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Studying the impact of a medication use evaluation by the community pharmacist (Simenon): Drug-related problems and associated variables

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ABSTRACT

Background: A medication use review (MUR) aims to optimize medication use, patient knowledge and can improve health outcomes. This pharmaceutical care service is not yet available in Belgium.
Objectives: To describe drug-related problems (DRPs) detected during a MUR, subsequent interventions proposed by pharmacists and evolution of DRPs until follow-up and to identify patient-related variables associated with the number of reported DRPs.
Methods: Belgian community pharmacists provided a MUR to older polymedicated ambulatory patients and registered DRPs, interventions and resolution at follow-up using the PharmDISC classification. The relationship between 14 patient-related variables and the number of reported DRPs was investigated with univariate analysis. A prediction model was developed with significant variables using negative binomial regression analysis.
Results: Across 56 pharmacies, 453 patients received a MUR and 1196 DRPs were registered (median 3DRPs/patient, range 0–10). Only for 11.7% of patients no problems were identified. The top-3 causes were interaction (15.2%), inappropriate timing or frequency (13.5%) and adverse effect (11.9%). The top-3 recommended interventions by pharmacists were transmission of information (25.1%), in-depth patient counselling (15.0%) and therapy stop (8.2%). After six weeks, 42.6% of DRPs were resolved; data was missing for 33.3%. A higher number of chronic drugs, female gender and living alone were associated with more DRPs. The prediction model found that per additional chronic drug, the number of problems increases by 4.3% (95% CI: 2.0–6.6%). Male gender decreases DRPs by 22.1% (95% CI: 10.4–32.0%). Living alone provided no additional predictive value in the prediction model. Confounding process- and pharmacist-related variables also influenced the number of reported DRPs.
Conclusion: A MUR appears an effective strategy to detect and resolve DRPs. The number of chronic medications and female gender predict a higher number of DRPs. These findings are a starting point for evidence-based eligibility criteria for a MUR service in Belgium.

Introduction

Aging populations, non-communicable diseases and polypharmacy, usually defined as using five or more drugs on a regular basis,[1] challenge healthcare systems worldwide. All three factors may contribute to the risk for drug-related problems (DRPs).[2] A DRP is 'an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes'.[3] Drug-related problems are responsible for 5–17% of acute hospitalizations.[4–6] The economic impact of avoidable drug-related hospitalizations is estimated to be 200 million euros per year in Belgium.[7]

A medication review (MR) is a promising service to proactively detect drug-related problems, to support evidence-based medication use and to provide individualized counselling to vulnerable patients. It

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is defined as 'a structured evaluation of a patient's medicines with the aim of optimizing medicines use and improving health outcomes. This entails detecting drug-related problems and recommending interventions'.[8] A medication use review (MUR) is an intermediate medication review in which the medication history and a patient interview are consulted to optimize the patient's knowledge and use of medication.[9]

Research shows that medication reviews by pharmacists can positively impact adherence, improve appropriateness of prescribing and may potentially reduce emergency department (ED) visits.[10–12] These studies emphasize the importance of providing the service to high-risk populations to maximize the impact.[12–14] However, there is no consensus which population is at high risk. Medication reviews are implemented and reimbursed in the primary care setting in several countries (e.g. The Netherlands, Switzerland, the United Kingdom, France, Australia, New Zealand and the United States of America) although the patient eligibility criteria vary.[9,15–20] Recurring criteria are: number of chronic medications, use of specific medication classes, advanced age, number of chronic diseases and additional risk factors. To estimate the eligible population in Belgium, two criteria can be applied: age and polypharmacy. Over two million people (18.5% of the Belgian population in 2017) are aged 65 or older and at least 19% of this aged population is polymedicated (estimated eligible population: 380.000 patients).[21,22] To further reduce the eligible population, the age criterion can be set at 70 years or older (13.1% of the population in 2017), and additional more restrictive criteria can be explored.[21]

In 2016, a consortium was set up with three universities and the Association of Pharmacists Belgium to investigate the effectiveness and implementation of a MUR in Belgian community pharmacies. Within this consortium, the objective of the SIMENON study (Studying the impact of a medication use evaluation by the community pharmacist) was to acquire insight in the burden of DRPs for older polymedicated patients and the effect of a pharmacist-led intervention to tackle them. More in detail, the aim was to describe the type and number of DRPs detected by community pharmacists during a MUR, the proposed interventions and evolution of DRPs until follow-up.[23] A second objective was to identify patient-related variables that predict a high number of DRPs and to investigate what confounding variables (i.e. process-, pharmacy- and pharmacist-related variables) mediated the relationship between the patient-related variables and the number of reported DRPs.

Methods

Design, setting and intervention

The SIMENON study is a longitudinal pre-post intervention study with a single group design. A detailed description of the study methodology is provided in the protocol manuscript.[23] The MUR intervention consisted of a 6-step process: 1. Patient recruitment; 2. Preparation of the review; 3. Patient interview (defined as $T_{0\ weeks}$); 4. Pharmacotherapeutic analysis; 5. Discussing the medication list and DRP(s) with the patient and reaching an agreement on the intervention(s) to be performed (at $T_{2\ weeks}$); 6. Follow-up (at $T_{6\ weeks}$) (Fig. 1).[23] During the process both contact with other healthcare professionals (HCPs) and use of an explicit medication appropriateness tool (e.g. the Ghent Older People's Prescriptions community Pharmacy Screening-tool (GheOP^{3}S-tool)) were advised but not compulsory.[24]

Participants

A convenience sample of Belgian community pharmacists participated to the study. The participants received an education program, including how to conduct a MUR and how to prioritize DRPs, to ensure the quality of the MUR and detection of DRPs.[23] Ambulatory patients who used five or more chronic medications (prescription or non-prescription medication) and were 70 years or older, were recruited by their regular community pharmacist on fixed inclusion days.[23]

