and PPV and negative NPV for four indirect methods tested

	Adherence		Diagnostic parameters							
	Yes	No	Sensitivity		Specificity		PPV		NPV	
	n	n	%	95% CI	%	95% CI	%	95% CI	%	95% CI
<i>HBP control</i>										
Controlled	19	22	55.9	38.1–72.4	70.7	58.9–80.3	46.40	31.0–62.4	77.9	65.9–86.7
Not controlled	15	53								
<i>Knowledge of HBP medication</i>										
Yes	28	63	82.4	64.8–92.6	16.0	8.9–26.7	30.8	21.7–41.4	66.7	41.2–85.6
No	6	12								
<i>Self-report</i>										
Yes	30	61	88.2	71.6–96.2	18.7	10.9–29.7	33.0	23.7–43.7	77.8	51.9–92.6
No	4	14								
<i>Morisky–Green test</i>										
Positive attitude	25	41	73.5	55.3–86.5	45.3	33.9–57.2	37.9	26.5–50.7	79.1	63.5–89.4
Negative attitude	9	34								

Abbreviations: CI, confidence interval; HBP, high blood pressure; NPV, negative predictive value; PPV, positive predictive value.

Discussion

The adherence to hypertension medication in this study was 31.2%, which is just below the lower value of the reported adherence range of one-third to one-half of the patients with HBP.^{1,2,5,6} It is also noticeable that more than two-thirds of the population studied did not receive any visit from a health visitor in the previous month.

The higher the number of pills to be taken per day, the lower the chance that the patients studied would adhere to treatment. This result is consistent with

that of the other study,⁷ although it was not statistically significant. We also found similar results that suggest that side effects of the medication are the principal cause of non-adherence.⁹

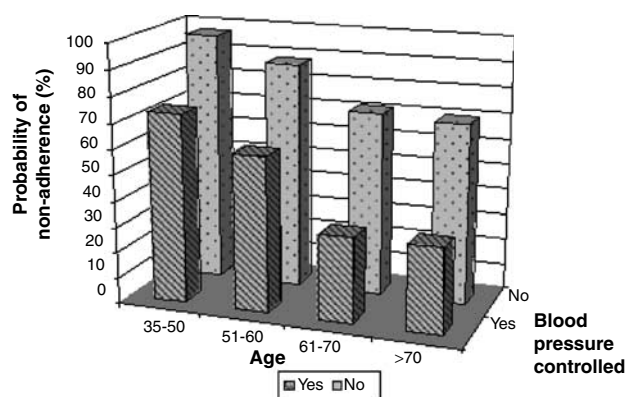
Very few studies about the diagnostic performance of the Morisky–Green test have generated conflicting results. Although in this study the association between the result of the test and adherence to medication was marginally significant, another study clearly confirmed this association.⁸ We found values that conflicted with the latter: a sensitivity of 32% (compared with 73.5%), specificity of 94%

Table 4 Relationship between medication adherence and risk factors using multiple logistic regression, with corresponding 95% CI and *P*-values

Risk factors	N	OR	95% CI	<i>P</i> -values
<i>Control of HBP</i>				
No	67	1.00 ^a		
Yes	41	4.88	1.82–14.29	0.002
<i>Age</i>				
35–50 years	19	1.00 ^a		
51–60 years	31	1.73	0.40–7.50	0.463
61–70 years	34	5.26	1.24–22.30	0.024
> 70 years	24	5.43	1.14–25.95	0.034

Abbreviations: CI, confidence interval; HBP, high blood pressure; OR, unadjusted odds ratio.

^aReference category.

**Figure 1** Probability of non-adherence based on multivariate logistic regression.

(compared with 45.3%), positive predictive value of 91.6% (compared with 37.9%) and negative predictive value of 42% (compared with 79.1%). The differences in diagnostic performance may be due to the differences between settings (clinical trial versus primary care health centre) and the time span of three decades between the studies. A recent validation study⁴ used correlations instead of sensitivity and specificity measures for Morisky–Green and other indirect methods of medication adherence, thus preventing a direct comparison with present study results.

A particularly troublesome finding was the lack of adherence to medication of 78% of patients with HBP from 35 to 60 years of age. This group accounted for 46% of those studied. The consequence of non-adherence was a lack of HBP control. Community health programmes should give special attention to this segment of the population, given that the high risk of non-controlled HBP in this group is rarely perceived.

