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Original research paper

Prescribers' approval rate of pharmacist-initiated interventions to optimise patients' clinical status of hypertension in the ambulatory care setting

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ABSTRACT

This perspective, pre- and post-intervention study with a one-year follow-up primarily aimed to ascertain prescribers' approval rate of pharmacists' interventions and clinical status of hypertension following comprehensive medication management (CMM) intervention in the ambulatory care clinic. Between January 2018 and January 2022 overall 100 patients with hypertension and other comorbidities were referred to the CMM services at the Health Centre Zagreb – Centar (HCZC). Out of 275 interventions directed to prescribers, 73.1 % of interventions were approved, 12.4 % were rejected and 14.5 % were not reviewed. The percentage of patients with a blood pressure goal increased from 45 % at the initial consultation to 82.5 % at the patients' latest encounter ($p < 0.001$). The average number of drug therapy problems (DTPs) per patient totaled 3.53 ± 1.80, where 98 % of patients had one or more DTPs, 48 % had 4 or more DTPs, whereas 26 % had 5 or more DTPs. Subtherapeutic dosage (32.6 %) and the need for additional drug therapy (30.9 %) were the two most commonly identified DTPs. These results reinforce the need to integrate pharmacy-led services in the primary care setting with the aim of improving patients' health outcomes.

Keywords: hypertension, comprehensive medication management services, pharmaceutical care, prescriber's approval rate, primary care, clinical outcomes

INTRODUCTION

According to the World Health Organization, around 16 % of the world population is diagnosed with hypertension with only 20 % being effectively managed. It presents a major cardiovascular (CV) risk factor amplifying the likelihood of various CV diseases, stroke, and kidney failure occurrence, thus leading to death (1). In 2021, hypertensive diseases presented the fifth most lethal cause of all deaths in Croatia, more affecting women

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and patients over the age of 60 (2). Management of diverse comorbidities in hypertensive patients very often necessitates intricate medication regimens, causing patients to face an escalated risk of drug-therapy problems (DTPs) that can lead to disease control failure, a higher rate of adverse drug events, and hospital admissions (3–7). Thus, to enhance medication mismanagement of CV disorders there was an imperative demand to introduce a new pharmacist-led service at the primary care level. In accordance with the global growth of healthcare demands and an increase in complex therapies, the 2021–2027 National Health Development Plan supported the implementation of the patient-centred pharmaceutical care practice (Comprehensive Medication Management services, CMM) into a multidisciplinary primary healthcare setting in Croatia (8).

Namely, the CMM services present a viable, evidence-based patient care practice delivered by pharmacist practitioners in partnership with patients, general practitioners, and other medical professionals (9–12). Being responsible for patients' medication optimisation and minimisation of drug-related morbidity, the pharmacist's key input and central commitment is the identification, prevention, and resolution of DTPs. This patient care framework introduced by Cipolle *et al.* includes the identification of medication-related problems, construction of the care plan, and continuous follow-up which allows the determination of actual health outcomes (13). Until now, the CMM practice inclusion into healthcare systems has shown a beneficial effect in each of the quadruple aim components by improving patients' clinical outcomes and health-related quality of life, contributing to cost-savings, and enhancing patients' care experience and health professionals' work lives (14).

Regardless of the existing evidence demonstrating how pharmaceutical care practitioners add significant value to the healthcare team (15–17), there is still insufficient evidence of prescribers' acceptance of proposed interventions in the ambulatory care setting (18, 19). Hence, the primary aim of this study was to ascertain prescribers' intervention acceptance rate among hypertensive patients at the primary care level in Croatia. Moreover, various studies have confirmed a high incidence of identified DTPs in patients with chronic diseases, whereby low drug doses and the need for new therapy were the most common DTPs (20–24). Additionally, large study databases published to date have demonstrated improvement in patients' medical conditions, including hypertension, confirming thus the value of pharmacist clinical judgement on patients' pharmacotherapy outcomes (13, 22, 25–30). Therefore, the second aim of our study was to evaluate patients' clinical status of hypertension following CMM intervention and determine the frequency and type of the DTPs with their in-depth description according to Cipolle *et al.* classification.