Data collection

Drug-related problems

The community pharmacist registered the drug-related problems that he/she judged to be a priority for the patient, taking into account all the available information. In addition to the reported DRPs, the interventions proposed to resolve the problem, and the evolution of the DRPs throughout the review were registered by the pharmacist (see Fig. 1). Pharmacists used an adapted, simplified version[1] of the PharmDISC classification for the registration of the cause of the intervention and intervention itself (Pharmacists' Documentation of Interventions in Seamless Care).[25] It classifies DRPs into problems related to therapy choice, drug choice, dose choice, drug use or patient-related problems.[25] Only one cause and intervention could be registered per DRP. The validated French version was used in the French-speaking part of Belgium; A Dutch translation was prepared by one researcher (JW), reviewed by a second researcher (VF) and optimized through discussions between both researchers. No back translation was made. The PharmDISC classification was chosen as it is intervention-oriented with an emphasis on DRPs and interventions related to medication use by the patient. Furthermore, the instrument has been validated in the community pharmacy setting.[25]

Variables associated with the number of reported DRPs

Aside from the DRP data, 14 patient-related variables were collected: 3 demographic, 8 medication-related and 3 clinical variables. Demographic variables were age, gender and living situation. Four medication-related variables, based on the eligibility criteria for a medication use review in the United Kingdom,[9] reported on the use of specific medication classes (antiplatelet medication (ATC code B01AC), anticoagulants (ATC code: B01AA, B01AE, B01AF), nonsteroidal anti-inflammatory medication (ATC code M01) and diuretics (ATC code C03)). Other medication-related variables were the number of chronic medications, the need for medication assistance by a caregiver, the use of medication assistance materials (e.g. pill box) and the availability of a medication list before the MUR. The clinical variables were limited to the occurrence of hospitalizations, ED visits or fall incidents within the last three months, as reported by the patient during the interview. The confounding variables consisted of 8 variables related to the MUR process and 8 pharmacy- and pharmacist-related variables. The variables are listed in Appendix 6. All data were coded and registered by the pharmacist using a secure webtool.

Data analysis

Drug-related problems

Frequencies and percentages were used to describe nominal and categorical data. Depending on the distribution of the continuous data, median and range or means and standard deviations were reported. When reporting percentages, the study population was consistently chosen as the denominator irrespective of missing data.

Variables associated with the number of reported DRPs

For the second objective, the association between the number of reported DRPs (the discrete dependent variable) and each independent patient-related variable was investigated in a univariate analysis with a model for count data. A negative binomial regression model was used, which can handle the presence of overdispersion (as opposed to a Poisson model). A significance level of 0.05 was chosen. Process-, pharmacy- and pharmacist-related variables (also referred to as confounding variables) were tested as they may influence the number of detected DRPs.

[1] Minor adaptations were made to the PharmDISC classification for the causes: the option 'not applicable' was added and the technical causes for an intervention (i.e. logistic issues and problems related to the prescription quality) were not included as the MUR, performed in this study, was independent from the dispensing process.

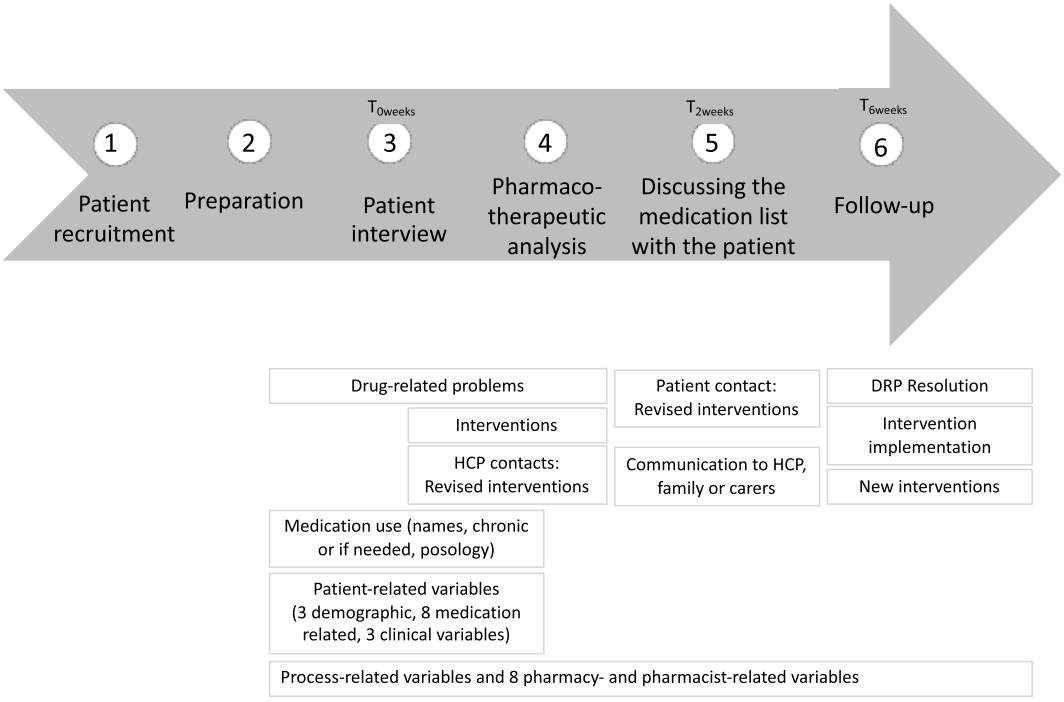

Fig. 1. Overview of the 6-step medication use review process and the data collected at the different timepoints.

