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ORIGINAL ARTICLE

Nature and frequency of prescription modifications in community pharmacies: A nationwide study in the Netherlands

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Aims: To investigate the nature and frequency of prescription modifications in Dutch community pharmacies.

Methods: In this cross-sectional study, Dutch community pharmacists documented prescription modifications in their pharmacy during 1 predetermined day. Pharmacists from all Dutch community pharmacies were invited to participate. A prescription modification was defined as any modification in a prescription for a medicine or other healthcare product because of an administrative problem, logistic issue or potential drug-related problem (DRP). All documented modifications were assessed to establish the nature and frequency of prescription modifications.

Results: Pharmacists in 275 pharmacies completed the study. A modification was performed in 5.5% of all prescriptions. 1.3% of the prescriptions contained an administrative problem, of which insufficient specification of the dosing regimen was most common (63.1%). A modification was performed due to a logistic issue in 2.4% of the prescriptions. The most frequently recorded issues were unavailability of medication (40.9%) and obligatory product substitutions due to reimbursement policies (33.2%). A modification was performed in 1.8% of the prescriptions to solve or prevent potential DRPs. Of these, 69.2% was potentially clinically relevant according to the pharmacist concerned. The most frequently prevented potential DRP was an incorrect strength or dose (31.9%).

Conclusion: Dutch community pharmacists modified almost 1 in 20 prescriptions per pharmacy. The nature of the modifications reflects current community pharmacy practice, in which pharmacists frequently deal with logistic issues and intervene to solve or prevent for DRPs several times a day. The majority of the DRPs were considered to be potentially clinically relevant.

KEYWORDS
prescription modifications, interventions, medication errors, prescribing errors, community pharmacy, pharmacists, drug-related problems, primary health care, medication safety

1 | INTRODUCTION

For decades, pharmacists have checked every prescription for administrative correctness, logistic availability and pharmacotherapeutic appropriateness, and they have modified prescriptions upon encountering problems, usually after consulting the prescriber.[1] In 1999, a Dutch study by Buurma et al revealed that community pharmacists modified 4.3% of all prescriptions and 4.9% of prescriptions for prescription-only medicines. The majority of the prescription-only medicine prescription modifications concerned administrative inaccuracies, and nearly a quarter of these modifications corrected a prescription error.[2] A large panel of medico-pharmaceutical professionals consistently judged that almost 60% of the latter modifications positively contributed to patients' quality of pharmacotherapy.[3] Approximately 10 years later, studies in Norway and Spain showed comparable rates of prescription modifications in community pharmacies of 2.6 and 5.0%, respectively.[4,5]

In the last decade, the provision of pharmaceutical care by community pharmacists has become more challenging. An aging population with high levels of multimorbidity has led to increased use of medication.[6] Another consequence of multimorbidity has been the fragmentation of pharmaceutical care resulting from the involvement of a wide range of health-care professionals.[7] At the same time, an enlarged therapeutic arsenal has become available, including complex drugs like biologicals. Research continuously provides new evidence for drug interactions and contraindications, and clinical parameters have become available to monitor individual patient's outcomes. These developments are supported by technology, such as electronic prescribing and advanced clinical decision support systems.[8,9]

In this context, community pharmacists' focus has shifted from product care towards optimizing drug therapy and medication safety for individual patients in close collaboration with physicians and other health-care professionals. Compared to the previous Dutch study in 1999, the quantity and quality of tasks such as patient counselling and education, patient adherence monitoring and medication reviews increased.[1,10–16] However, this clinical role of pharmacists is increasingly challenged by limited availability of medicines. This is caused by global shortages as well as by health-care politics that influence reimbursement policies with preferences for specific labels.[17–20]

Due to the aforementioned changes, the nature and frequency of prescription modifications are likely to be different from those reported in earlier studies. Insight regarding current prescription modifications by community pharmacists is needed to illustrate the extent of logistic problems in daily practice and to develop strategies to further improve medication safety. Therefore, in this study we investigate the nature and frequency of prescription modifications in community pharmacies in the Netherlands.

