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Corresponding Author	FamilyName	**González-Bueno**
	Particle	
	Given Name	**J.**
	Suffix	
	Division	Pharmacy Department
	Organization	Consorci Hospitalari de Vic
	Address	Vic, Barcelona, Spain
	Division	Central Catalonia Chronicity Research Group (C3RG)
	Organization	University of Vic - Central University of Catalonia (UVIC-UCC)
	Address	Vic, Barcelona, Spain
	Phone	
	Fax	
	Email	javigbueno@gmail.com
	URL	
	ORCID	http://orcid.org/0000-0003-2474-5413
Author	FamilyName	**Sevilla-Sánchez**
	Particle	
	Given Name	**D.**
	Suffix	
	Division	Central Catalonia Chronicity Research Group (C3RG)
	Organization	University of Vic - Central University of Catalonia (UVIC-UCC)
	Address	Vic, Barcelona, Spain
	Division	
	Organization	Pharmacy Department
	Address	Parc Sanitari Pere Virgili, Barcelona, Spain
	Phone	
	Fax	
	Email	
	URL	
	ORCID	http://orcid.org/0000-0003-2993-6200
Author	FamilyName	**Puigoriol-Juvanteny**
	Particle	
	Given Name	**E.**
	Suffix	
	Division	Epidemiology Unit
	Organization	Consorci Hospitalari de Vic
	Address	Vic, Barcelona, Spain
	Division	Tissue Repair and Regeneration Laboratory (TR2Lab) Group, Faculty of Sciences and Technology & Faculty of Medicine
	Organization	University of Vic - Central University of Catalonia (UVIC-UCC)
	Address	Vic, Barcelona, Spain

	Phone	
	Fax	
	Email	
	URL	
	ORCID	http://orcid.org/0000-0002-5510-2480
Author	FamilyName	**Molist-Brunet**
	Particle	
	Given Name	**N.**
	Suffix	
	Division	Central Catalonia Chronicity Research Group (C3RG)
	Organization	University of Vic - Central University of Catalonia (UVIC-UCC)
	Address	Vic, Barcelona, Spain
	Division	Department of Geriatrics
	Organization	Consorci Hospitalari de Vic & Fundació Hospital de La Santa Creu de Vic
	Address	Vic, Barcelona, Spain
	Phone	
	Fax	
	Email	
	URL	
	ORCID	http://orcid.org/0000-0003-0138-6278
Author	FamilyName	**Codina-Jané**
	Particle	
	Given Name	**C.**
	Suffix	
	Division	Pharmacy Department
	Organization	Consorci Hospitalari de Vic
	Address	Vic, Barcelona, Spain
	Division	Central Catalonia Chronicity Research Group (C3RG)
	Organization	University of Vic - Central University of Catalonia (UVIC-UCC)
	Address	Vic, Barcelona, Spain
	Phone	
	Fax	
	Email	
	URL	
	ORCID	http://orcid.org/0000-0003-4688-1803
Author	FamilyName	**Espaulella-Panicot**
	Particle	
	Given Name	**J.**
	Suffix	
	Division	Central Catalonia Chronicity Research Group (C3RG)
	Organization	University of Vic - Central University of Catalonia (UVIC-UCC)
	Address	Vic, Barcelona, Spain
	Division	Department of Geriatrics
	Organization	Consorci Hospitalari de Vic & Fundació Hospital de La Santa Creu de Vic
	Address	Vic, Barcelona, Spain
	Phone	
	Fax	
	Email	
	URL	
	ORCID	http://orcid.org/0000-0002-7057-0901

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Abstract

This study aimed to assess the impact of the patient-centered prescription (PCP) model in medication adherence and effective prescribing in patients with multimorbidity.Uncontrolled before–after study in an intermediate care facility in a mixed urban–rural district. Inpatients aged ≥ 65 years with multimorbidity exposed to polypharmacy before hospital admission were consecutively enrolled. Every patient's treatment plan was analyzed through the PCP model, which includes interventions aimed at improving medication adherence. The primary endpoint was the change in the proportion of adherent patients between pre-admission and after discharge for all regularly scheduled long-term medications, using the proportion of days covered (PDC). Secondary endpoints included the change on mean PDC for all long-term medications, number of long-term medications, proportion of patients with hyperpolypharmacy, medication regimen complexity index (MRCI) score, drug burden index (DBI) score, number of potential inappropriate prescribing (PIP), and proportion of patients with ≥ 2 PIPs.Ninety-three non-institutionalized patients were included (mean age 83.0 ± SD 6.1 years). The proportion of adherent patients increased from 22.1 to 51.9% ($P < 0.001$). Intervention also improved mean PDC [mean difference (95% CI) 10.6 (7.7, 13.5)] and effective prescribing through a reduction on the number of long-term medications [− 1.3 (− 1.7, − 0.9)], proportion of patients exposed to hyperpolypharmacy (− 16.1%, $P < 0.001$), MRCI score [− 2.2 (− 3.4, − 1.0)], DBI score [− 0.16 (− 1.8, − 1.3)], number of PIPs [− 1.6 (− 1.8, − 1.3)], and proportion of patients with ≥ 2 PIPs (− 53.7%, $P < 0.001$).Studied intervention provides significant effective prescribing and medication adherence enhancements in non-institutionalized older patients with multimorbidity and polypharmacy.

