Review

Drug-related Problems in Home-dwelling Older Adults: A Systematic Review

Ana I. Plácido, PhD[1]; Maria Teresa Herdeiro, PharmD, PhD[2]; Manuel Morgado, PharmD, PhD[1,3,4]; Adolfo Figueiras, PharmD, PhD[5,6,7]; and Fátima Roque, PharmD, PhD[1,3]

[1]Research Unit for Inland Development, Polytechnic of Guarda, Guarda, Portugal; [2]Institute of Biomedicine, Department of Medical Sciences, University of Aveiro, Aveiro, Portugal; [3]Health Sciences Research Centre, University of Beira Interior, Covilhã, Portugal; [4]Pharmaceutical Services of Hospital Centre of Cova da Beira, Covilhã, Portugal; [5]Department of Preventive Medicine and Public Health, Faculty of Medicine, University of Santiago de Compostela, Santiago de Compostela, Spain; [6]Consortium for Biomedical Research in Epidemiology and Public Health (CIBER en Epidemiología y Salud Pública-CIBERESP), Santiago de Compostela, Spain; and [7]Institute of Health Research of Santiago de Compostela, Santiago de Compostela, Spain

ABSTRACT

Purpose: The complex combination of medicines associated with age-related physiological alterations leads older adults to experience drug-related problems (DRPs). The goal of this study was to review the frequency and type of DRPs and DRP risk factors in home-dwelling older adults.

Methods: A MEDLINE PubMed and EMBASE scientific databases search was performed. Articles published from January 2000 through December 2018 reporting DRPs in home-dwelling older adults were included.

Findings: From 668 articles screened, 13 met the inclusion criteria and were included in this study. Overall, the studies included 8935 home-dwelling patients. The mean number of DRPs per patient observed was 4.16 (1.37−10). The main causes of DRPs were "drug selection" (51.41%), "dose selection" (11.62%), and "patient related" (10.70%) problems. The drug classes more frequently associated with DRPs were "cardiovascular system," "alimentary tract and metabolism," and "nervous system," and they represented 32.1%, 29.4%, and 16.5% of all drug selection problems, respectively. Respiratory system medicines accounted for 6.65% of all DRPs, of which "patient related" problems accounted for 97.28%.

Implications: Despite the heterogeneity of methodology of the included studies and the heterogeneity of tools used to identify DRPs, this analysis clearly shows the high prevalence of DRPs in home-dwelling older adults and highlights the need for interventions to improve medicine use in this population. This work also provides useful information for the development of strategies to improve medication use in home-dwelling older adults. (*Clin Ther*. 2020;42:559−572) © 2020 Published by Elsevier Inc.

Key words: drug-related problems, home-dwelling patients, medication review, older adults.

INTRODUCTION

The World Health Organization (WHO) estimates that >50% of all medicines are prescribed, dispensed, or sold inappropriately, and more than one half of patients fail to take them properly.[1] Drug-related problems (DRPs) are responsible for an increased risk of hospital admissions and emergency department

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visits.[2] Moreover, adverse drug events account for >3.7% of all hospital admissions. Medication nonadherence and monitoring problems account for 31% and 22%, respectively, of preventable drug-related admissions.[3]

Older adults are more likely to take multiple medications and metabolize medications differently than younger adults, and this may exacerbate DRPs as well as drug-related hospital admissions.[2,4] In the last decade, several strategies have failed the attempt to improve elderly patient well-being and reduce health care costs[5]; however, these patients account for 15%−30% of all drug-related hospital admissions.[6]

Regarding health concerns associated with DRPs in home -dwelling older patients, the identification and prevention of DRPs and DRP risk factors is essential to find effective strategies to improve DRPs-related outcomes. Accordingly, the aim of the present study was to review the frequency and type of DRPs and the risk factors associated with DRPs in home-dwelling older adults. This study also sought to describe the acceptance of the prescribers to proposed interventions.

MATERIALS AND METHODS

Search Strategy and Inclusion Criteria

A literature search was conducted in January 2018 and updated in February 2019 on the MEDLINE PubMed and EMBASE databases. Articles published from January 2000 through December 2018 were included. The search strategy was designed to identify relevant studies addressing DRPs in home-dwelling older patients. The following search terms were used: "drug-related problems" AND "elderly" OR "drug-related problems" AND "older" OR "medication-related-problems" AND "older" OR "medication-related problems" AND "elderly." Research studies were eligible for inclusion if they were in accordance with the following selection criteria: (1) language (papers had to be published in English, French, Spanish, or Portuguese); (2) target population (home-dwelling older people); and (3) outcome measures (DRPs in home-dwelling adults). To avoid the selection bias associated with patients who are not representative of an older population, studies were excluded if their focus was to evaluate DRPs with a specific medical condition or a specific nature of DRPs.[7] Insofar as study design of included studies was concerned, no inclusion or exclusion criteria were specified because the aim of the present study was to conduct a critical review of all published studies.

Study Selection

Two researchers (A.I.P. and F.R.) independently screened all titles and abstracts retrieved from electronic databases accordingly with the inclusion criteria. The full text of potentially eligible articles was then screened independently by 2 researchers to further evaluate its appropriateness for inclusion in this work. All discrepancies were resolved through discussion with the help of a third researcher (M.T.H.). Preferred Reporting Items for Systematic Reviews and Meta-Analyses standard guidelines were followed when applicable as per recommended practice.[8]

Quality Assessment of Included Studies

Three researchers independently evaluated the quality and susceptibility to bias of the included studies using Appraisal Tool for Cross-Sectional Studies (AXIS).[9] In interventional studies, the authors extracted only the preintervention data.

Data Extraction and Analysis

A single researcher extracted data from the included studies. Subsequently, another investigator checked the extracted data. The data extracted from each article included authors, publication year, study design, country, sample size, patients' age and sex, DRPs identified during medication review (MR), main DRP risk factors, medicines implicated in DRPs, and number of proposed and accepted interventions. All DRPs were classified/reclassified by 2 independent investigators according to the Pharmaceutical Care Network Europe (PCNE) classification for DRPs[10]; all DRP classification discrepancies were resolved through discussion with other researchers. The advantage of this classification system lies in its hierarchical design, with separated codes: 3 primary domains for problems (P1−P3), 8 primary domains for causes (C1−C8), 5 primary domains for interventions (I0−I4), and 3 primary domains for acceptance of the intervention proposals (A1−A3). For each domain, several categories are available. For each problem detected, a cause can be applied and an intervention proposed. Taking into account that the

included studies did not use PCNE classification system version 8.03, the investigators had difficulty in establishing an unequivocal cause to each problem. Therefore, based on a peer review panel decision, DRPs were only classified in one of the primary domains (in the primary domain "problems" or the primary domain "causes"). Moreover, whenever the extracted data had not allowed the unequivocal classification of DRPs in a specific subdomain, DRPs were only classified in its primary domain. In interventional studies, only DRP preintervention data were extracted. Medicine-related DRPs were categorized according to the Anatomical Therapeutic Chemical (ATC) classification system.[11]

RESULTS

Study Selection

The search of the databases yielded 1610 citations (Figure 1). After screening titles and abstracts, 55 articles potentially met the inclusion criteria. After full reading, 42 articles were excluded, and 13 studies[12–24] met the inclusion criteria and were included in this systematic review (see Table S1 in the