What is already known about this subject

- Community pharmacists modify prescriptions for administrative, logistic and therapeutic reasons.
- Worldwide drug shortages are a major issue; however, it is unknown how shortages impact prescription modifications in community pharmacies.
- Community pharmacists increasingly adopt a more clinical role for which they are supported with technology.

What this study adds

- Dutch community pharmacists modify 5.5% of prescriptions, almost 20 per pharmacy per day on average.
- Compared to 15 years ago the proportion of administrative modifications has decreased sharply, probably due to improved technology. Logistic issues emerged as a new problem, and prescription modifications for therapeutic purposes increased.

2 | METHODS

2.1 | Setting, design and data collection

In September 2016, Dutch community and hospital outpatient pharmacists (i.e. pharmacists working in community pharmacies located in hospitals) from all 1981 Dutch pharmacies were invited to participate in the study by email, newsletters and advertisements through the Royal Dutch Pharmacists Association. Pharmacists subsequently registered themselves for the study. For each pharmacy, 1 pharmacist could enrol in the study; each pharmacist therefore reflects 1 pharmacy. The participating pharmacies were located in strong urbanized areas as well as in rural areas, and were evenly distributed across the Netherlands. They did not differ statistically from the national average with respect to the number of prescriptions dispensed (357 *vs* 341).[21]

Participating pharmacists were asked to register all prescription modifications in their pharmacy on a single assigned study day within the study period from 10 October to 4 November 2016. These study days were equally assigned across the week. For each prescription modification performed on the study day, the pharmacists completed an online registration form and uploaded a scan of an anonymised copy of all modified prescriptions. The pharmacists were asked to judge the potential clinical relevance of any identified drug-related

problem (DRP). In addition, pharmacists provided the postal code of their pharmacy, the estimated number of registered patients in their pharmacy and the total number of prescriptions processed on the study day. All data was required to be uploaded to a secure online registration platform within 2 weeks after the study day. Pharmacists were reminded of the procedure 5 days before and 2 days and 2 weeks after their study day. Incomplete data after the deadline resulted in exclusion of the pharmacy. Pharmacists were informed in advance of the expected time investment of 3–6 hours and received compensation of €75 after completing the study.

The study design was based on prior research from 1999.[2] Given the nature of current practice and possibilities for (online) data collection, a limited number of changes in the data collection method and the data collection sheet were made (Appendix 1). The study protocol and online registration form were tested in 10 pharmacies. All study materials, including the study protocol and an instructional video were available on the online platform. A telephone helpdesk was available before and during the study for both technical and substantive questions.

2.2 | Ethics and confidentiality

Characteristics that could identify individual patients (e.g. date of birth, address, postal code or social security number) were removed by participating pharmacists before they uploaded the data. The research proposal was approved by the Institutional Review Board of the Division of Pharmacoepidemiology and Clinical Pharmacology of Utrecht University with reference number UPF1607.

2.3 | Selection of prescription modifications

A prescription modification was defined as a modification in the prescription for prescription only medicines or for other health-care products (e.g. over-the-counter drugs, continence-care materials and wound dressings) due to an administrative problem, logistic issue or potential DRP. In the Netherlands, pharmacists use clinical decision support systems that are integrated in the pharmacy information system and that help them to identify DRPs, and also some administrative and logistic issues. The system provides real-time alerts for e.g. drug–drug interactions, contraindications and dosing problems. A signal is also generated in case of a change compared to the previous delivery, for e.g. change in strength or alteration of manufacturer. As not all potential DRPs and administrative/logistic issues are signalled by the decision support system, pharmacists check all prescriptions manually for DRPs.

The pharmacists received instructions to only include prescriptions that were processed in the pharmacy information system on the study day (even if actual dispensing occurred on another day). Prescriptions that were not dispensed within 2 weeks after the study day were considered as not being dispensed and had to be excluded from the study by the pharmacists. Further exclusion criteria were minor modifications with lack of relevance for patient safety: no or incorrect address, no or incorrect insurance data, incorrect package size (e.g. 28 instead of 30 pieces), incorrect or impossible dosage units (e.g. mL instead of mg), and incomplete legal requirements regarding the prescription (e.g. no date, no signature).