Keywords (separated by '-') Multimorbidity - Polypharmacy - Inappropriate prescribing - Patient-centered care - Medication adherence

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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Improving medication adherence and effective prescribing through a patient-centered prescription model in patients with multimorbidity

J. González-Bueno[1,2] · D. Sevilla-Sánchez[2,3] · E. Puigoriol-Juvanteny[4,5] · N. Molist-Brunet[2,6] · C. Codina-Jané[1,2] · J. Espaulella-Panicot[2,6]

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Abstract

Purpose This study aimed to assess the impact of the patient-centered prescription (PCP) model in medication adherence and effective prescribing in patients with multimorbidity.

Methods Uncontrolled before–after study in an intermediate care facility in a mixed urban–rural district. Inpatients aged ≥ 65 years with multimorbidity exposed to polypharmacy before hospital admission were consecutively enrolled. Every patient's treatment plan was analyzed through the PCP model, which includes interventions aimed at improving medication adherence. The primary endpoint was the change in the proportion of adherent patients between pre-admission and after discharge for all regularly scheduled long-term medications, using the proportion of days covered (PDC). Secondary endpoints included the change on mean PDC for all long-term medications, number of long-term medications, proportion of patients with hyperpolypharmacy, medication regimen complexity index (MRCI) score, drug burden index (DBI) score, number of potential inappropriate prescribing (PIP), and proportion of patients with ≥ 2 PIPs.

Results Ninety-three non-institutionalized patients were included (mean age 83.0 ± SD 6.1 years). The proportion of adherent patients increased from 22.1 to 51.9% ($P < 0.001$). Intervention also improved mean PDC [mean difference (95% CI) 10.6 (7.7, 13.5)] and effective prescribing through a reduction on the number of long-term medications [− 1.3 (− 1.7, − 0.9)], proportion of patients exposed to hyperpolypharmacy (− 16.1%, $P < 0.001$), MRCI score [− 2.2 (− 3.4, − 1.0)], DBI score [− 0.16 (− 1.8, − 1.3)], number of PIPs [− 1.6 (− 1.8, − 1.3)], and proportion of patients with ≥ 2 PIPs (− 53.7%, $P < 0.001$).

Conclusion Studied intervention provides significant effective prescribing and medication adherence enhancements in non-institutionalized older patients with multimorbidity and polypharmacy.

Keywords Multimorbidity · Polypharmacy · Inappropriate prescribing · Patient-centered care · Medication adherence

✉ J. González-Bueno
javigbueno@gmail.com

[1] Pharmacy Department, Consorci Hospitalari de Vic, Vic, Barcelona, Spain

[2] Central Catalonia Chronicity Research Group (C3RG), University of Vic - Central University of Catalonia (UVIC-UCC), Vic, Barcelona, Spain

[3] Pharmacy Department, Parc Sanitari Pere Virgili, Barcelona, Spain

[4] Epidemiology Unit, Consorci Hospitalari de Vic, Vic, Barcelona, Spain

[5] Tissue Repair and Regeneration Laboratory (TR2Lab) Group, Faculty of Sciences and Technology & Faculty of Medicine, University of Vic - Central University of Catalonia (UVIC-UCC), Vic, Barcelona, Spain

[6] Department of Geriatrics, Consorci Hospitalari de Vic & Fundació Hospital de La Santa Creu de Vic, Vic, Barcelona, Spain

Introduction

Despite four decades of research, medication adherence in patients with chronic conditions remains suboptimal [1]. Medication non-adherence is a complex process determined by many modifiable and unmodifiable determinants which can be categorized into five dimensions (socio-economic, patient-related, therapy-related, condition-related, and health system–related) [2]. Non-adherence can occur due to a late or non-initiation of the prescribed treatment, suboptimal implementation of the dosing regimen, or early discontinuation [3]. Factors influencing medication non-adherence may also be categorized as intentional (e.g., patients are influenced by knowledge or beliefs about medications and do not voluntarily adhere) or unintentional (e.g., patients are unable to manage their medicines because the treatment workload exceeds patient capacity) [4, 5]. Non-adherence negative effects include increased morbidity, mortality, and costs [2]. Patients with multimorbidity are more likely to have polypharmacy and to be frail, making them particularly vulnerable to non-adherence and the associated consequences [6, 7].

A range of simple to complex behavioral and educational interventions have been tested, individually or in combination, to improve medication adherence in patients with multimorbidity, yet most show only modest efficacy [8, 9, 10]. Interventions are usually not matched to patient determinants for non-adherence despite the importance of tailoring interventions to patient characteristics [4]. Medication use is a complex process that involves different healthcare professionals so non-multidisciplinary interventions have been stressed as another limitation [11].

