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Study on the use of multi-compartment compliance aids to improve blood pressure values in hypertensive patients

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KEYWORDS

Community Pharmacies, Professional Pharmaceutical Services, Patient Compliance, Medication Adherence

ABBREVIATIONS

AHT: arterial hypertension
BP: blood pressure
CF: Community Pharmacists
CVD: cardiovascular diseases
DBP: diastolic blood pressure
ESH: European Society of Hypertension
HDL: high-density lipoproteins
HT: hipertensión
MCA: Multi-compartiment Aids
PA: presión arterial
PRM: problems related to the medication
SBP: systolic blood pressure

ABSTRACT

Objectives: To analyse the improvement of adherence in non-adherent patients with uncontrolled HT, polymedicated and older than 55 years after the use, or not, of Multicompartment compliance aids (MCA).

Design: Longitudinal research (6 month). Levels of adherence to treatment were analysed using an adapted version of Morisky-Green test, counting of returned medication (MCA group) and blood pressure (BP) values. Site: Multicentre study in 35 community pharmacies in Spain. Participants: 195 participants (88 MCA group and 107 control group) older than 55 years, polymedicated, non-adherent to medication, with uncontrolled hypertension and using electronic prescription. Interventions: MCA group received their medication in MCA while control group received their medication as usual. Main measurements: Systolic BP/Diastolic BP was recurrently measured with a digital tensiometer in both groups.

Results: MCA group obtained a significant decrease in BP values compared to the control group (Systolic BP decreased by 18.3 mmHg in the MCA group vs. 9.9 mmHg in the control group and Diastolic BP by 9.9 mmHg vs. 8.9 mmHg). Both groups increased their adherence to over 90%.

Conclusions: The use of MCA controlled BP levels in almost 50% of the participants. For this fact, MCA is postulated as a good tool (cost-effective, well tolerated by users, easy to use ...) to improve the adherence of patients and control their hypertension, although more studies are necessary.

INTRODUCTION

Arterial hypertension is the leading preventable cause for cardiovascular diseases and mortality worldwide (1). In Spain, 42.6% of the population of people >18 is hypertensive, being more frequent in men than in women. AHT rarely occurs alone and sometimes it is associated with other pathologies like dyslipidemia or diabetes that also increase the cardiovascular risk. AHT prevalence increases with age, thus >60% of people of 60 or older suffer from it (2).

At present, adults aged 65 or older represent 20% of the population according to the census in Spain (3). This population group represents two important characteristics strongly related: polypathology (e. i., simultaneous presence of 2 or more chronic diseases) and polymedication (taking 5 or more drugs for 6 months or more) (4).

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In this regard, it has been demonstrated the existence of a relation between advanced age, polypathology and polymedication with an increase in the lack of adherence (5) responsible of multiple clinical and economic consequences derived from the increase of morbidity and mortality seen in non-adherent patients (6). In fact, reducing the lack of adherence to medication and specifically to the medication for AHT control is one of the objectives proposed by the World Health Organisation (WHO) since 2003 (7).

According to the National Analysis of Treatment Adherence in Chronic Pathologies, which analyses data of 12 chronic diseases, including AHT, 51.6% of Spanish patients are non-adherent to the treatments (8). In fact, although 88.3% of diagnosed hypertensive patients are prescribed with a drug to control AHT, only 30% of them have controlled arterial blood pressure, maybe due to a lack of treatment adherence (2).

In the last years, multiple interventions haven been conducted in order to improve these adherence data and different results have been obtained (7.9-14). A meta-analysis assessed 771 of these interventions conducted worldwide and the results suggested that those interventions conducted by community pharmacists (CF) significantly increased patient's treatment adherence compared to those conducted by other healthcare professionals (15). Some of the interventions conducted by CF include implementation of multi-compartment compliance aids (MCAs), which not only allows improvement of treatment adherence but also prevents the occurrence of problems related to the medication (PRM) like taking the wrong drug or overdoses, frequent in polymedicated elderly people (16).

Elaboration of MCAs is a post-dispensing action conducted by the CF under its personal responsibility, regulated by Article 86.1 of the Royal Legislative Decree 1/2015 of 14 July by means of which the revised text of the Protection and Rational Use of Drug Products and Medical Devices Act is approved (17). Despite the potential improvement in adherence that can be obtained with the implementation of MCAs, only a few studies evaluating the improvement in adherence with this system have been found in the literature (18,19). Therefore, the objective of the analysis in this work was improvement in adherence of polymedicated patients with uncontrolled AHT by means of the implementation of MCAs compared to a control group, and it was measured by an improvement in patients' arterial blood pressure (BP) values. Additionally, as supplementary objectives, other parameters were assessed, including knowing the degree of patient's satisfaction with the MCA (assessed in a Likert scale in the last visit) as well as estimation and comparison of the cost of the described antihypertensive agents (these objectives will be described in detailed in the following publications).