2.4 | Nature of the prescription modifications

The nature of prescription modifications was classified by participating pharmacists as either an administrative problem, logistic issue or potential DRP and accompanied by a brief free text description. Appendix A presents all (sub)categories. Subcategories of administrative problems were based on Buurma et al[2] and adjusted to 3 changes in regulations in the Netherlands since 1999 (indicated with *). First, physicians are obliged to share the indication for the prescribed medicine with pharmacists for a set of 23 medicines since 2013. These medicines are prescribed in varying dosages for multiple indications and have a small therapeutic range or high risk for side effects. A second change is that some medicines in contrast to 1999 are only reimbursed in case of a repeated prescription for chronical use; for example, a proton-pump inhibitor is only reimbursed for a chronical stomach disorder and not for incidental heartburn. Third, prescriptions are offered both electronically and presented by the patient in person since the extensive use of electronic prescribing. In contrast to some other countries, dosage information still is a mandatory part of a prescription in the Netherlands. Subcategories within the potential DRP category were based on the DOCUMENT classification system,[22] the categorization used by Buurma et al[2] and the Dutch guideline for the management of DRPs.[23] These categories are familiar terms for the pharmacists and are used in the clinical decision support systems. Subcategories of logistic issues were based on practical experience of the researchers and the pilot study.

2.5 | Classification, validation and analysis

The documented registrations were entered in Microsoft Excel 2010. Two researchers (E.v.L., G.B.) confirmed whether the prescription modifications met the inclusion criteria and if they were classified correctly according to the brief description of the modification. If congruency was doubted, the anonymised copy of the prescription was consulted. Mistakes in inclusion and classification were recoded, and registrations were excluded when they met the exclusion criteria. To validate the checking and recoding by the researchers, the inter-rater reliability (Cohen's κ) was determined using IBM SPSS Statistics 23 in an at random sample of 4 cases from each subcategory (unless there were <4), totalling 120 cases (approximately 2% from 6142 registrations). In this sample, there was substantial agreement for all categories: the average user agreement was very good ($K = 0.95$).[24] To validate the reliability of the registration of modified prescriptions by the pharmacists, the researchers contacted the 10 pharmacists with the lowest number of modifications. The pharmacists were asked by phone whether there were obstacles in the detection and registration of prescription

modifications to ensure the results of these pharmacists there was no underreporting. Pharmacists with the highest number of modifications provided proof for the modifications (uploaded prescriptions).

Characteristics of the pharmacies and modified prescriptions were analysed by computing frequency tables in Microsoft Access 2010.

3 | RESULTS

In total, pharmacists of 365 pharmacies agreed to participate. Due to later nonresponse (18.4%) and incomplete data delivery (6.3%), 90 pharmacies were excluded. The 275 pharmacies (75%) in which the pharmacists adhered to the study protocol represented 13.9% of all Dutch pharmacies. The included pharmacies were community pharmacies (n = 254) and hospital outpatient pharmacies (n = 21) and were evenly distributed across the Netherlands. The 10 contacted pharmacists with the lowest number of modifications in their pharmacy indicated that there were no obstacles in following the study protocol. After checking the registrations, 757 out of 6142 (12.3%) registrations were excluded following the exclusion criteria. The remaining 5385 registrations were analysed.

An average of 357 (range: 65–1013) prescriptions per pharmacy were processed on the study day. Frequency of prescription modifications is presented in Table 1. Of all prescriptions, 5.5% were modified (range: 0–42%), corresponding to a mean of 19.6 modifications per pharmacy per day (range: 0–94).

Approximately 3/4 (77%) of the modified prescriptions were offered electronically. In 40% of the modified prescriptions, it concerned a first prescription of the medicine for the patient.

3.1. | Reasons for prescription modifications

Table 2 summarises the reasons for prescription modifications and presents examples. Insufficient specification of the frequency, duration, maximum or strength of the prescribed dose were the most common administrative problems (63.1%). In addition, 19.8% of all administrative problems were aimed at reduction of patient co-payment. The logistic issues that were recorded most frequently were unavailability of a product due to drug shortages and a compulsory change in label due to reimbursement policy of the insurance company concerned (40.9 and 33.2% of logistic issues, respectively). Incorrect strength or dose was the most frequently encountered potential DRP (31.9%). The second most common potential DRP (13.8%) was duplication (i.e. a combination of drugs containing the same active ingredients: the patient had sufficient stock or already used the drug via another route of administration) or pseudo duplication (i.e. 2 drugs with active ingredients from the same therapeutic category, such as 2 proton-pump inhibitors). In about half of the potential DRPs (44.4%) the modification was based upon a computer signal (under- or overdosing, [pseudo] duplication, drug interaction, contraindication, hypersensitivity, preventive therapy required).

