Patient Education and Counseling 101 (2018) 1654–1660

Contents lists available at ScienceDirect

Patient Education and Counseling

journal homepage: www.elsevier.com/locate/pateducou

Validation of the electronic prescription as a method for measuring treatment adherence in hypertension

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ARTICLE INFO

Article history:
Received 7 November 2017
Received in revised form 18 April 2018
Accepted 21 April 2018

Keywords:
Medication adherence
Patient compliance
Health promotion
Primary health care
Hypertension

ABSTRACT

Objective: To validate electronic prescriptions (e-prescriptions) as a method for measuring treatment adherence in patients with hypertension.
Methods: This prospective study initially included 120 patients treated for hypertension in primary care centers. Adherence was measured using the gold standard, the medication event monitoring system (MEMS), versus the index test, the e-prescription program, at baseline and at 6, 12, 18 and 24 months. We calculated the adherence rate using the MEMS and the medication possession ratio (MPR) for the e-prescriptions. We considered patients adherent if they had an adherence rate of 80% to 100%. To validate the e-prescription, we obtained measures of diagnostic accuracy, the Kappa concordance index, and the area under the ROC curve (AUC).
Results: We included 102 patients. Overall adherence was 77.4% by MEMS (95%CI: 66.8-88) and 80.4% (95%CI: 70.3-90.5) by MPR. At 24 months, sensitivity was 87% and specificity, 93.7%. The AUC was 0.903 (95%CI: 0.817-0.989).
Conclusion: Measures of treatment adherence were not significantly different between e-prescription and gold standard at most visits, and the e-prescription showed good discriminatory diagnostic capacity.
Practice implications: If patients are included in an e-prescription program for at least 2 years, e-prescription is an inexpensive method to measure adherence in hypertension.

1. Introduction

Control of hypertension, together with control of different vascular risk factors, is essential for preventing cardiovascular disease [1,2], which have a great impact on society in terms of both morbidity and mortality [3,4]. Achieving good control of blood pressure (BP) requires knowing the possible causes associated with poor control. Among the main causes are therapeutic inertia [5,6] and non-adherence to treatment [7]. The World Health Organization (WHO) defines adherence as "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" [8]. Adherence to medication is a crucial part of patient care and indispensable for reaching clinical goals [9]. There are many reasons why patients do not take their medication properly, such as forgetfulness, changes in dosage, and time periods when they do not experience symptoms. Indeed, sometimes the patient is not even aware of being non-adherent [10]. Accurate estimates of medication adherence will provide better evidence on the consequences, predictors/risk factors, and strategies to improve medication adherence [9].

Diagnosing non-adherence is complex, and there are no completely reliable or universally applicable methods that can be used in daily practice [11]. An ideal medication adherence measure should be low-cost, user-friendly, easy to carry out, highly

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[1] All authors have approved the final version of the manuscript.

https://doi.org/10.1016/j.pec.2018.04.009
0738-3991/

reliable, flexible, and practical [12]. The medication event monitoring system (MEMS) is one of the more reliable methods to measure adherence, but it is expensive to use. Thus, accurate indirect methods to measure adherence are needed.

Electronic prescriptions (e-prescriptions) are emerging as an important strategy to enhance the safety and quality of the prescribing process, for example in the United States [13,14]. This system allows for prescribing the most medically appropriate and cost-effective prescription at the point of care and transmitting the prescription electronically to the patient's preferred pharmacy [15]. At the end of 2010, over 230,000 physicians and other clinicians, or about one-third of practicing physicians, were actively e-prescribing [16]. Prescription refill records and electronic lids on medication containers provide similar estimates of overall adherence [17], and Porterfield et al. [14] has suggested that e-prescribing has the potential to increase patient safety and medication adherence. This measure of adherence assumes that prescription refilling corresponds to medication-taking behaviour, and that patients are taking drugs according to prescription. This low-cost method can identify patients at risk for treatment failure, show medication-refilling patterns and provide third-party verification of data [9].