Appropriate measurement of medication adherence in patients receiving polypharmacy remains a challenge. Although self-report methods are the most commonly reported in the literature, this is probably due to convenience rather than the validity of such approaches [12, 13, 14].Nonetheless, self-report adherence scales may help inform tailored interventions to improve medication adherence by identifying barriers and beliefs that are influencing adherence [15]. In contrast, quasi-objective adherence measures, such as proportion of days covered (PDC), are less subject to bias and provide a more conservative estimate of adherence than self-report methods [12, 13, 14]. Multiple discretized PDC might be considered an estimate of choice regarding its sensitivity, specificity, and applicability [16].

Medication appropriateness has been commonly outside of the traditional purview of medication adherence. However, treatment optimization by reducing inappropriate prescribing and, when achievable, reducing polypharmacy has been recommended within patient-centered strategies to improve medication adherence in older persons [11]. Effective prescribing additionally considers patient understanding about medications [17]. Both concepts involve medication appropriateness as a key element for approaching non-adherence. Optimized treatment could be reached through explicit criteria based on drug medication lists or by person-centered frameworks which consider life expectancy, time to benefit, goals of care, and appropriate treatment while ensuring patient values guide all clinical decisions [18].

The patient-centered prescription (PCP) model is a systematic 4-stage process, carried out by a multidisciplinary team, which centers therapeutic decisions on the patient's global assessment. Such an approach represents an advanced medication review framework [19], which has been associated with reducing inappropriate prescribing and medication burden in patients with multimorbidity [20, 21, 22].The PCP model was developed by the Central Catalonia Chronicity Research Group (C3RG), and its implementation in clinical practice is recommended by the Department of Health, Government of Catalonia (Spain) for elderly and frail patients with multimorbidity [23]. More recently, the PCP model has been proposed as an useful strategy to enhance both effective prescribing and adherence by including a qualitative assessment of non-adherence and a set of interventions aimed at improving medication adherence [24, 25, 26].

The aims of the study were to assess the impact of the PCP model in medication adherence and effective prescribing in patients with multimorbidity.

Methods

Study design and setting

This was a quasi-experimental (uncontrolled before–after) study in patients with multimorbidity admitted in a convalescent and rehabilitation ward in Sant Jaume de Manlleu Hospital, a 66-bed intermediate care step-down community hospital located close to Vic University Hospital, an acute care teaching hospital. Both are referral care centers for the Osona county, a mixed urban–rural district in Barcelona, Spain, population 160,000 inhabitants (3.3% aged 85 years or more). Older patients with complex needs are eligible for intermediate care when a functional decline due to an acute episode recommends rehabilitation and/or longer lengths of stay before hospital discharge. Recommendations from the CONSORT extension guidelines for pilot and feasibility trials adapted for quasi-experimental studies and ESPACOMP medication adherence reporting guideline (EMERGE) were followed [27, 28].

Journal : Large 228 | Article No : 3207 | Pages : 11 | MS Code : 3207 | Dispatch : 26-8-2021

Participants

Patients were consecutively considered for inclusion if they met the following eligibility criteria: older people (≥ 65 years) with ≥ 2 chronic conditions (from the expanded diagnostic clusters within the Johns Hopkins University Adjusted Clinical Groups (ACG) system) [29] who were receiving polypharmacy (≥ 5 regularly scheduled long-term (≥ 3 months) medications) before hospital admission. Patients were excluded from study participation if any of the following was applicable: limited life expectancy (using NECPAL CCOMS-ICO® tool criteria) [30], nursing home residents, or hospital admissions during the 6 months prior to inclusion in the study (to ensure an appropriate assessment of medication adherence prior to study intervention).

From April 2019 to February 2020, potential participants were enrolled in the study if informed consent was provided by them, or by their relatives in case of them being unable to provide consent, as approved by the ethics committee.

Intervention: patient-centered prescription model

Every patient's treatment plan was analyzed prior to discharge by a geriatrician and a hospital pharmacist through the 4-stage PCP model.

(i) Patient-centered step: A patient's global assessment by comprehensive geriatric assessment and calculation of the frailty index (Frail-VIG) [31] determines an individual therapeutic goal (prolonging survival, maintaining functionality, or prioritizing symptomatic control). This step additionally includes a qualitative assessment of patient adherence performed by a hospital pharmacist with the Spanish-version ARMS [24], helping to identify main non-adherence determinants (including high complexity medication regimens, adverse drug events, or poor knowledge or false beliefs about medications) and allowing subsequent tailored interventions. Written permission for conducting adherence assessments was obtained from the original developer of the English-version ARMS [32].

(ii) Diagnosis-centered step: Aims to guarantee medications fit individual therapeutic goal. It includes deprescribing strategies, thus simplifying regimen complexity. Both in this step and in the following, decisions concerning changes in the treatment plan are debated through a consensus meeting and agreed on by the geriatrician and the hospital pharmacist.

(iii) Medication-centered step: Reassess high-risk medications to prevent adverse events and simplify dosing regimens.