In a next step, a multiple regression model was built to predict the number of DRPs using only the significant patient-related variables from the univariate analysis. A forward stepwise approach was applied and a significance level threshold of 0.157 was chosen for the rejection or acceptation of each variable in the model. This threshold corresponds to the Akaike Information Criterion for a variable with one degree of freedom. Interaction terms were not added as there was already a risk for overfitting the model due to the high number of variables. A per protocol analysis was predefined, therefore no imputation of missing data was performed. Consequently, different samples were used in the model development. Linearity was verified for the continuous variable(s) in the model. No sensitivity analysis was performed. All analyses were executed using SPSS (IBM SPSS Statistics version 25).

Ethical considerations

The SIMENON study was reviewed and approved in November 2016 by the Ethics Committee of KU/UZ Leuven (S59676 V3). The study was retrospectively registered at www.ClinicalTrials.gov NCT03179722 on June 7, 2017. The intervention was executed between December 2016 and June 2017.

Results

Study population

Between December 2016 and June 2017, 453 patients received a medication use review across 56 participating community pharmacies (median of 9 reviews per pharmacy, range 1–15). The median age was 79 years, 61.4% of the patients were female and a minority lived alone. The median number of chronic medications at baseline was 8 [3–20]. An overview of the characteristics of the study population is provided in Table 1.

Table 1
Description of the study population.

Patient-related variable (N)	Frequency (%) Median [range]
Dependent variable	
Number of drug-related problems (453)	3 [0–10]
Demographic variables	
Age (years) (453)	79 [68–100]
Gender (female)	277/451 (61.4%)
Living situation (living with others)	280/443 (63.2%)
Medication-related variables	
Number of chronic medications (447)	8 [3–20]
Medication assistance by people	
- No assistance	291/389 (74.8%)
- Assistance by family	75/389 (19.3%)
- Assistance by a healthcare professional	12/389 (3.1%)
- Assistance by both	11/389 (2.8%)
Medication assistance materials (yes)	192/413 (46.5%)
Medication list before the review (yes)	119/437 (27.2%)
Use of antiplatelet medication	245/453 (54.1%)
Use of anticoagulants	101/453 (22.3%)
Use of nonsteroidal anti-inflammatory drugs	55/453 (12.1%)
Use of diuretics	131/453 (28.9%)
Clinical variables	
Hospitalization in the last three months (yes)	34/416 (8.2%)
ED visits in the last three months (yes)	20/409 (4.9%)
Fall incident in the last three months (yes)	54/419 (12.9%)

Drug-related problems

Detection of drug-related problems

In the SIMENON study, 1196 DRPs were registered. One or more DRPs were registered for 400/453 patients (88.3%) with a median of 3 DRPs per patient (range 0–10). Table 2 displays the components of the intervention, available data, type of data collected and the main findings per patient and per DRP. The most common causes for an intervention were (1) interaction (N = 182; 15.2%), (2) inappropriate timing or frequency (N = 162; 13.5%) and (3) adverse effect (N = 142; 11.9%) (Table 3). Overall, 44.4% of the problems were related to the therapy choice, 25.6% was related to drug use and 15.4% was patient-related. For 156 patients (34.4%), at least one DRP was detected with the help of the GheOP^{3}S-tool. The tool assisted in the detection of half of the DRPs related to no concordance with guidelines, contraindication and inappropriate therapy duration. The medication most often involved in a DRP were (1) proton pump inhibitors (N = 126 DRPs; 8.1%), (2) HMG CoA reductase inhibitors

Table 2
Overview of the findings for the six steps of the MUR process with an indication of the patient flow and the evolution of the detected DRPs.

Intervention component	Findings
1. Patient recruitment at T_{-1week}	Agreement to participate: 453 patients
2. Preparation	
3. Patient interview at T_0	Available patient data: 453 patients
4. Pharmacotherapeutic analysis	Available patient data: 453 patients Total of 1196 DRPs
Detection of DRPs	- No DRP: 53 patients (11.7%) - One or more DRPs: 400 patients (88.3%)
Use of the GheOP^{3}S-tool for the detection of DRPs	- Yes: 296 DRPs (24.7%) - No: 674 (56.4%) - Unknown: 226 DRPs (18.9%)
Discuss interventions with other HCPs	- Yes: 173 patients (38.2%) ○ Number of interventions adjusted after HCP contact: 163 DRPs for 90/173 patients (52.0%) - No: 221 patients (48.8%) - Unknown: 59 patients (13.0%)
5. Discussing the medication list with the patient at T_{2weeks}	Available patient data: 393 patients Total of 1091 DRPs
Discuss interventions with the patients	- Number of interventions adjusted: 155/1091 DRPs (14.2%) for 93/359 (25.9%) patients
Communication of the interventions to others	- Yes: 205 patients (52.2%) ○ Healthcare professional: 146 (37.2%) ○ Family or caregiver: 39 (9.9%) ○ Both: 20 (5.1%) - No: 151 patients (38.4%) - Unknown: 37 patients (9.4%)
6. Follow-up at T_{6weeks}	Available patient data: 393 patients Total of 1091 DRPs
Implementation of interventions	- Fully implemented interventions: 562 (51.5%) - Partially implemented interventions: 121 (11.1%) - Implementation started but failed: 25 (2.3%) - Not implemented: 208 (19.0%) o Problem no longer present 27 (2.5%) ○ Postponed 79 (7.2%) ○ Other reason 102 (9.3%) - Missing data: 175 (16.0%)
Resolution of DRPs	- Resolved: 465 (42.6%) - Not resolved: 274 (25.1%) - Missing data: 352 (23.3%)
New interventions	- New intervention recommended to patients: 60/393 (15.3%) - New intervention recommended for DRPs: 78/1091 (7.1%)

MUR: medication use review.
HCP: healthcare professional.
DRP: drug-related problem.
GheOP^{3}S-tool: Ghent Older People's Prescriptions community Pharmacy Screening-tool.

