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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Optimizing elderly pharmacotherapy: polypharmacy vs. undertreatment. Are these two concepts related?

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Abstract
Purpose This study aimed to estimate the prevalence of polypharmacy and potential prescribing omissions (PPO) and their related factors in community-dwelling elderly patients and to examine any possible relationship between these two concepts.
Methods A cross-sectional study was carried out including patients 65 years of age or over living on the island of Lanzarote (Spain). Sociodemographic, clinical and functional variables were collected, together with full data on drug therapy. The percentage of patients receiving ≥5 medications (polypharmacy) and the percentage of patients receiving at least one PPO according to Screening Tool to Alert doctors to Right Treatment (START) criteria (underprescription) were the two primary endpoints.
Results A total of 1844 medications were prescribed to the 407 patients included in our study. The overall prevalence of polypharmacy was 45 %. The risk factors associated with polypharmacy were comorbidity (OR 1.98, 95 % CI 1.63–2.44), limitations in activities of daily living (ADL; OR 3.0, 95 % CI 1.51–6.11), and being prescribed a drug in the Anatomical Therapeutic Chemical classification (ATC) C group (OR 7.92, 95 % CI 4.10–16.25) or in the N group (OR 3.80, 95 % CI 2.25–6.55). START criteria identified a total of 303 PPO in 170 (41.8 %) subjects. The risk of PPO increased by 60 % for every additional point in the Charlson Comorbidity Index (OR 1.60, 95 % CI 1.35–1.91). Polypharmacy also independently predicted the odds of at least one PPO according to START criteria (OR 2.19, 95 % CI 1.36–3.55).
Conclusion Our findings show high rates of polypharmacy and PPO, as well as a clear relationship between these two concepts.

Keywords Polypharmacy · Undertreatment · Potential prescribing omissions · START · Elderly · Spain

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Introduction

There has been a steady increase in drug consumption over the past few years. This may be related to different factors, such as the development of new drugs, changes in prescribing recommendations, pharmacological approaches to certain conditions that have not been treated to date, the increase in preventive therapies and the introduction of new clinical practice guidelines [1]. Higher consumption rates are particularly relevant in the elderly population, leading to an increase also in the number of patients with polypharmacy [2].

The term polypharmacy refers to the use of multiple medicines and/or the administration of more medicines than is clinically indicated, representing unnecessary medication use. However, for many years, there has been no agreement regarding the number of concomitant medications a person is taking that could be defined as "polypharmacy". Indeed, some investigators have chosen three or more medications as the threshold for polypharmacy [3], or four or more [4, 5], five or more [2, 6–15] and even six or more medications [16–18]. The cut-off point that is most often selected in the scientific

literature is five or more medications [19]. Indeed, a recent study concluding that five was an optimal discriminating number of concomitant medications associated with geriatric syndromes and functional outcomes, and mortality [20] has recently lent credibility to this figure as the best definition for polypharmacy. It is generally agreed that excessive polypharmacy refers to ongoing treatment with over 10 drugs [9–11, 14–16]. There are enormous differences in the prevalence of polypharmacy in the different studies, which may range between 5 and 78 % [21], due to differences in cut-off points, age groups, study settings, data sources and type of medications in each publication.

Probably, the main reasons for polypharmacy are longer life expectancy, the accumulation of comorbidities and the implementation of evidence-based clinical practice guidelines. In any event, polymedication is associated with greater complexity in clinical management and a higher rate of adverse events. A higher risk of adverse drug reactions (ADR), drug interactions, non-adherence, diminished functional status and various geriatric syndromes, such as cognitive impairments, falls, urinary incontinence and poor nutritional status, are among such negative health outcomes [22–25]. As a result, recent studies have given consideration to polypharmacy as an indicator of high-risk prescribing, together with the Drug Burden Index and the Beers criteria [26].

Many researchers have examined potentially inappropriate medication and polymedication jointly. However, only a few cases have also included the concept of underprescription. Treatment omissions are nonetheless very important to value the quality of pharmacological therapy. In fact, *suboptimal prescribing* has been defined as overuse (polypharmacy), inappropriate prescribing (drug whose risks are greater than the benefits in older adults) and underuse of indicated medications [27, 28]. This omission of drug therapy indicated for the treatment or prevention of a disease or condition may be linked to certain health outcomes in older patients, such as, for instance, the greater risk of cardiovascular events and mortality [13]. Until recently, when the Screening Tool to Alert doctors to Right Treatment (START) was published, underprescription had been evaluated with inconsistent definitions and focused on the omissions of selected medications for specific diseases [8, 13, 18, 29, 30]. START assesses the underuse of medicines for several common conditions simultaneously and incorporates 22 evidence-based indicators of prescribing omissions in older people [31].

