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EVIDENCE-BASED DEVELOPMENT OPPORTUNITIES FOR MEDICATION REVIEW IN THE FRAMEWORK OF BASIC PHARMACEUTICAL CARE IN HUNGARIAN COMMUNITY PHARMACIES

Ph.D. thesis

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LIST OF ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ATC	Anatomical Therapeutic Chemical
BEGONIA	Beteg Gondozás Informatikai Alapprogram (Patient Care Informatics Basic Program)
BELLA	Betegellátók Akkreditációja a biztonságos betegellátásért (Accreditation of Caregivers for Safe Patient Care)
COPD	Chronic obstructive pulmonary disease
DRP	Drug-related problem
EESZT	Elektronikus Egészségügyi Szolgáltatási Tér (Electronic Health Service Space)
EGYGYSZI	Egyetemi Gyógyszertár Gyógyszerügyi Szervezési Intézet (University Pharmacy Department of Pharmacy Administration)
GP	General practitioner
GYGSZB	Gyógyszerészi Gondozás Szakmai Bizottsága (Hungarian National Committee of Pharmaceutical Care)
HLS-EU	Health Literacy Survey - European Union
MGYK	Magyar Gyógyszerészi Kamara (Hungarian Chamber Of Pharmacists)
MGYT	Magyar Gyógyszerésztudományi Társaság (Hungarian Society of Pharmaceutical Sciences)
MHT	Magyar Hypertonia Társaság (Hungarian Society of Hypertension)
MOSZ	Magángyógyszerészek Országos Szövetsége (Hungarian Private Pharmacist Association)
NEAK	Nemzeti Egészségbiztosítási Alapkezelő (National Institute of Health Insurance Fund Management)
NSAID	Nonsteroidal anti-inflammatory drugs
OTC	Over-the-counter
PCNE	Pharmaceutical Care Network Europe
Rx	Prescription drug
SD	Standard deviation
SE	Semmelweis Egyetem (Semmelweis University)
VKA	Vitamin K antagonist

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1. INTRODUCTION

1.1. Health literacy

1.1.1. Definition, integrated model, and factors of health literacy

There are several approaches in the literature to define health literacy. By integrating 17 different definitions, as formulated by Sorensen et al. “health literacy is linked to literacy and entails people’s knowledge, motivation and competences to access, understand, appraise, and apply health information in order to make judgments and take decisions in everyday life concerning healthcare, disease prevention and health promotion to maintain or improve quality of life during the life course (1).”

In addition to the definition, Sorensen et al. created an integrated model of health literacy. This model builds on the dynamic process nature of health literacy.

The components of the process are:

- Access: information-seeking behavior, finding and obtaining information,
- Understand: perception of information,
- Appraise: interpreting, filtering, and judging information,
- Apply: the individual communicates information and uses it in decision-making to maintain or improve their state of health (1).

As a result of this process, the individual becomes able to thrive in healthcare, disease prevention, and health promotion.

Determinants influencing health literacy can be divided into three major groups:

- social and environmental determinants: demographics, culture, language, political forces, social system,
- personal determinants: age, gender, race, socio-economic status, education, occupation, employment, income, or literacy,
- situational determinants: social support, family and peer influences, media use, and physical environment (1).

1.1.2. The importance of low health literacy

The level of health literacy of the European population was assessed in 2015 by the Health Literacy Survey - European Union (HLS-EU). The research included 8 countries and 8,000 patients. The questionnaire survey classified participants into four levels of health

literacy: insufficient, problematic, sufficient, and excellent. The results showed that 47% of patients had low health literacy (insufficient or problematic), which varied significantly from country to country (29-62%). Financial problems, low social status, low education, or old age were predisposing factors for low health literacy (2).

Although Hungary did not participate in the original research, Koltai and her colleagues filled the missing domestic data with the same methodology. As a result of their survey, it turned out that the proportion of patients with limited health literacy in Hungary is 52%, which is better than Bulgaria alone among the countries surveyed (3).

Low health literacy has an impact on a patient's health. The consequences are unhealthy lifestyles, poorer health, more hospitalizations, higher healthcare costs, poorer patient adherence, and patient safety (4), making the issue inevitable for pharmacists working in community pharmacies.

1.1.3. The importance of health literacy in pharmaceutical counseling

Patient-centered community pharmacy services, such as pharmaceutical counseling, require pharmacists to have strong communication skills (5), thus ensuring the optimal exchange of information and the full participation of patients in their recovery (6, 7). Pharmacists' communication has to adapt to the different needs of patients to achieve patient-centeredness (8), in particular their different levels of health literacy. On this basis, pharmacists should provide clear and easy-to-understand information on the correct use of medicines to prevent, protect and improve patients' health so that patients can get the most out of it (9). In its report of 1997, the World Health Organization made it clear that the pharmacists of the future should be effective communicators. They have to focus on the involvement of open information exchange and patients in handling decision-making (10). According to a survey, 40-80% of the information provided by health professionals is immediately forgotten by patients, while nearly half of the information is poorly remembered (11). Inadequate and inaccurate communication, self-medication, and limited health literacy can easily lead to misunderstandings of medical recommendations and deviations from prescribed treatment regimens (9), in addition, it can harm pharmacists, as poor communication can lead to a deterioration in their judgment and a loss of confidence in their knowledge (12). In contrast, a pharmacist who is capable of effective patient-centered communication can improve patient adherence and health outcome (13), and can also increase patient satisfaction (12, 14).

However, to achieve all these goals, it is essential that both graduate and postgraduate pharmacy training adapt to changing needs. Various international pharmacist competence frameworks define communication as the core competence of pharmacists (15-19). However, these requirements are not always met in practice (8, 20-22). Education and training can improve the communication skills of pharmacists (7, 23, 24), which both pharmacy students and graduate pharmacists need (25).

1.1.4. Communication techniques supporting health literacy in pharmaceutical counseling

Properly clean, oral, and written communication techniques are essential during pharmaceutical counseling to enable the patient to become more involved in their therapy. The basis of successful communication is the use of appropriate, nonmedical language, short and simple conversations, images, and illustrations. It is also important to encourage patients to ask questions (26).

Several oral communication techniques that can be used in pharmaceutical counseling have been described in the literature. One of the most widely used effective approaches is the Indian Health Service model. This methodology is based on three open-ended questions ("What were you told this medication is for? How were you told to use it? What were you told to expect?"), based on which the pharmacist can provide advice appropriate to the patient's knowledge and health literacy (27).

In addition to this approach, a well-used structured communication technique is the "teach-back" (28) and the "Ask Me 3" methods (29). The Ask Me 3 method encourages patients to ask three simple questions to better understand their health and what they need to do to stay healthy ("What is my main problem? What do I need to do? Why is it important for me to do this?"). These questions help patients participate in their healing team, raise awareness of health literacy among professionals, and provide a platform for communication between patients, relatives, and healthcare workers (29).

The "teach-back" method allows the healthcare professional to assess whether the patient has understood the information provided. In this method, the practitioner explains something to the patient and then immediately asks it back with open-ended questions (e.g. "if you had to explain to your wife how this medicine works, how would you tell her?"). If the patient responds incorrectly, the healthcare professional will re-explain the

information and ask back. Open-ended questions should be topic-specific, thus providing more effective education to the patient (30).

In addition to oral techniques, the use of written tools is also important in pharmaceutical counseling and education (31). These tools are especially useful in case of lack of time, but there are many limitations when using them. Due to the complexity of the diseases and treatments and the potential for legal consequences, these leaflets often contain too much information, leading to misunderstandings, especially in patients with low health literacy (31, 32). Creating appropriate written materials is a challenge as their comprehensibility depends on many factors (cultural appropriateness, relevance, context, and the audience to whom the message is sent). Shortening the text is not a sophisticated approach enough, as it can lead to oversimplification, omission of important facts, and deteriorating readability. For example, the use of phonetically spelling long words with multiple syllables, placing important points at the beginning of the text, and pictograms improve the comprehensibility of written materials (33, 34). For the latter, they must be simple and straightforward for all groups of patients, especially those who are illiterate, elderly, or visually impaired (35). It is important to note that oral explanation is also necessary if we develop written materials and pictograms that are fundamentally accessible and useful to patients (36, 37).

These oral and verbal communication techniques, in combination with pictograms, provide a basis for good quality pharmaceutical counseling (38) and, more specifically, for pharmaceutical care services.

1.2. Pharmaceutical care

1.2.1. Pharmaceutical care in general

From the 1990s onwards, the development of pharmaceutical science and pharmacy practice took a new direction worldwide, responding to changes in the environment surrounding the profession and the needs of patients. The focus has shifted from the distribution and preparation of medicines to patient-centered care and counseling, where pharmacists assess the necessity, effectiveness, and safety of patients' medications, ensure that they understand their therapy, and monitor changes in their condition (39-42).

The establishment of a framework for pharmaceutical care has begun in the United States, as defined by Hepler and Strand (43). The meaning of pharmaceutical care has evolved

from their basic idea over the years, so today we use the definition of Pharmaceutical Care Network Europe (PCNE) as “pharmaceutical care is the pharmacist’s contribution to the care of individuals to optimize medicine use and improve health outcomes (44).”
Within the framework of pharmaceutical care, three elements can be distinguished: the management of drug therapy, the cooperation with physicians, and the education of patients (45).

1.2.2. Domestic definition of pharmaceutical care

In Hungary, Act XCVIII of 2006 on the General Provisions Relating to the Reliable and Economically Feasible Supply of Medicinal Products and Medical Aids and on the Distribution of Medicinal Products laid down the definition of pharmaceutical care. The law emphasizes that this is an activity of a pharmacist aimed at providing the necessary, effective, safe, and cost-effective drug therapy, advising on the use of drugs, and healthy lifestyle, and increasing the patient's adherence and quality of life. An important element of the service is the documentation, and the collaboration with the general practitioner (GP) (46).
Pharmaceutical care is a professional activity prescribed by law in Hungary, which can only be performed by a pharmacist in a community and branch pharmacy, as well as in a unit of institutional pharmacy engaged in supplying medicinal products directly to the general public (47). Regulation No 41/2007 Ministry for Health (on the operation, service, and registration of public, branch, manual and institutional pharmacies) distinguishes between two types of pharmaceutical care: basic and advanced (disease-specific) (47).

1.2.3. Basic pharmaceutical care

In the dispensing of prescription (Rx) and over-the-counter (OTC) medicines and other products (e.g. dietary supplements), it is the responsibility of all pharmacists to provide basic pharmaceutical care to patients visiting the pharmacy without a medical diagnosis or by prescription (47).
In the case of a patient visiting the pharmacy without a medical diagnosis, the pharmacist is responsible for:

- providing professional assistance in assessing the symptoms and referring the patient to a doctor, if necessary,

- recommending symptomatic relief therapy, including methods that can be used without medical intervention, and OTC medications,
- providing information on the use of OTC medicines and other products, including knowledge to identify drug-related problems (DRPs), what to do if they occur, and cases of suspension or discontinuation of therapy (47).

If the patient arrives at the community pharmacy with a prescription, it is the pharmacist's responsibility to:

- identify and resolve existing DRPs related to drug dispensing and prescription validation, in particular for certain specific diseases and conditions (e.g. infancy, pregnancy, lactation, geriatrics, liver and kidney disease, drug allergy),
- promote the safe, cost-effective, and continuous use of generic drugs by assessing the patient's previous medication, identifying and resolving DRPs,
- provide advice on how to improve adherence,
- give information on risk factors and advice for the continuation of health-conscious behavior, prevention of the development of certain diseases and their complications (47).

1.2.4. Advanced (disease-specific) pharmaceutical care

Advanced (disease-specific) pharmaceutical care is an activity related to public health programs. Part of this (in collaboration with the patient's GP) is to assess the risk factors for a particular disease, educate the patient, manage their medication use, improve their adherence, and refer them to a doctor if they have a problem. The purpose of the service is to identify risks at an early stage, maintain the patient's health, and prevent complications (47). While basic pharmaceutical care is the responsibility of all pharmacists, advanced pharmaceutical care can only be provided by a pharmacist, who has completed an education program to this end. In addition, to perform advanced pharmaceutical care, it is essential to have a counseling room in the pharmacy. This room must be accessible by the patients without disturbing the pharmacy work or entering rooms isolated from them. The private space can be designed in the public part of the pharmacy if it is at least 25 m^2 (47).

1.2.5. Summary of Hungarian programs for the introduction of pharmaceutical care

Efforts to introduce pharmaceutical care in Hungary began in the early 2000s. The first Hungarian project was the Pharmacist Diabetes Prevention Program launched in November 2005 by the Hungarian Private Pharmacist Association (Magángyógyszerészek Országos Szövetsége, MOSZ) in cooperation with the "Egy Csepp Figyelem" (One Drop of Attention) Foundation, during which nearly 100,000 blood glucose control measurements were performed in 500 pharmacies, as a result of which 19.0% of the patients were referred to the GP by pharmacists (48). In 2006, the Hungarian Chamber of Pharmacists (Magyar Gyógyszerészi Kamara, MGYK), together with the Hungarian Society of Hypertension (Magyar Hipertónia Társaság, MHT), launched its pharmaceutical care program for people with hypertension (PIPACH study). The study showed that patients in the intervention group (pharmaceutical care service) had a significant improvement in blood pressure compared to the control group. Furthermore, as a result of the activities of pharmacists, patient satisfaction also increased (49). The Hungarian Society of Pharmaceutical Sciences (Magyar Gyógyszerésztudományi Társaság, MGYT) joined the series of Hungarian care programs in 2007 in the field of self-medication, including headaches, sunbathing, and sunburn. In their program involving 50 pharmacies, 90% of patients in the field of headache requested specific medication to relieve their pain. However, following the consultation, the pharmacist did not give the requested product to half of the patients for professional reasons and referred 25% of the patients to a doctor. In addition, in the case of documented consultations in the field of sunburn, half of the patients received a different from the originally requested product, and 12% of the patients had to be referred to a physician (50).