(N = 99; 6.4%) and (3) selective beta blocking agents (N = 57; 3.7%) (Appendix 1).

Interventions recommended by the pharmacist

The top-3 interventions recommended by the pharmacist to handle DRPs were (1) transmission of information to other HCPs or to the patient (300; 25.1%), (2) in-depth patient counselling (179; 15.0%) and (3) stopping therapy (98; 8.2%) (Table 4). In addition, Appendix 2 shows the top-3 interventions proposed by the pharmacist to mitigate the top-3 DRPs. Transmission of information could refer to the pharmacist recommending the patient to discuss the problem with the treating physician for further actions. Likewise, the pharmacist referred patients to the general practitioner (GP) for therapy monitoring in 89 DRPs (7.4%). The medications for which the pharmacist most often recommended to stop therapy are psycholeptics (N05), psychoanaleptics (N06), medication for acid related disorders (A02), antithrombotic agents (B01) and anti-inflammatory and antirheumatic products (M01).

Discussion and communication of interventions

A multidisciplinary contact to discuss DRPs and interventions was initiated by the pharmacist for 173 patients (38.2%). It predominantly concerned contacts with general practitioners, with the aim to reach an agreement on the intervention to be performed. For half of the patients (90/173; 52.0%), one or more interventions were revised after HCP discussions. Similarly, for a quarter of the patients (93/359; 25.9%) at least one proposed intervention was modified when the pharmacist discussed the DRPs with the patient (Table 2). In both situations, all top-3 DRPs with modified interventions were related to therapy choice: interactions, no concordance with guidelines and adverse effects. The pharmacist provided feedback about his/her discussion with the patient and the agreed upon interventions to another HCP in almost half of the medication use reviews (166/393; 42.2%), predominantly to the GP. There was communication with the patient's family or caregiver for 59 patients (15.0%) (Table 2).

Implementation of interventions at follow-up

Approximately six weeks after the MUR, 51.5% of interventions (562/1091) were fully implemented; 11.1% were partially implemented (121/1091), 2.3% had a failed implementation (25/1091), 19.1% were not implemented (208/1091) and for 16.0% of interventions the implementation status was unknown (175).

Table 3
Overview of the causes of the intervention using the PharmDISC classification.

Cause of the intervention	N	%
1. Theray choice	**531**	**44.4**
1.1. No concordance with guidelines, only suboptimal therapy possible	116	9.7
1.2. Contraindication	36	3.0
1.3. Interaction	182	15.2
1.4. Drug not indicated	26	2.2
1.5. Duplication	20	1.7
1.6. Adverse effect	142	11.9
1.7. Missing patient documentation	9	.8
2. Drug choice	**33**	**2.8**
2.1. Inappropriate dosage form/administration route	33	2.8
3. Dose choice	**70**	**5.9**
3.1. Underdose	19	1.6
3.2. Overdose	25	2.1
3.3. Inappropriate monitoring	16	1.3
3.4. Dose not adjusted to organ function	10	0.8
4. Drug use	**306**	**25.6**
4.1. Inappropriate timing or frequency of administration	162	13.5
4.2. Inappropriate application	50	4.2
4.3. Inappropriate therapy duration	94	7.9
5. Patient	**184**	**15.4**
5.1. Insufficient adherence	42	3.5
5.2. Insufficient knowledge	97	8.1
5.3. Concerns about the treatment	31	2.6
5.4. Financial burden (patient/public health)	14	1.2
Missing data	72	6.0
Total	**1196**	**100**

DRP resolution

At follow-up, 465 DRPs were resolved (465/1091; 42.6%). After correction for missing data (363/1091; 33.3%), DRP resolution rate increased to 62.9%. DRPs related to the patient and drug use were most often resolved at follow-up. Drug choice and therapy choice were the most often unresolved categories (Fig. 2). At least one DRP was resolved for 224/393 patients (57.0%) and 34 patients (8.7%) had no DRPs.

Variables associated with the number of reported DRPs

Patient-related variables

Based on the univariate analysis, three out of 14 patient-related variables were significantly associated with the number of registered drug-related problems (Appendix 3). Risk factors included female gender, living alone and a higher number of chronic medications. Non-significant variables were age, medication assistance by caregivers or through materials, the possession of a medication list before the MUR and the use of NSAIDs, anticoagulants, antiplatelet and diuretics. The occurrence of a previous hospitalization, ED visit or fall incident in the last three months was also not significantly associated with the number of reported DRPs. The multiple negative binomial regression model included two variables: gender and drug count (Appendix 4). Per additional chronic drug, the number of registered problems increases by 4.3% (95% CI: 2.0–6.6%). Male gender decreases the number of registered DRPs by 22.1% (95% CI: 10.4–32.0%) when the number of medications remains unchanged. Living situation provided no additional predictive value. However, there is strong variability between the predicted values and the actual values. (see scatterplot in Appendix 5).

Confounding variables

Aside from the patient-related variables, four process characteristics were also associated with a higher number of reported DRPs. The significant confounding variables were: an interview on appointment, the use of an explicit medication appropriateness tool, the duration of the interview and of the analysis (Appendix 6). Non-significant variables included location of the patient interview, asking the patient to bring his medication to the interview (brown bag method) or to fill in a medication list and the number of reviews that were performed in the pharmacy (i.e. pharmacists did not detect more problems when they had performed more MURs as part of the SIMENON study).

Table 4
Overview of the interventions proposed by the pharmacist using the PharmDISC classification.