EXPERIMENTAL

Study design and setting

This prospective, pre- and post-intervention study with a one-year follow-up was conducted at the primary care clinic, Health Centre Zagreb – Centar (HCZC) between January 2018 and January 2022. The study is part of a larger research designed as a prospective, open-controlled pre- and post-intervention study with a 1-year patient follow-up and it represents a secondary subset analysis of trial data evaluating CMM's impact on cardiovascular risk factors as a primary outcome measure (24). The full implementation

process and clinical and humanistic outcomes of this new practice management system of CMM services were described previously (23, 24).

Developed in partnership with the University of Zagreb Faculty of Pharmacy and Biochemistry (UoZ) in January 2018, the HCZC's CMM services are provided by four pharmacists, two of whom are fully employed by HCZC. HCZC, the largest county healthcare centre in Croatia, is the only healthcare centre providing CMM services in Croatia and the first clinical institution employing a pharmaceutical care practitioner providing direct patient care outside the community pharmacy premises. Even more, it is the only primary healthcare institution employing pharmacists who are providing CMM services in the European Union.

Study participants and data collection

Altogether, 100 patients referred to HCZC's CMM services with hypertension, at least one regular prescription medication, and 18 years or more of age were eligible for inclusion in our study. Exclusion criteria rendered patients with cognitive impairment, mental and behaviour disorders caused by psychoactive substances, behavioural syndromes associated with physiological disturbance and physical factors, and patients with impaired decision-making capacity.

To determine all DTPs, sociodemographic characteristics, anthropometric data, current and previous medical conditions, medication history (prescription and over-the--counter medications, herbal remedies), as well as history of relevant medication use, drug allergies, and adverse drug reactions were collected for each patient by four pharmaceutical care practitioners providing the service. Medicines were classified according to the Anatomical Therapeutic Chemical (ATC) Classification System and diseases according to the International Classification of Diseases (ICD-10 version:2019). At the initial assessment data were retrieved by a careful review of the patient's medical records and through the interview with the patient, the patient's family members, or a caregiver if needed. Detailed patient care process is described elsewhere (23, 24).

The study was approved by the Health Centre's Ethics Committee and the Ethics Committee of the University of Zagreb Faculty of Pharmacy and Biochemistry. Furthermore, the research was registered at clinicaltrials.gov (NCT04778891).

Drug therapy problem identification as a part of the patient care process

All pharmacists providing care were employing a structured, rational thought process, the Pharmacotherapy Workup, developed and adopted as a systematic problem-solving process, specific to the practice of pharmaceutical care. The process allows the practitioner to systematically and comprehensively determine if all of a patient's medications were appropriately indicated, the most effective and the safest possible, and if a patient was able and willing to take them (13). The classification of drug therapy problems was carried out using a Pharmacotherapy Workup according to which DTPs were divided into four major categories and seven subcategories.

There are three main steps in the process of pharmaceutical care including a) the assessment of the patient, his or her medical problems, and drug therapies leading to the DTP identification, b) care plan development, and c) follow-up evaluations. These steps are highly dependent upon each other, and completion of all steps is necessary to practice

pharmaceutical care and to have a positive impact on a patient's medication experience. Systematic identification of DTPs together with resolution and prevention of DTPs, represent the central value of all medication management services. Drug therapy problems identified at the first and the second consultations were analysed to ensure all medical conditions and medication history were encompassed and taken into account. The process of care and the outcomes were thoroughly documented in a standardized chart structured in the Microsoft Office Excel software (version 2016). The primary outcomes were the prescriber's proportion of accepted interventions and the proportion of patients with improved clinical status of hypertension.

Clinical Outcomes Assessment

The impact of CMM services was evaluated by comparing the clinical status of hypertension determined at the first as opposed to the last consultation through the 4-year follow-up. Change in clinical status was evaluated and documented by the CMM pharmacist at each consultation, thus achieving clinical outcomes. A clinical outcome status was denoted as 'achieved' if favourable therapy goals were reached (< 130/80 mmHg for patients younger than 65 years of age; < 140/80 mmHg for patients older than 65 years of age), and *vice versa*, as 'unachieved' in case of blood pressure values above the threshold.