Since the advent of e-prescribing [16] and, subsequently the use of the XXI Prescription (Receta XXI) program in Andalusia (Spain) [18], health professionals in this context have been able to use this electronic prescribing system as a tool to measure adherence in chronic disease. However, its validity as a method for measuring adherence is unknown.

In the primary care setting, clinician assessments and self-report are still the most commonly used methods to measure adherence [19]. These indirect methods are cheap and easy to administer, but they are also the least reliable, have poor sensitivity and specificity, and can depend on interviewers' communication skills and the questionnaire design [9]. Given these shortcomings, XXI Prescription may be a good alternative for use in medical consultation to rule out therapeutic non-adherence before making treatment decisions. Therefore, the aim of this study was to validate the e-prescription (XXI Prescription) as a method for measuring adherence to antihypertensive therapy in the treatment of mild-to-moderate hypertension in primary care.

2. Methods

This prospective, longitudinal, multicenter health outcomes research study took place in two primary care centers in Andalusia, Spain, and involved 12 primary care physicians (PCP). The study included outpatients who met the following criteria: aged 40 to 80 years; diagnosed with mild to moderate essential hypertension (mean sitting systolic BP/mean sitting diastolic BP, mild: 140–159/90–99 mmHg, moderate: 160–179/100–109 mmHg) according to the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC), ESH-ESC 2013 [1]; on antihypertensive therapy; with the diagnosis of hypertension registered in the medical record and incorporated in the e-prescription program at least three months before study baseline; and gave their written consent. Exclusion criteria were: pregnant or breastfeeding; disabling diseases (e.g. dementia, Alzheimer's disease, neurological diseases, terminal cancer, disabling heart disease); inability or unwillingness to give informed consent; participating in other research studies; or living with someone taking the same antihypertensive medications.

The study began in January 2010 and concluded in December 2012. The enrollment period was six months, and mean follow-up was two years. Patients visited the health center five times: at enrollment (baseline) and at 6, 12, 18, and 24 months. At the enrollment visit, each PCP obtained informed consent and took the medical history, recording in a data entry form patients' weight, height, waist circumference and the average of two BP readings taken with sphygmomanometer on the same arm. At this visit each patient was given a medication event monitoring system (MEMS) for each antihypertensive drug prescribed in the XXI e-prescription. The use of the MEMS was explained in accordance with the health center protocol on their use.

Variables were recorded again at each follow-up visit, with patients bringing their medication bottle to all visits for a computer reading. One PCP from each primary health center was designated to conduct follow-up visits in study patients from each center. The investigator downloaded and subsequently analyzed the MEMS reading using a computer program. The number of times the bottle was opened was validated, eliminating any erroneous openings. The drug dispensing records on Diraya, which is the digital medical record used in the Autonomous Community of Andalusia, were noted from the dispensation module in the pharmacy. This module allows pharmacists to retrieve the medication prescribed to the patient and also receive the information regarding the medication actually dispensed. Failure to achieve the therapeutic objectives [1] was reported to the attending physician, and if the physician prescribed a different drug, this was replaced in the MEMS bottle by the patient. At the final visit the MEMS bottles were collected.

Treatment adherence was measured by both the MEMS, as the gold standard [9], and by the e-prescription program (XXI Prescription), as the index test. In order to validate the e-prescription, its data were compared with the pill count using MEMS in a 2×2 table, and indicators of validity were calculated.

The investigator performed data entry, and the following variables were analyzed: age; gender; number of chronic diseases (diabetes, dyslipidemia, obesity, left ventricular hypertrophy, microalbuminuria, retinopathy, coronary heart disease, peripheral vascular disease, stroke, cancer and other); number of drugs taken; cardiovascular risk factors; body mass index (BMI); abdominal waist circumference; mean clinical BP (SBP and DBP) with their SD; and the differences between two consecutive visits and between baseline and study end.