Modifications were most frequently found for medications of the Anatomical Therapeutic Chemical (ATC) groups nervous system (ATC N, 18.7%), alimentary tract and metabolism (ATC A, 14.1%), and the cardiovascular system (ATC C, 12.1%). Four potential DRPs concerned biologicals. These prescriptions were modified because of an inappropriate dosage form, wrong medicine, incorrect strength and duplication (enough supply) respectively. Consultation partners for prescription modifications are shown in Table 3, whereby multiple partners could be consulted for each modification. In 1/5 of all modifications and in 1/3 of potential DRPs, the prescriber was consulted in advance. In these cases, the prescriber agreed with the proposed modification. In 60.3% of the modifications, the modification was discussed with the patient or informal caregiver. For 28.5% of the modifications, the pharmacist did not contact these persons.

3.2 | Types of modifications undertaken to reduce potential DRPs and their estimated relevance

Table 4 presents the modifications that were undertaken as a result of potential DRPs and their relevance as indicated by the reporting pharmacist. Modifying dosage, therapy duration or frequency of administration were the most common types of modification to solve or prevent DRPs (40.0%). The prescription was not dispensed in 15.9% of modifications. All potential DRPs were solved or prevented through multiple types of modifications, except for the potential DRP preventive therapy required. For this potential DRP 1 type of modification was undertaken, namely adding medication.

In 69.2% (n = 1228) of the modifications aimed at solving or preventing potential DRPs, the modification had potential clinical relevance according to the pharmacist. This corresponds to 4.5 potentially relevant prescription modifications per pharmacy per day (1228 modifications in 275 pharmacies).

TABLE 1 Frequency of prescription modifications per day (n = 275 pharmacies)

	Number of POM[a] modifications (%)	Number of N-POM[b] modifications (%)	Number of all modifications (%)
Total number of modifications	4943 (6.0)	442 (2.7)	5385 (5.5)
Administrative	1073 (1.3)	212 (1.3)	1285 (1.3)
Logistic	2219 (2.7)	107 (0.7)	2326 (2.4)
Potential drug-related problem	1651 (2.0)	123 (0.8)	1774 (1.8)

[a]POM = prescription only medicine(s).
[b]N-POM = other health care products (e.g. over-the-counter drugs, continence-care materials and wound dressings).

TABLE 2 Reasons and examples for prescription modifications in Dutch community pharmacies