The scant publications examining the relationship between polypharmacy and underprescribing show contradictory results. While for some researchers, the number of medications may act as a risk factor for underuse [8], for others, this association is not yet proven [29, 32–34]. Furthermore, we know there are major geographical differences in the distribution of polypharmacy and other prescribing indicators, which emphasizes the need to examine these with a view to targeting specific activities that may lead to improvements [35]. As a result, it is of interest to ascertain which pharmacological groups and risk factors are associated in each area with polypharmacy and underprescription, as well as to study the possible relationship between both these concepts that seem, at first sight, to be in opposition to one another. Bearing this in mind, the aims of this paper were (i) to determine the prevalence of polypharmacy and its predictive factors, (ii) to determine the rate of potential prescribing omissions (PPO) and its associated factors and (iii) to determine the relationship between polypharmacy and underprescription, in line with the PPO detected using the START.

Methods

Study setting and population

A cross-sectional study was performed. The study population comprised all community-dwelling residents over the age of 65 on Lanzarote (Canary Islands, Spain), where there are 15 primary healthcare centres. We used stratified random sampling to select a representative sample of the population, with proportional allocation of the population for each healthcare centre. Considering an expected prevalence of polypharmacy and PPO [12, 34] of p=40 %, a confidence level of $1-\alpha$= 0.95, absolute accuracy of 4.67 % and a design effect δ=1.0, we achieved an overall sample of 407 patients. Patients were selected randomly within each healthcare centre from a general list of healthcare cards issued by the National Health System and provided by the Primary Care Board.

Data collection

The selected patients were invited to participate in the study by phone and, if they accepted, were asked to attend their health centre with their medication. In cases of mobility impairment or health problems, our geriatrician conducted the evaluation in the patient's home. All patients were requested to provide their informed consent.

Our main source of data comes from the interviews with each patient using a structured questionnaire, further complemented by a review of the packaging of all medications and medical records. In many cases, the main carer was also present at the interview. This enabled us to ascertain as closely as possible the real medication taken by the patients. Full data were compiled on dosage and duration of drug treatment, while the corresponding Anatomical Therapeutic Chemical classification (ATC) code was duly assigned to each drug. In the questionnaire, besides full details of drug therapy, a wide range of variables were also included to see the patients' clinical and sociodemographic characteristics and functional evaluation. The clinical diagnoses were examined

and the Charlson Comorbidity Index (CCI) [36] was calculated for each patient. We analysed patients' independence in activities of daily living (ADL) with the Katz Index [37], their cognitive function with the Short Portable Mental State Questionnaire (SPMSQ) by Pfeiffer [38] and their mood status with the Geriatric Depression Scale (GDS-15) by Yesavage [39]. The Katz Index of ADL (defined as needing assistance with bathing, dressing, toileting, transferring, continence, feeding) was used to categorize patients into two functional groups: independent or those who only need help for one ADL vs. patients requiring assistance with at least two ADL. Cognitive levels were grouped in two further categories, namely patients with intact intellectual functioning or mild cognitive impairment (<5 errors in SPMSQ) and patients with moderate–severe cognitive impairment (≥5 errors).

Statistical analysis

Exploratory data analysis and frequency tables were used to describe all variables. Two analyses were performed, one using polypharmacy as the dependent variable (defined as concurrent use of five or more medications) and the other with PPO as a dependent variable (this concept was measured with START). The percentage of patients receiving ≥5 medications and the percentage of patients receiving at least one PPO were the two primary endpoints, respectively. According to each criterion, chi-square or Fisher tests were used to analyse the differences in polypharmacy and PPO prevalence rates across categories of independent variables. Multivariate logistic regression was used to examine independent risk factors that were associated with polypharmacy and PPO, also carrying out a further diagnosis of the models to ensure the goodness of fit [40]. A generalized standard error inflation factor was used to ensure there was no colinearity between independent variables. Linearity of the quantitative independent variables was checked through partial regression plots while goodness of fit was ensured with the Hosmer-Lemeshow test [40]. The results of the regression analysis are presented with odds ratios (OR) and their 95 % confidence intervals (CI). A 5 % significance level was used to establish statistical significance. Statistical data analysis was carried out with both SPSS (SPSS, Chicago, IL) and R language.