Prescribers' approval of pharmacist-initiated interventions

In collaboration with GPs from the study setting, a pharmacist-practitioner provided CMM to referred or self-referred patients at the private counselling area. As a part of the standardized patient care process, the pharmacist created an expert opinion and communicated it with the patient's authorised GP through the patient or email. The expert opinion included the patient's personal data, a list of current medications and up-to-date medical history, the latest laboratory parameters, a history of presenting complaints, and a short paragraph describing the rationale behind the suggested intervention. GPs were asked to respond to pharmacists' recommendations and the acceptance of interventions was evaluated by reviewing GPs' or patients' responses. The acceptance was established as definite implementation if the actual change in pharmacotherapy occurred. This was additionally confirmed at the follow-up visit when patients' clinical outcomes were assessed and documented.

Statistical analysis

IBM SPSS software, version 25.0 (IBM SPSS Statistics for Windows, Version 25.0.) was employed for data analysis and a $p < 0.05$ was considered statistically significant. Quantitative variables were described according to their mean, standard deviation, median, and interquartile range, while categorical variables were shown as frequency and percentage. The McNemar test was used to compare the pre- and postintervention clinical outcome status of hypertension.

RESULTS AND DISCUSSION

A total of 100 subjects were enrolled in the study, among which 60 % were female. The patients ranged in age from 41 to 86 years with only 8 % being younger than 65 years of age

(Table I). The average number of medical conditions was 7.8 ± 4.0, with 80 % of patients having 5 or more conditions and 17 % having 10 or more conditions. Diseases of the circulatory system were the most prevalent diagnostic group (32.3 %), followed by endocrine, nutritional, and metabolic diseases (19.3 %) and diseases of the musculoskeletal system and connective tissue (10.4 %). All subjects suffered from arterial hypertension, while 80 % of them had resistant hypertension. Systolic and diastolic blood pressure values ranged from 99 to 195 mmHg and from 58 to 113.5 mmHg, respectively (Table II).

Table I. Participants' demographic, anthropometric, and clinical characteristics

Characteristics		Participants (N = 100)
Age, median		73.5 (41–86)
Sex, *n* (%)	Male	40 (40)
	Female	60 (60)
Smoking	Yes	5 (5.2)
	No	59 (61.5)
	Stopped smoking	32 (33.3)
Physical activity	Yes	44 (44)
	No/weak	56 (56)
Alcohol consumption	Yes	70 (70)
	No/occasionally	30 (30)
BMI (kg m^{-2}), mean value ± SD		28.8 ± 4.9
Total number of consultations, median (range)		4 (1–16)
Number of prescription medications at the initial visit (ATC[a]), *n*		919
Number of all medications at the initial visit (ATC + OTC[b]), *n*		1022
Number of medications per patient at the initial visit, median (range)		10 (2–21)
Use of medication with an effect on the heart and blood vessels, *n* (%) (ATC C)		371 (36.3)
Use of medication with an effect on the digestive system and metabolism, *n* (%) (ATC A)		184 (18)
Use of medication with effects on the nervous system, *n* (%) (ATC N)		126 (12.3)
Diagnoses at the initial visit, *n*		767
Number of diagnoses per patient at the initial visit, median (range)		7 (2–23)
The most common diagnostic groups[c], *n* (%)		
Diseases of the circulatory system (ICD-10 I00-I99), *n* (%)		248 (32.3)
Endocrine, nutritional and metabolic diseases (ICD10 E00-E99), *n* (%)		148 (19.3)
Diseases of the musculoskeletal system and connective tissue (ICD-10 M00-M99), *n* (%)		80 (10.4)
Number of drug therapy problems per patient at the initial visit, mean value ± SD		3.5 ± 1.8

[a] Anatomical Therapeutic Chemical Classification
[b] Over-the-Counter medications
[c] International Statistical Classification of Diseases and Related Health Problems, 10th Revision

The average number of medications per patient, including prescription and over-the--counter, totalled 10.2 ± 3.8. Accordingly, medicines affecting the heart and blood vessels were the most frequently prescribed group of medicines, followed by the group of medicines affecting the digestive system and metabolism and medicines affecting the nervous system (Table I).