	Total *n* = 5385 (%)	Example of prescription modification	
		Reason	Action of pharmacist
Administrative problem	*1285 (100)*		
- frequency, duration, maximum or strength of dose insufficiently or not specified	811 (63.1)	Prescribed regimen for eardrops with dexamethasone/antibiotic combination was unspecified	Dose adjustment to 3 drops 3 times a day in the left ear
- prescription modification aimed at reducing patient co-payment	255 (19.8)	No reimbursement for the prescribed omeprazole tablets	Adjusted to over-the-counter package, resulting in lower costs for the patient
- insufficient or wrong patient data	102 (7.9)	Medicine was prescribed for the father instead of his child	Prescription moved to the correct dossier
- indication lacking although legally required	42 (3.3)	The indication was missing on a prescription for ciclosporin for a 25-year-old patient. For ciclosporin assigning indication is obligatory in the Netherlands.	Consulted prescriber for indication in order to check the dose
- prescription offered more than once	38 (3.0)	Prescription for amoxicillin/clavulanate tablets was both sent electronically and presented by the patient in person	Cancelled the double prescription
- health care product not specified	37 (2.9)	Type and size of the catheter was missing	Consulted prescriber for specification
Logistic issue	*2326 (100)*		
- off market or currently not deliverable	951 (40.9)	Specific brand of levothyroxine was temporarily unavailable	Substituted for a generic alternative
- alteration in label of refill prescription due to low-price policy or generic substitution	773 (33.2)	Insurer preference-policy appointed other label of acetylsalicylic acid for reimbursement	Change of label
- alteration in prescribed product or brand/manufacturer due to pharmacy's available assortment	479 (20.6)	The specific prescribed device of salmeterol/fluticasone was not available in the established pharmacy assortment	Changed the device to another dry powder inhaler
- alteration in brand/manufacturer of refill prescription due to patient's preference	123 (5.3)	Due to nausea in the past, patient requested tablets instead of ibuprofen granulate	Dispensed tablets instead of granulate
Potential drug-related problem	*1774 (100)*		
- incorrect strength or dose	566 (31.9)	Incorrect dosage of metformin was prescribed	Dose adjustment from metformin 850 mg to metformin 500 mg according to patient's file
- (pseudo)duplication	245 (13.8)	Prescription for 90 tablets pantoprazole, but patient has enough supply for 8 weeks	Adjustment of number of tablets
- wrong duration or frequency of therapy	229 (12.9)	Therapy amoxicillin suspension prescribed for 3 days	After consulting prescriber, duration of therapy was adjusted to 7 days
- inappropriate dosage form	214 (12.1)	Prescription for nitrofurantoin 100-mg immediate-release tablets twice daily. Twice daily is an incorrect dosage interval for immediate-release nitrofurantoin tablets	Converted to Furabid 100-mg controlled release twice daily
- advance usability and/or therapy compliance	122 (6.9)	Prescription for half of a 10-mg tablet of enalapril per day, while 1 5-mg tablet per day is easier to use	Converted to 1 5-mg tablet of enalapril per day
- preventive therapy required	97 (5.5)	Fentanyl patches were prescribed. According to the guidelines, a laxative should be added to prevent constipation	Added macrogol
- wrong medicine/product	89 (5.0)	Prescription for tramadol, but the patient asked the physician for a refill prescription for naproxen	Dispensed naproxen instead of tramadol

(Continues)

TABLE 2 (Continued)

	Total *n* = 5385 (%)	Example of prescription modification	
		Reason	Action of pharmacist
- prescribed medication unnecessary	86 (4.8)	Prescription for perindopril tablets, but the therapy had already been discontinued	After consulting prescriber prescription not dispensed
- drug interaction	72 (4.1)	Prescribed colchicine interacts with simvastatin, resulting in risk for myopathy and rhabdomyolysis	Simvastatin temporarily discontinued
- contraindication apparent (incl. laboratory parameters)	39 (2.2)	Prescribed ciprofloxacin is associated with epileptic seizures	Substituted to cotrimoxazole
- hypersensitivity	15 (0.8)	Amoxicillin was prescribed, but patient is intolerant of penicillin	Substituted to clarithromycin

TABLE 3 Consultation partners for prescription modifications (multiple answers possible)

		Reason of prescription modification		
	Total	Administrative problem	Logistic issue	Potential DRP
	n = 5385	*n* = 1285	*n* = 2326	*n* = 1774
Consultation partner	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Patient/informal carer	3249 (60.3)	648 (50.4)	1495 (64.3)	1106 (62.3)
Prescriber	1091 (20.3)	247 (19.2)	222 (9.5)	622 (35.1)
No consultation with patient, care giver or prescriber	1535 (28.5)	457 (35.6)	718 (30.9)	359 (20.2)
Other	23 (0.4)	8 (0.6)	5 (0.2)	10 (0.6)
Unknown	4 (0.7)	1 (0.1)	3 (0.1)	-

4 | DISCUSSION

This study reveals that almost 1 in 20 prescriptions per day are modified in Dutch community pharmacies. Almost half of the modifications assessed in this study concerned logistic issues, 1/3 aimed to solve or prevent DRPs, and the remaining modifications addressed administrative problems. The nature of prescription modifications has changed considerably since the previous Dutch study in 1999.