The study protocol was approved by the local clinical research ethics committee.

Results

Population baseline characteristics

A total of 1844 medications were prescribed to the 407 patients included in our study. The median age of the participants was 79.3 (range 65–100) years, and 57.2 % were females (Table 1). The average CCI was 1.95 and 34.6 % of the patients had CCI scores >2. Hypertension was the most prevalent condition (57.2 %), followed by bone and joint disorders (53.3 %), heart disease (40 %) and peripheral vascular disease (38.8 %). Twenty-four per cent had diabetes mellitus while 19.4 % suffered from insomnia. During the preceding year, 26.2 % of the elderly patients had required hospitalization. As for the degree of dependency, about one third (32.6 %) of our sample needed assistance with at least two ADL. Over half the elderly patients had intact intellectual functioning (less than 2 errors in SPMSQ), while moderate to severe cognitive impairment was seen in 14.5 % (≥5 errors). There were 37.8 % of the patients who could be considered as likely to have depression (6–9 points on GDS-15) while 19 % were qualified as depressed (≥10 points on GDS-15).

The median number of medications per patient was 4.5 drugs (range 0–14). The most widely prescribed ATC groups were C (cardiovascular, 69.5 % of the patients had at least one drug from this group), A (digestive and metabolism, 53.6 %) and N (nervous system, 51.6 %). Omeprazole was the most

Table 1 Characteristics of community-dwelling older people population

Population characteristics	Total (*n*=407)
Age, mean (years±SD), range	79.3 (±8.0), (65–100)
Female gender, *n* (%)	233 (57.2 %)
Number of drugs prescribed	1884
Medications per patient, mean (±SD), range	4.5 (±2.9), (0–14)
Charlson Comorbidity Index, mean (±SD)	1.95 (±1.7)
Charlson Comorbidity Index, *n* (%)	
0	104 (25.6)
1–2	162 (39.8)
≥3	141 (34.6)
Most frequent diagnoses, *n* (%)	
Hypertension	233 (57.2)
Osteoarticular disease	217 (53.3)
Heart disease	163 (40)
Peripheral vascular disease	158 (38.8)
Gastrointestinal disease	129 (31.7)
Psychopathology	125 (30.9)
Diabetes mellitus	97 (23.8)
Katz Index (ADL), *n* (%)	
A–B	274 (67.4)
C–G	133 (32.6)
SPMSQ (cognitive function), *n* (%)	
0–2 errors	234 (57.5)
3–4 errors	114 (28)
≥5 errors	59 (14.5)

ADL activity of daily living, *SPMSQ* Short Portable Mental Status Questionnaire

frequently used drug followed by aspirin, furosemide and enalapril. The remaining drugs among the top ten were transdermal nitrates, acetaminophen, lorazepam, clopidogrel, digoxin and atorvastatin.

Polypharmacy

The prevalence of elderly people exposed to polypharmacy was 45 %, while 6 % of the participants usually took ≥10 drugs. The prescribing profile of polymedicated patients almost matches that of the overall sample, with omeprazole and aspirin as the most widely used drugs. The only difference was that digoxin now ranked as the sixth most frequently used drug.

In the multivariate analysis, once we had eliminated any colinearities, the risk factors associated with polypharmacy were (1) comorbidity (OR 1.98, 95 % CI 1.63–2.44), (2) limitations in ADL (OR 3.0, 95 % CI 1.51–6.11), (3) being prescribed a drug in the ATC C group (OR 7.92, 95 % CI 4.10–16.25) and (4) being prescribed a drug in the N group (OR 3.80, 95 % CI 2.25–6.55). In contrast, participants with moderate–severe cognitive impairment were less likely to have been prescribed multiple medications (OR 0.25, 95 % CI 0.10–0.63; Table 2). There was no statistically significant association between sex or age and polypharmacy. Indeed, the mean number of drugs taken by women was 4.6 compared with 4.4 drugs among men (the polypharmacy rates for women vs. men were 46 vs. 42 %, respectively, $p>0.05$). In our univariate analysis, the differences in rates of polypharmacy in the elderly over and under 85 years of age did not reach statistical significance either.

