

Assessing the impact of multi-compartment compliance aids on clinical outcomes in the elderly: a pilot study

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Abstract *Background* Medication non-adherence is a major problem for elderly people. Multicompartment compliance aids (MCAs) have been advocated as a solution for this problem. *Objective* To assess the impact of using MCAs in self-reported adherence and clinical biomarkers of elderly patients followed in a community pharmacy. *Setting* One community pharmacy at Sabugal (Portugal). *Methods* A four-month prospective, non-randomised, controlled study was performed. Autonomous patients aged 65 or more using 3 or more medicines and under follow-up in the pharmacy were invited to participate. All patients were offered to receive their medication in MCAs prepared in the pharmacy. Patients refusing the MCA were used as control. The intervention consisted of providing 4 weekly MCAs during the monthly visit. All patients received regular pharmacy counselling. Blood pressure (BP), lipid profile and glycaemia were assessed at baseline and monthly for all the patients. Morisky self-reported scale was applied at baseline and at the end of the study. Bivariate analysis and generalized estimation equations (GEE) were used. *Main Outcome Measure:* Self-reported medication adherence,

clinical biomarkers: BP, lipid profile, glycaemia. *Results* 54 patients between 65 and 90 years were under follow-up. 44 patients accepted the MCA, constituting the intervention group. No difference in the baseline biomarkers between both groups was found. The bivariate pre-post analysis yielded significant improvements in the intervention groups, but not in the control, for glycaemia ($p < 0.001$), HDL-c ($p = 0.018$), and systolic ($p < 0.001$) and diastolic ($p = 0.012$) BP. However, when introducing the ‘time in follow-up’ in the GEE model, all the differences became non-significant, except systolic BP, but the time remained significant for all the biomarkers. *Conclusion* MCAs apparently improve several clinical biomarkers in a cohort of patients under pharmacist’s follow-up. When including the time in pharmacist’s followup in a GEE, the effect of the MCA disappeared, remaining only the time as a significant variable. Not considering the time in follow-up may be overestimating the effect of MCAs.

Keywords Aged · Community pharmacy · Elderly · Medication adherence · Pharmaceutical services · Portugal

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Impacts of findings on practice

- The use of multi-compartment compliance aids does not seem to make a substantial difference on health outcomes in Portuguese patients receiving medication follow-up.
- Studies on pharmaceutical care or pharmacists’ intervention should take into consideration the effect of time under follow-up as a potential influencing variable.
- To ensure the sustainability of pharmaceutical services, the use of new procedures or instruments will require a careful evaluation of their benefits before the implementation stage.

Introduction

Population ageing is a topic that has quickly acquired extreme relevance in all developed countries. It is expected that by 2050 there will be 2 billion people aged 60 years or over worldwide [1]. Multimorbidity in the elderly has been estimated as ranging from 55 to 98 % and it is highest in very old people, in women, and in individuals from lower socioeconomic groups [2]. To deal with these concomitant multiple diseases, elderly people are required to take several medicines. Polypharmacy is therefore very common among older people. The results from the REPOSI study reveal that the prevalence of polypharmacy (defined as the concomitant use of five or more medicines) in elderly patients was 51.9 % at hospital admission and 67.0 % at discharge [3]. As a consequence, the risk of inappropriate medicine use, underuse of effective treatments, medication errors, adverse drugs reactions, drug–drug and drug–disease interactions, and poor adherence is high among the elderly [4].

Non-compliance, non-adherence and non-concordance are three terms used to define the situation when a patient fails to follow professional advice in less than 80 % or in more than 110 % of the times [5]. Although different definitions have been presented for these three terms [6], other authors regard them as synonyms [7], but the importance of paying attention to this problem has been recognised, whichever the term used [8]. The World Health Organization (WHO) has highlighted the consequences of the high prevalence of non-adherence among patients [9].