We calculated the adherence rate (AR) using MEMS and the medication possession ratio (MPR) for the e-prescription according to the formulas: AR per MEMS (total number of tablets presumably taken-MEMS openings/total number of tablets that should have been taken according to dosage [days elapsed] x 100) and MPR per e-prescription (total number of tablets presumably taken-purchased from the pharmacy/total number of tablets that should have been taken according to dosage [days elapsed] $\times$ 100). The AR between two consecutive visits was calculated from the MEMS, as well as the cumulative AR at each visit from the start. The final AR was considered to be the cumulative AR at study end or at withdrawal from the study for any reason, provided that a pill count was performed. The MPR was considered in a similar way. The degree of hypertension control was assessed as 'good' when SBP was less than 140 mmHg and DBP was less than 90 mmHg [20].

The primary outcome was the percentage of the patients who adhered to all the doses according to MEMS. This variable was used to classify the patients as adherent ($AR \geq 80\%$) or non-adherent ($AR < 80\%$). The MEMS was also used to determine the percentage of days the user took one tablet daily, the percentage of doses taken in the recommended time frame (7–9 h) and the therapeutic coverage or time during which the patient was pharmacologically covered by an antihypertensive drug, assuming the drug was effective for 24 h. We calculated all the variables overall and compared them between adherent and non-adherent patients.

To validate the e-prescription, we calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR +) and negative

likelihood ratio (LR−). We also determined the Kappa concordance index and the ROC curve or diagnostic performance curves to detect the discriminatory power of the index test. This is used to compare two diagnostic tests: the closer the value of the area under the curve (AUC) is to 1, the greater the discriminatory power of the test. In descriptive bivariate analyses, the Chi square test and the Student's *t*-test were used to compare qualitative and quantitative variables, respectively. In addition, we performed a backward stepwise multivariate logistic regression analysis, comparing the variables between adherent and non-adherent patients. P values less than 0.05 were considered significant, and confidence intervals were calculated at 95%. The Paradox 3.5 database and SPSS PC + s15 software were used for this study.

Using a 95% confidence interval, with a statistical power of 99% and expecting to find an area under ROC curve of 0.9, a sample size of 98 patients was needed for this study. We added 20% to take into account potentially missing data and attrition, resulting in a minimum sample size of 118. The study was conducted following the ethical standards for clinical research of the Declaration of Helsinki. The Research Committee of the Health Area of Huelva approved the study.

3. Results

Of the 120 patients initially included, we obtained data from 102 (85%). The other 18 patients were excluded due to: technical problems with the MEMS (n = 4), loss of the MEMS (n = 3), improper use of the MEMS (n = 6), patient request to withdrawal (n = 2), moved to another city (n = 1), development of a tumor (n = 1), and diagnosis of white-coat hypertension (n = 1), with the patient not requiring subsequent antihypertensive treatment. All 102 included patients completed the four follow-up visits over the two years.

3.1. Baseline characteristics of the study sample

Overall mean age was 61.06 years (SD 9.08; range 40–80); there were 32 men (31.4%) and 70 women (68.6%) (p = not significant for age or gender). The mean baseline SBP and DBP of the overall sample was 139.2 (SD 15.9) and 81.1 (SD 9.1), respectively, and the final means were 139.1 (SD 15.3) and 83 (SD 10.1). Table 1 shows the baseline characteristics of the study sample distributed into adherent (mean AR ≥ 80%; n = 79) and non-adherent participants (mean AR < 80%; n = 23) using MEMS. The bivariate and multivariate analyses showed differences between these groups only with regard to the number of drugs taken, with patients taking fewer prescriptions showing greater odds of being adherent (odds ratio [OR] 1.35, $p < 0.01$).

3.2. Adherence measurement during follow-up

MEMS indicators for adherent patients who were adherent at baseline showed that the mean cumulative percentage of doses taken was 89.1% (95% CI 81.0–97.0), the mean percentage of days on which the dose of antihypertensive medication was taken properly was 83.0% (95% CI: 73.6–92.6), and the percentage of days on which the medication was taken at the correct time was 79.4% (95% CI 69.1–89.7). The therapeutic coverage in adherent patients, assuming an antihypertensive effect of 24 h, was 89.1% (95% CI: 81.2– 97.0). According to the e-prescription, measured by MPR, adherence was 91.9% (95% CI: 85.0–98.8%).