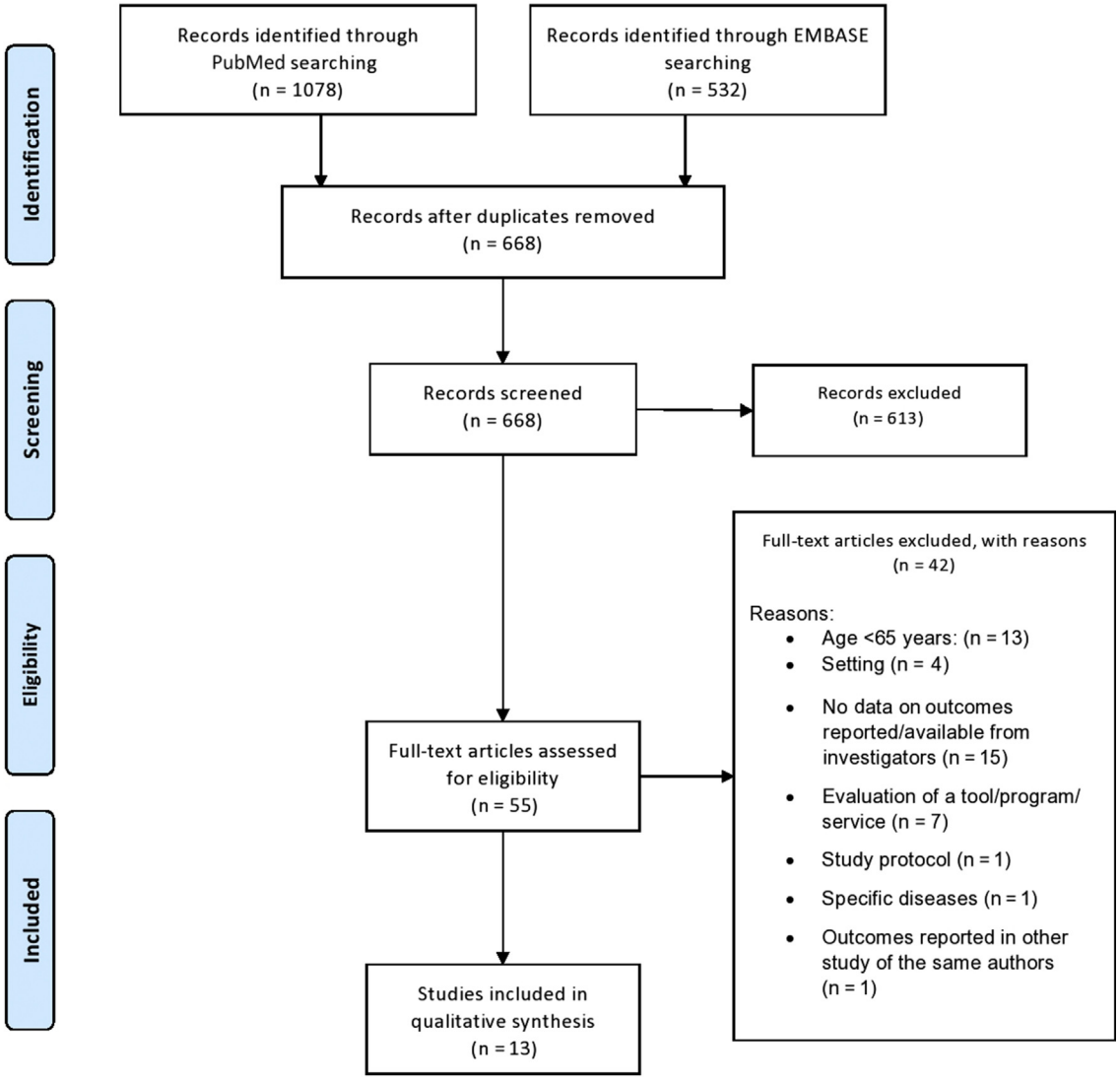

Figure 1. Selection of studies.

Table 1. Summary of key characteristics of the included studies.

Author, Year, Country	Study Design*	Sample Size; Age (mean ± SD; Range), y; % Female Sex	Medication Review			
			DRPs Mean Per Patient	Health Care Professional Involvement in MR and DR	Patient Interviews	Implementation Rate of Proposed Interventions (%)
Kari et al, 2018, Finland[15,†]	Randomized controlled trial	161 81.0 (75–98) 61.5	590 NA	MR: P; N; GP DR: P; N; GP	Yes	–
Rhalimi et al, 2018, France[20]	Multicenter Cross-sectional prospective	892 80.6 (66–102) 62	334 1.37[‡]	MR: P DR: P	Yes	78
Kovacevic et al, 2017, Serbia[16]	Prospective	388 72.1 (65–91) 55.9	964 2.5	MR: P DR: P	Yes	70.1
Chau et al, 2016, the Netherlands[14]	Cross-sectional	3807 78 (65–102) 57.9	11419 3.0	MR: P DR: P; GP	Yes	46.2
Chan et al, 2014, Taiwan[13]	Prospective case-series intervention	139 75.6 (NA) 44	297 2.1	MR: G, P, R DR: G, P, R	Yes	87
Kwint et al, 2012, the Netherlands[18]	Cross-sectional	155 (NA) (72–81) 54	1565 10	MR: P, GP DR: GP, P	Yes	–
Leikola et al, 2012, Finland[19]	Retrospective	70 79.6 (65–91) 75.7	505 7.2	MR: P, N, GP	Yes	55
Touchette et al, 2012, United States[23]	Randomized, controlled, clinical trial	637 74.6 (NA) 66.2	1083 (NA)	MR: P DR: P	Yes	~30[§]
Castelino et al, 2011, Australia[12]	Retrospective	224 74.6 (65–96) 52.7	1110 4.9	MR: P DR: P	NA	–
Kwint et al, 2011, the Netherlands[17]	Pragmatic randomized controlled Study	125 IG: 78.7 WG: 80.0	480 (NA)	MR: P DR: P	No	–
Vinks et al, 2006, the Netherlands[24]	–	196 77.0 (NA)	763 3.9	MR: P, R	No	–

Table 1. (*Continued*)

Author, Year, Country	Study Design*	Sample Size; Age (mean ± SD; Range), y; % Female Sex	Medication Review			
			DRPs Mean Per Patient	Health Care Professional Involvement in MR and DR	Patient Interviews	Implementation Rate of Proposed Interventions (%)
Roughead et al, 2004, Australia[21]	Retrospective	1000 (NA) 62	2222 (NA)	MR: P	NA	–
Sellors et al, 2003, Canada[22]	Randomized controlled trial	431 74.0 (NA) 64.3	1093 2.5	MR: P, N DR: P, GP	Yes	46.3

DR = decision about clinical relevance; DRPs = drug-related problems; G = Geriatrician; GP = general practitioner; IG = intervention group; MR = medication review; NA = information not available; N = nurse; P = physician; R = researcher; WG = waiting list group; (data from baseline).

* According to the authors' designation in the methods section.

† Classification of the most significant clinical DRPs; total of DRPs = 590.

‡ A total of 75 patients with DRPs.

§ Actual values: 28.8 in the basic medication therapy management group and 33.3 in the enhanced medication therapy management group.

online version at doi:10.1016/j.clinthera.2020.02.005).

Quality Assessment

Most of the studies (11 of 13) fulfilled >70% of the AXIS tool exploratory questions and were considered to have a good level of methodological quality. Results regarding our judgment about quality assessment, using the AXIS tool, are described in Table S2 (see the online version at doi:10.1016/j.clinthera.2020.02.005). Only one study[17] justified the number of participants included in the study. Measures to address and categorize nonresponders did not seem to be taken in any of the studies. All studies were included because the intent of the present analysis was to critically review all published studies in which the main theme was DRPs in home-dwelling older patients.

Study Characteristics

A description of the characteristics of the included studies is presented in Table I. Among the included studies, eight were conducted in Europe,[14–20,24] two in Australia,[12,21] two in North America,[22,23] and one in Asia.[13] Regarding the study design, three studies were retrospective,[12,19,21] three studies were prospective,[13,16,20] four studies were randomized controlled trials,[15,17,22,23] and two studies were cross-sectional.[14,18] The included studies identified DRPs during the MR process; according to the "PCNE statement on medication review 2013,"[25] four studies performed a PCNE type 1/basic MR,[12,17,21,24] two studies performed a PCNE type 2b/intermediate MR,[14,20] and six studies performed a PCNE type 3/advanced MR.[13,15,16,18,22] Three studies analyzed the impact of patients' participation in the improvement of the MR process. In nine studies, interventions to the prescriber were suggested.[13,14,16–20,22,23] Altogether, the studies included 8935 patients ranging in age from 65 to 102 years. The mean number of drugs used per patient was reported in 11 studies and varied from 7.6 to 12 drugs.[12–14,16–21,24] According to ATC code, drug classes most frequently used were "C-Cardiovascular," "A-Alimentary tract and metabolism," and "N-Nervous system" drugs.[12,15,17,18,24]

Study Outcomes

Only 4 studies reported the criteria used to identify the cause of DRP "drug selection."[13,17,18,24] Two

studies used implicit criteria based on a structural assessment of the rational order of indication, effectiveness, safety, and compliance.[17,18] One study[24] used the national prescribing guidelines ("The Standards for Dutch general practitioners and therapeutic handbooks"[26,27]) and one study used 2003 Beers criteria modified by National Taiwan University Hospital.[13] Concerning the DRP classification systems used, 4 studies used the PCNE classification system (versions 5.1, 6.2, and 7.0),[13,15,19,23] two studies used the DOCUMENT classification system,[17,18] and one study categorized the most relevant DRPs identified during the MR process.[15] One study only classified the most common DRPs identified during the MR process,[19] and another study reported the number of people associated with a specific DRP.[21] The remaining studies performed the classification of all DRPs identified during the MR process.