The prevalence of non-compliance among older people was estimated as ranging from 20 to 70 % [10]. There are a variety of reasons why patients do not adhere to their prescribed medication regimens: patient-related factors like socio-demographics, psychosocial profile, comorbidities, cognitive ability, and health beliefs; drug-related factors such as the number of medicines taken, adverse effects and administration regimes; and other factors such as patient–prescriber relationship, access to medication, or social support [10]. Several factors have been associated with poor compliance and early discontinuation of long-term treatments such as: therapeutic complexity, number of different prescribers, more visits to pharmacies and lower refill consolidation [4].

The literature has demonstrated the impact of pharmacists on improving medication adherence [11], although evidence in elderly patients is conflicting [12]. The use of multi-compartment compliance aids (MCAs) has been advocated as a potential benefit for patients and their use has increased in clinical practice [13]. However, a Cochrane review classified studies in this area from ‘low’ to ‘very low’ in terms of the quality of the evidence [14]. Another systematic review drew similar conclusions, both

about the utility of the devices and the quality of the studies [15]. Moreover, some authors stated that these devices can help some patients, but they are not a “panacea” [16]. As a result of this controversial evidence, the National Institute for Health and Clinical Excellence (NICE) was not able to produce a recommendation for the use of these devices [17].

Aim of the study

To assess the impact of using MCAs in self-reported medication compliance and clinical biomarkers of elderly patients followed in a community pharmacy.

Method

Study design

A prospective non-randomised controlled study was conducted from January to April 2011 in a community pharmacy (Central Pharmacy, Sabugal, Portugal). Individuals who met the following inclusion criteria were recruited: patients aged 65 years or over, autonomous, prescribed with 3 or more medicines, and being followed in the pharmacy for lipid profile, glycaemia or blood pressure. Medication follow-up is a pharmaceutical care service consisting of a continuous assessment of a patient’s medicines outcomes, and the implementation of the subsequent interventions to improve them. Written consent was obtained from all participants before being enrolled. All participants were offered the opportunity to receive their medication in a MCA. Allocation to intervention or control group was based upon acceptance of the MCA. The study was approved by the Portuguese Personal Data Protection Commission.

All patients had a baseline evaluation and one consultation with the pharmacist every month (a total of 4 consultations). In the first visit, a series of questionnaires were filled into record patients’ socio-demographic characteristics, medication, medical conditions and self-reported adherence. In addition, blood pressure, fasting glycaemia, total cholesterol (TChol), LDL cholesterol (LDL-c), HDL cholesterol (HDL-c) and triglycerides were measured. In subsequent monthly consultations, these laboratory parameters were assessed for all participants. At each monthly consultation, intervention group patients received four MCAs filled with the medication for the following 28 days. Patients in control group obtained their medication in standard retail boxes and received regular follow-up in the pharmacy.

Instruments

Patients' blood pressure was measured with a sphygmomanometer, which had been calibrated by a certified company. The value recorded was the mean of two measurements with a 5-minute interval, performed on the right arm of the patient while sitting down. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure was considered to establish blood pressure goals [18].

Lipid profile and fasting glycaemia were determined using two point-of-care instruments: Cardiocheck and Breeze2. Both instruments were validated by a clinical and pathology laboratory, holder of ISO 9001:2008 certification. Therapeutic goals for TChol, LDL-c, HDL-c, triglycerides, and glycaemia were established following the Third Report of the National Cholesterol Educations Program (NCEP) [19], the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [20] and the Portuguese General Health Directorate Guidelines on Diabetes Mellitus Diagnose and Classification [21].

To assess patient medication adherence and to classify patients as adherent or non-adherent, the Morisky Medication Adherence Scale was used [22]. This is a four-question scale, where each incorrect answer scores one point. Patients were classified as adherent to medication if the four questions scored zero.