Although the random sampling of the participants and the control of confounding variables in the data analysis have been strategies used to assure the internal validity of the study, some limits should be recognized. First, although the pill count is widely

used as gold standard in adherence validation studies, it is likely to overestimate the adherence.³ Direct methods such as biological assays or DOT may be more accurate than assuming that the pills were really ingested, although the applicability of these methods seems limited in primary care settings. Another possible limitation of this study is the short time between the initial and final visit. Although the same period was adopted by other authors⁹ and considered sufficient to evaluate adherence to medication, and although we selected patients who were using medication for more than 2 months, the regular use of medication can vary over time. Nevertheless, since nearly two-thirds of the sample in this study had used medication for more than 2 years, this factor was not likely to interfere significantly with the results. To minimize the Hawthorne effect, the patients were not informed that their pills would be counted, as this information could cause a systematic error of interference in their conduct because of their awareness that they were being studied. Nevertheless, it is possible that the perception of some patients about the study acted as an evaluative bias. Finally, the external validity of the study may be limited, because the characteristics of the population studied may be different from those in other areas.

Recent research directions in measuring antihypertensive medication adherence include development of reliable instruments⁵ and explicit criteria for the hypertension guidelines.⁶ It is essential that these efforts account for known influences on adherence, which include severity of HBP, comorbidity, age, health system barriers and physician knowledge and attitude.⁶ In addition, external validity of adherence questionnaires should be evaluated in primary care setting and expressed in terms of diagnostic performance measures such as sensitivity and specificity, thus providing a better

What is known about this topic

- Non-adherence to medication for systemic HBP is a significant public health problem as only about half of the patients use the medication as prescribed.²
- Very few studies that validated indirect methods of measuring adherence to antihypertension medication were conducted in a clinical trial setting, thus limiting their generalizability to primary care setting.
- There is a lack of diagnostic performance indicators such as sensitivity, specificity and predictive values of indirect measures of adherence to antihypertension medication.

What this study adds

- This study provides diagnostic performance indicators of indirect measures of adherence to antihypertension medication in a primary care setting, using random sampling and adjusting for many factors known to influence adherence.
- The study showed that none of the four indirect methods to measure adherence had satisfactory diagnostic performance and pointed to the utility of objective measures such as patient age and failure to control HBP.

Abbreviation: HBP, high blood pressure.

sense of its value in medical practice than correlations with other similar measures.

It was concluded that adherence to medication was low in the study population and that none of the indirect tests were good prognostic indicators of adherence. However, controlling HBP and patient age were found to be the most effective indicators of adherence. Among the associated risk factors, the absence of side effects was the best prognostic indicator of adherence to medication. Therefore, the reduction in these effects could have great potential for improving adherence to medication among hypertensive patients.

References

- 1 WHO. *Adherence to Long-Term Therapies: Evidence for Action*. World Health Organization: Geneva, 2003.
- 2 Pedoe HT. Hypertension. In: Miller DL, Farmer RDT (eds). *Epidemiology of Diseases*. Blackwell Scientific Publications: London, 1982, pp 122–135.
- 3 Braam RL, van Uum SH, Russel FG, Swinkels DW, Thien T. Bromide as a marker to measure adherence to drug therapy. *Eur J Clin Pharmacol* 2006; **62**: 285–290.
- 4 Hamilton GA. Measuring adherence in a hypertension clinical trial. *Eur J Cardiovasc Nurs* 2003; **2**: 219–228.
- 5 Krousel-Wood M, Muntner P, Jannu A, Desalvo K, Re RN. Reliability of a medication adherence measure in an outpatient setting. *Am J Med Sci* 2005; **330**: 128–133.
- 6 Milchak JL, Carter BL, Ardery G, Black HR, Bakris GL, Jones DW et al. Development of explicit criteria to measure adherence to hypertension guidelines. *J Hum Hypertens* 2006; **20**: 426–433.
- 7 Strelec MAAM, Pierin AMG, Mion Jr D. The influence of patient's consciousness regarding high blood pressure and patient's attitude in face of disease controlling medicine intake. *Arq Bras Cardiol* 2003; **81**: 349–354.
- 8 Sackett DL, Haynes RB, Gibson ES. Randomized clinical trial of strategies for improving medication compliance in primary hypertension. *Lancet* 1975; **1**: 1205.
- 9 Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 1986; **24**: 67–74.
- 10 Gomes MAM, Nobre F, Amodeo C, Kohlmann Jr O, Praxedes JN, Machado CA et al. IV Brazilian Guidelines on Hypertension. *Arq Bras Cardiol* 2004; **82**(Suppl 4): 7–14.