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ORIGINAL ARTICLE

Evaluation of drug-related problems in older polypharmacy primary care patients

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Abstract

Aims and Objectives: Targeting older patients with predictive factors for drug-related problems (DRPs) could make clinical medication reviews more cost-effective. The aim of this study was to identify the number, type, and potential predictive factors for DRPs in older polypharmacy patients.

Methods: Community pharmacists performed clinical medication reviews and documented DRPs, types of interventions, and their implementation in older patients.

Results: Three hundred eighty-eight medication reviews were analyzed, 964 DRPs (average 2.5 ± 1.9), and 1022 interventions (average 2.6 ± 2.0) were identified. The overall implementation rate of interventions was 70.1%, the highest was observed in interventions aiming to resolve the lack of therapy monitoring (86.8%). Patients with ≥ 12 medications had an increased risk of ≥ 5 DRPs ($P < .001$). Asthma was associated with lack of adherence ($P = .002$), lack of aspirin, statins, and proton pump inhibitors use with additional therapy needed ($P = .002-.004$). Predictive factors for drug interactions were antihypertensive medications and/or medications with narrow therapeutic index ($P < .05$). Lack of efficacy was associated with diabetes ($P = .006$). Nonsteroidal anti-inflammatory drugs were risk factors for inappropriate drug selection ($P = .002$). Lack of monitoring was associated with hypertension ($P = .013$), whereas benzodiazepines ($P < .001$) and aspirin ($P = .021$) were overused.

Conclusion: Patients with asthma, hypertension, and diabetes and lack of statin, antithrombotic agent, and/or proton pump inhibitor use were associated with higher risks for DRPs.

KEYWORDS

clinical medication review, community pharmacy, drug-related problems, older patients, polypharmacy

1 | INTRODUCTION

As the population is aging worldwide, polypharmacy is growing and leading to an increased risk for drug-related problems (DRPs).^{1,2} A DRP is defined as any undesirable event experienced by a patient, involving or suspected of involving drug therapy and actually or potentially interfering with the desired patient outcome.³ Identifying and reducing DRPs is possible through medication reviews conducted by pharmacists.⁴⁻⁶ In the United Kingdom, United States, Australia, and the Netherlands, the term clinical medication review (CMR) is

increasingly used and defined as a face-to-face cooperation between the pharmacist and/or general practitioner (GP) and the patient to systematically review a patient's medication and conditions.⁵ Kwint et al showed that more than 25% of DRPs were identified during the interview with the patient and they were frequently assigned a higher clinical relevance and associated with recommendations for drug change, compared to DRPs identified solely through reviewing patient medication and clinical records.⁷

Some studies have shown that medication reviews conducted by pharmacists can improve patients' health outcomes, especially in older

patients, while others reported different results.^{8–11} It has been argued that medication review services are time-consuming and are not likely to be cost-effective in all older patients.¹¹ Therefore, identifying and targeting patients with predictive factors for DRPs may yield better outcomes of the service. The aim of this study was to investigate the number and type of DRPs encountered in older polypharmacy patients in Serbian primary care and the implementation of proposed interventions. Moreover, we aimed at identifying potential predictive factors for DRPs to target patients who could benefit most from CMRs.

2 | METHODS

This prospective observational study was conducted within a larger study on indicators for patient involvement in the process of pharmaceutical care, initiated by the European Directorate for the Quality of Medicines and Healthcare (EDQM), during a 4-month period, between March and June 2014. After obtaining the Ethical Committee permission, the recruitment process was launched. The study was announced on the website and in the official journal of the Pharmaceutical Chamber of Serbia. All pharmacists working in community pharmacies in Serbia were eligible for the study. Pharmacists who initially applied were asked to confirm their participation by filling, signing, and sending an agreement form. After that, they were provided with all study materials and a training course for CMRs was organized. Pharmacists were instructed to check the patient's therapy for completeness and appropriateness and to ask about adherence and adverse reactions. Moreover, they were instructed to investigate the efficacy of treatment and how patients' outcomes were monitored. Educational materials regarding DRPs, as well as instructions suggesting procedures for recruiting patients, delivering consultations, and performing CMRs were also at pharmacists' disposal. Additionally, regular correspondence between members of the working group and participating pharmacists was maintained.