Intervention recommended by pharmacist	N	%
1. Substitution	58	4.8
2. Dose adjustment	74	6.2
3. Adjustment of package size/quantity	2	0.2
4. Optimization of administration/route	94	7.9
5. Therapy stopped/no delivery	98	8.2
6. Therapy started/continued	63	5.3
7. In-depth counselling of patient	179	15
8. Application instruction (training)	90	7.5
9. Delivery of adherence aid incl. counselling	33	2.8
10. Clarification/addition of information	15	1.3
11. Transmission of information	300	25.1
12. Proposition of therapy monitoring	89	7.4
13. No intervention: no priority	49	4.1
14. No intervention: other reason	28	2.3
15. Other intervention	14	1.2
Missing data	10	0.8
Total	**1196**	**100**

Five pharmacy and pharmacist-related variables significantly influenced the number of reported DRPs: years of experience in the pharmacy, province, previous knowledge or experience with medication review, polypharmacy or medication lists, the number of medication lists made in the last year and participation to a study workshop. Participation to a workshop reduced the number of registered problems. Non-significant variables were the number of pharmacists employed in the pharmacy, the function of the pharmacist who performed the review and previous education about an explicit medication appropriateness tool (Appendix 6).

Discussion

Findings

Drug-related problems

In the SIMENON study, community pharmacists provided a MUR to ambulatory polymedicated patients aged 70 or more. A median of 3 DRPs were registered per patient. The majority of the participants (88%) had at least one registered drug-related problem. Other studies show similar results with a mean number of DRPs ranging from 1.2 to 4.3.[16,26–29] Also, the proportion of patients with at least one DRP ranges between 18 and 94% depending on the inclusion criteria and the type of intervention.[30]

In the SIMENON study, almost half of the problems that were identified and registered by the pharmacist were related to the choice of therapy. Barely any DRPs were related to non-adherence, which is surprising as this MUR predominantly aimed to optimize the patient's drug use. In contrast, non-adherence was the most frequently reported DRP in the MUR service in Switzerland.[16] Plausible explanations for these contrasting findings are a lack of software support in the Belgian community pharmacy to detect non-adherence, limited education on adherence and limited experience to discuss non-adherence with patients. Furthermore, in Switzerland, pharmacists regularly prepare pill boxes and are remunerated for this care service which is not the case in Belgium.

Approximately half of the pharmacists' interventions related to communication and a quarter of the interventions involved drug alterations (e.g. dose adjustment, substitution, therapy stopped or started). A multidisciplinary contact was initiated for 38% of patients. HCP or patient contacts frequently led to intervention modifications, particularly for potential DRPs related to therapy choice (i.e. no concordance with guidelines, interactions and adverse effects). Interpreting and tackling these (potential) problems may require additional information that is not currently available to the community pharmacist

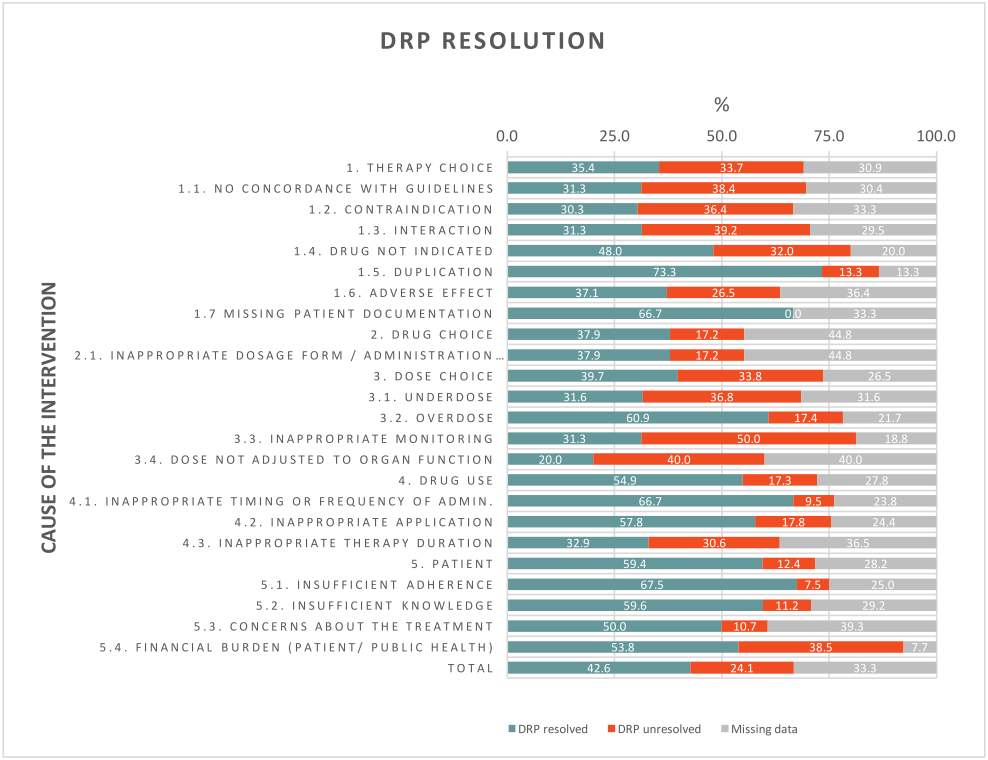

Figure 2. Overview of the DRP resolution rate at follow-up per drug-related problem.

(e.g. lab values, comorbidities and indications). These results are not surprising; other studies reporting on medication reviews led by GPs or hospital pharmacists have described that up to 30% of DRP interventions were altered upon discussion with the patient and/or GP.[31,32]

At follow-up, at least 43% of DRPs were resolved but lower resolution rates were observed for the aforementioned three therapy choice categories (no concordance with guidelines, interactions and adverse effects). The majority of new interventions at follow-up aimed to tackle these DRPs. These findings indicate that, at least, the resolution of DRPs related to therapy choice requires a multidisciplinary approach with patient involvement, multiple interventions and adequate follow-up. The findings also suggest that pharmacists are willing to take up an active role in this regard. Likewise, a systematic review by Kwint et al. describes a mean implementation rate and DRP resolution of 50% during a medication review (range 17–86%).[33] This implementation rate is positively associated with key elements of collaboration between GPs and pharmacists.[33,34] However, in spite of this benefit, the SIMENON feasibility study,[23] intervention study and implementation study[35] all pointed towards reservations among pharmacists regarding interprofessional collaboration. Pharmacists felt that collaboration should be stimulated where possible, but should certainly not be formalized or required for every patient. Furthermore, the level of multidisciplinary involvement in a MR differs across countries. Bulajeva found that only half (6/11; 55%) of intermediate MR services incorporate reporting to the physician and 3/11 (37%) include multidisciplinary case conferences during the review.[36] Although there is no consensus on how to collaborate with other healthcare professionals during a MR, interprofessional collaboration is an opportunity to maximize the impact of the service.