(iv) Therapeutic plan: Through this step, an individualized therapeutic plan is agreed with the patient and/or main caregiver. It includes motivational interviewing and pharmacotherapy counseling provided by the hospital pharmacist. To ensure an appropriate communication with community pharmacists and the primary care physician (which will be responsible for follow-up after the intervention), changes and suggestions relating to therapeutic plan are described and justified in a specific section as part of the hospital discharge report. Furthermore, ambulatory medication refilling by community pharmacies through multidose drug-dispensing systems is recommended for non-adherent patients with high medication regimen complexity (medication regimen complexity index (MRCI) [33] score ≥ 30) and/or very dependent for activities of daily living (Barthel index [34] < 40) and/or with cognitive impairment (Mini Mental State Examination score (MMSE) [35] < 25).

Data collection

Data collected are as follows: age, sex, length of stay, chronic conditions (from the expanded diagnostic clusters within the Johns Hopkins University ACG system), frailty index (Frail-VIG), Barthel index for activities of daily living, cognitive impairment (MMSE), individual therapeutic goal (based on the PCP model), medication management at home (medication administration (independent vs assisted), medication refill (independent vs assisted)), long-term medications (regularly scheduled and when required (*prn*) medications), hyperpolypharmacy (≥ 10 regularly scheduled long-term medications), medication adherence, regimen complexity, anticholinergic, and sedative risk exposure and potential inappropriate prescribing (PIP).

Demographic and medical data were collected from the patient's electronic medical records and by interviewing the patient and/or main caregiver. Frailty index, Barthel index, cognitive status, and medication management at home corresponded to the patient's status previous to hospitalization.

Medication adherence was assessed during a 6-month period before admission and 6-month period after discharge using the PDC [16]. PDC for all regularly scheduled long-term medications was estimated as the sum of the days supplied for each medication according with electronic linked pharmacy claim data. At least two prescription refill dates during a time period ≥ 90 days were required for each medication to calculate this ratio. The PDC rate was converted to a percentage based on the percentage of days covered by dispensed medication. Patients were considered adherent if PDC for each medication was ≥ 80% (excluding last refill).

Regimen complexity was assessed for all long-term medications (defined as regularly scheduled long-term

Journal : Large 228 | Article No : 3207 | Pages : 11 | MS Code : 3207 | Dispatch : 26-8-2021

medications plus when required (*prn*) medications) on admission and discharge using the Spanish-version MRCI [34].

Anti-cholinergic and sedative risk exposure for regularly scheduled long-term medications was assessed on admission and discharge using the drug burden index (DBI) [37, 38].

PIP was considered on admission and discharge in any of the following circumstances: absence of evidence-based indication, dosing unnecessarily high considering the patient's specific therapeutic objectives, unacceptable adverse drug event, contraindicated drug–drug interaction, unnecessary therapeutic duplication, inappropriate dosing or pharmaceutical dosage form, or any prescription characterized as potentially inappropriate by the American Geriatrics Society 2019 Updated Beers criteria® [39].

Endpoints

The primary endpoint was the change in the proportion of adherent patients between pre-admission and after discharge for all regularly scheduled long-term medications.

Secondary endpoints included the change between pre-admission and after discharge of the following variables: mean PDC for all regularly scheduled long-term medications, number of regularly scheduled long-term medications, proportion of patients with hyperpolypharmacy, MRCI score for all long-term medications, DBI score for all regularly scheduled long-term medications, number of PIPs, and proportion of patients with ≥ 2 PIPs.

Sample size and statistical analysis

A sample size calculation was performed to detect a decline in the proportion of non-adherent patients using a two-sided paired-*t*-test estimation method. The proportion of non-adherent patients prior to intervention was estimated to be 75% (own estimate based on routine clinical practice data). A sample size of 92 patients would be sufficient to detect a 30% reduction with 80% power and a 5% significance (estimating a 20% loss).

Statistical analysis was performed using SPSS version 27.0 (IBM SPSS Statistics, USA).

Results for categorical variables were expressed as absolute and relative frequencies and results for continuous variables as means and standard deviations (SDs) if they followed a normal distribution, or as the median and inter-quartile range (IQR) if they did not follow a normal distribution.

Comparisons between the pre-admission and after-discharge groups were performed using Student's *t* test for paired data for parametric continuous variables, or Wilcoxon signed-rank test for non-parametric continuous variables. McNemar's test was applied to analyze the changes on categorical variables. Losses to follow-up during the 6-month period after discharge were excluded from medication adherence analyses but included on effective prescribing analyses.

Subgroup analysis was performed to explore the consistency of the intervention on main and secondary outcomes depending on patient frailty (Frail-VIG index 0–0.19 vs 0.20–0.35 vs > 0.35). Medication adherence–related outcomes were also analyzed considering patient autonomy for medication administration at home (independent vs assisted), and medication refills at home (independent vs assisted).

Multivariable logistic regression analysis restricted to non-adherent patients before admission was conducted to identify variables that significantly predicted improvements on primary outcome measure after study intervention. Multivariate model was performed on variables which had a P value < 0.05 at the bivariate analyses using stepwise regression.