The procedure required the recruitment of 10 patients meeting the following inclusion criteria: minimum age 65 years; polypharmacy (ie, ≥ 5 medications for chronic conditions); and medications of interest: cardiovascular (The Anatomical Therapeutic Chemical Class (ATC): C01-C10), alimentary tract and metabolism (ATC: A1-A16), musculoskeletal system (ATC: M01-M09), and respiratory system (ATC: R01-R07). Exclusion criteria were no possibility for personal contact with the patient, physically frail older patients, those receiving palliative care, and patients with cognitive impairment.

The pharmacist briefly outlined the concept and purpose of the CMR and invited the patient to participate. If interested, the patient had to sign an informed consent and an appointment for the review was scheduled. The patient was asked to bring a list of all prescription medicines, over-the-counter products, vitamins, herbal products, and food additives used on a daily basis. Patient's complete medical and biochemical record from the past year, issued by their GP was also part of the review documentation. By examining the patient's current medication therapy and using a face-to-face interview, the pharmacist filled a Medication Review Form. This form included basic information about the patient, the general practitioner, and the community pharmacy, a list of all currently used medicines and a brief outline of the developed

action plan. During the CMR, if necessary, the pharmacist contacted the GP by telephone, or asked the patient to visit the GP and report the outcome of the intervention at the next appointment. General practitioners were contacted if the intervention for solving the DRP required their authorization or if the pharmacist needed additional information to complete the CMR. The implementation of proposed interventions was noted by the pharmacist during the CMR or at the next meeting. Data were collected anonymously; each patient and each pharmacy were assigned a unique number.

The DRPs and proposed interventions described in the action plan were subsequently analyzed and classified by an academic pharmacist. Drug-related problems could be categorized into 9 groups: problems with patient adherence, potential or actual adverse reactions, additional therapy needed, drug interactions, lack of efficacy of the prescribed treatment, inappropriate drug selection, lack of appropriate monitoring of the drug/disease, unnecessary drug, and treatment duplication. Proposed actions were categorized as adherence support, introduction of a new drug, revision of therapy (in changing an existing drug to another, which was deemed safer or more efficient), laboratory/parameter monitoring, referral to specialist (due to a potentially recognized new illness), discontinuation of drug, dose adjustment, regimen adjustment, and increased vigilance.

Statistical analysis was performed with PASW 18.0 (SPSS Inc., Chicago, Illinois). Continuous variables in the text and tables were expressed by mean $\pm$ SD, and categorical data were presented as percentage. Multivariate logistic regression was used to determine independent risk factors associated with the total number of DRPs. Drug or disease/condition with at least 5 DRPs, gender, age (65–74, 75–84, and ≥ 85 years), number of prescribed drugs (5–7, 8–11, and ≥ 12), and number of indications (1–3, 4–6, and ≥ 7) were entered in the logistic regression analysis, and a model was built using the stepwise method which excluded variables at a selection threshold of 0.1. We also examined associations between types of DRPs, using the Fisher exact analysis and potential risk factors for their occurrence. The results of the regression analysis and risk factors for DRPs are presented with odds ratios (ORs) and their 95% confidence intervals (CIs). A probability value of $< .05$ was considered to be statistically significant.

3 | RESULTS

Seventy-three pharmacists applied for participation in the EDQM study, out of whom 44 (60.3%) completed recruitment of 10 patients. Four hundred forty patients, who fulfilled the inclusion criteria, were asked to participate in the study, and CMR was finalized in 388 patients (88.2%). The mean age of the population was 72.1 ± 6.3 years; the mean number of medications was 7.6 ± 2.2 ; the characteristics of the population are presented in Table 1.