Table 2 shows the mean percentage counts of adherence and the proportion of adherent patients per visit, according to different variables calculated by MEMS (AR) and by e-prescription with the MPR per visit. Of the 102 total participants, 77.4% (95% CI: 66.8–88.0) were considered adherent during the overall study period; 70.6% (95% CI: 59.0–82.2), adherent once daily; and 60.8% (95% CI: 48.4–73.2), adherent at the correct time. According to the MPR, 80.4% of the patients (95% CI: 70.3–90.5) were adherent.

3.3. Blood pressure control per patient group

The percentage of hypertensive patients who had good BP control was: at the initial visit, 51% (95% CI: 41.4–60.5); at 6 months, 62.7% (95% CI: 53.0–71.7); at 12 months, 66.7% (95% CI: 57.0–75.0); at 18 months, 66.7% (95% CI: 57.0–75.0); and at 24

Table 1
Baseline characteristics of the study distributed into adherent and non-adherent participants.

	ADHERENT* PATIENTS N = 79	NON-ADHERENT* PATIENTS N = 23	P
Age (years), mean (SD)	60.7 (SD 9.5)	59.7 (SD 7)	NS
Gender, n (%)	M: 27 (34.2%) F: 52 (65.8%)	M: 5 (21.7%) F: 18 (78.3%)	NS
Number of diseases, mean (SD)	2.4 (SD 1.1)	3 (SD 1.4)	NS
Number of drugs taken initially, mean (SD)	1.9 (SD 1.2)	3.9 (SD 1.9)	0.02*
Initial BMI, mean (SD)	30.7 (SD 5)	32 (SD 5.5)	NS
Initial abdominal waist circumference, mean (SD)	101 (SD 10.2)	101.2 (SD 10.2)	NS
Initial SBP, mean (SD)	138.8 (SD16.8)	139.1 (SD13.4)	NS
Initial DBP, mean (SD)	80.6 (SD9.6)	81.6(SD7.6)	NS
Years with hypertension, mean (SD)	6.6 (SD 3.8)	6.9 (SD 4)	NS
Antihypertensive drugs added during the study, n (%)	15 (19%)	5 (21.7%)	NS
Age as CVRF, n (%)	37 (45.7%)	11 (52.4%)	NS
Cardiovascular risk factors			
Family history of CVD, n (%)	10 (12.6%)	2 (8.7%)	NS
Diabetes, n (%)	22 (27.8%)	3 (13%)	NS
Dyslipidemia, n (%)	39 (49.4%)	11 (47.8%)	NS
Smoker, n (%)	6 (7.6%)	2 (8.7%)	NS
Obesity, n (%)	41 (51.2%)	12 (52.2%)	NS
LVH, n (%)	9 (11.4%)	3 (13%)	NS
Microalbuminuria, n (%)	3 (3.8%)	2 (8.7%)	NS
Retinopathy, n (%)	2 (2.5%)	2 (8.7%)	NS
Coronary heart disease, n (%)	4 (5%)	3 (13%)	NS
PVD, n (%)	1 (1.2%)	2 (8.7%)	NS
Stroke, n (%)	3 (3.8%)	2 (8.7%)	NS

NS: Not significant. BMI: Body Mass Index. SBP: systolic blood pressure. DBP: diastolic blood pressure. CVD: cardiovascular disease. LVH: left ventricular hypertrophy. PVD: peripheral vascular disease. CVRF: cardiovascular risk factor. M: males. F: females.
* Adherence (AR ≥ 80%) and non-adherence (AR < 80%).

Table 2
Mean percentage counts of adherence and the proportion of adherent patients per visit, according to different variables calculated by the electronic monitors (MEMS) and by electronic prescription with the medication possession ratio (MPR).