In August 2007, the Hungarian National Committee of Pharmaceutical Care (Gyógyszerészi Gondozás Szakmai Bizottság, GYGSZB) was established with the participation of these three pharmaceutical organizations (MGYK, MGYT, MOSZ). The Committee's objectives included analyzing pharmaceutical care programs from a professional and cost-effectiveness perspective, developing uniform guidelines, supporting additional programs, and establishing a legal, educational, and funding framework for the service so that it can be provided by all pharmacies in the country (51).

As a result of the work of the Commission, the first official protocol for advanced pharmaceutical care in Hungary was established in 2010: the protocol for Metabolic Syndrome Pharmaceutical Care Program (52).

In 2012, the "Accreditation of Caregivers for Safe Patient Care" (Betegellátók Akkreditációja a biztonságos betegellátásért, BELLA) program was launched to improve patient and drug safety (53). The BELLA project aimed to lay down the principles of pharmaceutical care, and the development of pharmaceutical care guidelines for the most important diseases in terms of self-medication, which were tested with the participation of 52 pilot pharmacies. The program managers planned to develop a total of 16 pharmaceutical care guidelines in three major groups (guidelines for self-medication; for diseases with major public health consequences; for the care of pregnant and elderly patients). To date, only 5 of the 16 planned professional guidelines have been elaborated and officially published on the following topics:

- About pregnant care (54),
- Pharmaceutical counseling on the effective and safe use of drugs for the treatment of chronic obstructive pulmonary disease (COPD) (55),
- Pharmaceutical counseling to support the safe and effective use of medications for the treatment of adult asthma (56),
- Pharmaceutical counseling for self-treatment of acute non-specific low back pain (57),
- Pharmaceutical counseling on self-treatment of benign prostate enlargement (58).

The IT background of the project was provided by the development of the "Patient Care Informatics Basic Program" (Beteg Gondozás Informatikai Alapprogram, BEGONIA) software, which provided an opportunity to digitize paper-based pharmaceutical care (53).

Despite the availability of established professional protocols and IT background, the practical implementation of pharmaceutical care slowed down in the second half of the 2010s. Giving new impetus to the efforts, a "Complex Pharmacy Adherence Development Program" was launched in 2018 at the national level, to develop patient adherence in community pharmacies. Within the framework of the program, a public information leaflet and a professional aid were developed. The usefulness of the publications was studied including 1,082 patients and 205 pharmacies. The vast majority

of patients were helped to ask in pharmacies and pay more attention to their medication, and 52% of respondents found new information in the prospectus. The program has proven useful and has helped most in increasing therapeutic support for patients already known. The publication for patients was considered "very necessary" by most professionals and the aid for pharmacists was considered by most to be "essential". The importance of rethinking community pharmacy services and purposefully developing public information in Hungary has been proven, so the program continues to operate under the active care of MGYK and the University Pharmacy Department of Pharmacy Administration, Semmelweis University (Semmelweis Egyetem, Egyetemi Gyógyszertár Gyógyszerügyi Szervezési Intézet, SE EGYGYSZI), with the support of 9 professional organizations and institutions, focusing on adherence development (59).

1.3. Medication review

1.3.1. Medication review: definition and types

Based on the consensus definition of PCNE "medication review is a structured evaluation of a patient's medicines with the aim of optimising medicines use and improving health outcomes. This entails detecting drug-related problems and recommending interventions (60)." A good quality medication review requires a standardized, structured approach, covering prescription and OTC medicines, and other products (such as dietary supplements), their use, prescription, and optimization of administration. By health outcomes to be developed, we mean clinical, economic, and humanistic outcomes that include effectiveness, patient safety, and impact on quality of life. Part of this service is to detect DRPs *(see chapter 1.3.2.)* and to suggest solutions (60).

PCNE distinguishes between three types of medication reviews, assuming that all information about the medications taken by the patient is available to the pharmacist (61). A simple medication review (Type 1) is based on the patient's medication history. It can be used to find interactions, some side effects, unusual dosing, and some problems with adherence. In the case of an intermediate medication review, we have another source of information: a patient interview (Type 2A) or clinical data provided by a GP (Type 2B). By them, additional adherence problems, as well as drug-food interactions and efficacy problems can be eliminated. For Type 2A, additional side effects and problems with OTC use can be resolved, while for Type 2B, drugs without indication and indications without

medication can be found. In the case of an advanced (Type 3) medication review, all three pieces of information are available to us, so all of the above problems can be eliminated, in addition to the errors affecting the dosing of drugs (61) (*Table 1).*

Table 1: *Pharmaceutical Care Network Europe typology of medication reviews (61).*

Characterization		**Available information**		
Type	*Level*	*Medication history*	*Patient interview*	*Clinical data*
Type 1	Simple	X		
Type 2A	Intermediate	X	X	
Type 2B		X		X
Type 3	Advanced	X	X	X

From this classification, it can be seen that to carry out an effective medication review, the participation of the given patient and the patient's GP is essential (62-64).

1.3.2. Drug-related problems and their classification

Unexpected, adverse drug events are the fifth most common cause of death in the European Union, accounting for almost 200,000 deaths a year, resulting in additional costs of around € 80 billion per year. It is estimated that 5% to 10% of those taking drugs experience some form of side effect, which also causes 5% of hospital admissions (65).
There are several definitions of DRPs in the literature. One of the most commonly used terms is the PCNE definition, according to which DRP is defined as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes (66)." There can be several causes for DRPs, which can result in medication not achieving its goal or even being harmful.
Classifying DRPs is an essential pillar of the medication review. There are more than 20 types of DRP classification systems in the literature, which differ in e.g. DRP groups and methodology (67). In this thesis, we detail two classification systems: the PCNE Classification for DRPs (66), and the Third Consensus of Granada Drug-Related Problem Classification (68).

1.3.2.1. Pharmaceutical Care Network Europe Classification for DRPs

PCNE has been developing an internationally usable, standardized DRP classification system since 1999, which is regularly validated and modified. The current version is the PCNE Classification for Drug-Related Problems V 9.1 released in 2020 (66). The

classification can be used to investigate the nature, prevalence, and incidence of DRPs, for example, researches aimed at the results of pharmaceutical care. Its goal is also to help healthcare professionals document DRPs in care processes. The system is structured hierarchically, and it separates problems from causes. It classifies problems into 3 main and 6 subcategories, causes into 9 main and 38 subcategories, and interventions into 5 main and 17 subcategories. In addition, it discusses the acceptability of interventions (3 main and 10 subcategories) and the extent to which problems are solved (4 main and 7 subcategories) (66) *(Table 2).*

Table 2: *Pharmaceutical Care Network Europe Classification for Drug-Related Problems V9.1. – main categories (66).*

	Code V9.1	Primary domains
Problems (also potential)	**P1**	**Treatment effectiveness** There is a (potential) problem with the (lack of) effect of the pharmacotherapy
	P2	**Treatment safety** Patient suffers, or could suffer, from an adverse drug event
	P3	**Other**
Causes (including possible causes for potential problems)	**C1**	**Drug selection** The cause of the DRP can be related to the selection of the drug
	C2	**Drug form** The cause of the DRP is related to the selection of the drug form
	C3	**Dose selection** The cause of the DRP can be related to the selection of the dosage schedule
	C4	**Treatment duration** The cause of the DRP is related to the duration of treatment
	C5	**Dispensing** The cause of the DRP can be related to the logistics of the prescribing and dispensing process
	C6	**Drug use process** The cause of the DRP is related to the way the patient gets the drug administered by a health professional or carer, in spite of proper instructions (on the label)
	C7	**Patient related** The cause of the DRP can be related to the patient and his behavior (intentional or non-intentional)
	C8	**Patient transfer related** The cause of the DRP can be related to the transfer of patients between primary, secondary and tertiary care, or transfer within one care institution.
	C9	**Other**
Planned Interventions	**I0**	**No intervention**
	I1	**At prescriber level**
	I2	**At patient level**
	I3	**At drug level**
	I4	**Other**
Intervention Acceptance	**A1**	**Intervention accepted**
	A2	**Intervention not accepted**
	A3	**Other**
Status of the DRP	**O0**	**Problem status unknown**
	O1	**Problem solved**
	O2	**Problem partially solved**
	O3	**Problem not solved**

1.3.2.2. Third Consensus of Granada Drug-Related Problem Classification

The Third Consensus of Granada Drug-Related Problem Classification divides DRPs into six groups and an "Other" class for unmatchable cases, and it also identifies the cause of the particular DRP (68) *(Table 3).*

Table 3: *Drug-related problem classification and their underlying cause according to the Third Consensus of Granada Drug-Related Problem Classification (52, 68).*

	Drug-related problem		Underlying cause
Necessity	**DRP1**	Untreated health problem. The patient suffers from a health problem as a consequence of not receiving the medicine that he/she needs.	Medication is necessary (lack of the required medication)
	DRP2	Effect of unnecessary medicine. The patient suffers from a health problem as a consequence of receiving the medicine that he/she does not need.	Unnecessary taken drug
			Multiple drug use from the same pharmacological category
Effectiveness	**DRP3**	Non-quantitative ineffectiveness. The patient suffers from a health problem associated with the non-quantitative ineffectiveness of the medication.	Improper medication choice
			Non-adherence
	DRP4	Quantitative ineffectiveness. The patient suffers from a health problem associated with the quantitative ineffectiveness of the medication.	Improper dosage
Safety	**DRP5**	Non-quantitative safety problem. The patient suffers from a health problem associated with a non-quantitative safety problem of the medication.	Interaction
			Side effects
	DRP6	Quantitative safety problem. The patient suffers from a health problem associated with a quantitative safety problem of the medication.	Improper dosage
Other			

This classification system has already been the basis for several pieces of research in community pharmacies (69, 70) and emergency departments (71), and the system was

included in the protocol for Metabolic Syndrome Pharmaceutical Care Program (52). We also use it in the research of the thesis presented.

1.3.3. International results of medication review

Medication review in a community pharmacy can have several effects that can manifest themselves at the level of drug therapy, the patient's condition, health outcome, and the healthcare system.

Medication review at the level of drug therapy has a positive effect on anticoagulant therapy (optimization and management of International Normalized Ratio and associated outcome) (72) and reduces the number of drugs taken by reducing the number of potentially inappropriate medications (73-77). In addition, it is suitable for detecting and solving various DRPs (77-80), even in collaboration with hospital pharmacists (81).

Putting the issue in the broader context of the patient's condition and health outcome, medication review also has a positive effect on blood pressure (improved target systolic and/or diastolic pressure) (49, 82), cholesterol level (improved target cholesterol targets) (83), control of diabetes (reduction in HbA1c, improved blood glucose control) (84), and through them to cardiovascular diseases (reduction in cardiovascular events and risk assessments) (84), as well as to the management of asthma/COPD (improved symptom control and lung function) (85). In addition to disease management, medication review increases patient confidence in therapy (86) and adherence (82), however, its positive impact on patient satisfaction, drug knowledge, quality of life, and mortality is unclear (87).

Approached from a healthcare system perspective, it reduces the number of appearances in the emergency department (88, 89), hospital (re)admissions (89,90), and it increases the cost-effectiveness of the treatment (91).

1.3.4. Medication review in the framework of basic pharmaceutical care in Hungary

In Hungary, an important element of basic pharmaceutical care is medication review, the framework of which is set out in Regulation 44/2004 by the Ministry of Health, Social and Family Affairs on the ordering and issuing of medicinal products for human use (92). The regulation requires all medicines dispensed in a pharmacy to be subject to a medication review for medicines dispensed to the patient at the same time and determines

the tasks of the pharmacist or - under the professional supervision of the pharmacist - the technician who dispenses the medicine. During medication review the professional:

- provides detailed patient information,
- reveals clinically significant interactions,
- draws attention to the risks associated with the concomitant use of medicines with the same active ingredient but different brand names,
- informs the patient about possible ways to prevent disease,
- detects side effects,
- in the case of a regularly used drug, examines the patient's adherence with questions.

The regulation sets out certain cases in which the involvement of a pharmacist in the dispensing process is mandatory:

- clinically significant interaction during concomitant drug dispensing,
- clinically significant side effect,
- risk of duplication or an adherence problem,
- a prescription based on the name of the active substance,
- at the request of the patient,
- at the initiative of a drug dispensing technician.

As part of the medication review, the pharmacist should identify drug-related problems and suggest solutions (92).