Nine hundred sixty-four DRPs, classified in 9 categories, were identified in the cohort. The most common was lack of adherence (see Figure 1). Pharmacists proposed 1022 interventions, also classified in 9 categories, the most common were activities related to adherence support, such as using the pill box or education about the necessity of medication use (shown in Figure 1). On average 2.5 ± 1.9 (range

TABLE 1 Characteristics of the study population

Population characteristics	Total (n = 388)
Age, mean $\pm$ SD, range	72.1 $\pm$ 6.3 (65-91)
Sex (female), n (%)	217 (55.9)
Number of drugs prescribed	2933
Drug prescriptions per patient, mean $\pm$ SD, range	7.6 $\pm$ 2.2 (5-18)
Number of diseases/conditions per patient, mean $\pm$ SD, range	4.4 $\pm$ 1.5 (1-10)
Most frequent indications, n (%)	
Arterial hypertension	360 (92.8)
Diabetes mellitus	178 (45.9)
Primary prevention of cardiovascular events	151 (38.9)
Angina pectoris	133 (34.3)
Dyslipidemia	117 (30.2)
Cardiac arrhythmia	74 (19.1)
Most frequent medications/medication classes, n (%)	
Angiotensin-converting enzyme inhibitors	318 (82.0)
Beta blockers	278 (71.6)
Calcium channel blockers	225 (58.0)
Thiazide diuretics	193 (49.7)
Aspirin/Clopidogrel	189 (48.7)
Metformin	151 (38.9)

0-12) DRPs per patient and 2.6 ± 2.0 (range 0-11) interventions were observed, 381 patients (98.2%) had at least one DRP.

Using multivariate regression analysis, we identified independent risk factors for DRPs in our cohort. The count of medications and number of indications were predictors of the quantity of DRPs, whereas age and gender showed no significant influence. Patients with ≥ 12 medications had a significantly higher risk of ≥ 5 DRPs compared with patients with fewer medications (OR 5.4, 95% CI 2.12-13.78, $P < .001$). Similarly, patients with ≥ 7 indications had a significantly higher risk of ≥ 5 DRPs (OR 3.57, 95% CI 1.59-8.02, $P = .001$). Moreover, presence or absence of certain medications and/or indications was associated with a higher risk of a certain type of DRP as shown in Table 2. Asthma was associated with lack of adherence; additional

therapy was suggested for increased risk of cardiovascular events, dyslipidemia or presence of diabetes (statins), and dyspepsia or history of gastric ulcer (proton pump inhibitors). Most identified drug interactions were associated with antihypertensive medications and/or medications with narrow therapeutic index (warfarin, acenocoumarol, theophylline, amiodarone, and digoxin).^{12,13} In patients with cardiac failure, the risk of potassium imbalance was of concern. Pharmacists were concerned mostly due to additive hypotensive effects of medications in case of hypertensive patients. Lack of efficacy in adherent patients, was mostly associated with diabetes and the presence of metformin and sulfonylurea in therapy, whereas patients on insulin were not identified in this category. The presence of nonsteroidal anti-inflammatory drugs (NSAID) was often considered as inappropriate, usually associated with the use of this class of drugs in pain of different etiology (but not rheumatoid arthritis) in hypertensive patients, where paracetamol could have been considered as a safer alternative. Lack of monitoring was associated with lack of blood pressure monitoring in hypertensive patients, whereas benzodiazepines and aspirin were overused according to primary care pharmacists.

The overall implementation rate of the proposed interventions was 70.1%, whereas 10.0% of interventions were rejected and the outcome was unknown for the remaining 19.9%. Pharmacists were responsible for the implementation of 17.5% of interventions; patients for 29.6% and GP or specialist were required for 52.9% of proposed actions. Interventions, which aimed to resolve the lack of therapy monitoring, had the highest implementation rate (86.8%), whereas interventions concerning drug interactions were the least likely to be implemented (50.4%). Actions related to adherence support had the highest rate of acceptance, whereas the suggestion to refer the patient to a specialist was less likely to be accepted (81.0% vs 55.4%, respectively, $P < .001$). The interventions were more likely to be implemented if patients or pharmacists were responsible for it, compared with GP or specialist ($P < .001$).