Number and Nature of the Potential DRPs

The mean number of DRPs per patient was reported in nine studies and ranged from 1.37 to 10[12–14,16,18–20,22,24] (Table I), with a median of 3 (25th percentile, 2.30; 75th percentile, 6.05). Overall, the main causes of DRPs were "drug selection problems" (51.41%), "dose selection" (11.62%), "patient related" (10.70%), and "other" (5.73%) (Table II; see Table S3 in the online version at doi:10.1016/j.clinthera.2020.02.005). The subdomains "Inappropriate selection of drugs,"[12,14,15,19,22–24] "No or incomplete drug treatment in spite of existing indication,"[12,14,15,17,18,22] and "Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements"[13,20,24] were the most frequent cause of "drug selection," whereas "Patient uses/takes less drug than prescribed or does not take the drug at all," "Patient uses/takes more drug than prescribed or does not take the drug at all," and "Patient unable to use drug/form as directed" were the most frequent cause of "Patient related problems."[12,15,16,20,24] Regarding the domain problems, "Patient suffers, or could suffer, from an adverse drug event" and "Adverse drug event (possibly) occurring" were the most frequent subdomains observed in the domains "Treatment effectiveness" and "Treatment safety," respectively.

DRP Risk Factors

Four studies considered DRP risk factors as an outcome[16,20,21,24] and reported that patients with more prescribed drugs had more susceptibility to DRPs. Accordingly, patients with $\geq$12 prescribed drugs had a significant risk of $\geq$5 DRPs compared with patients with less medication use.[16] Patients with $\geq$7 prescribed drugs had a higher risk of DRPs than patients with $\leq$6 prescribed medicines.[20] However, prescription of $\geq$6 drugs increases the likelihood of patients to the DRPs "no indication for drug."[24] The number of indications and the lack of compliance were also associated with an increased risk of DRPs,[16,20] and, according to Rhalimi et al,[20] compliance was better among patients taking $\leq$6 drugs. Conversely, age and sex exhibited no significant influence. Five studies correlated the presence/absence of medicines with the risk of certain DRPs and observed that specific medicines/indications predisposed the patients to particular DRPs.[14–16,20,24] Overall, 2212 medicines were correlated with a specific DRP. The ATC drug classes "C-Cardiovascular system," "A-Alimentary tract and metabolism," "N-Nervous system," and "B-Blood and blood forming organs" medicines represented 32.1%, 29.4%, 17.0%, and 11.0%, respectively, of all DRPs. These data suggest that patients who took medicines from these ATC classes may have an increased risk for DRPs. However, we must keep in mind that medication from these ATC classes is the most frequently used. Regarding "Patient related problems," it was observed that in this subdomain, respiratory system medicines account for >85% of all "Patient related problems" (Table III).

Patients' Role in Identification of DRPs

Nine of the included studies reported an enrollment of patients in the MR process through an interview.[13–16,19,20,22–24] However, only three studies explicitly mentioned the advantage of patient involvement in the MR process.[15,16,18] Kari et al[15] endorses that most significant DRPs related to "No drug treatment in spite of existing indication," "Patient unable to use drug/form as directed," "Inappropriate drug according to guidelines," and "Problem with cost-effectiveness of the treatment" were only identified through face-to-face interviews.

Table II. Drug-related problems (DRPs) classified according to the Pharmaceutical Care Network Europe classification version 8.03.

DRPs Cause Domain (N)	Author and Year												
	Kari et al, 2018[15,*]	Rhalimi et al, 2018[20]	Kovacevic et al, 2017[16]	Chau et al, 2016[14]	Chan et al, 2014[13]	Kwint et al, 2012[18]	Leikola et al, 2012[19]	Touchette et al, 2012[23]	Castelino et al, 2011[12]	Kwint et al, 2011[17]	Vinks et al, 2006[24]	Roughead et al, 2004[21,†]	Sellors et al, 2003[22]
C1. Drug Selection	**39**	**226**	**408**	**6364**	**127**	**837**	**222**	**331**	**275**	**235**	**554**	**1008**	**662**
C1.1/C1.2 Inappropriate drug	17	67	86	971	–	74	82	224	61	9	158	268	212
C1.3 No indication for drug	6	19	38	–	32	323	29	–	35	78	181	103	98
C1.4 Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	2	133	125	664	35	15	33	107	–	13	136	30	47
C1.5 Inappropriate duplication of therapeutic group or active ingredient	2	–	12	–	34	12	–	–	–	14	71	31	–
C1.6 No or incomplete drug treatment in spite of existing indication	12	7	147	1814	16	402	78	–	179	121	8	454	305
C1.7 Too many drugs prescribed for indication	–	–	–	2915	–	–	–	–	–	–	–	122	–
C2. Drug Dosage Form	–	–	–	**96**	–	–	–	–	–	**8**	**89**	–	–
C2.1 Inappropriate drug form (for this patient)	–	–	–	96	–	–	–	–	–	8	89	–	–
C3. Dose Selection	–	**29**	–	**1190**	**27**	**105**	**111**	**149**	**262**	**97**	**69**	–	**197**
C3.1 Drug dose too low	–	–	–	622	20[‡]	72	51[‡]	149	77	26	69	–	108
C3.2 Drug dose too high	–	29	–	568	–	33	60[§]		62	48		–	89
C3.3 Dosage regimen not frequent enough	–	–	–	–	20[§]	–	–	–	–	–	–	–	–
C3.4 Dosage regimen too frequent	–	–	–	–	–	–	–	–	–	–	–	–	–
C3.5 Dose timing instructions wrong, unclear, or missing	–	–	–	–	–	–	–	–	123	23	–	–	–

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Table II. (*Continued*)

DRPs Cause Domain (N)	Author and Year												
	Kari et al, 2018[15,*]	Rhalimi et al, 2018[20]	Kovacevic et al, 2017[16]	Chau et al, 2016[14]	Chan et al, 2014[13]	Kwint et al, 2012[18]	Leikola et al, 2012[19]	Touchette et al, 2012[23]	Castelino et al, 2011[12]	Kwint et al, 2011[17]	Vinks et al, 2006[24]	Roughead et al, 2004[21,†]	Sellors et al, 2003[22]
5. Dispensing	4	–	–	–	–	73	–	–	46	–	–	178	–
C5.1 Prescribed drug not available	–	–	–	–	–	–	–	–	–	–	–	–	–
C5.2 Necessary information not provided	4	–	–	–	–	73	–	–	46	–	–	178	–
C6. Drug Use Process	–	19	–	–	–	–	–	250	–	–	–	–	–
C6.4 Drug not administered at all	–	–	–	–	98	–	–	250	–	–	–	–	–
C6.5 Wrong drug administered	–	–	–	–	–	–	–		–	–	–	–	–
C7. Patient Related	18		208	1401	–	96	–	–	205	3	125	329	144
C7.1 Patient uses/takes less drug than prescribed or does not take the drug at all	13	18	208	645	–	43	–	–	53	–	36	132	–
C7.2 Patient uses/takes more drug than prescribed	–		–	–	–	8	–	–		3			–
C7.3 Patient abuses drug (unregulated overuse)	–	–	–	–	–	–	–	–	–	–	–	9	–
C7.6 Patient stores drug inappropriately	–	–	–	–	–	–	–	–	21[‖]	–	–	98	–
C7.7 Inappropriate timing or dosing intervals	2	–	–	–	–	–	–	–	–	–	–	–	–
C7.8 Patient administers/uses the drug in a wrong way	2	–	–	–	–	–	–	–	–	–	–	90	144
C7.9 Patient unable to use drug/form as directed	1	–	–	756	–	45	–	–	58	–	–	–	–
8. Others	11	10	44	470	19	359	121	126	216	3	15	505	–