To unify the methodology of the activity, the Hungarian State Secretariat for Healthcare of the Ministry of Human Capacities issued a professional directive on medication review in the framework of basic pharmaceutical care in 2013. The directive aims to ensure the safety of medication use and patients through medication review in the framework of basic pharmaceutical care, helping to achieve necessary, effective, safe, and cost-effective drug therapy (65). The professional guideline sets out 29 recommendations, covering, in particular, the circumstances of refusing to dispense medicine and notifying the GP. The topics discussed are:

- general principles,
- assessment of drug interactions, in particular for active substances with clinically significant interactions,
- examination of parallel prescribing and drug use,

- reporting and investigation of suspected side effects,
- professional rules for dispensing medicines in the case of drug substitution and for prescribing medicines based on the name of the active substance,
- assessing and improving adherence,
- providing adequate patient information on the safety and potential problems of drug use (65).

Although the above-mentioned professional directive has been available since 2013, we have not found Hungarian studies and results in connection with this community pharmacy service.

2. OBJECTIVES

The thesis aimed to promote the wide-ranging practical feasibility of medication review in the framework of basic pharmaceutical care in Hungarian community pharmacies, by creating a unified communication base and evaluating the relevance, possibilities, results, and development directions of the service.

To create a unified communication base, our first goal was to introduce postgraduate training to promote the development of pharmacy communication that supports health literacy, and to assess its necessity and effectiveness (93).

Our next objective was to evaluate the relevance, possibilities, results, and development directions of the service. To this end, we launched a pilot project in a high-risk, specific patient population, the aims of which were as follows (94, 95):

- The qualitative and quantitative description of the discovered DRPs in community pharmacies, implementing the DRP classification used in previous domestic protocols (52) in practice.
- Analysis of pharmacists' interventions to solve DRPs to map the pharmacist-GP competence boundaries.

Our next goal was to support the results of the pilot project in a wider patient population. Therefore, we extended our studies to polypharmacy patients. The objectives of this research were as follows:

- Assessing the impact of medication review on the general drug knowledge of polypharmacy patients (96).
- Qualitative and quantitative analysis of DRPs revealed through medication review using the classification used in the pilot project (96, 97).
- Analysis of pharmacist interventions to address the DRPs found to support the results of the pilot project in a wider patient population (96, 97).
- A detailed survey of the main actors of the medication review (patients, pharmacists, and GPs), on the implementation and possibilities of the service, to learn about development potentials and barriers (98).
- Analysis of the most frequently discovered root cause of DRPs (interaction risks) in detail, in terms of their incidence, nature, clinical risk, and pharmacists' interventions to counter the identified risks to prepare a procedure for the uniform handling of drug interaction risks (97).

3. RESULTS

3.1. Results of the questionnaires about the establishment of a communication environment supporting low health literacy in community pharmacies

The research aimed to support the effectiveness and necessity of the health literacy-focused communication training and methodology introduced in the postgraduate pharmacy training and community pharmacy practice, with the participation of 69 pharmacies, 333 professionals (pharmacists and pharmacy technicians), 890 (at the beginning of the project) and 847 patients (at the end of the project). This study included two cross-sectional questionnaire surveys (patient and staff questionnaire) before and after the introduction of a methodological recommendation, which contains a 3-day postgraduate health literacy-focused communication training followed by the "train the trainer" teaching method at pharmacies, then the introduction of the learned methodology using uniform information materials and a communication checklist. For both the patient and staff questionnaire, a higher score indicates better communication. A detailed description of the methodology can be found in *Reference 93*.

3.1.1. Results of the patient questionnaire

The pre-intervention and post-intervention groups consisted of two different patient populations. Subgroups of these two different populations were compared using the Chi-square test and we could not detect statistical difference between basic demographic parameters in a significance level of 5% (sex: p=0.569; age: p=0.962; marital status: p=0.676; educational attainment: p=0.555; type of settlement: p=0.958).

The mean score of the pre-intervention patient group was 15.38 (standard deviation (SD)=4.89) points out of 24, which corresponds to 64.07%. At the end of the project, a new patient population completed the questionnaire, their mean score was 17.45 (SD=4.07) points, which is 72.72% of the total score, showing a significant ($p<0.001$) improvement of 8.65% (+2.07 points) between the two questionnaires. The improvement in the score of each question during the project has been examined, and these results are included in *Table 4* (maximum of 4 points per question). There was a significant improvement in all questions: the greatest was found in Question 2 (+17.58%). Questions 1 and 3 showed an improvement of 9.09% and 9.77% respectively, while the mean score of Questions 4-6 improved by 4-5% *(Table 4).*

Table 4: *Results of patient questionnaires. A self-developed questionnaire, containing 3 Likert-scale and 3 single-choice questions. Maximum total score: 24 points. Input and output populations differed. Significance level: 5% (n: data numbers) (98).*

Questions	Values of points available for the question	Mean pre-intervention score (point) n=889	Mean post-intervention score (point) n=846	Mean change (point)	Mean change (%)	p
1. Did the pharmacist or pharmacy technician use complicated terms or expressions during the consultation?	0/1/4 point(s)	2.94	3.31	+0.37	+9.09	<0.001
2. Did the pharmacist or pharmacy technician encourage you to ask questions during the consultation?		2.35	3.05	+0.70	+17.58	<0.001
3. Did your pharmacist or pharmacy technician emphasize the important information orally, with written help or graphics?		3.13	3.52	+0.39	+9.77	<0.001
4. How easy or difficult was it for you to understand the instructions given by your pharmacist or pharmacy technician on how to take/use the prescribed medication?	0-4 point(s)	3.06	3.29	+0.23	+5.75	<0.001
5. How much do you feel you know all the important information about your medicines?		2.04	2.26	+0.22	+5.58	0.002
6. How do you see your state of health?		1.86	2.02	+0.16	+4.16	0.027
TOTAL	**24 points**	**15.38**	**17.45**	**+2.07**	**+8.65**	**<0.001**

The improvement of the total score of each subpopulation has been analyzed to identify the groups of patients more or less affected by the project *(Table 5)*. The results showed that there was no significant difference between women and men ($p>0.05$). The total score of patients older than 40 years developed significantly more than those under 40 years ($p<0.001$). Also, the development of widows ($p<0.02$) and residents of county seats ($p<0.02$) was significantly higher. In contrast, patients who have university degrees improved less ($p=0.02$).

Table 5: *Change in the score for each patient subpopulation. (*: significantly higher improvement; n(pre-intervention): pre-intervention questionnaire data number; n(post-intervention): post-intervention questionnaire data number (98).*

Sex	**Mean change *(point)***	**Mean change *(%)***			
Male *n(pre-intervention)=368* *n(post-intervention)=362*	+2.02	+8.42			
Female *n(pre-intervention)=502* *n(post-intervention)=467*	+2.10	+8.75			
p>0.05					
Age	**Mean change *(point)***	**Mean change *(%)***	**Marital status**	**Mean change (point)**	**Mean change (%)**
18-25 years *n(pre-intervention)=106* *n(post-intervention)=105*	+1.39	+5.79	Other *n(pre-intervention)=21* *n(post-intervention)=15*	+1.93	+8.04
26-40 years *n(pre-intervention)=228* *n(post-intervention)=213*	+1.26	+5.25	Single *n(pre-intervention)=208* *n(post-intervention)=190*	+1.71	+7.13
41-65 years *n(pre-intervention)=332* *n(post-intervention)=318*	+2.43*	+10.13*	Married/long-term relationship *n(pre-intervention)=475* *n(post-intervention)=473*	+1.86	+7.75
65- years *n(pre-intervention)=220* *n(post-intervention)=202*	+2.59*	+10.79*	Widowed *n(pre-intervention)=171* *n(post-intervention)=156*	+2.84*	+11.83*
p<0.001			*p<0.02*		
Educational attainment	**Mean change *(point)***	**Mean change *(%)***	**Type of settlement**	**Mean change *(point)***	**Mean change *(%)***
Primary school *n(pre-intervention)=61* *n(post-intervention)=69*	+2.43*	+10.13*	Villages *n(pre-intervention)=30* *n(post-intervention)=30*	+0.97	+4.04
Vocational school *n(pre-intervention)=210* *n(post-intervention)=189*	+2.49*	+10.38*	Other cities *n(pre-intervention)=363* *n(post-intervention)=343*	+2.50	+10.42
Baccalaureate *n(pre-intervention)=301* *n(post-intervention)=292*	+2.39*	+9.96*	County towns *n(pre-intervention)=86* *n(post-intervention)=88*	+3.33*	+13.88*
University *n(pre-intervention)=303* *n(post-intervention)=266*	+1.67	+6.96	Capital city *n(pre-intervention)=410* *n(post-intervention)=385*	+1.67	+6.96
p=0.02			*p<0.02*		

3.1.2. Results of the staff questionnaire

The mean total score of the pre-intervention questionnaires was 18.61 points (SD=2.97; 74.47%) out of 25. The results of the repeated questionnaires at the end of the project were 21.30 points (SD=2.32; 85.21%), which is a significant ($p<0.001$) increase of 2.69 points (10.74%). Examining the individual questions, it can be stated that the mean score

of all questions increased significantly by the end of the project ($p<0.001$), the greatest improvement was in the case of Question 4 and the least in the case of Question 1 *(Table 6).*

Table 6: *Results of staff questionnaire. A self-developed questionnaire, containing 5 Likert-scale questions. Maximum total score: 25 points. Input and output populations were the same. Significance level: 5% (n(pre-intervention): pre-intervention questionnaire data number; n(post-intervention): post-intervention questionnaire data number) (98).*

Questions	**Mean pre-intervention score *(point)* n=889**	**Mean post-intervention score *(point)* n=846**	**Mean change *(point)***	**Mean change *(%)***	***p***
1. How typical are you to recognize patients with low levels of health literacy?	3.96	4.35	+0.39	+7.80	<0.001
2. How typical are you to know what communication techniques you can use to help the patient's health literacy?	3.69	4.26	+0.57	+11.40	<0.001
3. How typical are you of communicating with your patients in plain, everyday terms (e.g. not using technical terms)?	4.02	4.50	+0.48	+9.60	<0.001
4. How typical are you of encouraging your patients to ask questions?	3.29	4.04	+0.75	+15.00	<0.001
5. How typical are you to visually help your patient understand the information?	3.65	4.16	+0.51	+10.20	<0.001
TOTAL	**18.61**	**21.30**	**+2.69**	**+10.74**	**<0.001**

The statistical analysis pointed out that the results of professionals working in the county towns or the capital improved significantly more ($p<0.02$; *Table 7*).

Table 7: *Results of staff questionnaires by settlement type (*: significantly higher improvement ($p<0.02$); n(pre-intervention): pre-intervention questionnaire data number; n(post-intervention): post-intervention questionnaire data number) (98).*

Type of settlement	**Mean change *(point)***	**Mean change *(%)***
Villages *n(pre-intervention)=13* *n(post-intervention)=14*	+2.29	+9.16
Other cities *n(pre-intervention)=145* *n(post-intervention)=148*	+2.71	+10.84
County towns *n(pre-intervention)=30* *n(post-intervention)=30*	+3.23*	+12.92*
Capital *n(pre-intervention)=143* *n(post-intervention)=135*	+3.43*	+13.72*

3.2. Results of the pilot study about medication review in the framework of basic pharmaceutical care in community pharmacies

Medication reviews were done and data were collected by pharmacists participating in specialist training at Semmelweis University, who received training about the description and requirements of the project, the recommended methodology of medication review, and the DRP classification. The classification of DRPs was performed according to the Third Consensus of Granada on Drug-Related Problems classification system (68). In this study, we analyzed the DRPs identified by 61 pharmacists in 61 community pharmacies with 540 patients taking an angiotensin-converting enzyme (ACE) inhibitor in combination with a nonsteroidal anti-inflammatory drug (NSAID) and/or taking a vitamin K antagonist (VKA). A detailed description of the methodology can be found in *Reference 95*.

3.2.1. The results of descriptive analysis of the identified DRPs

On average, patients consumed 7.9 ± 3.2 medications and other products. From them, 6.3 were prescription drugs (SD=2.8), 1.1 OTC (SD=1.1) and 0.4 other product, for example dietary supplements (SD=0.8).

During the study, 769 DRPs were detected in these 540 patients, averaging 1.4 DRPs per patient (SD=1.1). The highest frequency category was DRP5 (non-quantitative safety problem: 63.6%), while 17.8% of cases belonged to DRP3 (non-quantitative ineffectiveness), 7.4% to DRP1 (untreated health problem) and 6.1% to DRP2 (effect of unnecessary medicine). DRP4 (quantitative ineffectiveness) and DRP6 (quantitative safety problem) were less frequent (3.4%; 1.7%) *(Figure 1).* One group of patients enrolled in the study was taking an ACE inhibitor with NSAID, which alone is considered a risk of interaction. Excluding these interactions from the results, pharmacists found 452 DRPs (0.8 ± 1.0 DRP/patient).