Variables associated with the number of reported DRPs

This study found that female gender, number of chronic medications and living alone were significantly associated with a higher number of registered DRPs. Literature confirms that **drug count**[37–43] is associated with more DRPs, drug-therapy problems, inappropriate medication use and potentially inappropriate medication. **Advanced age** is a proven risk factor for DRPs.[2,13] However, in studies with an older population, including this study, age is no longer a significant factor.[38,41] Some studies also suggest that **gender** is a relevant variable.[13,38,40] This may be attributed to the longer life expectancy in women and the differences in type of chronic conditions.[44] Finally, in this study **living alone** significantly increased the number of DRPs in the univariate analysis. We found no other medication (use) review studies that previously researched the impact of the living situation on the number of DRPs. Living alone was a risk factor in one study researching patients who benefit most of a geriatric assessment.[45] Future research should explore if living alone is indeed an independent risk factor for DRPs.

As to medication, proton pump inhibitors were most often involved in a DRP (8.1% of all DRPs). **High-risk medications** such as NSAIDs, anticoagulants, antiplatelet and diuretics were not associated with a higher number of drug-related problems. However, these medications were reported to be responsible for up to 50% of drug-related hospitalizations.[46] These findings emphasize the distinction between the frequency of DRPs and their clinical relevance. This can justify why these medications are an inclusion criterion for a medicines use review in the UK.[9] **Recent ED visits** and hospitalizations have been linked to a higher number of drug-related problems in two independent studies in patients aged 18–65years.[37,40] This was not confirmed in this study, potentially due to the low prevalence of ED visits and hospitalizations in this sample.

There is a strong evidence base for an age threshold as well as a minimum drug count as inclusion criteria for MR. Both criteria are used in The Netherlands and France, countries that both have nationally implemented, remunerated medication review services.[18,20] Future research should investigate and periodically review the eligibility criteria of a MR service and explore the patient's living situation as a potential criterion. Because a criterion related to drug count can lead to the exclusion of patients with low adherence and undertreatment,[47] it is also useful to explore the number of chronic diseases as an inclusion criterion in future studies. This criterion is already used for the medication therapy management service in the USA, New Zealand and Australia.[15,17,19]

In this study, a significant proportion of variability in the number of DRPs could not be attributed to the researched patient-related variables. Literature has identified additional risk factors that should be investigated further, including obesity, dyslipidemia, depression, diabetes, congestive heart failure, respiratory conditions, hypertension, poor functional status, frailty and reduced kidney function.[37,38,43,48] In a Delphi-study up to 27 risk factors were identified, including 14 specific medications, medical conditions and patient-related variables such as lack of knowledge, experience of adverse drug reactions, language issues, self-management and adherence.[49] However, this information that may not be accessible in the community pharmacy.

In addition, several confounding process- and pharmacist-related variables were identified in this study that explain a small proportion of the variability. During the implementation of a medication use review service, these process and pharmacist requirements should be clearly defined. Interestingly, participation to the study workshop led to less reported drug-related problems. However, his result should be interpreted with caution as only 5/56 pharmacies did not participate to the study workshop. A potential explanation for this result is that this workshop emphasized the importance of prioritizing DRPs, which could have influenced the number and type of registered DRPs among the participants.

Strengths and weaknesses

This large multicenter study provides insights in the potential effectiveness of a medication use review in Belgian practice. In parallel, the implementation of this service has also been researched, as recommended by the MRC framework for complex interventions.[35,50] A potential weakness is that selection bias may have occurred during recruitment on the level of the patient and pharmacist. The convenience sampling strategy for pharmacies has resulted in a sample of early adopters, which provides insights into the potential benefit but also limits the generalizability of the findings. The results of the study demonstrate the potential of a MUR service by the most motivated Belgian community pharmacists, but the results may not reflect the quality of care in each pharmacy. Furthermore, there may be variability among pharmacists in the execution of the MUR, including the detection and prioritization of DRPs. To mitigate this variability, pharmacists were provided with an education program and confounding pharmacist characteristics were investigated.

On the patient level, the data shows that a small number of patients did not meet all inclusion criteria. It is a strength that patients had a therapeutic relationship with the pharmacist who performed the review. In that case, there is a trust relationship between the patient and pharmacist, the patient may open up more easily about treatment questions or concerns and the pharmacist has knowledge of the patient's history and social context.