Table II. (*Continued*)

DRPs Cause Domain (N)	Author and Year												
	Kari et al, 2018[15,*]	Rhalimi et al, 2018[20]	Kovacevic et al, 2017[16]	Chau et al, 2016[14]	Chan et al, 2014[13]	Kwint et al, 2012[18]	Leikola et al, 2012[19]	Touchette et al, 2012[23]	Castelino et al, 2011[12]	Kwint et al, 2011[17]	Vinks et al, 2006[24]	Roughead et al, 2004[21,†]	Sellors et al, 2003[22]
C8.1 No or inappropriate outcome monitoring (including Therapeutic drug monitoring)	4	10	44	–	–	359	–	–	–	3	–	334	–
C8.2 Other cause; specify	Cost: 4								Investigation test request: 158		Drug treatment of an adverse reaction: 8	Patient fearful about taking medicines: 40	
	Others: 3	–	–	470	19	–	121	126	Referral to other health professional: 58	–	Off–label: 7	Need for additional therapy: 131	–

DRPs: Problems Domain (N)	Kari et al, 2018[15,¶]	Rhalimi et al, 2018[20]	Kovacevic et al, 2017[16]	Chau et al, 2016[14]	Chan et al, 2014[13]	Kwint et al, 2012[18]	Leikola et al, 2012[19]	Touchette et al, 2012[23]	Castelino et al, 2011[12]	Kwint et al, 2011[17]	Vinks et al, 2006[24]	Roughead et al, 2004[21,#]	Sellors et al, 2003[22]
P1. Treatment Effectiveness	**31**	–	**113**	**975**	–	–	–	–	–	**57**	–	–	
P.1.1 No effect of drug treatment	3	–	113	975	–	–	–	–	–	57	–	–	
P.1.2 Effect of drug treatment not optimal	–	–	–	–	–	–	–	–	–	–	–	–	
P. 1.3 Untreated symptoms or indication	28	–	–		–	–	–	–	–	–	–	–	

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Table II. (*Continued*)

DRPs Cause Domain (N)	Author and Year													
	Kari et al, 2018[15,*]	Rhalimi et al, 2018[20]	Kovacevic et al, 2017[16]	Chau et al, 2016[14]	Chan et al, 2014[13]	Kwint et al, 2012[18]	Leikola et al, 2012[19]	Touchette et al, 2012[23]	Castelino et al, 2011[12]	Kwint et al, 2011[17]	Vinks et al, 2006[24]	Roughead et al, 2004[21,†]	Sellors et al, 2003[22]
P2. Treatment Safety	**8**	**32**	**191**	**923**	**26**	**95**	**51**	**227**	**106**	**77**	–	**186**	**90**
P 2.1 Adverse drug event (possibly) occurring	8	32	191	923	26	95	51	227	106	77	–	186	90
% of DRPs Per Patients Weighted Per Study													
Domain: Cause	C1. Drug Selection 51.41	C2. Drug Form 0.90	C3. Dose Selection 11.62	C5. Dispensing 0.27	C6. Drug Use Process 3.15	C7. Patient Related 10.70	C8. Others 5.73	**Domain: Problems**	P1. Treatment Effectiveness 8.29	P2. Treatment Safety 7.93			

* Classification of the most significant clinical DRPs, total of DRPs –590.
† Number of patients with a DRP.
‡ C3.1 or C3.3.
§ C3.2 or C3.4.
‖ Defined in the original classification system as: Others (including out of date medicines/storage); according to the Pharmaceutical Care Network Europe classification system out of date medicines/storage must be classified in the domain "Patient stores drug inappropriately."
¶ Classification of the most significant clinical DRPs, total of DRPs –590.
# Number of patients with a DRP.

Two studies[16,18] found that "Patient-related problems," "Dose problems," and "Treatment safety problems" were more frequently identified during patient interviews, whereas "monitoring problems" were more frequently identified from medication and clinical records. Roughead et al[21] pointed out that patients' perception is essential to gaining insight regarding DRPs.

Proposed and Accepted Interventions

Nine studies described the rate of prescriber acceptance interventions.[13,14,16–20,22,23] The most suggested interventions were related to "drug selection problems" followed by "No or inappropriate outcome monitoring" and "dose problems." According to the included studies, highest implementation rates were observed in DRPs related to the lack of therapy monitoring, whereas interventions related to drug interactions were the least likely to be implemented.[14,16–18,20] Patients and pharmacists were more likely to accept interventions than general practitioners or specialists.[16] Regarding the acceptance of the proposed interventions, 3 studies[16,19,20] reported an implementation rate of >50% (Table I). Chau et al[14] reported that 46.2% of the interventions proposed were accepted; within these, 22.4% were implemented with modifications, and 31.3% were refused by the prescriber (27.5%) or patient (11.9%). In 2 randomized controlled trials, prescribers implemented only ~29.0% of all proposed interventions.[17,23] In other randomized controlled trials, it was observed that after 5 months, the physician had succeeded in fully implementing 46.3% of the recommendations and 9.3% were partially implemented; the most frequent intervention was related to inappropriate drug.[22] In general, the most suggested and the most rejected recommendations were related to "drug selection."[14,16–18,20] The most implemented intervention was related to "other" DRPs problems, namely "No or inappropriate outcome monitoring."

DISCUSSION

This systematic review analyzed studies that investigated DRPs, and it provides unique data on the characterization of DRPs and DRP-related causes in home-dwelling older patients. It highlights that almost one half of patients have a "drug selection problem" and ~1 in 8 have a "patient related

Table III. Medicines involved in drug-related problems (DRPs) classified through the groups of the Anatomical Therapeutic Chemical (ATC) classification system.

		Drug Classes (ATC)									
		Alimentary Tract and Metabolism	Blood And Blood Forming Organs	Cardiovascular System	Genito Urinary System and Sex Hormones	Musculo-Skeletal System	Nervous System	Respiratory System	Sensory Organs	Other OTCs	Total
DRPs: Cause Domain	Drug Selection	566 (25.6%)	243 (11.0%)	577 (26.1%)	(0.05%)	72 (3.3%)	366 (16.5%)	–	–	4 (0.18%)	1829 (82.7%)
	Dispensing	–	–	2 (0.09%)	–	–	1 (0.05%)	–	1 (0.05%)	–	4 (0.18%)
	Patient Related	2 (0.09%)	–	19 (0.86%)	–	–		143 (6.5%)	–	–	164 (7.4%)
	Drug and Dose Seletion	–	–	59 (2.7%)	–	3 (0.14%)	–	–	–	–	62 (2.8%)
	Others	2 (0.09%)	–	29 (1.3%)	–	–	1 (0.05%)	2 (0.09%)	–	–	34 (1.5%)
DRPs: Problems Domain	Treatment Effectiveness	81 (3.7%)	–	17 (0.77%)	3 (0.14%)	–	5 (0.22%)	2 (0.09%)	–	–	108 (4.9%)
	Treatment Safety	–	–	7 (0.32%)	–	2 (0.09%)	2 (0.09%)	–	–	–	11 (0.50%)
Total		651 (29.4%)	243 (11%)	710 (32.1%)	4 (0.18%)	77 (3.5%)	375 (17.0%)	147 (6.6%)	1	4	2212
									0.05	0.18%	

OTCs = over-the-counter drugs.
a- refers to other OTC medicines that are not classified in ATC code.

problem." If we consider that few studies enrolled the patients into the MR process, the number of patient-related problems is probably underrepresented.