4 | DISCUSSION

Our results show that pharmacist-initiated CMRs can be effective in detecting and resolving DRPs. The mean of 2.5 DRPs per review is in

FIGURE 1 A, Drug-related problems in older polymedicated patients and B, interventions proposed by primary care pharmacists

TABLE 2 Medication/indication associated with drug-related problems (DRPs)

DRP	No. of patients with DRP, N (%)	Medication/indication associated with DRP	OR	95% CI	P value
Adherence	141 (36.3)	Asthma	4.95	1.71-14.29	.002
Potential/actual adverse reaction	146 (37.6)	-	-	-	-
Additional therapy needed	112 (28.9)	Secondary prevention of cardiovascular events	2.42	1.34-4.36	.003
		Statins	2.36	1.31-4.25	.004
		Proton pump inhibitors	5.25	1.77-15.61	.002
		Primary prevention of cardiovascular events	2.88	1.53-5.44	<.001
		Gastrointestinal tract protection	7.60	2.07-27.89	.001
		Dyslipidemia	2.23	1.16-4.26	.015
Interactions	78 (20.1)	Anticoagulants	4.57	1.13-18.41	.028
		Theophylline	7.33	1.81-29.63	.003
		Amiodarone	5.00	0.81-31.00	.049
		Calcium channel blockers	7.72	3.57-16.69	<.001
		Beta blockers	2.57	1.36-4.88	.003
		Angiotensin-converting enzyme inhibitors	3.05	1.66-5.58	<.001
		Digoxin	6.72	1.52-29.61	.008
		Thiazide diuretics	4.00	1.90-8.39	<.001
		Spironolactone	3.76	1.01-14.10	.043
		Cardiac arrhythmia	6.33	2.28-17.59	<.001
		Heart failure	5.65	1.38-23.12	.011
		Hypertension	4.00	2.33-6.86	<.001
Lack of efficacy	81 (20.9)	Sulfonylurea	3.26	1.07-9.90	.032
		Metformin	4.17	1.85-9.40	<.001
		Diabetes	2.61	1.30-5.27	.006
Inappropriate drug	42 (10.8)	Nonsteroidal anti-inflammatory drugs	8.94	1.92-41.58	.002
		Pain of different aetiology	7.07	1.48-33.78	.007
Lack of therapy monitoring	29 (7.5)	Hypertension	2.72	1.21-6.13	.013
Unnecessary drug	67 (17.3)	Aspirin	2.47	1.13-5.40	.021
		Benzodiazepines	33.30	11.68-94.94	<.001
		Anxiety/sleep disorder	11.05	3.95-30.93	<.001
Treatment duplication	12 (3.1)	-	-	-	-

Abbreviations: CI, confidence interval; OR, odds ratio.

agreement with other investigators (2.0-6.5).^{4,6,14-18} Most common DRPs identified by pharmacists were lack of adherence, potential or actual adverse reactions, and the need for additional drugs, all of those accounted for more than a half of identified DRPs. These findings are in accordance with CMRs performed in community pharmacies, which included patient interviews.^{7,19-22} In contrast, non-adherence had less impact on overall DRPs when medication reviews were conducted without interviewing the patient.^{4,6,23-26} A possible explanation for the discrepancy was given by Kwint et al who showed that compliance issues, toxicity, over or underdose, and education were more likely to be identified during patient interviews.⁷

The count of medications and indications were predictors of the quantity of DRPs, which was expected and in line with literature data.^{23,27,28} We identified possible risk factors for most DRPs. Asthma was associated with lack of adherence, mostly due to inappropriate use of inhalers and treatment cost. Such findings are in accordance with several studies showing low adherence and persistence in asthma patients.²⁹⁻³² In contrast, Snyder et al reported a lack of predictors in their adherence-specific problems,²³ possibly because of an insufficient number of asthma patients. Interestingly, although potential/actual adverse reactions were observed in more than a third of the patients involved in medication reviews, there was no particular medication or indication associated with this DRP. The high prevalence of adverse reactions can be related to the large number of drugs used