Continuous data are presented as mean (standard deviation) or median (inter-quartile range) depending on the underlying distribution of the data. Categorical data are reported as numbers (proportion). Statistical significance was set at a two-sided P value of 0.05.

Results

Of the 256 patients discharged from the intermediate care facility during the study period, 93 non-institutionalized older patients with multimorbidity and polypharmacy were included (Fig. 1). The average age was 83.0 (SD 6.1) years, and the majority were female (66%, $n = 61$). The patients had a median number of chronic conditions of 7.0 (IQR 4–12). About 81% ($n = 75$) had mild or moderate frailty, 54% ($n = 50$) had mild-to-moderate dependence for activities of daily living, and 43% ($n = 40$) had cognitive impairment. Consequently, maintaining functionality was the most prevalent individual therapeutic goal (80%, $n = 74$). Regarding medication management at home, more than a half of patients required some assistance for medication administration (50.5%, $n = 47$) or prescription refills (62.4%, $n = 58$). Further characteristics are shown in Table 1. No significant differences in baseline characteristics were identified between losses to follow-up and patients included in the medication adherence analysis except for sex, as losses to follow-up were 31% in males and 10% in females.

Intervention resulted in both an enhancement in medication adherence and effective prescribing (Table 2). The proportion of adherent patients for all regularly scheduled long-term medications increased from 22.1 to 51.9% ($P < 0.001$). Intervention also improved mean PDC and effective prescribing through a reduction on the number of regularly scheduled long-term medications, the proportion

Journal : Large 228 | Article No : 3207 | Pages : 11 | MS Code : 3207 | Dispatch : 26-8-2021

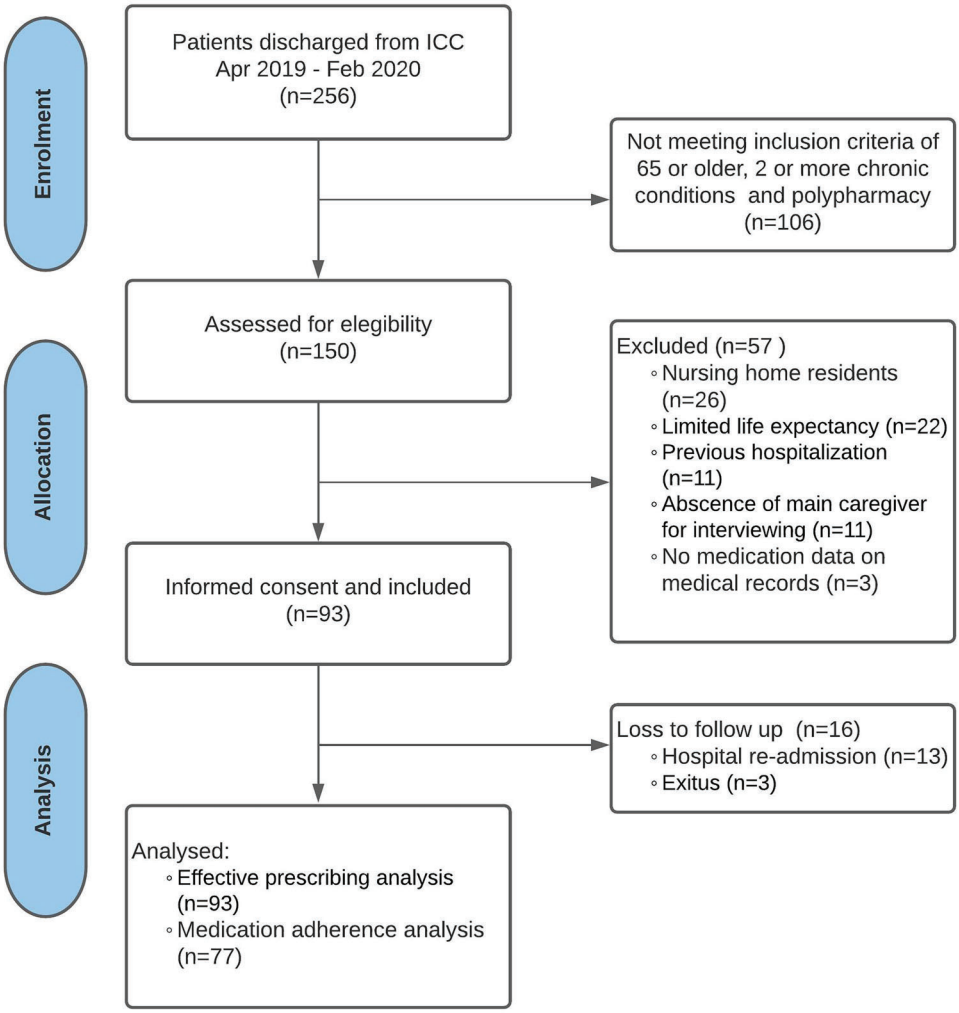

Fig. 1 Flow diagram: study participation and selection process. ICC Intermediate Care Center

of patients exposed to hyperpolypharmacy, the MRCI, the DBI, the number of PIPs, and the proportion of patients with ≥ 2 PIPs.