METHODS

General Information

Multicentric epidemiological study with 35 community pharmacies that were randomised to the intervention group (MCA group) or the control group and which made a follow-up on the patients for 6 months. Randomisation was made by grouping; e. i., each of the pharmacies included all its patients either in the control group or in the MCA group as per previous allocations. For the allocation of each pharmacy to the corresponding group, the pharmacies with similar population characteristics (neighbourhood, rural, urban or coast) were matched by pairs so that after randomisation one of them will be in the control group and the other in the intervention group (18 in the MCA group and 17 in the control group).

Study Inclusion/Exclusion Criteria

To be included either in the control group or the intervention group of the study, patients should meet the following criteria:

1. Adult patient aged 55 years old.
2. Polymedicated patient (taking >6 drugs daily uninterruptedly over a period of ≥6 months).
3. Patient receiving electronic prescription since at least 3 months.
4. Patient with AHT, not controlled at the baseline visit and with treatment for over three months
   It is considered uncontrolled AHT (1) when:
   a. Systolic blood pressure (SBP)/diastolic blood pressure (DBP) levels are above 140/90 mmHg.
   b. Limits of controlled SBP/DBP must be inferior to 130/80 when given the following circumstances: a previous cardiovascular event, stablished nephropathy, diabetes, patients with ≥3 cardiovascular risk factors (male, mean age 55 years old for men or 65 years old for women, smoking, dyslipidemia, family history of premature cardiovascular disease), heart failure or patients with metabolic syndrome.

Blood pressure must be measured with a sphygmomanometer validated by the European Society of Hypertension (ESH) and 2-3 measurements must be obtained in adequate conditions according to established international guidelines (1,20).

Study exclusion criteria:

1. Patients receiving antipsychotic agents.
2. Patients with any physical or mental disability preventing them from going to the community pharmacy and taking part in the project.

3. Patients who are already receiving the MCA preparation service.

The pharmacist counted the non-taken tablets found in the MCA the patient returned, and the patient's treatment adherence was estimated (it was considered a non-adherent patient if the adherence was below 80%).

Adherence was assessed using a version of Morisky-Green test **(Annex)** (21,22) applied in every visit (baseline visit, Month 1 visit, Month 3 visit and Month 6 visit).

Study Development

FIRST VISIT

The following data were obtained:

- Sociodemographic variables: age, sex, level of education, province/state/county, country of origin.
- Number of hospital admissions during the previous year. These data were obtained by asking the patient.
- Cardiovascular risk factors, diabetes mellitus, previous acute myocardial infarction, substance abuse, nephropathies, dyslipidemia, cardiac illness, strokes, weight, and size. These data were obtained by asking the patient.
- Active principle (antihypertensive or non-antihypertensive agent) the patient takes based on the electronic prescription information and asking directly to the patient.
- Blood pressure measurement (3 measurements as per the recommendations of the ESH Guidelines), always with the same device and in the same time interval. The mean value of the three measurements was obtained.
- Patient had to present the results of recent lab tests and the total cholesterol and HDL data were documented.
- Patients had to fill out an adapted Morisky-Green test to assess the degree of baseline treatment adherence.
- Patients of the pharmacy randomised to the control group were given the medicine in the traditional way as the other patients of the pharmacy.
- All the patients (MCA group and control group) were provided standardised information about hypertension and signed the informed consent.
- Suspected adverse reactions were assessed and documented.

SECOND AND SUCCESSIVE VISITS (Month 1 and Month 3)

Both groups

- Blood pressure measurement (3 measurements as per the ESH recommendations).
- Adapted Morisky-Green test.
- Measurement changes were documented.
- Suspected adverse reactions were documented.

In the group with MCA intervention

- Medication with MCA was dispensed.

LAST VISIT (Month 6)

Both groups

- Adapted Morisky-Green test.
- An evaluation of HDL level was made using the cobas b 101 system (Roche Diagnostics) for those patients who had no lab tests at the end of the study.
- Blood pressure measurement (3 measurements as per the ESH recommendations).
- Measurement changes were documented.
- Suspected adverse reactions were documented.
- Pharmacist's satisfaction survey.

In the group with MCA intervention

- Medication with MCA was dispensed.
- Assessment of patient's satisfaction with the MCA system.
- Time spent dispensing the medication with the MCA system.