per patient (≥ 5), which is consistent with other authors.^{33,34} In pharmacists' opinion, almost every fourth patient needed at least 1 additional medication, usually an antithrombotic agent, statin and/or proton pump inhibitor. In a previous study, we reported a high rate of prescription omissions particularly in patients with diabetes (statins) and in secondary prevention of cardiovascular events.³⁵ Moreover, lipid modifying agents, antithrombotics, H₂-inhibitors, and proton pump inhibitors were most frequently associated with DRPs in Dutch CMRs as well.⁴ Pharmacists were concerned about potential adverse outcomes of interactions, mostly between antihypertensive medications and/or medications with narrow therapeutic index. The rate of interactions 0.3 per patient was similar to the study of Ahmad et al³³ and in line with other studies ranging from 0.05 to 1.4 interactions per patient.^{16,36} Diabetes was associated with lack of efficacy, NSAIDs with inappropriate drug use, hypertension with the lack of monitoring, benzodiazepines, and aspirin were overused according to primary care pharmacists. Such results were comparable with our previous study and literature data which associated diabetes and hypertension with DRPs.^{9,17,33} However, the potential risk factors for DRPs in our study were not similar to the study of Snyder et al.²³ Only 33% complied to the risk factors contributing to the occurrence of DRPs agreed by an expert panel in the study of Kaufmann et al.³⁷ Although similar types of DRPs were observed as in other studies, this indicates that a difference in prescribing patterns may exist among different health care

systems leading to various specific DRPs as well as a difference in detecting DRPs between experts and community pharmacists.

According to the type of DRPs, most common pharmacists-suggested interventions were adherence support, the introduction of a new drug, or revision of existing therapy regarding drug change. Similarly, medication change, monitoring, and provision of information/advice were the most common interventions proposed by pharmacists during CMRs in Dutch pharmacies.⁴ The overall implementation rate of proposed interventions was 70.1%, similar to acceptance and implementation rates reported in the literature (56%-75%).^{6,38-40} The DRPs with the highest implementation rate of interventions were a lack of monitoring (86.8%) followed by interventions to resolve non-adherence (76.9%). In contrast, interventions, which included medication change and referral to a specialist, were least likely to be implemented. The rate of intervention implementation was higher if it depended solely on the pharmacist and patient. However, this observation was to some degree biased by the fact that pharmacists often lacked knowledge about the outcome of the proposed action to GP or specialist (29.3%), whereas the rejection rate by GPs and specialists was 14%.

There are some limitations to this study that should be addressed. First, we targeted patients with medications belonging to defined ATC groups, which resulted in a population with most prevalent diseases. However, we had a small proportion of patients with nervous system diseases where DRPs can be expected as well. Second, taxonomies for defining DRPs differ in literature, and we used one which was suitable for the results encountered in our population. Therefore, direct comparisons to other studies should be interpreted carefully. Finally, there is a high possibility that the number of DRPs identified in our study was underestimated and biased by the knowledge and skills of the individual pharmacist. However, the study reflects the real-life situation regarding CMRs in community pharmacy practice.

5 | CONCLUSION

This is the first study which investigated DRPs detected by community pharmacists' during a CMR, in Serbia. Risk factors were associated with specific DRPs. Higher prevalence of non-adherence was seen in asthma and lack of treatment efficacy in diabetes. Additional therapy was needed to prevent cardiovascular events and/or bleeding, whereas NSAIDs (including aspirin) and benzodiazepines were associated with inappropriate or unnecessary treatment. Pharmacists were concerned about interactions in patients with cardiovascular diseases and identified lack of therapy monitoring in hypertensive patients. Clinical medication reviews performed by community pharmacists are a useful tool in detecting and solving a variety of DRPs in older multimorbid patients. Further research is necessary to investigate the impact of community pharmacists' CMRs on health-related outcomes of older patients.

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The authors declare that they have no conflict of interest.

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CONTRIBUTION OF AUTHORS

MĆ, MK, BG, KV, and MJ collected and analyzed the data; SVK analyzed the data and wrote the manuscript; BM and JJG revised the manuscript.