Potential prescription omissions (PPO)

START identified a total of 303 PPO in 170 (41.8 %) subjects. The mean was 0.74 (range 0–4) START criteria per patient (Table 3). Sixteen of the 22 START criteria (72.7 %) were used to identify these PPO.

Table 4 presents the prevalence of each of the individual START criterion by physiological system. The most frequent PPO was metformin with type 2 diabetes mellitus ± metabolic syndrome, statin therapy in diabetes mellitus with coexisting major cardiovascular risk factor and antiplatelet therapy in diabetes mellitus if one or more coexisting major cardiovascular risk factors were present (hypertension, hypercholesterolaemia, smoking history). The endocrine system accounted for over half the omissions (51.8 %), followed by the cardiovascular system (26.7 %), where the main omission was anticoagulants in the presence of chronic atrial fibrillation. In terms of cardiovascular therapy, statins were also omitted.

Multiple logistic regression analysis revealed that the risk of PPO increased by 60 % for every additional point in the CCI, as measured by the START criteria (OR 1.60, 95 % CI 1.35–1.91). Polypharmacy also independently predicted the odds of at least one PPO according to START criteria (OR 2.19, 95 % CI 1.36–3.55; Table 5). In the univariate analysis, the proportion of patients with at least one omission was 59 % in polymedicated patients, while in patients with no polypharmacy, this proportion was 27 % ($p<0.05$).

Table 2 Multivariate logistic regression. Factors associated with polypharmacy

Patient characteristic	Polypharmacy[a]	
	OR	95 % confidence interval
Age	0.99	0.95–1.02
Gender		
Man	Reference	
Woman	0.87	0.51–1.47
CCI	1.98*	1.63–2.44
Katz Index of ADL[b]		
A–B	Reference	
C–G	3.00**	1.51–6.11
SPMSQ[c]		
0–4 errors	Reference	
≥5 errors	0.25**	0.10–0.63
ATC group C medication[d]		
None	Reference	
≥1 (at least 1)	7.92*	4.10–16.25
ATC group N medication[e]		
None	Reference	
≥1 (at least 1)	3.80*	2.25–6.55

OR odds ratio, *CCI* Comorbidity Charlson Index, *ADL* activities of daily living, *SPMSQ* Short Portable Mental State Questionnaire by Pfeiffer (cognitive function), *ATC* Anatomical Therapeutic Chemical classification

*$p<0.001$; **$p<0.01$

[a] Patients receiving ≥5 medications

[b] A–B: independent patients or those who only need help for one ADL; C–G: patients requiring assistance with at least two ADL

[c] 0–4 errors in SPMSQ: patients with intact intellectual functioning or mild cognitive impairment; ≥5 errors: patients with moderate–severe cognitive impairment

[d] Being prescribed a drug in the ATC C group (cardiovascular)

[e] Being prescribed a drug in the ATC N group (nervous system)

Table 3 Number of patients with potential prescribing omissions identified by START

Number of PPO	No. of subjects (%)
0	237 (58.2)
1	85 (20.9)
2	46 (11.3)
3	30 (7.4)
4	9 (2.2)
≥1 (at least 1)	170 (41.8)

PPO potentially prescribing omissions, *START* Screening Tool to Alert doctors to Right Treatment