VISIT EVERY 15 DAYS

Only the group with MCA intervention

- Medication dispensing (MCA delivery and collection every 15 days for 6 month of follow-up).

Table 1 summarises the data collected in each of the visits carried out.

Sample Size Estimation

Since the intervention consisted of a medication preparation service that does not modify the antihypertensive treatment, but could only improve adherence, the impact that it could have on blood pressure was estimated to be less than that of comparative clinical trials with different active principles. For this reason, the sample size was estimated to detect a change of 8 mmHg between the systolic blood pressure and final blood pressure (at Month 6). Accepting a bilateral alpha error at 0.05 and a beta error at 0.2, 123 patients would be necessary in the first group and 123 patients in the second group to detect a similar difference or superior to 8 units (in mmHg) between baseline blood pressure value and final systolic blood pressure (SBP) value. An estimated common standard deviation would be 20. The estimated loss to follow-up rate was 20%.

The last final sample valid for the analysis was 88 patients in the MCA group and 107 in the control group.

Analysis

A descriptive analysis of all the variables was conducted and comparability between groups at baseline was evaluated. Blood pressure assessment was made by calculating the mean of the 3 measurements of sitting blood pressure for each patient. For the analysis of the primary variable,

Table 1 Data obtained in each visit

Procedures	Baseline visit (Day 0)	Visit 1 (Month 1)	Visit 2 (Month 3)	Visit 3 (Month 6)
Inclusion/exclusion criteria	X			
Informed consent and patient information sheet	X			
Sociodemographic variables	X			
Cardiovascular risk factors	X			X
Number of hospital admissions during current/previous year	X			X
Antihypertensive treatment: • Control group • MCA group	 X X	 X X	 X X	 X X
Concomitant medication: • Control group • MCA group	 X X	 X X	 X X	 X X
Blood pressure measurement	X	X	X	X
Recent total cholesterol and HDL values	X			X
Morisky-Green test	X	X	X	X
Only the group with MCA intervention Medication dispensing (MCA delivery and collection every 15 days for 6 month of follow-up)	X	X	X	X
Standardised information about AHT	X			
Only the group with MCA intervention Indicator of time spent dispensing the medication with the MCA system	X			X
Suspected adverse reactions: • Control group • MCA group (assessment every time the medication is dispensed)	 X X	 X X	 X X	 X X
Only the group with MCA intervention Satisfaction assessment of patient with MCA				X

a covariance analysis was carried our taking the baseline measurement of blood pressure as the covariable, the intervention group as the independent variable and final measurement at Month 6 as the dependent variable (prior normality verification). Change of measurement at Month 3 was also evaluated. Continuous variables were categorised and the association between primary outcomes and independent variables were assessed using a univariate logistic regression analysis. Subsequently, all variables with a $p < 0.05$ were included in a multivariate model to estimate the odds ratio and the corresponding 95% confidence intervals. To do so a forward stepwise regression model of variables was used. Analysis was conducted with Statistical Analysis Software, version 9.4. Those in charge of the statistical analysis were blinded as to the patient's identity and the group the patients were randomised to.

Study Classification and Evaluating ECCR

The study protocol was sent to the Spanish Agency of Medicines and Medical Products (AEMPS) for its classification and it was classified as an EPA SP study since it is a prospective follow up of patients, given that the primary factor of exposition is not a drug but the assessment of the clinical and economic impact of the implementation of the MCA service.

The study was approved by the regional ECCR of the Madrid Community of Castilla-La Mancha and Cataluña.

Ethical Aspects and Protection of Study Participants

The study was conducted in accordance with the requirements provided in the Declaration of Helsinki (Seoul revision, October 2008) and the current Spanish Legislation pursuant to the disposition in the Ministerial Order SAS/3470/2009 regarding observational studies. Treatment, communication, and transfer of personal data of all participants comply with the Organic Law 15/1999 of 13 September for the protection of personal information. As general considerations, all parties involved in the study accepted the national and international ethical rules for clinical research. An ECCR evaluated the protocol prior to patient inclusion to the study. Any data required by protocol was subjected to audits by the sponsor, independent organisations and/or competent authorities, but the confidentiality of the data was an indispensable condition in accordance with the previously cited law.