REFERENCES

1. Stuck A, Beers M, Steiner A, Aronow H, Rubenstein L, Beck J. Inappropriate medication use in community-residing older persons. *Arch Intern Med*. 1994;154:2195-2200.
2. Noble RE. Drug therapy in the elderly. *Metabolism*. 2003;52(10 Suppl 2):27-30.
3. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. *Am J Hosp Pharm*. 1990;47:533-543.
4. Kempen TG, van de Steeg-van Gompel CH, Hoogland P, Liu Y, Bouvy ML. Large scale implementation of clinical medication reviews in Dutch community pharmacies: drug-related problems and interventions. *Int J Clin Pharmacol*. 2014;36:630-635.
5. Geurts MME, Talsma J, Brouwers JR, de Gier JJ. Medication review and reconciliation with cooperation between pharmacist and general practitioner and the benefit for the patient: a systematic review. *Br J Clin Pharmacol*. 2012;74:16-33.
6. Milos V, Rekman E, Bondesson A, et al. Improving the quality of pharmacotherapy in elderly primary care patients through medication reviews: a randomised controlled study. *Drugs Aging*. 2013;30:235-246.
7. Kwint HF, Faber A, Gussekloo J, Bouvy ML. The contribution of patient interviews to the identification of drug-related problems in home medication review. *J Clin Pharm Ther*. 2012;37:674-680.
8. Niquille A, Bugnon O. Relationship between drug-related problems and health outcomes: a cross-sectional study among cardiovascular patients. *Pharm World Sci*. 2010;32:512-519.
9. Roughead EE, Barratt JD, Ramsay E, et al. The effectiveness of collaborative medicine reviews in delaying time to next hospitalization for patients with heart failure in the practice setting: results of a cohort study. *Circ Heart Fail*. 2009;2:424-428.
10. Holland R, Lenaghan E, Harvey I, et al. Does home based medication review keep older people out of hospital? The HOMER randomised controlled trial. *Br Med J*. 2005;330:293
11. Lenaghan E, Holland R, Brooks A. Home-based medication review in a high risk elderly population in primary care-the POLYMED randomised controlled trial. *Age Ageing*. 2007;36:292-297.