Exploratory subgroup analyses for frailty status and patient autonomy with medication management at home were in most cases consistent with primary analyses (Online Resource). Frailty (mild or moderate to severe) versus non-frailty resulted in an increase in the proportion of patients with hyperpolypharmacy, number of regularly scheduled long-term medications, MRCI, DBI, and number of PIPs at pre-admission. Mildly frail patients compared with non-frail or moderately to severely frail patients showed a higher benefit from the intervention in terms of greater reduction on the number of regularly scheduled long-term medications and in the proportion of patients with hyperpolypharmacy. Declines on MRCI, number of PIPs, and proportion of patients with ≥ 2 PIPs were greater on frail versus non-frail patients. Furthermore, greater improvement in the proportion of adherent patients was shown in patients partially or totally assisted with medication management at home.

Twenty-eight (47%) out of 60 patients with non-adherence for all regularly scheduled long-term medications before admission became adherent after discharge due to study intervention. In multivariate analysis, being partially or totally assisted for medication refills at home [odds ratio (OR) = 5.5, 95% confidence interval (CI) 1.5, 20.0), $P = 0.010$], having ≤ 1 PIPs after discharge (OR = 14.5, 95% CI 1.8, 112.1, $P = 0.011$), and experiencing 1-point reduction on DBI between pre-admission and after discharge (OR = 6.2, 95% CI 1.5, 24.7, $P = 0.010$) significantly predicted improvements in the primary outcome measure.

Discussion

Findings from the present study support the benefit of a patient-centered prescription model for improving medication adherence and effective prescribing in non-institutionalized older patients with multimorbidity and polypharmacy discharged

Journal : Large 228 | Article No : 3207 | Pages : 11 | MS Code : 3207 | Dispatch : 26-8-2021

Table 1 Characteristics of non-institutionalized older patients with multimorbidity and polypharmacy discharged from a convalescent and rehabilitation ward in an intermediate care center ($N = 93$)

Characteristic	
Age in years (mean (SD))	83.0 (6.1)
Sex (*n* (%))	
Male	32 (34.0)
Female	61 (66.0)
Length of stay in hospital, days (median (IQR))	37 (24.0–58.5)
Chronic conditions (median (IQR))	7.0 (4.0–12.0)
Frailty (Frail-VIG) (mean (SD))	0.28 (0.11)
No frailty (Frail-VIG < 0.2) (*n* (%))	15 (16.1)
Mild frailty (Frail-VIG 0.2–0.35) (*n* (%))	50 (53.8)
Moderate frailty (Frail-VIG 0.36–0.50) (*n* (%))	25 (26.9)
Severe frailty (Frail-VIG > 0.50) (*n* (%))	3 (3.2)
Activities of daily living (Barthel index) (median (IQR))	85 (15–100)
No dependency (Barthel index ≥ 95) (*n* (%))	26 (28.0)
Mild–moderate dependency (Barthel index 90–65) (*n* (%))	50 (53.8)
Moderate–severe dependency (Barthel index 60–25) (*n* (%))	15 (16.1)
Absolute dependency (Barthel index ≤ 20) (*n* (%))	2 (2.2)
Cognitive impairment	
Absence (equivalent to MMSE > 24) (*n* (%))	53 (57.0)
Mild (equivalent to MMSE 21–24) (*n* (%))	23 (24.7)
Moderate (equivalent to MMSE 10–20) (*n* (%))	17 (18.3)
Individual therapeutic goal (based on the PCP model)	
Prolonging survival (*n* (%))	17 (18.3)
Maintaining functionality (*n* (%))	74 (79.6)
Prioritizing symptomatic control (*n* (%))	2 (2.2)
Medication administration at home	
Independent (*n* (%))	46 (49.5)
Assisted (*n* (%))	47 (50.5)
Medication refill at home	
Independent (*n* (%))	35 (37.6)
Assisted (*n* (%))	58 (62.4)

SD standard deviation, *IQR* inter-quartile range, *MMSE* Mini Mental State Examination, *PCP* patient-centered prescription

from an intermediate care facility. In a cohort of patients, most of them with clinical frailty and dependence for activities of daily living, the study intervention appears to be consistently effective regardless of frailty severity or patient autonomy with medication management at home.

A growing literature has suggested the existence of a close link between effective prescribing and medication adherence in older patients with multimorbidity [11, 17, 25, 40]. To the best of our knowledge, this is the first clinical study to verify through routine practice conditions previous theoretical frameworks. Evidence from randomized controlled trials is still not available [41].

Comparisons between the current study and published literature for improvement in the proportion of adherent patients secondary to study intervention are challenging due to unclear adherence definitions, inadequate measurement of adherence outcomes, or heterogeneity of methods used for reporting multiple medication adherence [12, 28]. Multiple discretized PDC has shown to double specificity as compared to other quasi-objective adherence measures as the mean PDC [16]. This fact would justify the low adherence rates seen in the current study. Cross et al. reported an average increase in the absolute number of adherent participants of 12.8% for mixed educational and behavioral interventions aimed at improving medication adherence in older community-dwelling adults prescribed multiple long-term medications [10].In the light of previous result, the magnitude of the effect showed in current study seems to be of great importance.