RESULTS

Participation and Follow-Up

A total of 35 community pharmacies participated in the study, 17 in the control group and 18 in the MCA, with a recruitment of 107 and 88 patients, respectively. All of the participants remained in the study till its completion and there were no significant differences between both groups. Participants mean age was 76.4 SD 8.9 and 57.4% were women. At the beginning of the study, no significant differences were seen regarding patient's comorbidities; but patients included in the MCA group had a higher number of hospital admissions in the 12 months prior to the study. Comorbidities in each study group and the progression were similar in both groups as well as the hospital admissions. All these data are presented in Table 2.

Table 2 Summary of comorbidities/history and hospital admissions at baseline

History and hospital admissions		MCA Group: 88 (45.1%)	Control Group: 107 (54.9%)	Total Sample 195 (100%)	*p*-value
Diabetes *mellitus*, n (%)		35 (40.0%)	46 (43.0%)	81 (41.5%)	0.6642 (b)
Previous acute myocardial infarction, n (%)		14 (15.9%)	17 (15.9%)	31 (15.9%)	1.0000 (b)
Smoking, n (%)		6 (6.8%)	11 (10.3%)	17 (8.7%)	0.4502 (b)
Nephropathy, n (%)		4 (4.6%)	11 (10.3%)	15 (7.7%)	0.1792 (b)
Dyslipidemia, n (%)**		55 (64.0%) Respondent: 86	79 (74.5%) Respondent: 106	134 (69.8%)	0.1177 (b)
High Total Cholesterol (>240 mg/dl), n (%)**		3 (9.1%) Respondent: 33	7 (13.5%) Respondent: 52	10 (11.8%)	0.7337 (b)
Low HDL-Cholesterol (<40 mg/dl), n (%)**		4 (14.8%) Respondent: 27	0 (0%) Respondent: 27	4 (7.4%)	0.1109 (b)
Heart disease, n (%)		41 (46.6%)	40 (37.4%)	81 (41.5%)	0.2427 (b)
Stroke, n (%)		8 (9.1%)	14 (13.1%)	22 (11.3%)	0.4962 (b)
Overweight (BMI >25), n (%)		54 (67.5%)	60 (76.9%)	114 (72.1%)	0.2161 (b)
Hospital admissions in the last 12 months, mean (SD)		0.64 (1.98)	0.23 (0.58)	0.42 (1.41)	0.04880 (a)*
Hospital admissions in the last 12 months, n (%)	0	64 (74.4%)	86 (83.5%)	150 (79.4%)	0.2004(b)
	1-2	17 (19.8%)	16 (15.5%)	33 (17.5%)	
	3-4	3 (3.5%)	1 (1.0%)	4 (2.1%)	
	5+	2 (2.3%)	0 (0%)	2 (1.1%)	

a: t-test for independent groups; b: Fisher test.
* Statistically significant differences ($p < 0.05$).
** Percentage of total of patients per group, but these are not mandatory variables in the CRD.
Blood cholesterol levels were not obtained from all the patients because it was not mandatory for the participants of the study.

Adherence

At baseline, and according to the study screening criteria, 0% of patients were adherent to the medication. Adherence increased in both groups after the first visit (100%, 100% and 98.9% in the MCA group and 92.5%, 96.3% and 95.3% in the control group at Month 1, Month 3 and Month 6, respectively). Significant differences were seen only regarding adherence in the visit at Month 1 after study initiation (*p*-value between groups = 0.00087).

Treatments

Total number of prescribed treatments for BP decreased significantly during the study in the control group (8.5 *vs.* 7.8 between the first and the last visit; $p = 0.0075$) but not in the MCA group which remained constant (8.9 *vs.* 8.9; $p = 0.9321$). Non-antihypertensive medication increased significantly during the study in the MCA group (4.7 *vs.* 6.5), but not in the control group (5.3 *vs.* 5.6). With respect to the medication for AHT control, a significant decrease was observed in both groups, but not between groups (4.3 *vs.* 2.4 in the MCA compared to 3.1 *vs.* 2.3 in the control group).

Blood Pressure Progression

As can be seen in Table 3, BP decreased in both groups.

Patients in the MCA group presented a lower SBP of 18.3 mmHg *vs.* 11.5 mmHg in the control group from baseline to Month 6. Both data are statistically significant and the difference between groups is also statistically significant ($p = 0.0020$).

Similarly, patients in the MCA group presented a lower DBP of 9.9 mmHg *vs.* 8.9 mmHg in the control group from baseline to Month 6. Both data are statistically significant and the difference between groups is not statistically significant.

47.7% of patients in the MCA group reached blood pressure control at Month 6 compared to 39.3% in the control group. A significant increase was seen in the MCA group (Table 4).