The number of reported DRPs may have been an underestimation because only DRPs that the community pharmacist could identify, in the absence of clinical data, and that they considered a priority, were counted. It is a strength that the DRPs were registered with a validated instrument, but registration bias and burden may have occurred. There was no imputation of missing data and therefore, the analysis assumes that the data were missing completely at random. Furthermore, the choice of the number and typology of drug-related problems as the primary outcome measure has the advantage that it encompasses all types of problems that can be identified during a medication review (ranging from appropriateness to adherence). However, it is a disadvantage that this outcome measure does not address the clinical relevance of the problems and that the relationship between the different types of problems and hard endpoints such as hospitalizations is unclear. Therefore, a substudy has evaluated the impact of the MUR service on patient-reported outcome measures, as described in a separate manuscript.[51]

In the regression analysis, a large number of variables were explored. However, the reported p-values should be interpreted with caution as there was no correction for multiple testing and the model is subjected to overfitting due to the high number of variables researched. Another limitation is that the model did not consider potential correlations within the pharmacy. It is plausible that pharmacists who have been performing excellent usual care, may have found less DRPs during the medication use review service than others. Overall, the authors acknowledge that the usability of the developed model is limited and requires optimization. Nonetheless, this research is an important first step towards evidence-based eligibility criteria as only few studies have investigated inclusion criteria for a medication review.[40,47] Given that the primary objective of this study was not the model development, the study design was not adapted to this objective. Future research should minimize variability between pharmacists, mitigate the risk of confounding factors and explore additional potential risk factors.

Conclusions

This research indicates that MURs can be an effective strategy to detect and resolve drug-related problems. The number of chronic medications and female gender predict a higher number of DRPs. There is strong literature evidence that advanced age is also a risk factor for DRPs. However, a significant proportion of variability in the number of reported DRPs could not be attributed to patient-related variables. Confounding variables such as process- and pharmacist-related variables also influenced the number of detected DRPs. Future research should investigate the eligibility criteria of a MR service and explore the patient's living situation as a potential criterion.

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Declaration of competing interest

The authors report no conflicts of interest in this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sapharm.2019.11.008.

Appendix 1. Overview of the medication involved in the DRPs and prevalence of the medication in the study sample using Anatomical Therapeutic Chemical (ATC) classification level 1. The top-10 of the ATC codes level 4 involved in a DRP are also displayed in the table with the ranking between brackets

Anatomical Therapeutic Chemical Classification	DRP		Sample	
	N	%	N	%
A Alimentary tract and metabolism	307	19.7	759	17.5
A02BC Proton pump inhibitors (1)	126	8.1	220	5.0
A10BA Biguanides (7)	45	2.9	108	2.5
B Blood and blood forming organs	95	6.1	391	9.0
B01AC Platelet aggregation inhibitors excluding heparin (4)	55	3.5	269	6.2
C Cardiovascular system	515	33.1	1352	31.2
C03CA Sulfonamides, plain (6)	37	2.4	82	1.9
C07AB Beta blocking agents, selective (3)	57	3.7	217	5.0
C08CA Dihydropyridine derivatives (8)	37	2.4	111	2.6
C10AA HMG CoA reductase inhibitors (2)	99	6.4	288	6.6
D Dermatologicals	2	0.1	7	0.16
G Genito-urinary system and sex hormones	31	2	98	2.3
H Systemic hormonal preparations, excluding sex hormones and insulins	31	2	124	2.9
J Antiinfectives for systemic use	5	0.3	28	0.65
L Antineoplastic and immunomodulating agents	5	0.3	31	0.71
M Musculo-skeletal system	82	5.3	184	4.2
N Nervous system	336	21.6	738	17.0
N05BA Benzodiazepine derivatives (5)	56	3.6	124	2.9
N06AB Selective serotonin reuptake inhibitors (9)	35	2.3	53	1.2
N06AX Other antidepressants (10)	34	2.2	58	1.3
P Antiparasitic products, insecticides and repellents	0	0	2	0.05
R Respiratory system	70	4.5	186	4.3
S Sensory organs	20	1.3	73	1.7
V Various	0	0	6	0.14
Uncategorized (e.g. food supplements or pharmaceutical compounding)	57	3.7	359	8.3
Total number of registered medications	**1556**	**100**	**4338**	**100**

Appendix 2. Overview of the top-3 interventions proposed by the pharmacist to mitigate the top-3 DRPs

Cause of the intervention			Intervention		
Type	N	% of all DRPs	Type	N	% within the cause
Interaction	182	15.2%			
			Transmission of information	68	37.4%
			Proposition of therapy monitoring	34	18.7%
			In-depth counselling of patient	21	11.5%
Adverse effect	142	11.9%			
			Transmission of information	52	36.6%
			Therapy started/continued	20	14.1%
			In-depth counselling of patient	12	8.5%
			Therapy stopped/no delivery	12	8.5%
Inappropriate timing or frequency of administration	162	13.5%			
			Optimization of administration/route	56	34.6%
			Application instruction (training)	41	25.3%
			In-depth counselling of patient	25	15.4%

Appendix 3. Results of the univariate analysis of the patient-related variables. The significance level for univariate analysis was set at $p < 0.05$. Significant p-values are indicated in bold

Variable	N	p-value	Exp (B)	95% CI Exp (B)
Demographic variables				
Age	453	0.500	0.996	0.985–1.007
Gender (reference: female)	451	**< 0.001**	0.764	0.666–0.878
Living situation (reference: living with others)	443	**0.019**	1.174	1.027–1.341
Medication-related variables				
Number of chronic medications	447	**< 0.001**	1.048	1.025–1.071
Medication assistance by people	389	0.705	0.777	0.489–1.235
- No assistance			0.758	0.468–1.227
- Assistance by family			0.738	0.406–1.343
- Assistance by a healthcare professional			1.000	
- Assistance by both (reference)				
Medication assistance materials*	413	0.676	1.029	0.900–1.177
Medication list before the review*	437	0.578	0.959	0.829–1.111
Use of antiplatelet medication*	453	0.876	0.989	0.866–1.131

Use of anticoagulants*	453	0.350	1.080	0.919–1.270
Use of nonsteroidal anti-inflammatory drugs*	453	0.140	0.863	0.710–1.050
Use of diuretics*	453	0.412	0.941	0.814–1.088
Clinical variables				
Hospitalization in the last three months*	416	0.990	0.998	0.780–1.278
ED visits in the last three months*	409	0.695	1.067	0.772–1.473
Fall incident in the last three months*	419	0.575	0.945	0.775–1.152