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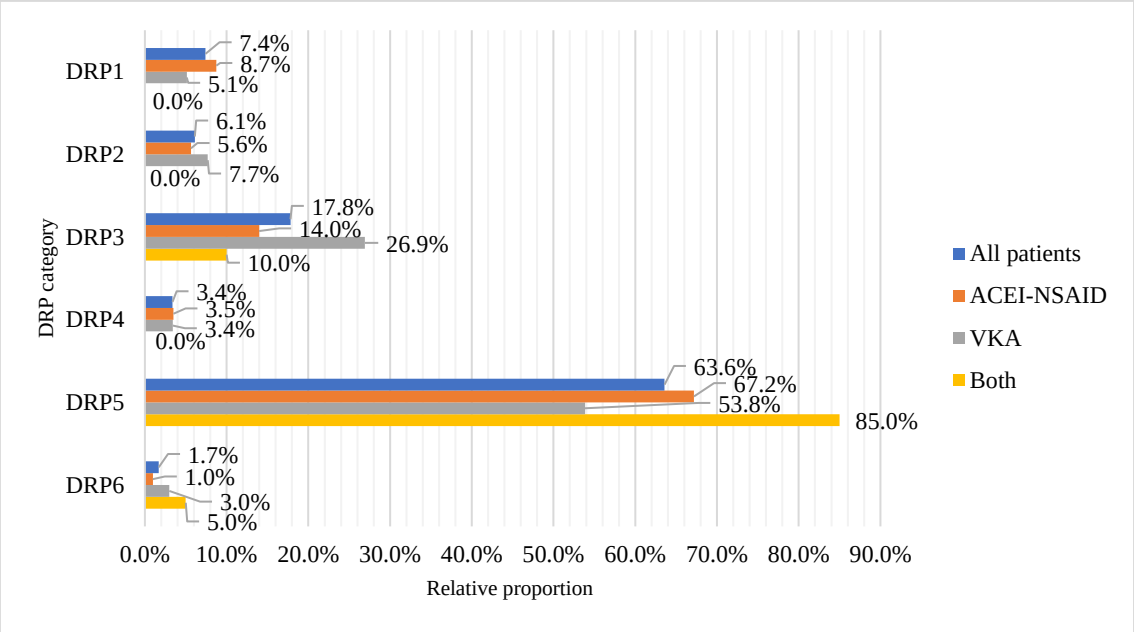

***Figure 1**: The proportion of each DRP category relative to total DRPs per patient group. All patients: all the participating patients (n=769 DRPs); ACEI-NSAID: patients taking ACE inhibitor and NSAID simultaneously (n=515 DRPs); VKA: patients taking vitamin K antagonist (n=234 DRPs); Both: patients included in both categories (n=20 DRPs) (95).*

Analyzing the root causes of DRPs, the most common was drug-drug interaction (57.0%). If we do not count in the ACE-NSAID interaction, this cause remains the most common (26,8%). The second was non-adherence (14.4%), while the quantitative safety problem caused by improper dosage was the rarest (1.7%) *(Figure 2).*

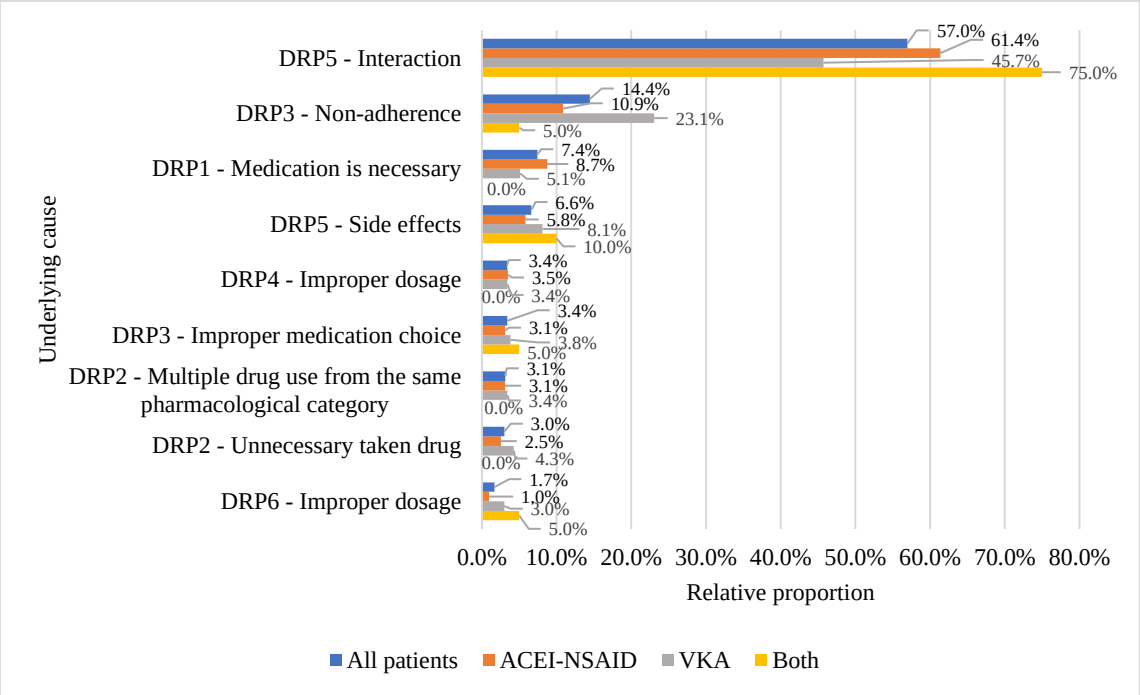

Figure 2: *The proportion of each underlying cause of DRPs relative to total DRPs per patient group. All patients: all the participating patients (n=769 DRPs); ACEI-NSAID: patients taking ACE inhibitor and NSAID simultaneously (n=515 DRPs); VKA: patients taking vitamin K antagonist (n=234 DRPs); Both: patients included in both categories (n=20 DRPs) (95).*

In the case of ACEI-NSAID patients, the DRP1 category appears to be higher (8.7%) than in the case of VKA patients (5.1%). The ratio was reversed in the case of DRP3 (14.0% and 26.9%) *(Figure 1* and *2).* The ratio of interaction was extremely high for those patients who were in both categories, but only 10 patients were included in this group (85.0%; *Figure 2*). However, these differences are not significant either in the number of DRPs or in the occurrence of the individual categories and causes. There was no "other" problem that cannot be categorized elsewhere.

3.2.2. Results of statistical analysis of DRPs found

There are no differences in the prevalence of DRPs between men and women (p=0.070) and between the patients over and under 65 years (p=0.552).

There is a significant difference between the types of settlement in the occurrence of the DRP. In the capital city, the pharmacists have found two DRPs per patient in a significantly higher ratio, while in other settlements it was markedly higher, that the pharmacist found no mistake in the medication (p<0.001). There is a correlation between

the higher number of DRPs and the higher total number of used medications, but the correlation is weak (Pearson correlation coefficient=0.214 ($p<0.005$)). The relationship between the number of prescription drugs and the number of DRPs is similar, somewhat lower (Pearson correlation coefficient=0.152 ($p<0.005$)). *Table 8* summarizes the rates of interventions used to eliminate DRPs.

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Table 8: *Drug-related problems (DRPs) and the ratio of the interventions used with each other for the total study population (Green cells: the most common intervention for the elimination of each underlying cause; Yellow cells: the interventions for each underlying cause with an incidence higher than 10% (n=562 interventions) (95).*

DRPs	Root causes	Pharmacist interventions												
		Dosage change	**Dose escalation**	**Dose reduction**	**Drug recommen-dation**	**Drug replacement**	**Education**	**Helping with device**	**Not necessary**	**Not happened**	**Notification of the GP**	**Sending to the doctor**	**Stop drug**	**SUM**
DRP1	Medication is necessary	-	-	-	42.1%	1.8%	1.8%	-	-	-	12.3%	42.1%	-	**10.0%**
DRP2	Unnecessary taken drug	-	-	-	-	4.5%	9.1%	-	18.2%	-	13.6%	9.1%	45.5%	**3.9%**
	Multiple drug use from the same pharmacological category	-	-	-	-	4.2%	-	-	29.2%	-	12.5%	4.2%	50.0%	**4.2%**
DRP3	Improper medication choice	-	-	-	3.8%	19.2%	3.8%	-	3.8%	7.7%	30.8%	30.8%	-	**4.6%**
	Non-adherence	-	-	-	-	2.8%	85.0%	8.4%	-	-	1.9%	1.9%	-	**18.8%**
DRP4	Improper dosage	-	3.8%	-	3.8%	3.8%	15.4%	-	3.8%	3.8%	34.6%	30.8%	-	**4.6%**
DRP5	Interaction	-	-	-	-	38.8%	16.9%	-	21.5%	0.8%	10.7%	6.2%	5.0%	**42.6%**
	Side effects	-	-	-	9.8%	17.6%	5.9%	-	7.8%	3.9%	13.7%	37.3%	3.9%	**9.0%**
DRP6	Improper dosage	7.7%	-	23.1%	-	-	15.4%	-	-	-	15.4%	38.5%	-	**2.3%**
	Other	-	-	-	-	-	-	-	-	-	-	-	-	**0.0%**
SUM		**0.2%**	**0.2%**	**0.5%**	**5.5%**	**20.2%**	**25.5%**	**1.6%**	**12.1%**	**1.2%**	**11.8%**	**14.8%**	**6.3%**	**100.0%**

3.3. Results of study about medication review in the framework of basic pharmaceutical care in community pharmacies with polypharmacy patients (polypharmacy study)

The research was carried out in the framework of the training of specialist pharmacists at Semmelweis University. At the beginning of the project, pharmacists received a one-day course at Semmelweis University, during which participating pharmacists were introduced to the detailed goals, implementation steps, and professional content (DRP classification, medication review methodology, questionnaires) to be used. In this study, we analyzed 755 polypharmacy (continuous concomitant use of 5 or more drugs) patients' knowledge of medicines and the DRPs identified by 78 pharmacists in community pharmacies of 35 settlements, especially regarding interaction risks. Also, we surveyed the opinions of key actors (patients, GPs, pharmacists) in medication review done in the framework of basic pharmaceutical care on the widespread implementation of the service. A detailed description of the methodology can be found in *References 96, 97,* and *98*.

3.3.1. Results of the drug knowledge questionnaire

On average, patients consumed 9.3 ± 3.3 medications and other products. From them, 7.7 were prescription drugs (SD=2.8), 1.1 OTC (SD=1.2) and 0.5 other product, for example dietary supplements (SD=0.9).

The self-developed drug knowledge questionnaire was completed by 755 patients. At the beginning of the project, the patients' average drug knowledge was 67.9% (SD=21.6%). As a result of monthly pharmacist consultations, this result increased to 78.2% (SD=19.0%), which is a significant improvement of 10.3% ($p<0.001$).

3.3.2. Results of the comprehensive analysis of DRPs and underlying causes

A total of 984 DRPs (1.3 DRPs per patient) were registered during the survey. The vast majority of DRPs were non-quantitative safety problems (DRP5; 62.6%). The second most common was non-quantitative ineffectiveness (DRP3; 11.6%). In 8.2% of cases, untreated health problem (DRP1) was detected, and the effect of unnecessary medicine (DRP2) was detected with the same frequency. Quantitative ineffectiveness (DRP4; 5.0%) and quantitative safety problems (DRP6; 4.4%) were detected with the lowest frequency. Uncategorized, "other" problems did not occur. Looking at the underlying causes of DRPs, interaction was by far the most common cause (54.0%), with a total of

531 interaction risks (0.7 per patient) found by participating pharmacists. The distribution and order of occurrence of the underlying causes are shown in *Figure 3.*

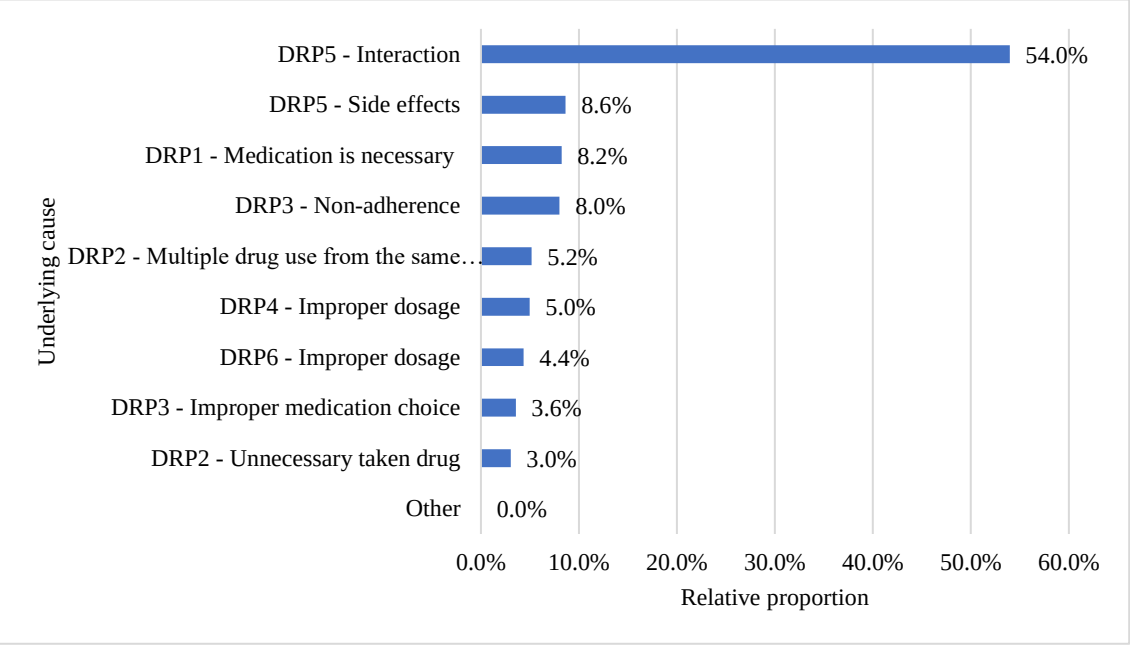

Figure 3: *The proportion of each underlying cause of DRPs relative to total DRPs (n=984 DRPs) (97).*

3.3.3. Results of detailed analyzes of interaction risks

3.3.3.1. Active substances participating in interaction risks

A total of 135 active substances were identified in 531 interaction risks. The five most common of these were amlodipine (13.7% of interactions), perindopril (13.6%), acetylsalicylic acid (11.7%), metformin (9.8%) and bisoprolol (9.2%).