Table 3 Summary of mean BP values in the different groups during the study

Visit	MCA Group: 88 (45.1%)		Control Group: 107 (54.9%)	
	SBP	DBP	SBP	DBP
Baseline	151.6 (11.3)	85.4 (10.2)	147.6 (12.0)	83.7 (11.7)
Month 1	139.7 (14.3)	78.2 (9.7)	139.3 (14.0)	78.4 (12.1)
Difference (SD) *p*-value between baseline and Month 1	-11.8 (13.8) 0.0000 (b)*	-7.2 (9.9) 0.0000 (b)*	-8.3 (13.4) 0.0000 (b)*	-5.3 (12.3) 0.0000 (b)*
	0.0723 (a) 0.2303 (a)			
Month 3	137.2 (14.8)	77.3 (8.7)	138.4 (16.1)	76.1 (11.6)
Difference (SD) *p*-value between baseline and Month 3	-14.4 (15.2) 0.0000 (b)*	-8.2 0.0000 (b)*	-9.1 (16.1) 0.0000 (b) *	-7.7 (13.3) 0.0000 (b) *
	0.0289 (a)* 0.7722 (a)			
Month 6	133.3 (13.7)	75.6 (8.3)	136.1 (15.7)	74.9 (10.4)
Difference (SD) *p*-value between baseline and Month 6	-18.3 (14.3) 0.0000 (b)*	-9.9 (11.0) 0.0000 (b)*	-11.5 (15.6) 0.0000 (b)*	-8.9 (11.8) 0.0000 (b) *
	0.0020 (a)* 0.5402 (a)			

a: t-test for independent groups; b: paired t test.
* Statistically significant differences ($p < 0.05$).
Data in parentheses indicate standard deviation.

Table 4 Progression of blood pressure control per study group

Prescribed active principles	MCA Group: 88 (45.1%)	Control Group: 107 (54.9%)	p-value between groups
Baseline Visit, n (%)	0 (0%)	0 (0%)	--
Visit at Month 1, n (%)	25 (18.4%)	30 (28.3%)	1.0000 (b)
Visit at Month 3, n (%)	37 (42.1%)	35 (32.7%)	0.1840 (b)
Visit at Month 6, n (%)	42 (47.7%)	42 (39.3%)	0.2482 (b)
p-value between Month 1 and Month 6	0.0016 (c)*	0.0630 (c)	

Letter "n" indicates how many patients presented normal blood pressure values in the different visits.
Percentage of total of patients per group that had normal blood pressure values are between parentheses.
b: Fisher test; c: McNemar's test.

DISCUSSION

This work shows controversial results regarding our initial hypothesis. On the one hand, both the control group and the MCA group showed a decrease in the BP levels (SBP and DBP), though it was significantly higher in the MCA group. This can be so for several reasons. Firstly, some studies have demonstrated that the correct dispensation by the CF (providing information about the medicine, the pathology and healthcare education) as well as conducting pharmacist-patient interviews, improves patients BP levels compared to those who only receive the medication without any further information (9,15). Another fact that could also be responsible for this BP decrease is the regular measurement of blood pressure, measured in both groups at least 4 times and that has become one factor influencing BP level reduction (11), maybe patients being more aware that their BP values are not appropriate decide to take the medication to compensate for this. On the other hand, another factor that seems decisive in this work is the increase of adherence levels; however, despite both groups have reached practically the same levels of adherence, BP values in the MCA group are significantly lower than in the control group. This may be due to the different way in which adherence levels have been evaluated in both groups. In the MCA group, levels of adherence have been assessed by objective methods like counting the medication in the returned MCA, while in the control group, only the adapted Morisky-Green test has been used, a test that even though it's validated, it's not effective detecting lack of adherence like direct methods (23,24).

The implementation of the MCA system and the pharmaceutical intervention derived from its preparation improves the control of different chronic diseases evaluated in different scientific literature (25) and of the SBP levels as it was demonstrated in this work; however, further studies are necessary. Another factor that favours the use of the MCA system is that they are cost-effective. In our work, the cumulative cost for antihypertensive medication was approximately 100 euros less in the MCA group than in the control group (201.03 € in the control group *vs.* 109.34 € in the MCA group), fact that was demonstrated in multiples works (19,26,27). What seems undebatable is that the use of the MCA system has been postulated as an easy-to-use tool that improves patients' life making them more autonomous and improves their perception about their health status, and at the same time decreases side effects associated with the medication (28,29).

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Annex. Morisky-Green Test

- Do you sometimes forget to take your medicines?
- Do you take your medication every day at the indicated time?
- When you feel well, do you stop taking your medication?
- If the medication makes you feel bad, do you stop taking them?

RETURN