While prescription modifications due to logistic issues were not addressed separately in the 1999 Dutch study or in studies from abroad, most modifications in our study involved logistic issues. Drug shortages pose increasing logistic problems for pharmacists worldwide. In the Netherlands, 769 new drug shortages were reported in 2018, 8 times the amount of 2004.[25] Although finding suitable alternatives in the best interest for the patient is part of the clinical role of pharmacists, it takes a substantial part of pharmacists' time.[26] Furthermore, switching medication because of drug shortages or switching between generics on behalf of insurers can lead to misunderstanding by the patient and therefore might complicates the relationship between patient and pharmacist.[27] Switching labels may alter the effects of the drug therapy, and because switching is associated with an increase in adverse effects, patient dissatisfaction may increase.[28–30]

The frequency of potential DRPs was approximately 30% higher in our 2016 data compared to 1999. Also compared to more recent studies in Denmark, Norway and Spain, our study showed a higher frequency of modifications to solve or prevent DRPs.[4,5,31] This may be attributable to the more clinical role of the community pharmacist, which has been furthered by several developments in the Netherlands. Many professional guidelines on the quality of pharmacotherapy have been developed for pharmacists in the Netherlands,[32] clinical decision support rules have been implemented in computer systems to identify potentially inappropriate therapy, and the quality of pharmacy practice is measured through indicators linked to these guidelines and rules. In addition, although still to a limited extent, physicians increasingly share certain clinical data with pharmacies such as relevant laboratory values and the reasons for use of medicines. For a small set of medicines, this also is mandatory in the Netherlands.[33] It is likely that the availability of this information enables pharmacists to better monitor drug therapy and to detect more potential DRPs.[34] Furthermore, pharmacists may feel encouraged to further develop their clinical role due to the formal acknowledgement of the community pharmacist as a specialty in the Netherlands, which was finalised in 2016. Another reason for the increase of potential DRPs might be the ageing population with higher risks because of polypharmacy.[12] The introduction of new highly effective drugs did not result in a relevant change of prescription modifications.

Interestingly, in about half of the potential DRPs (44.4%), the modification was based on a computer signal. This means that the clinical

TABLE 4 Type of prescription modifications for potential drug-related problems (DRPs) and estimated clinical relevance

	Total (*n*)	Relevance = yes (%)	Dose, frequency or duration modified	Prescription not dispensed	Medication substituted by other medication	Strength of medication modified	Dosage form modified	Medication added	Comedication modified	Other
Potential DRP	1774	1228 (69.2)	709 (40.0)	282 (15.9)	180 (10.1)	176 (9.9)	161 (9.1)	103 (5.8)	79 (4.5)	84 (4.7)
Incorrect strength or dose	566	466 (82.3)	452 (79.9)	11 (1.9)	2 (0.4)	100 (17.7)	-	-	-	1 (0.2)
(pseudo)duplication	245	108 (44.1)	17 (6.9)	157 (64.1)	3 (1.2)	3 (1.2)	1 (0.4)	1 (0.4)	54 (22.0)	9 (3.7)
Wrong duration or frequency of therapy	229	137 (59.8)	204 (89.1)	3 (1.3)	1 (0.4)	3 (1.3)	-	-	1 (0.4)	17 (7.4)
Inappropriate dosage form	214	125 (58.4)	1 (0.5)	3 (1.4)	26 (12.1)	2 (0.9)	138 (64.5)	2 (0.9)	-	42 (19.6)
Advance usability and/or therapy compliance	122	62 (50.8)	23 (18,9)	1 (0.8)	11 (9.0)	62 (50.8)	19 (15.6)	2 (1.6)	-	4 (3.3)
Preventive therapy required	97	94 (96.9)	-	-	-	-	-	97 (100.0)	-	-
Wrong medicine/product	89	63 (70.8)	-	11 (12.4)	72 (80.9)	-	-	-	-	6 (6.7)
Prescribed medication unnecessary	86	48 (55.8)	1 (1.2)	83 (96.5)	-	-	-	-	2 (2.3)	-
Drug interaction	72	71 (98.6)	8 (11.1)	7 (9.7)	31 (43.1)	2 (2.8)	2 (2.8)	-	20 (27.8)	2 (2.8)
Contraindication apparent (incl. laboratory parameters)	39	39 (100.0)	3 (7.7)	5 (12.8)	22(56.4)	4 (10.3)	-	1 (2.6)	2 (5.1)	2 (5.1)
Hypersensitivity	15	15 (100.0)	-	1 (6.7)	12 (80.0)	-	1 (6.7)	-	-	1 (6.7)