Table 4 Details of potential prescribing omissions (PPO) identified by the START

Criteria	Number of PPO (%)
Cardiovascular system	81 (26.7)
Warfarin in the presence of chronic atrial fibrillation	22 (7.2)
Aspirin in the presence of chronic atrial fibrillation	4 (1.3)
Aspirin or clopidogrel with atherosclerotic disease	10 (3.3)
Statin therapy with known coronary, cerebral or peripheral vascular disease	19 (6.3)
ACE inhibitor with congestive heart failure	9 (2.9)
ACE inhibitor following acute myocardial infarction	17 (5.6)
Respiratory system	22 (7.2)
Inhaled β_2-agonist or anticholinergic for mild-moderate asthma or COPD	22 (7.2)
Central nervous system	24 (7.9)
L-Dopa in idiopathic Parkinson's disease	3 (0.9)
Antidepressant drug in the presence of moderate/severe depressive symptoms	21 (6.9)
Gastro-intestinal system	2 (0.7)
PPI with severe GERD or peptic stricture requiring dilatation	2 (0.7)
Musculoskeletal system	17 (5.6)
Biphosphonate in patients taking glucocorticoids for more than 1 month	5 (1.6)
Ca^{2+} and vit. D_3 supplement in patients with known osteoporosis	12 (3.9)
Endocrine system	157 (51.8)
Metformin with type 2 diabetes mellitus ± metabolic syndrome	72 (23.7)
ACE inhibitor or ARB in diabetes with nephropathy	22 (7.2)
Antiplatelet therapy in diabetes mellitus with major cardiovascular risk factors	23 (7.6)
Statin therapy in diabetes mellitus and ≥1 major cardiovascular risk factor	40 (13.2)
Total PPO	303

START Screening Tool to Alert doctors to Right Treatment, *ACE* angiotensin converting enzyme, *COPD* chronic obstructive pulmonary disease, *PPI* proton pump inhibitors, *GERD* gastroesophageal acid reflux disease, *ARB* angiotensin receptor blocker

Table 5 Multivariate logistic regression for having at least one PPO according to START

Patient characteristic	Potentially prescribing omission (PPO)[a]	
	OR	95 % confidence interval
Age	0.99	0.96–1.02
Gender		
Man	Reference	
Woman	0.99	0.63–1.57
CCI	1.60*	1.35–1.90
Polypharmacy	2.19**	1.36–3.55
Katz Index of ADL[b]		
A–B	Reference	
C–G	0.62	0.34–1.12
SPMSQ[c]		
0–4 errors	Reference	
≥5 errors	1.41	0.67–2.98

PPO potentially prescribing omissions, *START* Screening Tool to Alert doctors to Right Treatment, *OR* odds ratio, *CCI* Charlson Comorbidity Index, *ADL* activities of daily living, *SPMSQ* Short Portable Mental State Questionnaire by Pfeiffer (cognitive function)

*$p<0.001$;**$p<0.01$

[a] Patients receiving at least one PPO according to START

[b] A–B: independent patients or those who only need help for one ADL; C–G: patients requiring assistance with at least two ADL

[c] 0–4 errors in SPMSQ: patients with intact intellectual functioning or mild cognitive impairment; ≥5 errors: patients with moderate–severe cognitive impairment

Discussion

Principal findings and comparisons in the context of current literature

About polypharmacy

We found that around half of the patients were being polymedicated (45 %). The prevalence of polypharmacy is known to vary widely for different reasons. Among these is the type of healthcare setting (the elderly who have been hospitalized differ enormously from community-dwelling or nursing home residents). All this makes the results more difficult to compare, but if we focus on the outpatient setting, our figures are moderate and similar to those reported in other papers [12, 41]. Despite the frequency of polypharmacy on Lanzarote, the overall consumption of drugs cannot be seen as excessive if we consider the mean number of drugs per patient (4.5), or the discreet rate of excessive polypharmacy (6 %) and the level of comorbidity in this patient population. As for the prescribing profile, it is reasonable that ATC group C was the most widely used, in line with the most prevalent diseases seen in our elderly population. This outcome also coincides with other studies such as EPIFARM [42]. A high level of use of proton pump inhibitors (A group), basically omeprazole, [43] has been recognized in Spain for some time now, even though a major increase is being seen in the use of these drugs in other European countries, such as Italy [42].

An increase in comorbidity is associated with greater polypharmacy, a result that has already been described elsewhere [2, 4, 9, 11] and which is logical. In fact, we saw rates of polypharmacy of 70.2 % in patients with a high comorbidity rate, compared with only 31.6 % in patients with no or low comorbidity rates. The relationship seen with limitations in ADL is less well known, probably due to the fact that the Katz Index has not been assessed in many studies on

polypharmacy, especially studies derived from prescribing databases that contain few or no clinical or functional details. What is novel and remarkable is that a greater risk of polypharmacy stems from being prescribed a drug from the cardiovascular or nervous system groups. The most likely explanation is a kind of *pull effect* (i.e. some conditions involve more than one disease or more than one risk factor to be prevented) or of *prescribing in cascade* (the use of a medication that results in an adverse drug event that is mistaken for a new diagnosis and treated with another medication). Moreover, cognitive impairment protected patients from accumulating drugs, a finding already described by Kuzuya [18], although no final conclusions may be drawn on the controversial issue of whether physicians prescribe differently for patients with advanced-stage dementia.