12. Blix HS, Viktil KK, Moger TA, Reikvam A. Drugs with narrow therapeutic index as indicators in the risk management of hospitalised patients. *Pharm Pract (Granada)*. 2010;8:50-55.
13. Trujillo TC, Nolan PE. Antiarrhythmic agents: drug interactions of clinical significance. *Drug Saf*. 2000;23:509-532.
14. Denneboom W, Dautzenberg MG, Grol R, De Smet PA. Treatment reviews of older people on polypharmacy in primary care: cluster controlled trial comparing two approaches. *Br J Gen Pract*. 2007;57:723-731.
15. Leikola SN, Virolainen J, Tuomainen L, Tuominen RK, Airaksinen MS. Comprehensive medication reviews for elderly patients: findings and recommendations to physicians. *J Am Pharm Assoc* (2003). 2012;52:630-633.
16. Vinks TH, Egberts TC, de Lange TM, de Koning FH. Pharmacist-based medication review reduces potential drug-related problems in the elderly: the SMOG controlled trial. *Drugs Aging*. 2009;26:123-133.
17. Stafford AC, Tenni PC, Peterson GM, et al. Drug-related problems identified in medication reviews by Australian pharmacists. *Pharm World Sci*. 2009;31:216-223.
18. Jokanovic N, Tan EC, van den Bosch D, Kirkpatrick CM, Dooley MJ, Bell JS. Clinical medication review in Australia: a systematic review. *Res Social Adm Pharm*. 2016;12:384-418.
19. Chua SS, Kok LC, Yusof FA, et al. Pharmaceutical care issues identified by pharmacists in patients with diabetes, hypertension or hyperlipidaemia in primary care settings. *BMC Health Serv Res*. 2012;12:388.
20. Lenander C, Elfsson B, Danielsson B, Midlov P, Hasselstrom J. Effects of a pharmacist-led structured medication review in primary care on drug-related problems and hospital admission rates: a randomized controlled trial. *Scand J Prim Health Care*. 2014;32:180-186.
21. Ocampo CC, Garcia-Cardenas V, Martinez-Martinez F, Benrimoj SI, Amariles P, Gastelurrutia MA. Implementation of medication review with follow-up in a Spanish community pharmacy and its achieved outcomes. *Int J Clin Pharmacol*. 2015;37:931-940.
22. Sturgess IK, McElnay JC, Hughes CM, Crealey G. Community pharmacy based provision of pharmaceutical care to older patients. *Pharm World Sci*. 2003;25:218-226.
23. Snyder ME, Frail CK, Jaynes H, Pater KS, Zillich AJ. Predictors of medication-related problems among Medicaid patients participating in a pharmacist-provided telephonic medication therapy management program. *Pharmacotherapy*. 2014;34:1022-1032.
24. Nicolas A, Eickhoff C, Griesse N, Schulz M. Drug-related problems in prescribed medicines in Germany at the time of dispensing. *Int J Clin Pharmacol*. 2013;35:476-482.
25. Haemmerlein A, Griesse N, Schulz M. Survey of drug-related problems identified by community pharmacies. *Ann Pharmacother*. 2007;41:1825-1832.
26. Brulhart MI, Wermeille JP. Multidisciplinary medication review: evaluation of a pharmaceutical care model for nursing homes. *Int J Clin Pharmacol*. 2011;33:549-557.
27. Alkema GE, Wilber KH, Simmons WJ, Enguidanos SM, Frey D. Prevalence of potential medication problems among dually eligible older adults in medicaid waiver services. *Ann Pharmacother*. 2007;41:1971-1978.
28. Pit SW, Byles JE, Cockburn J. Prevalence of self-reported risk factors for medication misadventure among older people in general practice. *J Eval Clin Pract*. 2008;14:203-208.
29. Covey JR, Mullen AB, Ryan M, et al. A comparison of medication adherence/persistence for asthma and chronic obstructive pulmonary disease in the United Kingdom. *Int J Clin Pract*. 2014;68:1200-1208.
30. Sumino K, Cabana MD. Medication adherence in asthma patients. *Curr Opin Pulm Med*. 2013;19:49-53.
31. Moldrup C, Stein J, Sondergaard B. "Patients don't lie"; a view on adherence in asthma. *Pharm World Sci*. 2010;32:795-798.
32. Haupt D, Krigsman K, Nilsson JLG. Medication persistence among patients with asthma/COPD drugs. *Pharm World Sci*. 2008;30:509-514.
33. Ahmad A, Mast MR, Nijpels G, Elders PJ, Dekker JM, Hugtenburg JG. Identification of drug-related problems of elderly patients discharged from hospital. *Patient Prefer Adherence*. 2014;8:155-165.
34. Cresswell KM, Fernando B, McKinsty B, Sheikh A. Adverse drug events in the elderly. *Br Med Bull*. 2007;83:259-274.
35. Vezmar Kovacevic S, Simicic M, Stojkov Rudinski S, et al. Potentially inappropriate prescribing in older primary care patients. *PLoS One*. 2014;9:e95536.
36. Paulino EI, Bouvy ML, Gastelurrutia MA, Guerreiro M, Buurma H. ESCP-SIR Rejkjavik Community Pharmacy Research Group. Drug related problems identified by European community pharmacists in patients discharged from hospital. *Pharm World Sci*. 2004;26:353-360.
37. Kaufmann CP, Stampfli D, Hersberger KE, Lampert ML. Determination of risk factors for drug-related problems: a multidisciplinary triangulation process. *Br Med J*. 2015;5:e006376.
38. Nishtala PS, McLachlan AJ, Bell JS, Chen TF. A retrospective study of drug-related problems in Australian aged care homes: medication reviews involving pharmacists and general practitioners. *J Eval Clin Pract*. 2011;17:97-103.
39. Freeman CR, Cottrell WN, Kyle G, Williams ID, Nissen L. An evaluation of medication review reports across different settings. *Int J Clin Pharmacol*. 2013;35:5-13.
40. Zermansky AG, Alldred DP, Petty DR, et al. Clinical medication review by a pharmacist of elderly people living in care homes-randomised controlled trial. *Age Ageing*. 2006;35:586-591.

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