Included Studies' Methods

Most studies failed to justify the sample size, which can affect the significance of the outcomes of the study. Although randomization of samples affects the sample frame and leads to a nonrepresentative sample, only four studies reported these types of data.[15,22–24] Most of the studies failed to report the nonresponders, which can lead to a bias of results. Only four of the studies described the nature of prescribed and drug selection DRPs.[13,17,18,24] Coding systems are critical tools to register DRPs, and thus it was expected that all studies would mention the coding system used; however, three studies failed to report it.[14,16,22]

Results of the Review

The included studies suggested that the number of medicines is associated with increased difficulty in the management of medicines by patients; however, studies performed in different settings failed the attempt to relate the number of drugs used to the risk of undesirable health outcomes.[28,29] Older adults are more likely to have multiple medical problems, multiple medications, and cognitive impairment, and these factors can predispose to the occurrence of DRPs. In the included studies, no correlation between "age" and "susceptibility to risk factors" was observed. This lack of correlation is not a surprise, because aging itself is not a disease. The included studies show that the use of some medicines is associated with an increased risk for DRPs. It was observed that drugs for the central nervous system and cardiovascular drugs were the most consumed drugs and account for 15%–30% of all drug-related hospital admissions.[3] An association was found in the included studies between the use of inhalers and the PCNE cause category "drug administered/used in a wrong way." The underuse of "R-respiratory system" drugs is frequently observed, suggesting difficulties by patients with techniques of respiratory devices. These observations underline the necessity of recognizing this problem and implementing measures to improve the management of respiratory devices. Concerning "N-05 psycholeptic drugs," it was observed that these drugs were associated with an

overuse and with the occurrence of adverse drug reactions. "C-Cardiovascular system" drugs were not only associated with adverse reactions but also with "no or inappropriate monitoring," "drug selection," and "dose selection."

Another finding of our review was that patient interviews were essential for the identification of 27%−73% of DRPs; however, due to time consumption and costs, the involvement of patients during the MR process is not usually used in most of the studies. The active participation of patients during the process of MR is also an opportunity for the medication reviewers' teams to empower older patients in the appropriate use of drugs and self-management to identify concerns and fears and improve drug therapy control, resulting in better therapy outcomes.

Study Limitations

The main limitation of this review is the heterogeneity of methodology of the included studies, the lack of randomization of respective populations, and the heterogeneity of tools used to identify DRPs. Some studies failed to report the DRP classification system used, and, when reported, they were not consistent among studies. We had to reclassify all DRPs reported in the results of the studies according to the PCNE classification. This coding system is updated regularly and has been tested regarding its usability in practice and internal consistency. It is important to use a universal classification system to allow comparison. The data regarding the interventions recommended must be considered carefully because they are highly dependent on several extrinsic variables, such as: the internal political measures, the country where the study took place, the communication between health care professionals, and the design of the MR process. The most suggested intervention was related to "drug selection problems"; however, the most accepted interventions were related to "therapy monitoring."

Despite all limitations, this systematic review summarizes and highlights the relevant studies that can help to develop health strategies to improve medication use in the older adults.

Future Perspectives

It was found that "drug selection" and "dose problems" account for the majority of DRPs observed, suggesting that the use of preventive strategies targeting systems rather than individuals could be effective in reducing DRPs. Computerized expert clinical decision support systems are a promising strategy that targets the ordering stage of medication, when the most DRPs occur.[30] However, to improve the prescription process, it is essential that patient information in the patient data system is updated, structured, and accessible to all health professionals who participate in patients' care. The combination of the computerized expert clinical decision support systems and patient interviews, together with health care teamwork, will allow the achievement of a rational use of medicines that will improve clinical, economic, and humanistic outcomes.

CONCLUSIONS

This study provides useful information for the development of health promotion strategies to improve medication use in home-dwelling older adults. The huge number of drug selection problems observed suggests that more studies regarding the implementation of strategies that decrease inappropriate prescription should be performed. However, we must take into consideration that ongoing vigilance and support for older adults at risk of DRPs will always be necessary.

DISCLOSURES

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors have indicated that they have no conflicts of interest regarding the content of this article.

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Address correspondence to: Fátima Roque, Research Unit for Inland Development, Polytechnic of Guarda (UDI-IPG), Avenida Dr. Francisco Sá Carneiro, No. 50, 6300-559, Guarda, Portugal. E-mail: froque@ipg.pt

APPENDIX A. TABLE S1: SCREENING OF FULL TEXT FOR POTENTIAL INCLUSION/ EXCLUSION IN THE REVIEW.

AUTHOR AND YEAR	TITLE	INCLUDED	EXCLUDED (Why?)
Alderman CP, et al; 2013	Medication-related problems identified in home medicines reviews conducted in an Australian rural setting	No	yes (Age: range [50—99]
Benson H, et al; 2018	Pharmacists in general practice: a focus on drug-related problems	No	yes (Age: mean 67.7 ± 13.6)
Bonner CJ and Carr B; 2002	Medication compliance problems in general practice: detection and intervention by pharmacists and doctors	No	yes (no Data on Outcomes Reported/Available from Investigators)
Campins L, et al; 2017	Randomized controlled trial of an intervention to improve drug appropriateness in community dwelling polymedicated elderly people	No	yes (No Data on Outcomes Reported/Available from Investigators)
Castelino RL, et al; 2011	Are interventions recommended By pharmacists during Home Medicines Review evidence-based?	Yes	No
Castelino RL, et al; 2010	Retrospective evaluation of Home medicines reviews by pharmacists in older Australian patients using the medication appropriateness index	No	X no Data on Outcomes Reported/Available from Investigators
Chan DC, et al; 2014	Effectiveness of the medication safety review clinics for older adults prescribed multiple medications	yes	No
Chan DC, et al; 2012	Drug related problems (DRPs) identified from geriatric medication safety review clinics	No	yes (These data are the baseline data of Chan et al 2014)
Chan WWT, et al 2018	Evaluation of collaborative medication reviews for high-risk older adults	No	yes (setting tertiary care hospital)
Chau SH, et al; 2016	Clinical medication reviews in elderly patients with polypharmacy: a cross-sectional study on drug-related problems in the Netherlands	yes	no
Elliot RA, et al; 2012	Pharmacist-led medication review to identify medication-related problems in older people referred to an Aged Care Assessment Team: a randomized comparative study	No	Yes (compare pharmacist HMR with general practitioner HMR)
Fick DM, et al; 2008	Health outcomes associated with potentially inappropriate medication use in older adults. Research in nursing & health	No	yes (no Data on Outcomes Reported/Available from Investigators)
Galato D, et al; 2010	Study of the use of medicine in elderly living in a city in the South of Santa Catarina (Brazil): a look at the polymedication	No	yes (age> 60)
Griffiths R, et al; 2004	Nursing intervention for the quality use of medicines by elderly community clients	No	yes (no Data on Outcomes Reported/Available from Investigators)

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AUTHOR AND YEAR	TITLE	INCLUDED	EXCLUDED (Why?)
Jameson JP and VanNoorda GR; 2001	Pharmacotherapy consultation on Polypharmacy patients in ambulatory care	No	yes (age> 5)
Kari H, et al; 2018	Patient involvement is essential in identifying drug-related problems	yes	no
Kheir N, et al; 2014	Drug-related Problems identified by pharmacists conducting medication use reviews at a primary health center in Qatar	No	yes (age > 18)
Kiel WJ and Phillips SW; 2018	Impact of pharmacist-conducted comprehensive medication reviews for older adult patients to reduce medication related problems	No	yes (no Data on Outcomes Reported/Available from Investigators)
Huysmans K et al 2014	Drug related problems in Belgian community pharmacies	No	yes (age)
Kongkaew C, et al; 2017	Drug-Related Problems Identified at Patients' Home: A prospective Observational Study in a Rural Area of Thailand	No	yes (age)
Kovacevic SV, et al; 2017	Evaluation of drug-related problems in older polypharmacy primary care patients	yes	
Kwint HF, et al; 2014	Completeness of medication reviews provided by community pharmacists.	No	yes (compare pharmacist HMR with expert reviewers HMR)
Kwint HF, et al; 2011	Effects of medication review on drug-related problems in patients using automated drug-dispensing systems: a pragmatic randomized controlled study.	yes	no
Kwint HF, et al; 2012	The contribution of Patient interviews to the identification of drug-related problems in home medication review	yes	no
Laaksonen R, et al; 2010	Performance of community pharmacists in providing clinical medication reviews	No	Yes (compare clinic pharmacist HMR with community pharmacists HMR)
Leikola SNS, et al; 2012	Comprehensive medication reviews for elderly patients: Findings and recommendations to physicians	yes	No
Lenander C, et al; 2017	Effects of an intervention (SÄKLÄK) on prescription of potentially inappropriate medication in elderly patients	No	Yes (PIMS)
Lenander C, et al; 2018	Effects of medication reviews on use of potentially inappropriate medications in elderly patients; a cross-sectional study in Swedish primary care.	No	Yes (setting: nursing home or home care service)
Malet-Larrea A, et al; 2017	Cost analysis and cost-benefit analysis of a medication review with follow-up service in aged polypharmacy patients	No	yes (no Data on Outcomes Reported/Available from Investigators)
Mamen A.V., et al; 2015	Norwegian elderly patients' need for drug information and attitudes towards medication use reviews in community pharmacies	No	yes (no Data on Outcomes Reported/Available from Investigators)
McCarthy L, et al; 2007	Frequency of risk factors that potentially increase harm from medications in older adults receiving primary care	No	yes (no Data on Outcomes Reported/Available from Investigators)