By grouping the drugs according to the third level of Anatomical Therapeutic Chemical (ATC) classification system, it can be stated that the most common groups were antithrombotic agents, beta-blocking agents, and ACE inhibitors *(Table 9).*

Table 9: *Incidence of active substances in interactions relative to the number of interaction risks (n=531) grouped according to Anatomical Therapeutic Chemical (ATC) classification system level 3 (incidence>10%) (96).*

ATC	Group name	%
B01a	Antithrombotic agents	25.0
C07a	Beta blocking agents	22.2
C09a	ACE inhibitors, plain	20.5
A10b	Blood glucose lowering drugs (excluding insulins)	17.9
C08c	Selective calcium channel blockers with mainly vascular effects	14.4
M01a	Anti-inflammatory and antirheumatic products, non-steroids	13.1
C03b	Low-ceiling diuretics (excluding thiazides)	10.7

3.3.3.2. Analysis of interaction risks based on the prescribing and dispensing category of the drugs

The distribution of interaction risks is grouped by prescribing and dispensing category of the interacting medicines shown in *Figure 4*. The highest proportion of interactions were between two prescription drugs (Rx-Rx) that could be solved in most cases in collaboration with GP (66.7%). The incidence of interaction risk types (Rx-OTC, OTC-OTC, Rx/OTC-Other) that can be solved primarily by pharmacists was 31.1%. Most of the latter were interactions between prescription and OTC medications (25.8%).

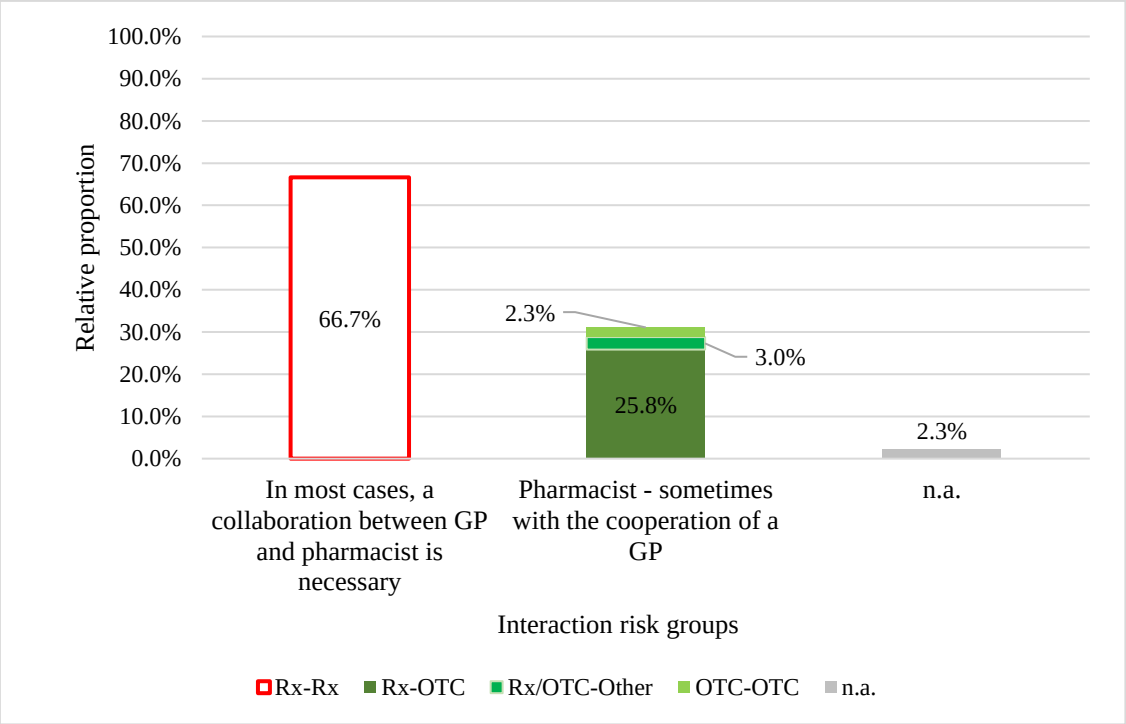

Figure 4: *The proportion of interaction risks relative to all interaction risks, grouped by the competent healthcare professional providing the necessary intervention and a complete solution, and by the prescribing and dispensing category of the drugs involved. Rx: prescription drug; OTC: over-the-counter medicine; Other: other products (e.g. dietary supplements); n.a.: not available; GP: general practitioner; n=531 interaction risks (97).*

3.3.3.3. Analysis of interactions and major active substances involved, grouped by clinical risk

According to the risk classification of the interactions, 42.0% of the cases (would have) made it necessary to monitor the therapy (Grade C in UpToDate Lexicomp® classification system (99)). In 30.7% of cases, although the pharmacist suspected a clinically relevant problem, according to the UpToDate Lexicomp® database, there was no known negative outcome using the two substances together (Grade A). Moreover, in 6.4% of cases, although there was an interaction, no further action was required (Grade B). In contrast, in 13.0% of interactions it was (would have been) recommended modifying therapy (Grade D), and in 1.9% the cessation of interaction was (would have been) possible only by the complete elimination of one active substance (Grade X). A small proportion of interaction risks recorded by participating pharmacists (6.0%) could not be categorized because one of the participants was not in the UpToDate Lexicomp® database *(Figure 5).*

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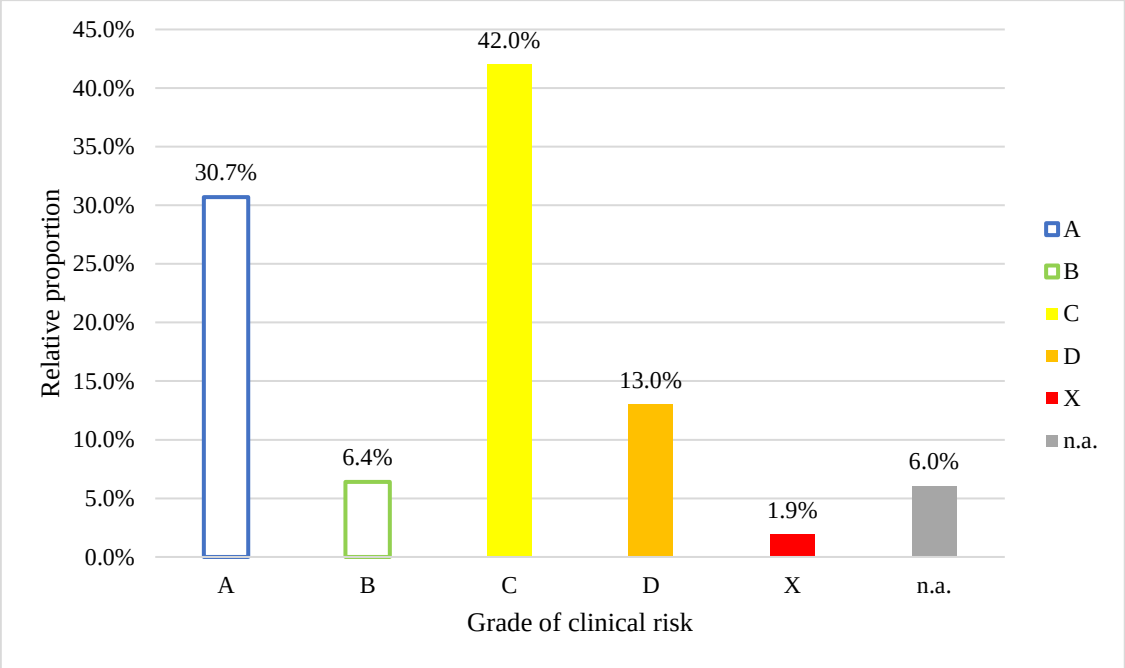

Figure 5: *The proportion of interaction risks grouped by UpToDate Lexicomp® clinical risk classification grades (99), relative to all interaction risks. A: no known interaction, B: no action needed, C: monitor therapy, D: consider therapy modification, X: avoid combination; n.a.: not available; n=531 interactions (97).*

Grade A or Grade B interactions were caused by 77 active substances. The most common active substances (more than 10.0% of the Grade A or Grade B interactions) were amlodipine (32.0%), bisoprolol (17.8%) perindopril (12.7%), and metformin (11.2%). Of these, three agents have highly associated with Grade A or Grade B interaction by participating pharmacists: 71.2% of amlodipine cases; 71.4% of bisoprolol cases; and 42.3% of metformin cases were not clinically relevant. Compared to them, perindopril had a lower rate of Grade A or Grade B interactions (22.2%) *(Figure 6/A).*

By examining the active substances that cause serious (Grade D or Grade X) interactions, we found that acetylsalicylic acid (22.8%), acenocoumarol (17.7%), and diclofenac (13.9%) were the most common (more than 10.0% of Grade D and Grade X interactions) of the approximately 56 active substances causing such interactions. Of these active substances, a high percentage of acenocoumarol interactions belonged to Grade D or Grade X (60.9%), but the ratio of serious interaction of diclofenac (36.7%) and acetylsalicylic acid (29.0%) was also high *(Figure 6/B).* The Grade D or Grade X interaction pairs of these three agents found in the study are shown in *Table 10*.

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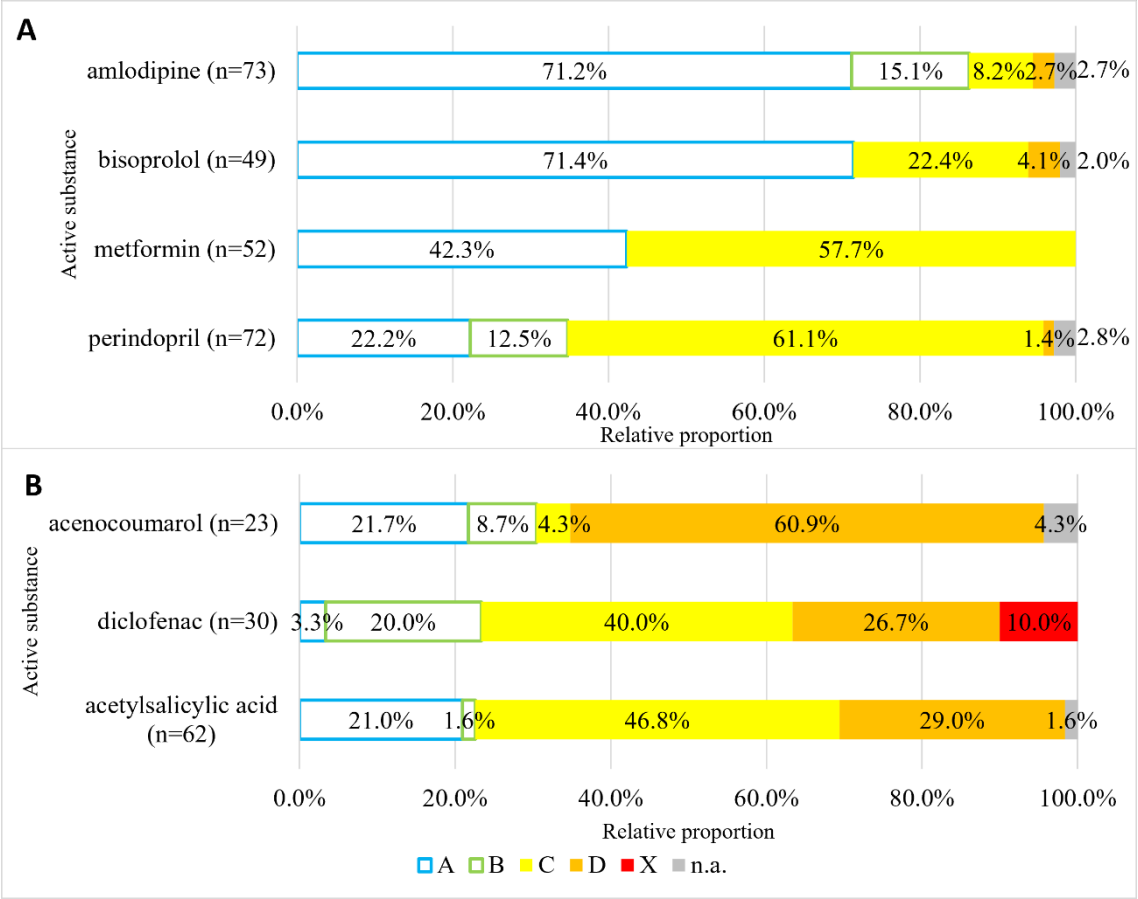