For patients in the intervention group, MCAs (ApoWare DOSI 35, Lauer-Fischer GmbH) were prepared in the pharmacy. These MCAs are blisters that contain 35 cells arranged in five administrations per day for a whole week. This device meets the definition of MCA [14], although the physical aspect is that of a blister instead of a box with sliding lid. However, they cannot be considered to be “calendar blisters” since they contain all the medicines to be taken placed together in a cell in their “units of use” [14]. Four of these MCAs were provided to the patient once a month with instructions for their use.

Statistical analyses

Descriptive statistics were carried out presenting absolute values and relative frequencies for categorical variables, and central tendency with dispersion for continuous or discrete variables. An independent χ^2 test was used to analyse associations between categorical variables, using the Fisher exact test or the χ^2 exact test when frequencies were lower than 5. The Mann–Whitney or Kruskal–Wallis tests were used to test hypotheses in continuous variables with skewed distribution. The McNemar and the McNemar–Bowker tests were applied to compare two time-points of categorical variables in the same subjects, and the Wilcoxon test was used to compare continuous variables in two time-points.

To identify the potential effect of the ‘time in follow-up’ (i.e. time under medication follow-up) as a confounder, multivariate generalised estimating equations (GEE) were used. Identity was considered for the link function which implies assuming a linear evolution over time. GEEs allow the analysis of repetitive longitudinal measurements, providing consistent estimations of parameters associated to the covariates even when covariance structure is not specified correctly [23]. Following Pepe and Anderson [24] recommendations, an independent correlation matrix was used.

All statistical analyses were performed using SPSS for Windows, version 18.0 and a p value <0.05 was considered to indicate statistical significance.

Results

A total of 54 patients were included in the study. The age of participants ranged from 68 to 78 years old (mean = 72), and 67 % were females. The vast majority (89 %) suffered from a cardiovascular disease (Table 1), with 74 % with hypertension, 52 % with dyslipidemia and 24 % with diabetes. After offering the MCA, 44 (81.5 %) patients accepted and were allocated to the intervention group. The remaining 10 constituted the control group. Of the 24 characterising variables (socio-demographic and lifestyles), no statistical differences appeared between intervention and control groups (see Online Appendix 1), except for the self-control of blood pressure, which was higher in the control group ($p = 0.001$). No differences were found in the medical conditions suffered by patients allocated to both groups (Table 1).

The mean number of medicines in use by patients was 5.1 (SD 2.1), the anti-hypertensive being the most prevalent (Table 2). No difference in the number of drugs used was found between the intervention and control groups ($p = 0.356$).

Following the administration of the self-reported adherence scale, 38 (70 %) were classified as adherent at baseline. At the end of the study period, 89 % ($n = 48$) patients were classified as adherent, resulting in a significant difference ($p = 0.002$). No difference was found in the adherence rate between intervention and control patients at month four ($p = 1.000$).

Table 3 presents the results of clinical biomarkers from baseline and at the end of the study, both for the intervention and control groups. After the 4-month follow-up, slight improvements appeared in the vast majority of the biomarkers for both control and intervention groups. However, after a bivariate pre-post analysis in the control group, a significant difference appeared only for systolic blood pressure, while in the intervention group differences

Table 1 Health problems reported by study participants (n = 54)

	Total (n = 54)		Medication in MCAs				p*
	n	%	Yes (n = 44; 82 %)		No (n = 10; 18 %)		
			n	%	n	%	
Health problems							
Rheumatology	10	19	8	18	2	20	0.760
Respiratory	4	7	3	7	1	10	0.735
Cardiovascular diseases	48	89	40	91	8	80	0.658
Endocrine diseases	21	39	16	36	5	50	0.645
Blood diseases	11	20	9	20	2	20	0.661
Oncology	4	7	2	5	2	20	0.345
Gastrointestinal diseases	6	11	4	9	2	20	0.658
Central nervous system	6	11	5	11	1	10	0.637
Urinary diseases	1	2	1	2	0	0	0.351
Another	4	7	3	7	1	10	0.735