Due to the complex nature of the study intervention, it is difficult to state which of the features were most responsible for the benefit in adherence we saw. In our view, main reasons for the success of study intervention include the following: a mixed approach with both behavioral and educational

Journal : Large 228 | Article No : 3207 | Pages : 11 | MS Code : 3207 | Dispatch : 26-8-2021

Table 2 Impact of the intervention on medication adherence and effective prescribing scores between pre-admission and after discharge

	Change in scores between pre-admission and discharge (n (%)) or (mean ± SD))		Difference (n (%)) or (mean (95% CI))	P value
	Pre-admission ($n_1 = 77$) ($n_2 = 93$)*	After discharge ($n_1 = 77$) ($n_2 = 93$)*		
Adherent patients[a]	17 (22.1)	40 (51.9)	+23 (+29.8)	< 0.001
PDC[b]	81.0 ± 15.7	91.6 ± 9.9	+10.6 (+7.7, +13.5)	< 0.001
No. of regularly scheduled long-term medications[b]	8.8 ± 2.8	7.5 ± 2.7	−1.3 (−1.7, −0.9)	< 0.001
Patients with hyper-polypharmacy (≥ 10 medications)[a]	35 (37.6)	20 (21.5)	−15 (−16.1)	< 0.001
MRCI[b]	24.8 ± 10.7	22.5 ± 9.4	−2.2 (−3.4, −1.0)	< 0.001
DBI[b]	0.99 ± 0.81	0.83 ± 0.69	−0.16 (−0.27, −0.05)	0.004
No. of PIPs	2.6 ± 1.5	1.0 ± 0.89	−1.6 (−1.8, −1.3)	< 0.001
Patients with ≥ 2 PIPs[a]	68 (73.1)	18 (19.4)	−50 (−53.7)	< 0.001

PDC proportion of days covered, *MRCI* medication regimen complexity index, *DBI* drug burden index, *PIP* potentially inappropriate prescribing, *SD* standard deviation, *CI* confidence interval

*Medication adherence and effective prescribing analyses are performed on a sample of $n_1 = 77$ and $n_2 = 93$ patients, respectively

[a]Categorical data and differences between pre-admission and post-discharge are presented as numbers (proportion)

[b]Continuous data are presented as mean (SD) and differences between pre-admission and post-discharge as mean (95% CI)

[c] + and − symbols signify the direction of change/difference between pre-admission and post-discharge scores

components, the development of patient-specific care plans based on patient's barriers identified through the qualitative assessment of medication adherence, the active involvement of patients and/or main caregivers with treatment choices, and multidisciplinary collaboration.

Published literature shows that mixed interventions are more effective at improving the proportion of people who satisfactorily adhere to their prescribed medications than educational or behavioral interventions alone [10]. Study intervention includes a range of behavioral (simplification of medication regimen, prevention of adverse drug events, and recommendation for ambulatory refilling through multidose drug-dispensing systems in patients who had a decreased medication management capacity) and educational/counseling strategies selected following a comprehensive and standardized methodology [25],thus confirming the previous statement. Moreover, matching interventions and factors related to patients' adherence has also been proposed as a key ingredient for successful interventions to improve adherence [42].For this purpose, a qualitative assessment of medication adherence through the Spanish-version ARMS scale was performed, aiming to provide tailored care [26]. Furthermore, shared decision-making to agree on an individualized care plan has been highlighted as main component for an optimum care model for patients with multimorbidity [43, 44].Shared decision-making is also considered a critical element of successful medication adherence by enhancing patient's active involvement in treatment choices [40]. In line with previous considerations, the PCP model pursues a shared decision-making by improving patient's knowledge and satisfaction with treatment choices through a motivational interview. Finally, the provision of coordinated care by multidisciplinary teams has been proposed as a strategy that could maximize the effectiveness of care for patients with multimorbidity [45, 46].Due to the complex nature of medication management of patients with multimorbidity, multidisciplinary collaboration involving geriatricians and hospital pharmacists is essential to achieve the best health outcomes.

In addition to the above potential drivers of intervention success, we cannot exclude the possibility that high prevalence of non-adherence before admission could have maximize the benefit derived from study intervention. This is supported by the fact that including non-adherent patients has been significantly associated with effective adherence interventions [47].

Numerous studies have evaluated efforts to reduce inappropriate prescribing, with most interventions focused on the use of explicit criteria and only a few considering patient-centered approaches [48, 49, 50]. Although most of the studies reported improvements in medication appropriateness, including reductions in medication burden or PIP,

just a few were performed in a hospital setting and even fewer in intermediate care facilities [51]. Because hospitalization often leads to increased medication burden for older patients, the benefits from the intervention are of even more significance. Furthermore, reduction shown in the proportion of patients with ≥ 2 PIPs might be clinically relevant considering the association of PIP with negative health outcomes and its cumulative effect [52, 53, 54]. Longer lengths of hospital stay in intermediate care facilities versus acute care settings is possibly an important facilitator for effective prescribing enhancements, allowing for greater time for optimizing the treatment plan. However, the number of PIPs which still prevails after hospital discharge warrant ambulatory interventions for further improvements in medication appropriateness.