decision support system provides important support to pharmacists and pharmacy assistants, but cannot replace these professions in the delivery of pharmaceutical care. Dosage problems were the most frequently encountered potential DRP as seen in previous studies.[2,4,31,35] Most potential DRPs were solved or prevented by modifying dose, frequency or duration, which was also observed in other studies.[4,31,36] Not dispensing the prescribed product was common as well. The conversation with the patient and/or informal carer was sufficient for the pharmacist to modify a prescription in 60% of the cases. The prescriber was consulted in a minority of the cases. Several explanations can be given. This may be a result of medication appointments that doctors and pharmacists make in periodic pharmacotherapeutic consultations. Furthermore, apparently small clarifications of for example the dosage in order to achieve proper use and prevent misunderstanding of the patient can be done without consulting the prescriber. However, it also reflects the professional autonomy of the pharmacist.

For a first impression of the relevance in this study, we asked the pharmacists to judge the clinical relevance of the prescription modifications themselves. The pharmacists estimated 69.2% of the modifications to be potentially clinically relevant. A follow-up study using specific methods, such as evaluation of cases by a multidisciplinary expert panel,[11,37] could be considered to provide more objective insight of the clinical relevance of the prescription modifications.

As expected, administrative problems were less frequent in 2016 than in the Dutch study of 1999.[2] We estimate that administrative problems decreased by approximately 60%; however, due to some other categories in reasons for prescription modifications, exact comparison cannot be made. This tendency can also be observed in comparable studies from Denmark, Norway and Spain.[4,5,31] The decrease in administrative problems is most likely to be attributable to the widespread implementation of electronic prescribing, which is currently obligatory in the Netherlands.[9] Dutch electronic prescribing systems are well developed with integrated formularies to help prescribers to select the right drug and dosage for the indication. However, it can also introduce new errors like provider order entry errors and transcription errors.[38,39] Since the majority of administrative problems concerned missing or incomplete dosage information, they could result in potential DRPs if they were not noticed. Therefore, despite the reduction of administrative problems achieved, further improvement is desired, for example by the development of specific alerts for administrative issues in prescribing systems.

Although we categorized the modifications into 3 domains, they are all connected to a certain extent. Regardless of the domain of the modifications, there is a potential impact on medication safety: unclear dosage or usage instructions can result in several type of DRPs; availability problems can result in treatment interruptions or undesirable medication changes; switching generics can reduce patient's confidence in the drug and different packaging of the same drug can confuse the patient and for example result in taking the same drug twice. Therefore, opportunities to improve medication safety must be explored in all aspects and requires attention from healthcare providers to the medicine (logistics, pharmacology) as well as to the patient (information, shared decision making). Combining existing signals in 1 alert, which can also arise apart from logistic processing, may improve medication safety as well as the efficiency of the professionals. This development is already in an advanced stage. The problem of drug shortages is recognized and currently politics are working on a plan in which a larger stock of medication will be built up in the chain. This would solve short-term drug shortages. Besides, careless manufacturer policies causing drug shortages result in fines. Nevertheless, the Dutch market remains vulnerable due to the low drug prices in the Netherlands. Plans for a new medication process called Medication Process 9.0 are currently being worked out.[40] This plan enables better recording and exchange of medication data between healthcare providers and healthcare providers and patient. In this plan, medication appointments are separated from delivery requests. Although this requires major modifications of current systems, it has the potential to reduce medication errors of repeated prescriptions.

There was large variation in the proportion of prescriptions that were modified in each pharmacy. There are several possible reasons for this variation. The number of registered patients and number of prescriptions per day per pharmacy varied widely. Moreover, differences in patient population, alertness of pharmacists and prescribers, good cooperation with the prescribers, and the presence or absence of linked medication records may have contributed. Furthermore, contractual arrangements with the most prominent local health insurance companies affected the number of logistic modifications.