Figure 6: *Distribution of interactions by clinical risk caused by active substances causing the most Grade A/B or Grade D/X interactions.* ***6/A:*** *Distribution of interactions by clinical risk caused by active substances causing the most Grade A/B interactions.* ***6/B:*** *Distribution of interactions by clinical risk caused by active substances causing the most Grade D/X interactions. A: no known interaction; B: no action needed; C: monitor therapy; D: consider therapy modification; X: avoid combination; n.a.: not available (97).*

Table 10: *Grade D or X interaction pairs of the three most common D or X interacting agents (acenocoumarol, acetylsalicylic acid, and diclofenac) (97).*

Active substances causing Grade D or X interaction with acenocoumarol	**Active substances causing Grade D or X interaction with acetylsalicylic acid**	**Active substances causing Grade D or X interaction with diclofenac**
5-aminosalicylic acid	aceclofenac	acetylsalicylic acid
acetylsalicylic acid	acemetacin	metamizole
allopurinol	acenocoumarol	furosemide
garlic	apixaban	aceclofenac
Ginkgo biloba	diclofenac	heparin
ginseng	enoxaparin	nimesulide
ibuprofen	garlic	warfarin
metamizole	Ginkgo biloba	
piroxicam	metamizole	
	nimesulide	

3.3.3.4. Results of comparative statistical analysis of interaction risks

In comparative studies by gender, the incidence of Grade C, D, or X interaction risks was examined separately and then aggregated (C+D+X). No significant difference was found between men and women in either case ($p>0.05$). Examining the age groups (≥65 years or <65 years) found that there was a more frequent Grade C interaction risk in the age group 65 years or older, with a significant difference ($p=0.05$), while no significant difference was found for Grade D or X interaction risks. Looking at the combined incidence of Grade C, D, and X interaction risks, it can be assumed in professional practice that the older age group (≥65 years; n=512 patients) is more likely to have clinically relevant interaction risks than the younger age group (<65 years; n=243 patients) ($p=0.076$, close to the significance limit).

3.3.4. Results of analysis of pharmacist interventions to solve DRPs, including interaction risks

A total of 1045 pharmacist interventions were applied by 78 pharmacists to solve the 984 DRPs identified by pharmacists. Pharmacists notified the GP about the problem in 32.5% of cases, compared with nearly two-thirds (64.7%) solved the problem without the GP's involvement. Based on pharmacist reports GPs were notified mainly by telephone or in-person, pharmacists did not prefer written contact.

In most of the latter solutions, “education” (28.0%) and “dosage change” were used (8.0%). In the education of the patients, pharmacists used the information materials developed for the project.

The rates of pharmacist interventions to address the risks of interactions do not differ significantly from those of other DRPs: dosage changes were used more often (interaction risks: 11.6%; all DRPs: 8.0%), while drug recommendation was used - not surprisingly - less often (interaction risks: 2.5%; all DRPs: 5.5%) by pharmacists. In the case of interactions, a higher proportion of cases did not require pharmacist intervention (interaction risks: 10.5%; all DRPs: 6.2%) *(Figure 7).*

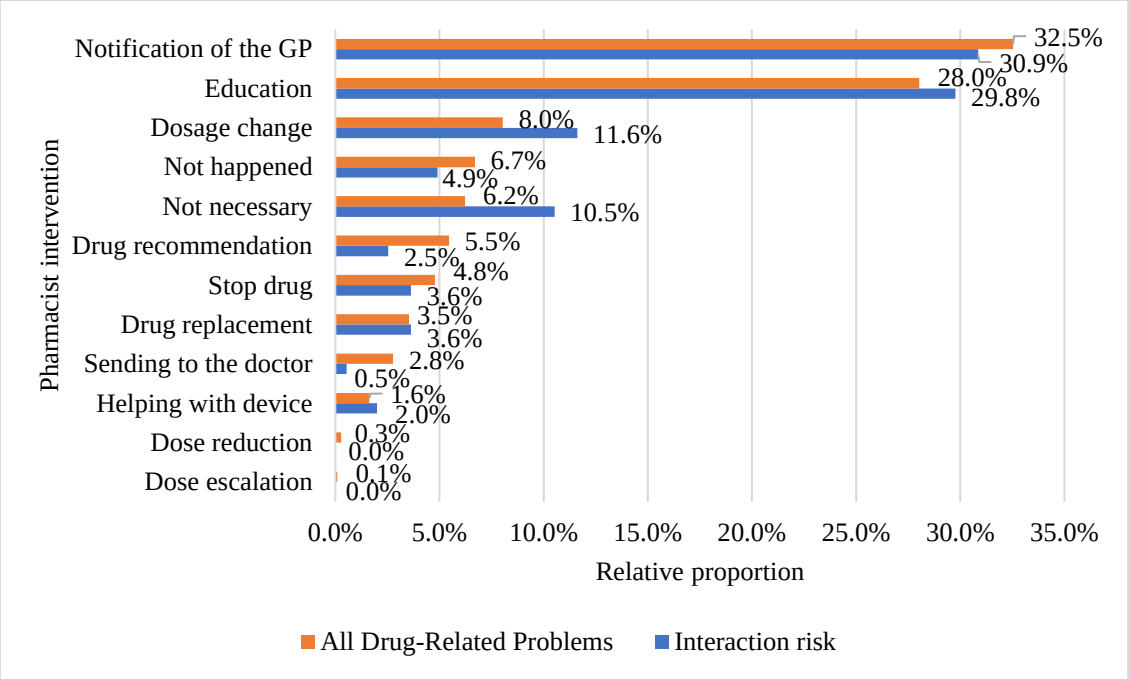

Figure 7: *The relative proportion of pharmacist interventions to solve all DRPs (n=1045 all interventions), especially interaction risks (n=551 interaction risks interventions); GP: general practitioner.*

3.3.5. Satisfaction and opinion of participating pharmacists, patients, and GPs on medication review in the framework of basic pharmaceutical care

3.3.5.1. Results of the patient questionnaire

The patient questionnaire was completed by 670 of the 755 participating patients (88.7%). The answers to each question were shown in *Table 11*, *Figure 8*, and *Figure 9*. Detailed information on the incorporation of medication into everyday life (38.5% of the

respondents), side effects (37.7%), interactions (35.0%), and medicines taken (34.7%) was a novelty for many patients in the uniform procedure used in the research, the frequency of these responses was significantly higher than the incidence of the other responses *(Figure 8;* p<0.001). Significantly more patients would like to receive a medication recommendation for mild symptoms (57.1%), to be consulted about the disease or medication (55.1%), to check their regular medications (53.3%) as well as their blood pressure in community pharmacies (51.4%) (p<0.001) *(Figure 9).*

Table 11: *Results of the patient questionnaire (*: significantly different frequencies) (98).*

Question	Response options and results				Number of patients responding
1. How satisfied were you with the medication review and medication monitoring provided by your pharmacist?	*Four-point Likert scale (1 point: I was not satisfied, 4: I was very satisfied)*				*n=670*
	Mean: 3.37 ± 0.65 points				
2. Would you recommend a medication review provided by your pharmacist to someone else?	*Yes*		*No*		*n=666*
	97.1%		2.9%		
3. To what extent have you accepted your pharmacist's advice about your medication?	*Four-point Likert scale (1 point: never accepted, 4 points: always accepted)*				*n=666*
	Mean: 3.41 ± 0.61 points				
4. In the activity of your pharmacist, what was <u>new</u> to you in the recent period from any of the following (e.g. compared to your previous pharmacy visits)?	***see Figure 8***				
5. Would you like to receive new services provided by your pharmacist in pharmacies in the future (e.g. in connection with your health or medication)?	*Yes*		*No*		*n=663*
	94.7%		5.3%		
6. How much time can / do you want to consult a pharmacist at the pharmacy?	*I don't have more than the time I've spent so far*	*5-10* minutes*	*15-20 minutes*	*I need more than 20 minutes*	*n=667*
	23.2%	43.0%* (p<0.001)	27.3%	6.5%	
7. What types of services would you like to use at the pharmacy?	***see Figure 9***				
8. What type of solution would you prefer when using the services?	*When I come in, be available to me immediately*		*I will be happy to come in at a mutually agreed time (by phone or in person) to make sure they can spend enough time with me in calm conditions*		*n=662*
	39.9%		60.1%		
9. How important is it for you to be able to talk to the pharmacist in a private setting (a separate room in the pharmacy)?	*Four-point Likert scale (1 point: not important at all, 4 points: very important)*				*n=665*
	Mean: 2.60 ± 0.89 points				

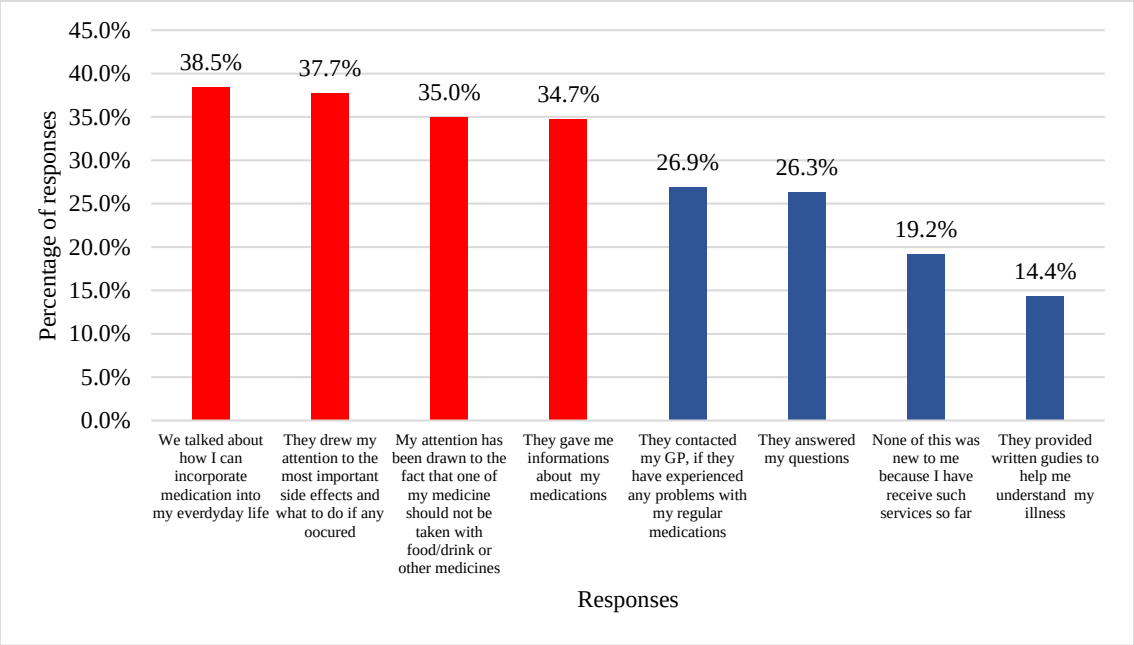

Figure 8: *Percentage of different responses to Question 4 of the patient questionnaire ("In the activity of your pharmacist, what was new to you in the recent period from any of the following (e.g. compared to your previous pharmacy visits)?") relative to the number of patients completing the questionnaire. The red bars indicate the answers that were chosen significantly more often than the other options (GP: general practitioner; p=0.001; n=668 patients; multiple-choice question) (98).*

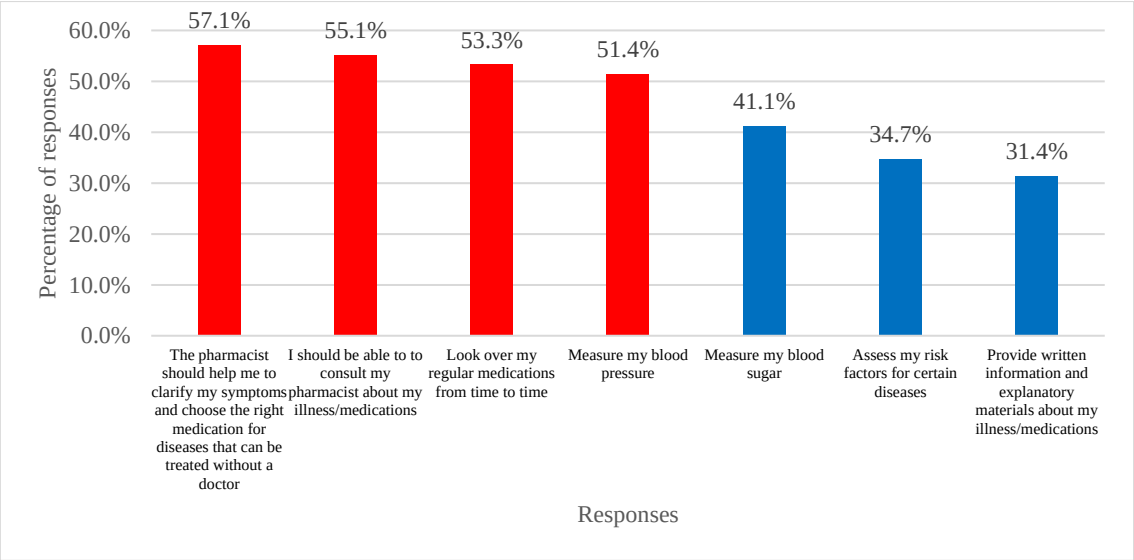

Figure 9: *Percentage of different responses to Question 7 of the patient questionnaire ("What types of services would you like to use at the pharmacy?") relative to the number of patients completing the questionnaire. The red bars indicate the answers that were chosen significantly more often than the other options (p=0.001; n=666 patients; multiple-choice question) (98).*