	VISIT 1 (6 m)	VISIT 2 (12 m)	VISIT 3 (18 m)	VISIT 4 (24 m)	p
Total doses taken (by MEMS), % ± SD	86.5 ± 24	89 ± 22.3	90.5 ± 15.3	90.2 ± 17.5	<0.01
Days on which 1 tablet was taken daily by MEMS, % ± SD	79 ± 24.9	83.2 ± 21.3	85.7 ± 14.5	84.8 ± 16.1	<0.01
Days the medication was taken during the prescribed time by MEMS (7–9 h), % ± SD	76 ± 30	80.2 ± 25.1	77.2 ± 25.1	84.0 ± 17.7	<0.01
24- hour therapeutic coverage (MEMS), % ± SD	86.6 ± 22.1	88.8 ± 19.9	90.2 ± 13.1	90.8 ± 14	<0.05
MPR, % ± SD	92.6 ± 11.5	92.3 ± 13.8	90.7 ± 14.1	92.1 ± 11.7	NS
Adherent patients who took all their doses by MEMS (AR), % (N)	78.4(80)	80.4(82)	74.5(76)	77.5(79)	NS
Days on which adherent patients took 1 tablet daily by MEMS, % (N)	66.7 (68)	70.6(72)	72.5(74)	74.5(76)	NS
Adherent patients who took medication during the correct time by MEMS, % (N)	62.7(64)	60.8 (62)	58.8(60)	60.8(62)	NS
Adherent patients by MPR, % (N)	89.2(91)	83.3(85)	73.5(75)	75.5(77)	<0.05

NS: non-significant; m: month; m: months

months, 42.2% (95% CI: 33.0–51.8). Table 3 shows blood pressure values per visit for adherent and non-adherent participants. Over the course of the study, there was a non-significant decrease in SBP in the adherent group, for whom baseline SBP was 138.8 (SD 16.8) and baseline DBP was 80.6 (SD 9.6), compared to 136.5 (SD 13.6) and 80.9 (SD 9.1), respectively, at study end. In contrast, in the non-adherent group there was a significant increase in BP between these two time points, both for SBP (139.1 [SD 13.4] versus 150.6 [17.3], p = .04) and DBP (81.6 [SD 7.6] versus 92.2 [SD 9.2], p = .007). There were no differences between the groups at intermediate time points, but at the final visit, the non-adherent group had a higher BP (p < 0.0001). Control of hypertension at the initial visit was higher in the adherent group than in the non-adherent group, though the difference was not significant. However, we did observe significant differences between the two groups at 6 months, 12 months, and 24 months, with the non-adherent group achieving a lower degree of control. Thus, at 6 months, 68.3% had good BP control in the adherent group compared to 43.4% in the non-adherent group; at 12 months, 70.8% of the adherent group had good control versus 52.2% in the non-adherent group. On completion of the study, control of hypertension in the adherent group was 50.6% (95% CI: 37.9–63.3) versus 13% (95% CI: 4.4–21.6) (p < 001) in the non-adherent group. The percentage of patients with good control decreased at the final visit (p = .01).

3.4. Validation indicators of the e-prescription

Table 4 shows the validation indicators for e-prescription as a method for measuring adherence. At the final visit at 24 months, sensitivity was 87% (95% CI 65.3–96.6); specificity, 93.7% (95% CI: 85.2–97.7); PPV, 80% (95% CI: 58.7–92.4); NPV, 96.1% (95% CI: 88.3–99.0); LR+, 13.8; and LR−, 0.1. Kappa concordance improved from the initial 0.292 until reaching good agreement at the last visit of 0.782 (Table 4). The following AUC values were obtained for e-prescription: 0.618 (95% CI: 0.471–0.766) at 6 months, 0.695 (95% CI: 0.596–0.844) at 12 months, 0.813 (95% CI: 0.705–0.922) at 18 months, and 0.903 (95% CI: 0.817-0.989) at 24 months (Fig. 1).

4. Discussion and conclusion

4.1. Discussion

This study showed that e-prescription (XXI Prescription) is an effective method for measuring adherence to antihypertensive therapy in the treatment of mild-to-moderate hypertension in primary care setting. The overall adherence measurements within the adherent group of hypertensive patients did not show significant differences between e-prescription method and the reference (MEMS) method at 18 and 24 months. The e-prescription system showed very good discriminatory diagnostic capacity as a method for measuring adherence in the primary care setting.