Despite the fact that polypharmacy is often considered to be among the most important risk factors for ADR and medication-related hospital admissions in older people [44], a high use of drugs should not necessarily be taken as inappropriate. In fact, it may become necessary to add on medication for patients with various comorbidities, based on an appropriate benefit/risk evaluation. However, there is limited data to guide the use of medications in older adults and a lack of age-specific guidelines. Quite the opposite, available clinical guidelines are disease specific, which predisposes physicians to add on drugs to therapeutic regimens without fully understanding the interactions these may have with other medications and diseases.

About potential prescription omissions and their relationship with polypharmacy

Using the START, we have identified a high percentage of omissions (41.8 %), a slightly higher prevalence than most results published in the primary care setting [32, 45–47], except for a recent Serbian study reporting a rate of 50 % [48]. We believe that some of these studies show a lower prevalence of omissions because the patient population is younger and healthier [32], while in others there may have been an underestimation of PPO where the required clinical and therapeutic information was unavailable to be able to assess all START criteria, and not just a subset of this tool [47]. In other more complex settings, such as hospitalization or nursing homes, the percentage of patients not receiving an effective, evidence-based drug treatment shows even higher figures [33, 34, 49–52] (summary in Table 6). It is likely that the baseline characteristics of our elderly population, with a high mean age and level of comorbidities, may partially account for the frequency of omissions we found, given that their clinical and functional status comes closer to that of elderly patients with greater clinical and therapeutic complexity. Also, there are studies that have pinpointed PPO with methods other than START, which may hinder comparison of data. However, we would like to stress that we also found very high omission rates, around 60 % [13, 29, 30].

The highest volume of underprescription of beneficial agents was seen in the endocrine system. This finding follows a different pattern to most studies where the cardiovascular system was usually the most severely affected by omissions [32–34, 47–49, 51]. This can be due to the fact that the main PPO in our study referred to metformin, statins and aspirin, all in diabetic patients. As a result, 84.5 % of the diabetic patients had at least one PPO, compared with only 28.4 % in non-diabetics (mean of 1.92 vs. 0.37 PPO in diabetics vs. non-diabetics). Diabetes mellitus was also a significant determinant of PPO in the study by Dalleur, although this was not shown to be a predictive factor for PPO-related hospital admissions [52]. Of all our diabetic patients, 29 % were treated with insulin and 56 % received some oral antidiabetic drug, sulphonylureas, mainly glibenclamide, being the most widely prescribed. We do not know what motivated the physicians' selection of certain medications or whether the patients were overweight, but we feel that it is likely the profile has changed over the past few years, as in the rest of Spain, with metformin being favoured as the first-line option.

We would need a prospective study to understand the real impact of underprescribing on health outcomes, but an increase in ischaemic strokes is likely given the lack of antithrombotic therapy in older patients with atrial fibrillation. Bearing in mind the most common omissions, the clinical implications are generally associated with a greater risk of cardiovascular events and mortality [13].

Regardless of applying START criteria, we should like to point out that antidepressant therapy had been started in 24.6 % of subjects with clear symptoms of depression (patients with ≥10 points on GDS-15). This seems to be more closely related to a lack of any formal diagnosis of depression (reported in only 15 % of clinical records).

Our study shows the possible association between polypharmacy and underprescription of indicated medicines since the probability of PPO increased significantly with polypharmacy. These two apparently opposing concepts have already been reported by other authors [46, 47, 51], though not by others [29, 30, 32–34, 52, 53]. The relationship between polypharmacy and potentially inappropriate medication (PIM) is more widely known and easier to understand in principle. Indeed, also in our study population on Lanzarote, the number of drugs was associated with a risk of PIM (with a prevalence of 35.4 %) [54]. However, it is also reasonable to think that physicians may be discouraged from adding more medications to an already long prescription list. Faced with a clinical case of comorbidity and polypharmacy, it is likely that priorities for therapy are set and, as a result, other therapies intended for prevention are sacrificed. Indeed, antiplatelet drugs and statins are among the most

common omissions seen in the scientific literature on this topic (Table 6).