3.3.5.2. Results of the GP questionnaire

The GP questionnaire was completed by 88 of the 98 participating GPs (90%). The mean (and SD) of the answers to each question are shown in *Table 12.*

Table 12: *The results of the general practitioner questionnaire (n=88 general practitioners).* GP: general practitioner, SD: standard deviation *(98).*

Question	Likert scale scoring	Mean (points)	SD (points)
1. How would you characterize the GP-pharmacist working relationship formed during the project (medication review)?	*1 point: did not happen* *...* *4 points: it was good*	3.90	0.30
2. How often was there an oral consultation between the GP and the pharmacist regarding the medication review?	*1 point: did not happen* *...* *4 points: it happened often*	3.02	0.56
3. How often was there a written consultation between the doctor and the pharmacist regarding the medication review?	*1 point: did not happen* *...* *4 points: it happened often*	1.59	0.78
4. How useful do you find the medication review and follow-up carried out during the project?	*1 point: it was not useful* *...* *4 points: It was very helpful*	3.10	0.69
5. To what extent do you consider the medication review of pharmacists, in general, to be useful from a medical point of view?	*1 point: it causes more problems* *...* *4 points: clearly useful*	3.86	0.34
6. In general, how useful do you find the advice of pharmacists on medication?	*1 point: not supported* *...* *4 points: really useful*	3.17	0.73
7. In your opinion, which statement is generally true for pharmacists regarding medication review?	*1 point: pharmacists are not suitable for reviewing medication* *...* *4 points: pharmacists are in a good position and able to review the patient's drug-related problems*	3.30	0.91

3.3.5.3. Results of the pharmacist questionnaire and opinion survey

The pharmacist questionnaire was completed by 73 of the 78 pharmacists involved in the project (94%). The results are listed in the order of the average scores for each question in *Table 13.*

Table 13: *Results of the pharmacist questionnaire, in descending order of mean scores (SD: standard deviation; n=73 pharmacists) (98).*

Statement	Likert scale (agreement level)	Mean (points)	SD (points)
Medication review helps pharmacists assess their patients' knowledge of medication.	*1: I do not agree at all; … 5: I totally agree*	4.3	1.4
Medication review is an excellent opportunity to demonstrate the professional knowledge of pharmacists to the general public.		4.2	1.4
Medication review improves inappropriate medication use.		4.2	1.4
Medication review improves patient adherence.		3.8	1.4
I could do more medication reviews if it were a funded activity.		3.4	1.5
Medication review improves the cost-effectiveness of prescription drugs.		3.4	1.3
The professional and material conditions in the pharmacy are adequate for me to perform the medication review at the appropriate standard.		3.4	1.3
I simply don't have time to do a medication review.		2.8	1.1
In my opinion, patients do not require this service from a pharmacist.		2.5	1.1
Medication review by pharmacists is just a waste of time.		1.7	0.9

Opinions on the implementation of medication review were expressed in writing by 57 pharmacists (73%). These opinions could be divided into two major groups: problems and proposals.

A problem was identified by 42% of pharmacists. The biggest obstacles were the lack of time and the lack of specialists (19%; 19%, respectively).

Proposals to help implementation were made by 91% of respondents (52 people), which can be divided into five major groups: software development, work organization, training development, information, and service development proposals. The largest proportion of pharmacists made software development proposals (51%), including the various suggestions for the development of the EESZT (Elektronikus Egészségügyi Szolgáltatási

Tér; Electronic Health Service Space (37%)). The most common (>5%) groups of proposals are illustrated in *Table 14.*

Table 14: *Distribution rates of the most common pharmacist proposals on the implementation of medication review. One pharmacist could make several suggestions (n=57 pharmacists) (98).*

Proposal group	**%**	**Proposals**	**%**
Software development proposals	**51**	Development of EESZT services: • Background for pharmaceutical care, cloud-based storage, and documentation • Online connection to the GP • The pharmacist can see the patient's data, laboratory results, medical history, medicines purchased elsewhere	37
		Integrated, practical, and unified interaction in the pharmacy software	18
Work organization proposals	**35**	Pharmacist care at a pre-arranged date or separate care time	19
		Employment of a pharmacist providing pharmaceutical care only	7
Training development proposals	**25**	In-depth drug delivery training for pharmacist assistants: interactions, glucose, and blood pressure measurement	12
		Development of postgraduate training for pharmacists	9
Information proposals	**18**	Informing patients about the service: advertising, patient clubs, lecture with a doctor, written materials	16
Service development proposals	**9**	Blood sampling, blood pressure, blood sugar, body fat measurement, and allergy test in the pharmacy	7

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4. DISCUSSION

The concept of medication review has long been present in Hungarian professional public discourse and regulation, however, very little real-life data on the service has been available so far, which makes it difficult to develop the service and put it into practice.

Medication review is based on proper communication, so we focused on postgraduate education of communication, and patient health literacy. In Hungary, detailed training in the development of pharmacists' communication skills has recently started in undergraduate education, for example in the practice of Semmelweis University, starting in the 2020/2021 academic year. Graduated pharmacists have access to many communication trainings, which are often not patient-centered but product- or marketing-focused. Based on the results of the patients' input questionnaires in our research, there were shortcomings in pharmacists' communication in all matters (64.07%), in particular in encouraging the patients to ask questions. Our results are in line with international trends in the communication skills of community pharmacists and pharmacy technicians (22, 100). Interestingly, this result is not fully reflected in the results of the staff questionnaire, which showed that pharmacists and pharmacy technicians rated their skills higher (74.47%). It seems that the postgraduate, patient-focused communication training aimed at health literacy presented in our research (93) may provide a partial solution to this problem, with the help of which the training of a large number of professionals could be solved with a small number of instructors in a short time. These results are also supported by the results of the patients' post-intervention questionnaires: professionals have improved in encouraging asking questions, avoiding technical terms, and emphasizing important information. Given that the pre-, and post-intervention patient groups differed, this development is clearly due to the methodology introduced. The results also showed that pharmacy workers should pay special attention to patients over 40 years, and those with a low level of education. The development was also supported by the results of the staff questionnaire: although the professionals did not consider their communication skills to be poor, progress was made by the end of the project, especially in encouraging patients to ask questions. The greatest development was experienced by professionals living in the capital or county seat, since during the project they tried to devote an adequate amount of time to patients, despite the higher number of patients in these settlements. Overall, the project has supported the necessity and legitimacy of the

methodology introduced, its integration into everyday life, and its contribution to improving the effectiveness of educational interventions.

The results of this thesis show that the medication of patients entering the community pharmacy may contains many DRPs (1.4 and 1.3/patient), which would probably go undetected for a long time without pharmacists. This prevalence found is as described in the literature, although the number of DRPs varies widely between different patient groups and research methods (101-103). One of the possible reasons for their development is the large number of drugs taken by patients (103, 104). It can be seen that the pilot project also involved mainly polypharmacy patients. In developed countries, the number of drugs taken is increasing as the population ages (105). Between 1995 and 2010, the number of patients taking more than 5 medicines doubled, affecting more than 20% of the population (106). Several factors play a role in the development of polypharmacy such as poor medical record-keeping, poor transitions of care, use of automated refill systems (107). The high number of OTC and other drugs purchased at the pharmacy also contributes to the high number of drugs, the average volume of which did not differ between the populations of the pilot and polypharmacy study. Given that these medicines are obtained by patients in a pharmacy without a doctor's supervision, a pharmacist working in a community pharmacy is best placed to complete the full list of medicines (Rx, OTC, and other products) and to perform medication review both in special patient groups (e.g. patients taking ACE inhibitor with NSAID and/or VKA), and in a more general patient population (e.g. polypharmacy patients).

Given the high number of medications taken, patients' drug knowledge is paramount. The impact of medication review on drug knowledge is unclear, with a quarter of studies showing significant improvement in this area (87). According to our results, regular medication review alone can improve this knowledge.

However, recognizing DRPs alone is not enough. We need to know the incidence of pharmacist interventions to solve them, and the extent to which they resolve the situation on their behalf or together with the patient's GP. It is important to map the competence boundaries of pharmacists and GPs. From the results presented in the thesis, it can be seen that the pharmacists solved most of the problems in their own right, and only in 25-35% of the cases sought the help of a GP. In the pilot project, most of these requests were made by sending the patient to a GP (without notice). This proportion was reversed among

polypharmacy patients, thanks to the emphasis on the topic in the preparation of participants: most problems were resolved by notifying the physician (primarily in person), which is a positive change for pharmacist-GP collaboration.

Of the pharmacist interventions, the most common in both projects was patient education (pilot study: 25.5%, polypharmacy study: 28.0%), which is an obvious pharmacist competence, but the quality of its implementation can vary widely. There are several ways to improve the quality of education, for example by developing appropriate information materials (37, 59), improving the communication skills of pharmacy staff in general (one approach is presented in this thesis), or focusing on a topic/patient group.

The big difference between the distribution of pharmacist interventions described in the two projects was that in the pilot project, pharmacists did drug replacement more frequently, due to the participation of patients taking an ACE inhibitor with NSAID, where one of the most obvious ways to reduce the risk of interaction was to change the NSAID to paracetamol.

To determine the further development directions of the pharmacists' medication review, we analyzed in detail the composition of the DRPs found. For this, we used the classification of the DRPs used in a previous Hungarian protocol, which has a great advantage over the PCNE classification (which is widely used internationally and presented in this thesis in chapter 1.3.2.1) as it has a simpler structure, and therefore, it is easier to use in everyday life. Although the patient populations of the two studies targeting medication review were different, we found similarities in the composition of DRPs identified. The most common category was by far the non-quantitative safety problem (DRP5), which was due mainly to interaction risks, so we retrospectively performed further analyses on the interaction data of the polypharmacy study.

The prevalence of interaction risks in the pilot (0.81/patient), and polypharmacy study (0.70/patient) is consistent with the literature (108-111). Based on our analysis, we can conclude that interactions are more common in elderly patients (≥65 years). The difference is presumably due to more drugs taken by the elderly: those over 65 used an average of 9.78 drugs, while those younger patients used 8.41. Multiple drugs are associated with a higher number of Grade C interactions, requiring continuous monitoring of therapy, resulting in a significantly higher risk of interactions. The monitoring of these

therapies is within the competence of the pharmacist, during which, if the problem manifests itself, it is important to involve the GP according to a uniform procedure.

The importance of the latter is underlined by the fact that two-thirds of the risks of interaction occur between two prescription drugs. There are presumably two reasons for this: one is that the interaction is known to the GP, however, the benefits of therapy outweigh the risks, as evidenced by the number of Grade C (42.0%) and B (6.4%) interactions. However, due to the presence of Grade D and X interactions revealed in 79 cases (14.9%), the other reason might be the overload of GP care and the lack of medication review role of community pharmacists. For Grade C, D, and X interaction risks, the existence of an appropriate communication channel between the pharmacist and the GP is of paramount importance, which is currently unresolved. The solution to this task could be the development of the EESZT in this direction, as the implementation of the cooperation between the GP and the pharmacist is not an easy task in person and by telephone.

In one-third of our cases, OTC or other products (such as dietary supplements) caused an interaction, which reaffirms the role of pharmacists in detecting these problems. The solution to these DRPs is primarily the competence of pharmacists working in community pharmacies, since a significant part of these is not visible to the GPs, and they do not receive information about them unless the pharmacist indicates the problem.

Given the overburdening of the two professions (GPs, and pharmacists), pharmacists need to refer to GPs the relevant risks only. Our results show that 37.1% of the identified interaction risks were clinically irrelevant (Grade A and B). The time spent solving these interaction problems is an unnecessary burden for both pharmacists and doctors, which has a devastating effect on collaboration between the two professions in the long run. The high number of Grade A interaction risks also indicates that pharmacists should receive extensive and appropriate training to be able to determine the clinically relevant interactions. To do this, it would be important to have access to the patient's medical history and laboratory results, and to develop and integrate a unified interaction classification system into pharmacy software, as these, although still in some form, do not help pharmacists enough to filter out relevant interactions. Our results show that some groups of drugs, although present in many interactions, do not pose a real risk in most cases (beta-blocking agents, blood glucose-lowering drugs (excluding insulins), selective

calcium channel blockers with mainly vascular effects). However certain groups present a high risk (antithrombotic agents, anti-inflammatory and antirheumatic products, non-steroids), especially when OTC medications are available (e.g. diclofenac and acetylsalicylic acid). Until we have the right software support, handy spreadsheets like *Table 10* can help pharmacists filter out and learn the most relevant interactions.