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AUTHOR AND YEAR	TITLE	INCLUDED	EXCLUDED (Why?)
Messerli M, et al	Impact of a Community pharmacist-led medication review on medicines use in patients on polypharmacy—a prospective randomized controlled trial	No	yes (evaluation of a program/ service)
Metge C, et al; 2005	Pharmaceutical use among older adults: Using administrative data to examine medication-related issues	No	yes (no Data on Outcomes Reported/Available from Investigators)
Milos V, et al; 2013	Improving the quality of pharmacotherapy in elderly primary care patients through medication reviews: a randomized controlled study.	No	yes (no Data on Outcomes Reported/Available from Investigators)
Montiel-Luque A, et al; 2017	Medication-related factors associated with health-related quality of life in patients older than 65 years with polypharmacy.	No	yes (no Data on Outcomes Reported/Available from Investigators)
Ocampo CC, et al; 2015	Implementation of medication review with follow-up in a Spanish community pharmacy and its achieved outcomes	No	Yes (age)
Ong KY, et al; 2017	Effectiveness of a multidisciplinary home-based medication review program in reducing healthcare utilization among older adult Singaporeans	No	Yes (evaluation of a program/ service)
Parody, et al; 2005	Cost-effectiveness and cost calculation in an intervention on medication-related problems in primary care	No	Yes(age)
Pit SW, et al; 2007	Medication review: patient selection and general practitioner's report of drug-related problems and actions taken in elderly Australians	No	yes (no Data on Outcomes Reported/Available from Investigators)
Rhalimi M, et al; 2018	Drug-related problems identified during geriatric medication review in the community pharmacy	yes	No
Rose O, et al; 2015	Effect evaluation of an interprofessional medication therapy management approach for multimorbid patients in primary care: a cluster-randomized controlled trial in community care	No	yes (study protocol)
Roth MT and Ivey JL, 2005	Self-reported medication use in community-residing older adults: A pilot study.	No	yes (age)
Roth MT, et al; 2011	Racial disparities in the quality of medication use in older adults: baseline findings from a longitudinal study	No	yes (age)
Roughead EE, et al; 2004	Medication-related problems commonly occurring in an Australian community setting	yes	No
Sellors et al; 2003	A randomized controlled trial of a pharmacist consultation program for family physicians and their elderly patients	yes	no
Stafford et al 2009	Drug-related problems identified in medication reviews by Australian pharmacists	No	yes (age)
Tasaka Y, et al; 2018	Potential drug-related problems detected by routine pharmaceutical interventions: safety and economic contributions made by hospital pharmacists in Japan	No	Yes (setting: hospital)

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AUTHOR AND YEAR	TITLE	INCLUDED	EXCLUDED (Why?)
Touchette DR, et al; 2003	Safety-focused medication therapy management: a randomized controlled trial	Yes	No
Verdoorn S; et al; 2015	Majority Of drug-related problems identified during medication review are not associated with STOPP/START criteria. Eur J Clin Pharmacol	No	Yes (evaluation of a program/ service/tool)
Viktil KK, et al; 2006	Interview of patients by pharmacists contributes significantly to the identification of drug related problems (DRPs).	Yes	Yes (Setting hospital)
Vinks THAM., et al; 2006	Identification of potential drug-related problems in the elderly: The role of the community pharmacist	Yes	No
Vinks TH.M, et al; 2009	Pharmacist based Medication review reduces potential drug-related problems in the elderly: the SMOG controlled trial	No	yes (no Data on Outcomes Reported/Available from Investigators)
Willeboordse F,et al; 2017	The effectiveness of optimized clinical medication reviews for geriatric patients: Opti- Med a cluster randomized controlled trial	No	Yes (evaluation of a program/ service)
Xiong T, et al; 2014	Medication-related problems among community-dwelling older adults after recent hospital discharge in mainland China		yes (age)
Yang J, et al; 2018	Drug-related problems among community-dwelling older adults in mainland China	No	yes (only cardiovascular diseases)

APPENDIX B. TABLE S2- STUDY OF ASSESSMENT OF QUALITY AND SUSCEPTIBILITY TO BIAS OF QUANTITATIVE AND MIXED STUDIES: AXIS TOOL.

Author, year	Kari, K. et al, 2018[15]	Rhalimi, R. et al, 2018[20]	Kovacevic, M. et al, 2017[16]	Chau, J. et al, 2016[14]	Chan, C. et al, 2014[13]	Kwint, F. et al, 2012[18]	Leikola, V. et al, 2012[19]	Touchette, M. et al, 2012[23]	Castelino, B. et al, 2011[12]	Kwint, F. et al, 2011[17]	Vinks, de K. et al, 2006[24]	Roughead, B. et al, 2004[21]	Sellors, K. et al, 2003[22]
INTRODUCTION													
1. Were the aims/objectives of the study clear?	X	X	X	X		X	X	X	X	X	X	X	X
2. Was the study design appropriated for the stated aims?	X	X	X	X	X	X	X	X	X	X	X	X	X
3. Was the sample size justified?													
4. Was the target/reference population clearly defined? (Is it clear who the research was about?)	X		X	X	X	X	X	X	X	X	X	X	X
5. Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?	X	X	X	X	X	X	X	X	X	X	X	X	X
6. Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?	X	X	X	X	X	X	X		X	X		X	X
7. Were measures undertaken to address and categorise non-responders?											X	NA	
8. Were the risk factor and outcome variables measured appropriate to the aims of the study?	X	X	X	X	X	X	X	X	X	X	X	X	X
9. Is it clear what was used to determined statistical significance and/or precision estimates? (e.g. *p*-values, confidence intervals)	X	X	X	X	X	X	X	X	X	X	X	X	X
10. Were the methods (including statistical methods) sufficiently described to enable them to be repeated?		X	X		X	X	X	X	X	X	X		X
RESULTS													
11. Were the basic data adequately described?	X	X	X		X	X	X	X	X	X	X		X
12. Does the response rate raise concerns about non-response bias?	X	X	X	X	X	X	X	X	X	X	X	X	X
13. If appropriate, was information about non-responders described?									X		X		

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Author, year	Kari, K. et al, 2018[15]	Rhalimi, R. et al, 2018[20]	Kovacevic, M. et al, 2017[16]	Chau, J. et al, 2016[14]	Chan, C. et al, 2014[13]	Kwint, F. et al, 2012[18]	Leikola, V. et al, 2012[19]	Touchette, M. et al, 2012[23]	Castelino, B. et al, 2011[12]	Kwint, F. et al, 2011[17]	Vinks, de K. et al, 2006[24]	Roughead, B. et al, 2004[21]	Sellors, K. et al, 2003[22]
14. Were the results internally consistent?									NA				
15. If appropriate, was information about non-responders described?	X		X	X	X	X	X	X	X	X		X	X
16. Were the results presented for all the analyses described in the methods?	X	X	X	X		X		X	X	X	X	X	X
DISCUSSION													
17. Were the authors' discussions and conclusions justified by the results?	X	X	X	X	X	X	X	X	X	X	X	X	X
18. Were the limitations of the study discussed?	X				X	X		X	X	X	X		
OTHER													
19. Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?	X	X	X	X	X	X	X	X	X	X	X	X	X
20. Was ethical approval or consent of participants attained?	X	X	X	NA	X	X	X	X	NA	X	NA	X	X

Empty cell: The study did not comply with this exploratory question.
Cell marked with X: The study complied with this exploratory question.
Cell marked with NA: This exploratory question could not be appraised in this study.

APPENDIX C. TABLE S3 - CORRESPONDENCE BETWEEN RECLASSIFICATION FOR PCNE[A] AND CLASSIFICATION USED IN THE INCLUDED STUDIES.