Comparing the extent of non-adherence with previous studies on hypertension in Spain using pill count or MEMS shows that adherence has improved in recent years. The mean AR ranged from 74.04% in the Puras 2001 [21] study to 92.5% in the Cumampa 2005 [22] study. The percentage of adherent patients (with an AR higher than 80%) was similar to that found in other series, such as the Cumple II study [23], which reported an overall proportion of adherent patients of 73.3%. Likewise, measures for once-daily adherence and adherence to the prescribed time for taking medicine showed lower proportions of adherence than the measure of overall adherence. The same occurred in the Cumple II study [23], where the percentages of patients adherent to the correct dose and schedule were 52.8% and 46.5%, respectively. This reflects the general difficulty of taking medication, especially if it must be taken every day and in accordance with the schedule recommended by the physician. Regarding the percentage of adherent patients by MPR, we saw a significant decline over the course of the study, approaching the percentage obtained with the

Table 3
Mean systolic and diastolic blood pressure (SBP and DBP) values per visit for adherent and non-adherent participants.

	Baseline visit	Visit 1 (6 months)	Visit 2 (12 months)	Visit 3 (18 months)	Visit 4 (24 months)	p (Initial visit − Final visit)
Adherent						
SBP	138.8 ± 16.8	133.8 ± 17.6*	133.9 ± 14.6*	135.7 ± 14.5	136.5 ± 13.6	NS
DBP	80.6 ± 9.6	79.2 ± 9.6	78.8 ± 8.1	79 ± 7.4	80.9 ± 9.1	NS
Non-adherent						
SBP	139.1 ± 13.4	137 ± 14.5	133 ± 15.5	133.9 ± 14.8	150.6 ± 17.3	0.04
DBP	81.6 ± 7.6	82.3 ± 8.3	79.2 ± 8.9	80.7 ± 8	92.2 ± 9.2	0.007
p for differences in SBP by adherence groups	NS	NS	NS	NS	0.0001	
p for differences in DBP by adherence groups	NS	NS	NS	NS	0.0001	

NS: non-significant.
Note: In this table, adherent patient has been defined as the patient being adherent at the final visit.
* p < .05 compared to the value at the initial visit.

Table 4
Validation indicators for e-prescription as a method for measuring adherence.

	Visit 1 (6 months)	Visit 2 (12 months)	Visit 3 (18 months)	Visit 4 (24 months)
Sensitivity	28.6%	50%	73.1%	87%
Specificity	95.1%	91.5%	89.5%	93.7%
PPV	60%	58.8%	70.4%	80%
NPV	83.7%	88.2%	90.7%	96.1%
LR+	5.8	5.9	6.9	13.8
LR-	0.8	0.6	0.3	0.1
Kappa index	0.292	0.413	0.618	0.782

PPV (positive predictive value). NPV (negative predictive value). LR+ (positive likelihood ratio). LR- (negative likelihood ratio).

MEMS. Bivariate and multivariate analyses were performed between the different study variables to assess their impact on adherence. Significant differences were only observed for the number of drugs taken, an observation corroborating previous reports that therapeutic complexity affects adherence [24].

What was most striking about the relationship to BP control (Table 3) was the significant increase in both the mean systolic and diastolic BP in the non-adherent group at the final visit. We must emphasize that control of hypertension was higher in the adherent group from the first visit; though the differences were not significant, they were nevertheless evident at the first, second and final follow-up visits, with the non-adherent group showing poorer control. While only a small percentage of the non-adherent group was well controlled, half of the adherent group was, and half of these patients were still taking the correct drug treatment at the two-year follow up. This is higher than in previous studies such as the PREVENCAT [25], with 32.8% of hypertensive patients controlled; Prescap [26], with 41%; and Hicap [27], with 39.3%. Finally, we note that good BP control decreased the prevalence of other cardiovascular risk factors, while poor control was associated with increased cardiovascular risk [27].