In summary, it is important to develop tools for decision support that can be integrated into the pharmacy software, thus, the development of algorithms to support a uniform protocol for handling cases of varying severity (e.g. uniform interaction risk classification with the possibility of online notifying to the GPs). A possible IT algorithm for the pharmacist protocol is shown in *Figure 10,* based on a clinical classification of interaction risks according to the UpToDate Lexicomp® database (99).

In contrast to the high rate of Rx-Rx interaction risks experienced, taking into account the high proportion of prescription drugs in other interaction risks as well (Rx-OTC, RX/OTC-Other), the frequency of pharmacist interventions involving GP was low, even though the most complete and safest solution in these cases, due to the presence of a prescription drug, would be to inform the GP, in addition to other and necessary pharmacist intervention. Based on our research, it has been found that in addition to (or even instead of) "notification of the GP", a pharmacist can only use "education" (29.8%), or "dosage change" (11.6%) as an independent and professional competence. The need for a uniform pharmacist protocol is also supported by the quantitative characterization of the pharmacist interventions recorded in our research to solve the interaction risks, which are far from consistent and not very straightforward.

Recognition, classification, and resolution of DRPs are part of Semmelweis University's specialist pharmacist training (as in the case of the research presented). Based on the results of the polypharmacy study, pharmacy students need to be purposefully prepared to solve DPRs already at the undergraduate level, whose first steps have already been taken in the practice of Semmelweis University.

In many cases, the rights of the two disciplines (GPs and pharmacists) are not clearly defined in Hungary in solving the interaction risks (and other DRPs), so they need to be determined and widely introduced into the pharmacist practice, e.g. what interaction risks should be indicated to the GP in each case *(Figure 10).*

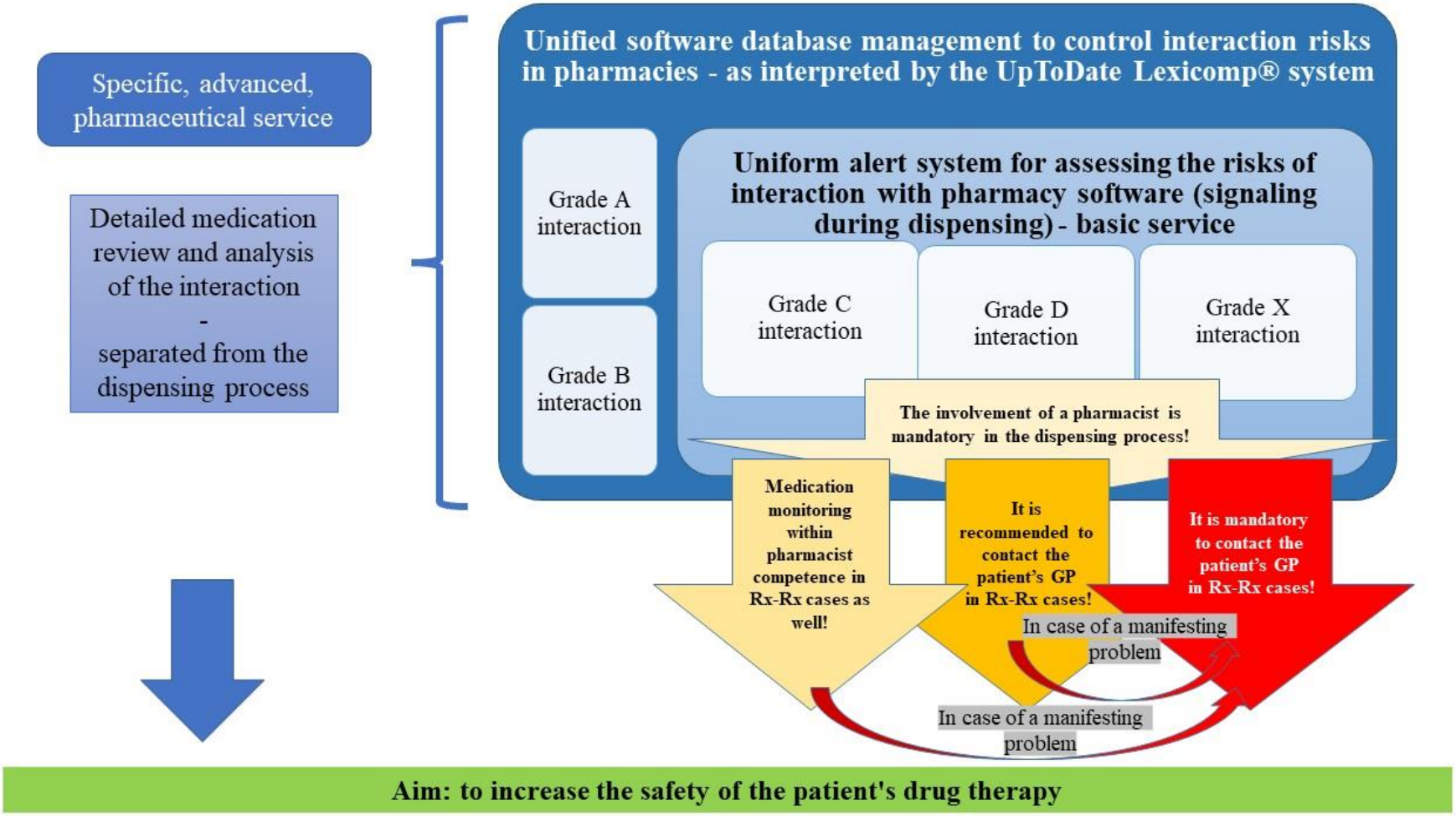

Figure 10: *Proposal for a uniform community pharmacy procedure for the management of interaction risks (97).*

Finally, all these efforts are worthless if the key players (doctors, pharmacists, patients) do not require a medication review from pharmacists. Based on our results, it can be stated in general that all three key actors influencing the success of pharmacotherapy had a positive opinion on the medication review performed with the presented procedure, but several shortcomings and the direction of the necessary improvements were also revealed. The responses provided by patients in *Figure 8* draw attention to several shortcomings in everyday drug-dispensing practices. About one-third of patients encountered novelty in the process of drug dispensing: the description of side effects and interactions by a pharmacist, as well as detailed information about medications. This rate, despite the publication of the "Professional directive on medication review in the framework of basic pharmaceutical care" nine years ago, highlights the failure to put this knowledge into practice, which pharmacist training needs to address. Improving the university training of pharmacists is particularly important in light of the answers shown in *Figure 9*: regular blood pressure measurement, regular consultation on diseases and medicines, self-medication without consulting a doctor in the case of mild illnesses, and the need to monitor medication taken every day draw attention to shortcomings in primary care, which can be addressed by cognitive services (e.g. medication review) provided by pharmacists working in community pharmacies. The above is also supported by the results of the GPs' questionnaires, as most of them found medication review to be useful, both for their work and for patients. These results, as well as the opinions of pharmacists about the benefits and barriers, are in line with the results of other articles (112). Pharmacists considered medication review to be a good opportunity to represent pharmacist expertise to the public. They thought that patients benefit from both the improvement of drug knowledge, the elimination of inappropriate drug use, and the development of adherence. In the experience of pharmacists, patients also require this service, the widespread use of which would be based on the provision of adequate funding, material, and professional conditions. The main obstacles were the lack of pharmacists and the lack of time. Patients would ideally take 5-10 minutes for a consultation at a pre-arranged time, a solution that pharmacists also prefer. An interesting result is that having a separate counseling room does not seem vital for patients. In addition to the ideas for overcoming the lack of time and professionals, the main proposals were to develop software support, including solutions for filtering and classifying

interactions and expanding the functions of EESZT, which are in line with the development needs already mentioned: developing cloud-based support and documentation for pharmaceutical care, online connection to the doctor for quick communication, and pharmacist access to the e-Profile (e.g. medical history), which logically includes real-time (online) pharmacist insight into the patients' entire drug list. The changes are ongoing: from 1 January 2020, the pharmacist will personally be entitled to view the patient's full medication data distributed in any pharmacy with the patient's Health Insurance Number (TAJ) for one year in the EESZT (with the patient's written consent), except for medications for sexually transmitted diseases and psychiatric disorders. Under previous regulations, this was only possible for pharmacists using the NEAK (Nemzeti Egészségbiztosítási Alapkezelő; National Institute of Health Insurance Fund Management) database for officially subsidized medicines. Negotiations are still underway to exploit the further potential of the system, and it is planned that "BEGONIA 2.0", which supports pharmaceutical care, may be included in the framework of EESZT.
The results of the presented thesis contain several novelties. A novelty is the methodology that underpins communication that supports health literacy, the results of which are confirmed by two types of questionnaires. In addition, a new result is the substantiation of the domestic relevance of medication review in community pharmacies with the large number of detected DRPs, as well as the knowledge of their qualitative composition, especially regarding interaction risks. Pharmacist interventions to solve DRPs were also described for the first time in Hungary, as well as the opinions of key players (GPs, pharmacists, patients) on the relevance of the service, barriers, and development opportunities. All these results provide a good basis for integrating the methodology of the researches into undergraduate and graduate education. All this process has already begun in the practice of Semmelweis University, which provides an opportunity to examine the longer-term impact of the developments.
However, the results of the thesis are limited by bias factors. Limitations of the communication project were the lack of control groups, selection bias, as no randomization was used in the professional, pharmacy, and patient enrolment method, and the fact, that the questionnaires used were self-developed, based on experience from previous projects, and were not validated. In addition, the long-term effects of the methodology have remained unexplored.

The bias factors for pilot and extended research on medication review were convenience sample technique in the pharmacist, pharmacy, GP, and patient enrolment. Further research is needed to explore the effectiveness of pharmacist interventions to solve DRPs. The questionnaires used (drug knowledge, patient, GP, and pharmacist questionnaires) were self-developed, unvalidated ones. The results of the GP and patient questionnaires may have been influenced by the fact that those who took part in the survey were presumably more positive about the service in advance. We did not examine the age of pharmacists but based on their average year of graduation younger age group than the national average was able to express their views on the project, which may have influenced the suggestions made (e.g. the high proportion of software proposals).

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5. CONCLUSIONS

It can be concluded that there are several benefits to medication review in the framework of basic pharmaceutical care, given the current community pharmacy context and regulatory environment. With its help, many DRPs can be found and eliminated, partly under the authority of a pharmacist and partly with the involvement of a GP. Most DRPs were caused by an interaction risk, while the most commonly used pharmacist intervention was patient education. Both patients, GPs, and pharmacists have had a positive view of the service, they need it, but several gaps and potential areas for development have been identified.

The most important areas to be developed are the improvement of communication in pharmacies to support patient education and health literacy, which can be addressed by the postgraduate methodology, presented in the thesis. In addition, special emphasis should be placed on the practical application and development of uniform procedures for each DRP, in particular for the resolution of clinically relevant interaction risks, as well as their effective teaching in undergraduate education.

To develop an effective medication review, it is also essential to improve the software background, e.g. EESZT, so that pharmacists can access patients' health data, communicate effectively with the GP and document their activities, thus ensuring the necessity, effectiveness, and safety of patients' pharmacotherapy at the highest professional level.

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6. SUMMARY

Medication review is “a structured evaluation of a patient‘s medicines with the aim of optimising medicines use and improving health outcomes. This entails detecting drug-related problems and recommending interventions.”

The thesis aimed to promote the wide-ranging practical feasibility of medication review in the framework of basic pharmaceutical care in Hungarian community pharmacies, by creating a unified communication base and evaluating the relevance, possibilities, results, and development directions of the service.

The health literacy-centered communication skills of graduated pharmacists participating are deficient: the results of the patients’ input questionnaire in our research were 64.07%, in which there were shortcomings in encouraging the patients to ask questions. Due to the postgraduate methodology presented, the mean score of the patient questionnaire was 72.72%, which is a significant improvement ($p<0.001$).

In our researches, the medication of patients entering the community pharmacy contained many DRPs (1.4 and 1.3/patient). The most common DRP category was non-quantitative safety problem, which was due to many interaction risks (57.0% and 54.0%). The highest proportion of interactions was between two prescription drugs (66.7%), 42.0% of the cases made it necessary to monitor the therapy, in 30.7% of cases the risk was irrelevant, while in 14.9% of interactions it was recommended modify or stop the therapy. The most common pharmacist intervention was patient education (25.5% and 28.0%).

All three key actors influencing the success of pharmacotherapy had a positive opinion on the medication review performed. Detailed information on the incorporation of medication into everyday life (38.5%), side effects (37.7%), interactions (35.0%), and medicines taken (34.7%) was a novelty for many patients. The main obstacles were the lack of pharmacists and the lack of time. The main proposals were to develop software support, including solutions for filtering and classifying interactions and expanding the functions of EESZT.

Overall, there are several benefits to medication review in the framework of basic pharmaceutical care. The most important areas to be developed are the improvement of communication in pharmacies, development of uniform procedures for each DRP, improvement of the software background (e.g. EESZT), thus ensuring the necessity, effectiveness, and safety of patients' pharmacotherapy at the highest professional level.

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