Authors, Year	Reclassification for PCNE[a]	Number of DRP[b]	Authors Classification
Kari, K. et al, 2018[15]	**C1. DRUG SELECTION**	**39**	
	C1.1/C1.2 Inappropriate drug	17	Drug used for wrong purpose Not recommendable for older people for regular use Nonoptimal drug
	C1.3 No indication for drug	6	Indication for use of medication is unclear Inappropriate use of dietary supplements
	C1.4 Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	2	Interaction with warfarin
	C1.5 Inappropriate duplication of therapeutic group or active ingredient	2	Use of several systemic NSAIDs
	C1.6 No or incomplete drug treatment in spite of existing indication	12	Additional drug needed
	C5. DISPENSING	**4**	
	C5.2 Necessary information not provided	4	Contradictions in counselling
	C7. PATIENT RELATED	**18**	
	C7.1 Patient uses/takes less drug than prescribed or does not take the drug at all	13	Intentional nonadherence
	C7.7 Inappropriate timing or dosing intervals	2	Inappropriate timing of administration furosemide administered in the late afternoon/evening
	C7.8 Patient administers/uses the drug in a wrong way	2	Patient administers the drug in a wrong way: improper asthma inhaler device use
	C7.9 Patient unable to use drug/form as directed	1	Patient has misunderstood the instructions: patient did not know that budesonide–formoterol turbuhaler should be used regularly
	C8. OTHERS	**11**	
	C8.1 No or inappropriate outcome monitoring (incl. TDM)	4	Need for monitoring Due to decreased health condition patient cannot drive a car anymore and has

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Authors, Year	Reclassification for PCNE[a]	Number of DRP[b]	Authors Classification
			difficulties to go to INR monitoring tests
	C8.2 Other cause; specify		
	Cost	4	Medication costs
	Other	3	Others
	P1.TREATMENT EFFECTIVENESS	**31**	
	P.1.1 No effect of drug treatment	3	(Possible) Lack of effect of pharmacotherapy
	P. 1.3 Untreated symptoms or indication	28	Poor therapy control
	P2. TREATMENT SAFETY	**8**	
	P2.1 Adverse drug event (possibly) occurring	8	(Possible) Adverse drug reaction
Rhalimi, R. et al, 2018[20]	**C1. DRUG SELECTION**	**226**	
	C1.1/C1.2 Inappropriate drug	67	Drug contra-indicated or not recommended
	C1.3 No indication for drug	19	Drug without indication
	C1.4 Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	133	Drug interaction
	C1.6 No or incomplete drug treatment in spite of existing indication	7	Untreated indication
	C3. DOSE SELECTION	**29**	
	C3.2 Drug dose too high	29	Supra-therapeutic dosage
	C6. DRUG USE PROCESS	19	Improper administration
	C7. PATIENT RELATED	**18**	
	C7.1 Patient uses/takes less drug than prescribed or does not take the drug at all	18	Non-compliance
	C8. OTHERS	**10**	
	C8.1 No or inappropriate outcome monitoring (incl. TDM)	10	Drug monitoring
	P2. TREATMENT SAFETY		
	P2.1 Adverse drug event (possibly) occurring	32	Adverse effect
Kovacevic, M. et al, 2017[16]	**C1. DRUG SELECTION**	**408**	
	C1.1/C1.2 Inappropriate drug	86	Inappropriate drug
	C1.3 No indication for drug	38	Unnecessary drug
	C1.4 Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	125	Interactions
	C1.5 Inappropriate duplication of therapeutic group or active ingredient	12	Treatment duplication
	C1.6 No or incomplete drug treatment in spite of existing indication	147	Additional therapy needed
	C7. PATIENT RELATED	**208**	
	C7.1 Patient uses/takes less drug than prescribed or does not take the drug at all	208	Adherence
	C8. OTHERS	**44**	
	C8.1 No or inappropriate outcome monitoring (incl. TDM)	44	Lack of therapy monitoring
	P1.TREATMENT EFFECTIVENESS	**113**	
	P.1.1 No effect of drug treatment	113	Lack of efficacy
	P2. TREATMENT SAFETY	**191**	
	P2.1 Adverse drug event (possibly) occurring	191	Potential/actual adverse reaction

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Authors, Year	Reclassification for PCNE[a]	Number of DRP[b]	Authors Classification
Chau, J. et al, 2016[14]	**C1. DRUG SELECTION**	**6364**	
	C1.1/C1.2 Inappropriate drug	971	Contra-indication
	C1.4 Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	664	Interaction
	C1.6 No or incomplete drug treatment in spite of existing indication	1814	Undertreatment
	C1.7 Too many drugs prescribed for indication	2915	Overtreatment
	C2. DRUG DOSAGE FORM	**96**	
	C2.1 Inappropriate drug form (for this patient)	96	Inappropriate dosage form
	C3. DOSE SELECTION	**1190**	
	C3.1 Drug dose too low	622	Dose too low
	C3.2 Drug dose too high	568	Dose too high
	C7. PATIENT RELATED	**1401**	
	C7.1 Patient uses/takes less drug than prescribed or does not take the drug at all	645	Non adherence
	C7.9 Patient unable to use drug/form as directed	756	Difficulty using dosage form
	C8. OTHERS	**470**	
	C8.2 Other cause; specify	470	Miscellaneous problem
	P1.TREATMENT EFFECTIVENESS	**975**	
	P.1.1 No effect of drug treatment	975	Drug not effective
	P2. TREATMENT SAFETY	**923**	
	P2.1 Adverse drug event (possibly) occurring	923	Side effect
Chan, C. et al, 2014[13]	**C1. DRUG SELECTION**	**127**	
	C1.3 No indication for drug	32	No clear indication for drug
	C1.4 Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	35	Potential interaction
	C1.5 Inappropriate duplication of therapeutic group or active ingredient	34	Inappropriate duplication of drug
	C1.6 No or incomplete drug treatment in spite of existing indication	16	No drug but clear indication
		10	Other drug choice problems
	C3. DOSE SELECTION	**27**	
	C3.1 Drug dose too low and/or C3.3 Dosage regimen not frequent enough	20	Drug dose too low/not frequent enough
		7	Other dosing problems
	C6. DRUG USE PROCESS	**98**	
	C6.4 Drug not administered at all	98	Drug not taken/administered
	C8. OTHERS	**19**	
	C8.2 Other cause; specify	19	Other problem
Kwint, F. et al, 2012[18]	**C1. DRUG SELECTION**	**837**	
	C1.1/C1.2 Inappropriate drug	74	Contra-indications apparent
	C1.3 No indication for drug	323	No indication apparent
	C1.4 Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	15	Drug interaction

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Authors, Year	Reclassification for PCNE[a]	Number of DRP[b]	Authors Classification
	C1.5 Inappropriate duplication of therapeutic group or active ingredient	12	Duplication
	C1.6 No or incomplete drug treatment in spite of existing indication	402	Undertreated
			Condition undertreated
			Condition untreated
			Preventive therapy required
		11	Other drug selection problem
	C3. DOSE SELECTION	**105**	
	C3.1 Drug dose too low	72	Prescribed dosage too low
	C3.2 Drug dose too high	33	Prescribed dosage too high
	C5. DISPENSING	**73**	
	C5.2 Necessary information not provided	73	Incorrect or unclear dosing instructions
			Disease management or Advice
	C7. PATIENT RELATED	96	
	C7.1 Patient uses/takes less drug than prescribed or does not take the drug at all	43	C(ompliance) Taking too little
	C7.2 Patient uses/takes more drug than prescribed	8	C(ompliance) Taking too much
	C7.9 Patient unable to use drug/form as directed	45	Difficulty using dosage form
	C8. OTHERS	**359**	
	C8.1 No or inappropriate outcome monitoring (incl. TDM)	359	Non-laboratory monitoring
			Laboratory monitoring
	P2. TREATMENT SAFETY	**95**	
	P2.1 Adverse drug event (possibly) occurring	95	Toxicity, allergic reaction or adverse effect present
Leikola, V. et al, 2012[19]	**C1. DRUG SELECTION**	**222**	
	C1.1/C1.2 Inappropriate drug	82	Inappropriate drug
	C1.3 No indication for drug	29	No clear indication for drug use
	C1.4 Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	33	Potential interaction
	C1.6 No or incomplete drug treatment in spite of existing indication	78	No drug prescribed but clear indication
	C3. DOSE SELECTION	**111**	
	C3.1 Drug dose too low and/or C3.3 Dosage regimen not frequent enough	51	Drug dose too low or dosage regimen not frequent enough
	C3.2 Drug dose too high and/or C3.4 Dosage regimen too frequent	60	Drug dose too high or dosage regimen too frequent
	C8. OTHERS	**121**	
	C8.2 Other cause; specify	121	Other DRPs
	P2. TREATMENT SAFETY	**51**	
	P2.1 Adverse drug event (possibly) occurring	51	Adverse effect suffered (nonallergic)
Touchette, M. et al, 2012[23]	**C1. DRUG SELECTION**	**331**	
	C1.1/C1.2 Inappropriate drug	224	Drug choice problem: patient gets or is going to get wrong (or no) drug for disease and/or condition