Medical conditions were classified following the therapeutic classification of the *Prontuario Terapêutico*, the drug reference book of the Portuguese Medicines Agency

* Test χ^2 independence

Table 2 Therapeutic classes of medicines prescribed to elderly patients (n = 54)

	Total (n = 54)		Medication in MCAs				p
	n	%	Yes (n = 44; 82 %)		No (n = 10; 18 %)		
			n	%	n	%	
Therapeutical groups							
Antithrombotic	17	6	15	7	2	3	
Anti-dyslipidaemic	33	12	26	12	7	12	
Oral antidiabetic, insulins	23	8	19	9	4	7	
Antihypertensive	61	22	49	23	12	20	
Another	140	51	106	49	34	58	
Total number of medicines per patient							
≤4	28	52	25	57	3	30	0.356***
5–7	18	33	13	30	5	50	
>7	8	15	6	14	2	20	

*** Exact χ^2 test

existed for fasting glycaemia, HDL-c, systolic and diastolic blood pressure (Table 3).

When generalised estimating equations were used to include the ‘time in follow-up’ in the analysis, the significance of the use of MCAs disappeared for all the biomarkers, with ‘time in follow-up’ remaining the only variable associated with the variance in three of the biomarkers analysed: fasting glycaemia, systolic and diastolic blood pressure (Table 4 and Online Appendix 2).

Discussion

Our study aimed to identify the impact of MCAs on clinical biomarkers of elderly patients who were being followed by a pharmacist in a community pharmacy during the four-month period. We found an apparent improvement in the intervention group when MCAs were used. However,

including time in a multivariate model demonstrated that the difference was not associated with the use of these devices, but with the ‘time in follow-up’. Time is a crucial variable to consider, because the longer the use of medicines, the greater the likelihood of misadministration [14].

Our study also aimed to identify the impact of MCAs on self-reported adherence of elderly patients. Although at baseline 70 % patients were adherent, overall adherence increased significantly after the study period. Nevertheless, at the end of the study, no difference was found in the self-reported adherence between intervention and control groups. This suggests that the pharmacist’s follow-up had an effect on medication adherence, but MCAs had no additional effect. We should bear in mind that MCAs may be beneficial for unintentional non-adherence, but may have no effects on intentional non-adherence [14]. A recent qualitative analysis concluded that MCAs can be helpful for patients who are motivated to adhere to their

Table 3 Values of clinical biomarkers at baseline and at the end of the study (n = 54)

Biomarker	Baseline			Month 4			Difference			p value
	Median	P25	P75	Median	P25	P75	Median	P25	P75	
TChol										
I	182	142	198	172	150	190	-1.50	-10.00	3.50	0.134
C	156	146	188	157	140	193	4.00	1.00	14.00	0.241
Glycaemia										
I	120	98	147	107	96	121	-11.00	-29.00	2.00	<0.001
C	111	97	148	131	100	168	2.00	-18.00	27.00	0.514
HDL-c										
I	51	42	58	54	45	60	1.50	-1.00	6.00	0.018
C	57	47	67	55	45	65	-0.50	-2.00	1.00	0.623
LDL-c										
I	79	64	113	80	66	107	1.50	-6.00	5.00	0.933
C	66	59	81	71	57	89	0.00	-1.00	4.00	0.933
DBP										
I	78	70	87	72	70	79	-4.00	-10.00	2.50	0.012
C	79	72	92	77	72	80	-1.50	-7.00	11.00	0.859
SBP										
I	142	130	155	137	127	143	-7.00	-13.00	3.00	<0.01
C	152	134	164	135	130	156	-7.00	-12.00	-2.00	0.028
TG										
I	154	115	207	150	117	183	-2.50	-30.50	6.00	0.060
C	145	86	188	144	90	182	-1.00	-4.00	4.00	0.919