As the frailty of patients increases, so does the number of long-term medications, prevalence of hyperpolypharmacy, regimen complexity, anticholinergic and sedative risk exposure, and PIP. This association has been previously documented [21, 55, 56],revealing that treatments are commonly not individualized, but rather are based on the same general recommendations for the whole population. Frail patients tend to show a higher benefit from the intervention in effective prescribing outcomes compared with non-frail individuals. This fact is highly significant due to increased vulnerability of frail patients to adverse drug events and to difficulties arising in self-managing complex regimens.

Subgroup analyses also raise the issue of caregiver influence on patient's medication adherence, as caregiver availability for medication management at home does not in itself guarantee an optimal medication adherence. These findings recognize the importance to engage them on strategies to improve medication adherence, as their own values and preferences might influence patient's medication adherence.

Furthermore, exploratory analysis suggests that the greater the impact of the intervention in improving effective prescribing in non-adherent patients, the greater the probability they benefit in terms of medication adherence. These results underscore the existence of a strong association between effective prescribing and medication adherence and the importance of address them as a whole.

Strengths and limitations

Study strengths include a pragmatic design, a frequently under-researched inpatient setting, and the use of reliable and validated medication adherence estimates. In addition, this study is the first to report results from an intervention arising from a qualitative assessment of medication adherence through the ARMS scale [24, 32].The PCP model has become a well-established therapeutic intervention for improving effective prescribing in our institution. This ensures the applicability of the study intervention. In any case, its adaptation to diverse settings will be feasible as long as the core components of the model are maintained.

Nevertheless, there are certain limitations that should be taken into consideration, mainly concerning study design and sample size. A quasi-experimental design was chosen due to ethical considerations, because a randomized design would have prevented some patients from benefitting from an intervention with known efficacy on medication appropriateness [21, 22, 57]. In addition, as the application of the PCP model has already been integrated in the routine clinical practice of our institution, randomization of patients to a control and intervention groups might have increased the risk of contamination bias. In any case, results must be interpreted in the context of main study limitations, including a small patient sample, the absence of a control group, and significant losses to follow-up. Although the sample size was valid to demonstrate improvements in medication adherence, the study was not powered enough for exploratory analysis. Thus, results from subgroups and multivariate analysis warrant further investigation.

Prescription refills are not equivalent to administration of medication so adherence measures might be overestimated. Nonetheless, the availability of adherence rates for each patient's medication to estimate primary outcome measure enhances confidence on its validity.

Medication appropriateness and effective prescribing are both close but not interchangeable terms. The latest additionally considers discussion of solutions to patients' perceived barriers to obtaining and taking medications that are part of an agreed-upon treatment plan [58]. We firmly believe study intervention fits previous definition despite not having capture this conceptual dimension through standardized measures.

Implications

In the light of present findings, comprehensive geriatric assessment should recognize patients' non-adherence determinants through qualitative adherence assessments to ensure tailored interventions for improving effective prescribing. Consideration of frailty status could be important for guiding effective prescribing interventions, as frail patients appear to obtain greater benefits from study interventions. Given the shorter life expectancy of frail patients, a lower time to benefit from effective prescribing improvements might minimize the impact of previous statement. Further research is needed to identify patients that would benefit the most from the intervention. Future efforts should be made in the context of multicenter cluster randomized

Journal : Large 228 | Article No : 3207 | Pages : 11 | MS Code : 3207 | Dispatch : 26-8-2021

trials to provide solid scientific evidence. Multilevel strategies and continuity of care involving primary care physicians and community pharmacists are mandatory to more effectively lessen PIP and to continue improving medication adherence rates. Research to better understand the implications of effective prescribing on medication adherence in older adults prescribed multiple medications would be well warranted.

Conclusions

The PCP model provides significant effective prescribing and medication adherence enhancements in non-institutionalized older patients with multimorbidity and polypharmacy, regardless of frailty severity or patient autonomy with medication management at home.

Mixed behavioral and educational interventions, tailored care based on patient's medication adherence barriers, agreement of patients and/or main caregivers with provided interventions, and multidisciplinary collaboration could be the core components for successful interventions aiming to improve medication adherence.

Our findings further suggest that frail patients tend to show a higher benefit from the intervention in effective prescribing.

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Author contribution All authors contributed to the study conception and design. González-Bueno J, Sevilla-Sánchez D, Puigoriol-Juvanteny E, and Molist-Brunet N performed material preparation, data collection, and analysis. González-Bueno J wrote the first draft of the manuscript, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and material The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Ethics approval This study (ID PR223) was approved by the Ethics and Clinical Research Committee of the Osona Foundation for Research and Health Education – Vic Consortium Hospital, Barcelona, Spain. The authors certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate and consent for publication Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare no competing interests.

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