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Authors, Year	Reclassification for PCNE[a]	Number of DRP[b]	Authors Classification
	C1.4 Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	107	Interactions: manifest or potential drug–drug or drug–food interaction
	C3. DOSE SELECTION	**149**	
	C3.1 Drug dose too low and/or C3.2 Drug dose too high	149	Dosing problem: patient gets more or less than the amount of drug required
	C6. DRUG USE PROCESS	**250**	
	C6.4 Drug not administered at all and/or C6.5 Wrong drug administered	250	Drug use problem: wrong or no drug taken/administered
	C8. OTHERS	126	
	C8.2 Other cause; specify	126	Other or unknown problem
	P2. TREATMENT SAFETY	**227**	
	P2.1 Adverse drug event (possibly) occurring	227	Adverse reaction to medication: patient suffers from potential or actual ADE
Castelino, B. et al, 2011[12]	**C1. DRUG SELECTION**	**275**	
	C1.1/C1.2 Inappropriate drug	61	Wrong or inappropriate medicine
	C1.3 No indication for drug	35	Unnecessary medicine
	C1.6 No or incomplete drug treatment in spite of existing indication	179	Need for additional medicine
	C3. DOSE SELECTION	**262**	
	C3.1 Drug dose too low	77	Dose too low
	C3.2 Drug dose too high	62	Dose too high
	C3.5 Dose timing instructions wrong, unclear or missing	123	Rationalization of drug therapy
	C5. DISPENSING	**46**	
	C5.2 Necessary information not provided	46	Lack of supporting information
	C7. PATIENT RELATED	**205**	Lifestyle issues
			Assistance required
	C7.1 Patient uses/takes less drug than prescribed or does not take the drug at all	53	Compliance problems
	C7.6 Patient stores drug inappropriately	21	Others (including out of date medicines/storage)
	C7.9 Patient unable to use drug/form as directed	58	Inappropriate technique
			Poor knowledge of the condition or treatment
	C8. OTHERS	**216**	
	C8.2 Other cause; specify|	216	Investigation test requested
			Referral to other health professionals
	P2. TREATMENT SAFETY	**106**	
	P2.1 Adverse drug event (possibly) occurring	106	Adverse drug reactions, drug–drug interactions and allergies
Kwint, F. et al, 2011[17]	**C1. DRUG SELECTION**	**235**	
	C1.1/C1.2 Inappropriate drug	9	Contraindication/intolerance
	C1.3 No indication for drug	78	Lack of indication or unclear indication
	C1.4 Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	13	Drug interaction

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Authors, Year	Reclassification for PCNE[a]	Number of DRP[b]	Authors Classification
	C1.5 Inappropriate duplication of therapeutic group or active ingredient	14	Duplication
	C1.6 No or incomplete drug treatment in spite of existing indication	121	Condition not adequately treated
			Preventive therapy required
	C2. DRUG DOSAGE FORM	**8**	
	C2.1 Inappropriate drug form (for this patient)	8	Wrong dosage form
	C3. DOSE SELECTION	**97**	
	C3.1 Drug dose too low	26	Dosage too low
	C3.2 Drug dose too high	48	Dosage too high
	C3.5 Dose timing instructions wrong, unclear or missing	23	Inappropriate dose frequency/ schedule
	C7. PATIENT RELATED	3	
	C7.2 Patient uses/takes more drug than prescribed	3	Taking too much
	C8. OTHERS	**3**	
	C8.1 No or inappropriate outcome monitoring (incl. TDM)	3	Non-laboratory monitoring required
	P1.TREATMENT EFFECTIVENESS	**57**	
	P.1.1 No effect of drug treatment	57	Lack of effectiveness
	P2. TREATMENT SAFETY	**77**	
	P2.1 Adverse drug event (possibly) occurring	77	Risk of adverse effects
			Possible drug treatment in response to adverse effect
Vinks, de K. et al, 2006[24]	**C1. DRUG SELECTION**	**554**	
	C1.1/C1.2 Inappropriate drug	158	Contraindication
	C1.3 No indication for drug	181	No longer existing indication
	C1.4 Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	136	Drug—drug interaction
	C1.5 Inappropriate duplication of therapeutic group or active ingredient	71	Therapeutic duplication
	C1.6 No or incomplete drug treatment in spite of existing indication	8	Undertreatment
	C2. DRUG DOSAGE FORM	**89**	
	C2.1 Inappropriate drug form (for this patient)	89	Inconvenience of use
	C3. DOSE SELECTION	**69**	
	C3.1 Drug dose too low	69	Inappropriate dosage
	C3.2 Drug dose too high		
	C6.5 Wrong drug administered	—	
	C7. PATIENT RELATED	**36**	
	C7.1 Patient uses/takes less drug than prescribed or does not take the drug at all	36	Non-compliance
	C8. OTHERS	**15**	
	C8.2 Other cause; specify	8	Drug treatment of adverse drug reaction
	- Drug treatment of an adverse reaction		
	- Off label	7	Off label use
Roughead, B. et al, 2004[21]	**C1. DRUG SELECTION**	**1008**	
	C1.1/C1.2 Inappropriate drug	268	Use of wrong or inappropriate medicine

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Authors, Year	Reclassification for PCNE[a]	Number of DRP[b]	Authors Classification
	C1.3 No indication for drug	103	Use of unnecessary medicine
	C1.5 Inappropriate duplication of therapeutic group or active ingredient	31	Duplication of medications
	C1.6 No or incomplete drug treatment in spite of existing indication	454	Need for additional medication 249 Use of too little medicine 205
	C1.7 Too many drugs prescribed for indication	122	Use of too much medicine
	C5. DISPENSING	**178**	
	C5.2 Necessary information not provided	178	Need for more information
	C7. PATIENT RELATED	**329**	
	C7.1 Patient uses/takes less drug than prescribed or does not take the drug at all	132	Compliance problems
	C7.3 Patient abuses drug (unregulated overuse)	9	Hoarding of medicines
	C7.6 Patient stores drug inappropriately	98	Expired medicines
	C7.7 Inappropriate timing or dosing intervals	—	
	C7.8 Patient administers/uses the drug in a wrong way	90	Administration problems
	C8. OTHERS	**505**	
	C8.1 No or inappropriate outcome monitoring (incl. TDM)	334	Need for additional test
	C8.2 Other cause; specify	40	
	- Patient fearful about taking medicines		Patient fearful about taking medicines
	- Need for additional therapy:	131	Need for additional therapy
	P2. TREATMENT SAFETY	**186**	
	P2.1 Adverse drug event (possibly) occurring	186	Adverse drug reactions present
Sellors, K. et al, 2003[22]	**C1. DRUG SELECTION**	**662**	
	C1.1/C1.2 Inappropriate drug	212	Patient is not taking an appropriate drug
	C1.3 No indication for drug	98	Patient is taking a drug for which he or she has no indication
	C1.4 Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	47	Patient is experiencing a drug interaction
	C1.6 No or incomplete drug treatment in spite of existing indication	305	Patient is not receiving a required drug
	C3. DOSE SELECTION	**197**	
	C3.1 Drug dose too low	108	Patient is taking too little drug
	C3.2 Drug dose too high	89	Patient is taking too much drug
	C7. PATIENT RELATED	**144**	
	C7.8 Patient administers/uses the drug in a wrong way	144	Patient is not taking a drug appropriately

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Authors, Year	Reclassification for PCNE[a]	Number of DRP[b]	Authors Classification
	P2. TREATMENT SAFETY	**90**	
	P2.1 Adverse drug event (possibly) occurring	90	Patient is having na adverse drug reaction

[a] Pharmaceutical Care Network Europe.
[b] Drug Related Problem.