With regard to the validity of the e-prescription, and comparing the overall measurements of the adherent group by MEMS (gold standard) and by MPR (e-prescriptions), significant differences were only present at the first follow-up visit (Table 2). At all other time points, the proportion of adherent participants remained similar, with no differences at the third and fourth follow-up visits. This might be due to the introduction of a copayment for medicines in Spain, implemented on July 1, 2012, requiring pensioners to contribute to the cost of their prescriptions [28,29]. There is evidence that copayments have an effect on adherence [30,31].

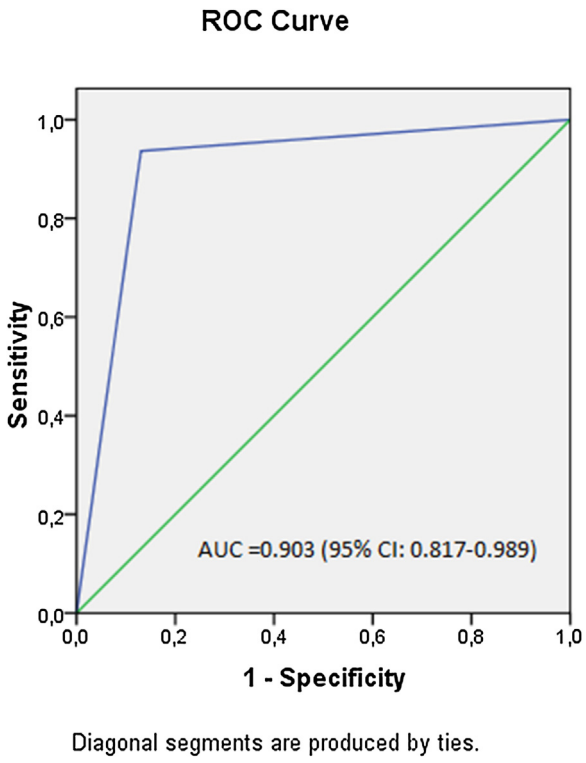

Fig. 1. ROC curve and area under the curve (AUC).

At the first follow-up visit, the Kappa index indicated weak agreement between adherence measures, but by the 18- and 24-month visits, concordance was much stronger. The validity of the test showed that the sensitivity, or the ability to detect non-adherent subjects, was low at the beginning of the study, owing to the high proportion of falsely adherent participants (false negatives), who accumulated drugs and were not detected by the method. However, sensitivity improved with successive visits and was high at study end, as the e-prescription (MPR) had detected the true non-adherent participants (true positives). The specificity, or ability of the test to detect the adherent patients, was high from the beginning. This is primarily because there were relatively few false non-adherent patients (false positives) in the sample. This is logical, as patients can generally not take medication if they do not collect it from the pharmacy.

The PPV of the test improved with successive visits. However, the NPV was high from the beginning and remained so throughout the study. At two years, we observed high values for all the study tests. Analysis of the AR showed that both the LR+ and the LR− improved during follow-up, such that at the final visit, non-adherence could be conclusively confirmed (LR+ > 10) or ruled out (LR− = 0.1) [32]. When compared with other indirect methods to measure adherence, the best validation indicators were obtained using e-prescriptions. In the Haynes-Sackett test, or self-reported adherence test, the estimated sensitivity (35%), specificity (95%), predictive values and likelihood ratios, as compared to pill counts, were taken as proof of certainty in patients being treated with antihypertensive drugs [33]. In assessing the AUC values, the XXI Prescription improved over the different visits, from an average (AUC = 0.618) to a very good diagnostic test at the fourth visit (AUC = 0.903). Thus, this test has very good discriminatory diagnostic capacity.

4.1.1. Limitations

Participants were included by consecutive sampling until achieving an adequate sample size based on prior calculation and were recruited from two different primary health care areas; all of those with pill counts attended every follow-up visit over the two-year study period. Nevertheless, this study might not be representative of the general population of hypertensive patients because the recruitment areas were limited. One of the main study limitations was that we did not adopt the new EU-funded taxonomy to describe and define adherence [33] because the study started before it had been published. However, our study methods met the criteria recommended by Haynes et al. [34] for