There may be other reasons besides this lack of conviction to start certain treatments, such as lipid-lowering drugs for secondary prevention [55], in the elderly population although these are beyond the scope of this study. We agree with Querubini's review that the main reasons for underprescription are comorbidity, polypharmacy, ageism, lack of or scanty evidence concerning the efficacy and safety of drugs in older patients, fear of ADR and economic constraints [56].

We detected high levels of omissions and polypharmacy, as well as the coexistence of both, meaning that efforts should focus on improving these two areas. However, we must be cautious when interpreting these markers of prescribing quality. We think they may not always be inappropriate and should be evaluated together with other major issues such as life expectancy, time to benefits, goals of care and patient preferences [57]. Therapy for the elderly should seek to strike a balance between therapeutic goals and possible risks as well as to perform a frequent review of medications and overall health status. It would also be reasonable not only to include standard efficacy variables within the therapeutic goals but also to give consideration to the possible improvement in functional status and the quality of life for the patients. This requires a highly individualized assessment for each patient as well as a far-from-easy treatment prioritization process. As a result, it would be useful to develop guidelines or consensus statements that help physicians identify diseases or symptoms with higher priority in elderly patients with high rates of comorbidities, as well as to select the best treatment options. However, further research is needed in this context. There are plenty of clinical guidelines to add on a new drug, but this is not the case for interventions to reduce medication exposure, where the evidence for their clinical effectiveness and sustainability is conflicting and lacking [58]. Meanwhile, we feel that the application of tools capable of identifying both PIM (mainly Screening Tool of Older Person's Potentially Inappropriate Prescriptions—STOPP—and 2012 American Geriatrics Society Beers Criteria) and PPO (START) may be extremely useful.

Therefore, optimizing pharmacotherapy is an extremely complex process, and we agree with other authors [59] that several healthcare professionals could be involved in a collaboration to implement a stepwise approach to geriatric drug treatment.

Strengths and weaknesses of the study

The strengths of the current study were mainly the use of stratified random sampling to select representative patients for the population, together with the quantity and quality of the data collected and our statistical analysis. We performed thorough, direct data collection as we wanted to look at what patients were really taking rather than looking at prescriptions recorded on the database. We have been able to examine clinical and functional data, geriatric evaluation and details of pharmacological therapy. All these data have contributed towards the applicability of the criteria and have probably assured a greater sensitivity to detect omissions. In fact, some publications stated that when START criteria are evaluated without clinical details, there is a decrease in the detection of PPO [60]. We were able to apply the 22 items within START; however, 6 of these did not reveal any PPO (for instance a beta blocker for chronic stable angina, inhaled corticosteroid for moderate–severe asthma or COPD, and home oxygen for respiratory failure), probably because these prescriptions are more difficult to omit. Most studies were unable to identify PPO with all the criteria, using only between 10 and 18 items [32, 34, 45–47, 51, 53]. There were also, however, some limitations to our study. Selecting a sample from a single region or country may lead to a lack of external validity, even though the participants' characteristics and values obtained can be seen to be consistent with those reported in other studies. We should also point out that we have no information available on the patients' preferences or on the reasons for omission by the physicians. These topics will be addressed in further studies.

Conclusion

Our findings show high rates of polypharmacy and PPO, as well as a clear relationship between these two concepts.

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Conflict of interest The authors declare that they have no conflict of interest.

Authors' contributions The proposed paragraph repeats some sentences. It could be changed by the following: EBR and GAZ were responsible for the concept and design of the study, application of START criteria and evaluation of prescriptions, analysis and interpretation of results, preparation of the manuscript and final approval of the version for publication. GAZ was also responsible for the data collection. Preparation of manuscript was also a responsability of ROR. MLO was also responsible for the application of START criteria and evaluation of prescriptions. ROR, MLO and IBE were also responsible for the analysis and interpretation of results and final approval of the version for publication.

Ethical standards The authors declare that this clinical research was devised in line with the ethical standards laid down in the Helsinki Declaration (Fortaleza 2013) and that special attention was paid to ensuring informed consent from all patients prior to their inclusion, as well as to the confidentiality of all personal data. This study was classified as a post-authorization, epidemiological study by the Spanish Medications and Healthcare Products Agency. The study was also approved by the Clinical Research Ethics Committee (Dr. Negrín Gran Canaria Universitary Hospital, code 120279).

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