This study has several limitations. Although we included a substantial proportion of pharmacies (13.9%), distributed evenly over the Netherlands, we cannot exclude selection bias in the participating pharmacists or pharmacies. The most plausible reason is the selection of pharmacies with relatively good procedures for checking the quality of prescribing. Hence, the findings might be an overestimation of the number of modifications in average pharmacies. By contrast, underreporting due to not signalling all modifications cannot be ruled out. However, the pharmacists indicated that there were no obstacles in following the study protocol. Furthermore, pharmacists were supported by Dutch clinical decision support systems, which generated potential DRP signals based on the Dutch Guideline for the management of drug related problems.[22] Since the frequency of potential DRPs was higher compared to the Dutch study of 1999 and more recent international studies, we have no strong clues to suspect underreporting.

Pharmacists only collected their modifications during 1 day. We choose for this short measurement time because we wanted to compare to the Dutch study of 1999 and therefore used the same design. Furthermore, the study was time consuming for the participating pharmacists. To achieve good cooperation of the pharmacists, the time investment must be limited. Because of the short time period, fluctuation within pharmacies and seasonal fluctuation could not be assessed. Equally, assigning all days of the week accounted for potential variation throughout the week.

The data collection took place in 2016. There have been no remarkable changes in the Dutch market since then. Electronic exchange of prescriptions was already extensively implemented in 2016 and could only have marginally increased at most. There were no new regulations in for example sharing patient information or reimbursement. Logistic issues

remain unabated. They may be slightly increased regarding the increasing global drug shortages, but, by contrast, preference policy has somewhat changed by assigning longer preference periods. Therefore, this study still fits the present practice in 2020.

Finally, this study does not describe all efforts of pharmacists during the dispensing process. Interventions that did not result in a prescription modification (e.g. advice regarding medication use) were not included in this study.

5 | CONCLUSION

Dutch community pharmacists modified almost 1 in 20 prescriptions per pharmacy. The nature of the modifications reflects current community pharmacy practice, in which pharmacists frequently deal with logistic issues and intervene to solve or prevent for DRPs several times a day. The majority of the detected potential DRPs were considered to be potentially clinically relevant.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

W.E.L., H.B., M.L.B. and A.F.S. conceived of the presented idea. W.E.L., H.B., P.A.G.M.S., A.C.G.E., M.L.B. and A.F.S. designed the study. The project was directed by W.E.L, under supervision of M.L.B. and A.F.S. W.E.L. and M.K. performed the pilot study. The study was performed by W.E.L. and G.W.B., with the assistance of M.K. W.E.L., M.K. and G.W.B. analysed the data. S.D.B. accompanied the data analysis and validation. W.E.L. and S.D.B. wrote the manuscript with input from all authors. All authors approved of the final version to be published.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, Dr A. Floor-Schreudering, upon reasonable request.

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APPENDIX A

Reasons for prescription modifications

Administrative problem
- insufficient or wrong patient data[1]
- frequency, duration, maximum or strength of dose not or insufficiently specified
- health care product not specified
- indication lacks although legally required*
- prescription modification concerning
- reimbursement of the product*
- prescription offered more than once*

*Logistic issue**
- off market or currently not deliverable
- alteration label of refill prescription due to low-price policy or generic substitution[2]
- alteration of prescribed product or alteration brand/manufacturer due to pharmacy's assortment
- alteration brand/manufacturer of refill prescription due to preference- or low-price policy

Potential drug-related problem (DRP)
- incorrect strength or dose
- wrong medicine/product
- inappropriate dosage form[3]
- wrong duration or frequency of therapy
- prescribed medication unnecessary
- (pseudo) duplication[4]
- contraindications apparent (incl. laboratory parameters)
- hypersensitivity
- drug interaction
- preventive therapy required*
- advance usability and/or therapy compliance*

*Additional categories of prescription modifications compared to 1999

1 Wrong patient data defined as *correction prescription error* in 1999; changed to administrative problem

2 Generic substitution was excluded in 1999

3 Defined as *clarification needed* in 1999; changed to potential DRP

4 Part of category duplication concerning enough supply defined as *clarification needed* in 1999; changed to potential DRP