P percentile, # Wilcoxon test, TChol total cholesterol, HDL-c HDL cholesterol, LDL-c LDL cholesterol, DBP diastolic blood pressure, SBP systolic blood pressure, TG triglycerides, I intervention, C control

Table 4 Results of the generalised estimating equations to estimate the effect of 'time in follow-up' on clinical biomarkers

	MCA			Time (in months)		
	β	CI 95 %	p value	β	CI 95 %	p value
Glycaemia	-13.360	-50.451; 23.731	0.480	-7.103	-12.298; -1.908	0.007
HDL-c	-3.425	-11.906; 5.415	0.463	0.459	-0.153; 1.071	0.141
DBP	0.328	-5.858; 6.515	0.917	-1.054	-1.940; -0.167	0.020
SBP	-5.004	-18.470; 8.462	0.466	-2.620	-3.720; -1.520	<0.001

MCA multi-compartment compliance aid, HDL-c HDL cholesterol DBP diastolic blood pressure, SBP systolic blood pressure

medication but have struggled to manage it [25]. Those patients who intended to take their medicines as advised, could also benefit from other interventions such as medication reminder cards, which are perceived by patients as interfering less with their independence and autonomy [26]. Additionally, patients who have difficulties managing their medication may also have problems when using MCAs [26].

Patients in our study were using on average more than five medicines. Medication regimen complexity has also been associated with poor adherence [27, 28]. Reducing the complexity has been advocated as an important way of improving unintentional non-adherence [16]. Even the WHO included the reduction of complexity as a means of improving several of the five dimensions that affect adherence [9]. Medication regimen complexity, although

strongly associated with the number of medicines used [29], should not be the only parameter to take into account. Reliable instruments for precisely measuring the complexity have been created and validated [30–32].

In the bivariate pre-post analysis we found significant differences in HDL-c and in both systolic and diastolic blood pressure in the intervention group. Evidence reports a significant difference in diastolic, but not systolic blood pressure after a 6- or 8-month follow-up [14]. We also found significant reduction of fasting glycaemia in the intervention group, but not in the control, which could be analogous to the significant reduction in glycated haemoglobin reported in the Cochrane review after a 3- and 6-month follow-up [14]. None of the studies included in this systematic review took into consideration the time in follow-up in the statistical analysis, probably based on the

rationale that a controlled study design would reduce the risk of bias.

When introducing time in follow-up in a GEE model, we found that significance disappeared for most biomarkers, with time being the only variable associated with the effect. Two potential effects of time in follow-up should be considered. First, the possible Hawthorne effect [33] may be more important in patients using the MCAs than in those in the control group. Patients in the intervention group come across the MCA at least once a day, while patients in the control group have only monthly encounters with the pharmacist. Second, and more importantly, both groups were followed by a pharmacist, and this intervention may have a greater effect on clinical biomarkers than the MCA itself. Substantial evidence exists concerning the effect of pharmacists' interventions on blood pressure and diabetes [34, 35]. Previous studies reported a significant association between the time that pharmacists spent with patients and the number of problems resolved [36]. Subsequently, our study poses a rational doubt on the effect of MCAs compared with the effect of pharmacists' interventions. Further studies assessing the efficacy of MCAs should take into account the time in follow-up as a potential confounder.

A limitation of our study may be the small number of patients included; however this small sample was enough to achieve significance in the improvement of the clinical biomarkers analysed.

Conclusion

The use of multi-compartment compliance aids in a group of patients under pharmacist follow-up was associated with an improvement of some clinical biomarkers, such as fasting glycaemia, HDL-c, and blood pressure. However, when introducing the variable time in a generalised estimating equation analysis, these improvements remained associated only with the 'time in follow-up'. Our study demonstrates the necessity to consider time in further analyses when assessing the efficacy of MCAs on patients' clinical outcomes.

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Conflicts of interest The authors declare not having any conflict of interest regarding this study.

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