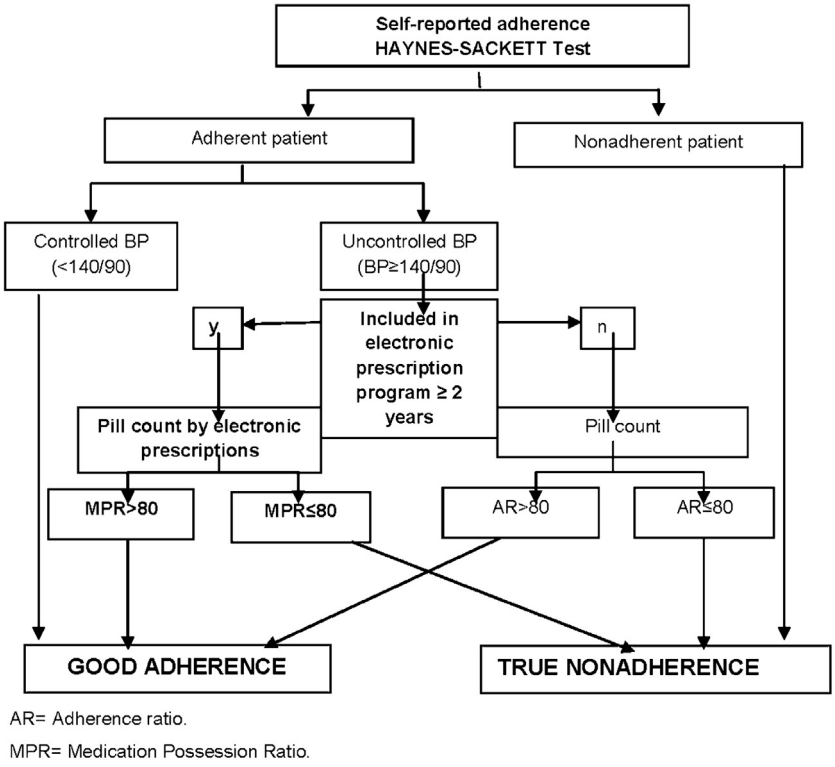

Fig. 2. Algorithm for measurement of adherence in hypertension recommended after the results obtained.

adherence studies: the diagnosis of hypertension was correct; the method of measuring adherence, the MEMS, has been validated; and the results on adherence and hypertension were assessed with a follow-up of at least 80% of the sample in over 100 individuals. Although the e-prescription is considered a measure of persistence [35], other studies have shown that this method provides a good estimate of adherence [17], and we compared the MPR with the MEMS. At the same time, clinicians' awareness of the study, the use of the MEMS, and control by two medical researchers may have conditioned a more intense performance of the intervention by the physician. However, these limitations are assumed in observational studies of health effectiveness in clinical practice and clinical effectiveness [36]. To minimize information bias, the first visit was carried out by the PCP from the health center, while the subsequent visits were conducted by two research physicians.

4.2. Conclusions

The measurements of treatment adherence by the XXI Prescription did not show significant differences with the gold standard at most visits, and the e-prescription showed good discriminatory diagnostic capacity as a method for measuring adherence in the primary care setting.

4.3. Practice implications

If patients are included in e-prescription program for at least two years, physicians can use e-prescribing as a method to measure adherence. Therefore, we propose that the Spanish Society of Hypertension (SHE-LELHA) adopts a practical modification to detect non-adherence (Fig. 2), the Haynes-Sackett self-reported adherence test. If the patient claims to be non-adherent, clinicians shall consider them as such. If the patient claims to be adherent and their BP levels are under good control, they can be classified as adherent, since the clinical objective is to control hypertension. If the patient claims to be adherent but has poor BP control, clinicians should suspect non-adherence and perform a subsequent query of their electronic health history in the medication module to verify whether the drug has been included in an e-prescription program for more than two years. If so, physicians can check the dispensing and obtain the MPR for the previous six months. If e-prescription has not been used or if the prescription has been in effect for less than two years, clinicians may conduct a pill count, either at home, at the office or by telephone interview.

I confirm all patient/personal identifiers have been removed or disguised so the patient/person(s) described are not identifiable and cannot be identified through the details of the story.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Declarations of interest

None.

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