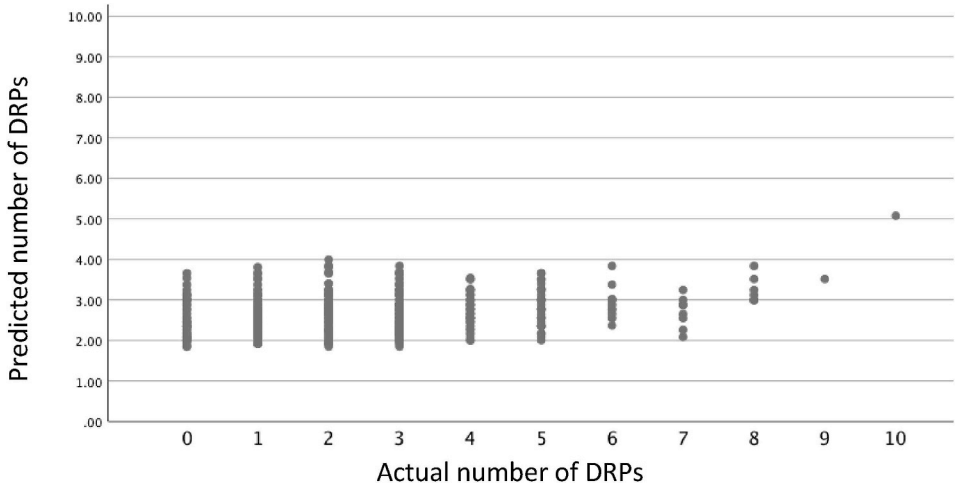
* Yes is reference value.

Appendix 4. Significant variables in the negative binomial regression models

Variable	p-value	B	Exp (B)	95% Confidence Interval for exp(B)
Model with patient-related variables (n = 446)				
Intercept	0.000	0.686	1.986	1.594–2.475
Gender (Female = 1 (reference value); male = 0)	0.000	−0.249	0.779	0.680–0.894
Number of chronic medications	0.000	0.042	1.043	1.020–1.066

The significance level for multiple regression analysis was set at $p < 0.157$.
Exp(B) is also referred to as the incidence rate ratio. For example, one unit increase in the number of chronic medication increases the predicted number of DRPs by 1.043 or 4.3% given the other variable gender remains unchanged. The model equation to estimate the number of DRPs is $Log(Number\ of\ DRPs) = 0.686 - 0.249 * (male) + 0.042 * (number\ of\ chronic\ drugs)$.

Appendix 5. Scatterplot visualizing the predicted number of DRPs with the developed model and the actual number of DRPs



Appendix 6. Description of the process-related, pharmacy- and pharmacist-related variables and results of the univariate analysis. The significance level for univariate analysis was set at $p < 0.05$. Significant p-values are indicated in bold

Variable	Descriptive statistics			Univariate analysis		
	N	Frequency (%)	Median [range]	p-value	Exp (B)	95% CI Exp (B)
Process-related variables						
Duration of patient interview	442		35 [10–120]	< **0.001**	1.009	1.007–1.012
Duration of the analysis (step 4)	390		30 [5–300]	< **0.001**	1.005	1.003–1.006
Number of the review**	453		5 [1–15]	0.101	0.982	0.962–1.003
Location of the patient interview: (reference: pharmacy)	443	333 (77.4%)		0.860	1.014	0.866–1.188
Interview on appointment*	444	395 (89.0%)		**0.003**	0.711	0.564–0.897
Use of an explicit medication appropriateness tool*	373	158 (42.4%)		< **0.001**	0.706	0.628–0.793
Use of a brown bag*	439	203 (46.4%)		0.117	0.900	0.790–1.027
Use of an empty medication list*	443	259 (58.5%)		0.928	0.994	0.869–1.136
Pharmacy- and pharmacist-related variables						
Years of experience in a pharmacy	309		14 [1.5–42]	< **0.001**	1.015	1.006–1.023
Number of fulltime pharmacist equivalents in the pharmacy	350		2 [0–4.75]	0.934	0.997	0.920–1.079
Previous education on an explicit medication appropriateness tool (GheOP^{3}S tool)*	315	227 (72.1%)		0.793	1.024	0.857–1.224
Participation to the workshop related to patient communication (as part of the SIMENON study)*	309	254 (82.2%)		< **0.001**	1.423	1.174–1.724
Knowledge: Previous experience with medication review, polypharmacy or medication list*	286	232 (81.1%)		**0.032**	0.782	0.624–0.981
Experience: number of medication lists made last year	309	14 (4.5%)		**0.001**	1.250	0.603–2.590
- No experience		153 (49.5%)			0.724	0.409–1.283
- Less than 10 patients		77 (24.9%)			0.733	0.409–1.313
- Between 10 and 20 patients						0.299–0.964

- Between 20 and 50 patients		57 (18.4%)		0.537	
- Over 50 patients (reference)		8 (2.6%)		1.000	
Function in the pharmacy	316	100 (31.6%)	0.108	1.088	0.855–1.384
- Pharmacist, employee		160 (50.6%)		0.897	0.720–1.116
- Pharmacist, supervisor and owner		56 (17.7%)		1.000	
- Pharmacy, supervisor non-owner (reference)					
Province	453		**0.004**	1.003	0.737–1.365
- Antwerp				1.375	1.026–1.843
- Brussels				1.343	1.068–1.687
- Hainaut				1.036	0.785–1.367
- Limburg				1.270	1.006–1.603
- East Flanders				1.242	0.986–1.564
- Flemish Brabant				0.638	0.425–0.957
- Walloon Brabant				1.038	0.807–1.335
- West Flanders				1.000	
- Liège (reference)					

* Yes is reference value.

** The number of reviews that the pharmacist had already conducted.

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