At the initial assessment, a total of 353 DTPs were identified with an average of 3.5 ± 1.8 per patient, where 98 % had one or more DTPs, 48 % had 4 or more DTPs, and 26 % had 5 or more DTPs. The most frequently involved drug therapy problems were subtherapeutic dosage (32.6 %) and the need for additional drug therapy (30.9 %) (Table III). The percentage of patients' goals of therapy achieved increased from 45 % at the initial consultation (36 patients with blood pressure values reaching target values) to 82.5 % at patients' latest encounters (66 patients with blood pressure values reaching target values) ($p < 0.001$). Altogether, 275 interventions were directed to the prescriber, out of which 73.1 % were accepted, 12.4 % were denied and 14.5 % were not evaluated by the prescriber. The most common interventions as a means of resolving DTPs were initiation of new drug therapy

Table II. Participants' systolic blood pressure, diastolic blood pressure, pulse and kidney function

Clinical parameters	Participants (N = 100)
Systolic blood pressure (mmHg), mean value ± SD	138.9 ± 17.7
Diastolic blood pressure (mmHg), mean value ± SD	79.5 ± 10.8
Heart rate (beats/minute), mean value ± SD	70.0 ± 10.8
eGFR categories[a] (mL/min/1.73m^2), (%)	
Stage 1 (≥ 90 mL/min/1.73^2) (normal or high)	19.4
Stage 2 (60–89 mL/min/1.73^2) (mild)	50
Stage 3 (30–59 mL/min/1.73^2) (moderate)	25.5
Stage 4 (15–29 mL/min/1.73^2) (severe)	5.1
Stage 5 (< 15 mL/min/1.73^2) (end stage)	0

[a] eGFR – estimated glomerular filtration rate

Table III. The frequency of drug therapy problems by category

Drug-related needs	Drug therapy problem category	n (%)
Indication	Unnecessary drug therapy	23 (6.5)
	Needs additional therapy	109 (30.9)
Effectiveness	Ineffective drug	32 (9.1)
	Dosage too low	115 (32.6)
Safety	Adverse drug reaction	26 (7.4)
	Dosage too high	37 (10.5)
Adherence	Nonadherence or noncompliance	11 (3.1)
Total		353 (100)

(26.1 %), change in drug dosage (25.6 %), change in drug product (12.5 %), change of dosage regimen (10.5 %), and discontinuation of drug therapy (9.4 %). Only 3.1 % of identified DTPs were associated with non-adherence. The most common examples of drug therapy problems are detailed in Appendix 1. Drugs most often associated with DTPs were calcium channel blockers (8.3 %), statins (7.2 %), and beta blockers (6.7 %), followed by moxonidine (6.2 %), ACE-inhibitors (5.3 %) and urapidil (4.8 %). During the 1-year study period, there was an average of 2.9 ± 2.3 visits per patient.

This study evaluated patients' clinical status of hypertension and general practitioners' acceptance rate of pharmacists' interventions provided to a group of ambulatory patients receiving CMM services in the primary care clinic. To the best of our knowledge, this is the only Croatian and European study that has explored the effects of CMM services on blood pressure control over a time period as long as 4 years. The present study demonstrated that CMM services substantially improve the clinical status of hypertension patients, hence confirming multiple previously published research (22, 24–33). By nearly doubling the percentage of patients achieving the goals of therapy in the treatment of hypertension, the percentage of patients' therapy goals in our study increased from 45 to 82.5 % following CMM services provision. This finding is similar and even surpasses results from previous studies (22, 26, 34–37). Namely, Bunting *et al.* reported an increase from 40.2 to 67.4 % in the percentage of patients at blood pressure goal (26), while Isetts *et al.* disclosed an increase from 76 to 90 % after medication therapy management (MTM) services were provided (22). In a study by Carter *et al.*, a physician and pharmacist collaborative model in community-based medical offices demonstrated controlled blood pressure in 29.9 % of patients in the control group as opposed to 63.9 % of patients in the intervention group (25). Such meaningful results provide relevant evidence for the Croatian policymakers to recognize CMM as a high-quality service with a proven positive impact among patients with high risk of DTPs, such as those living with hypertension, which will hopefully instigate and accelerate the adoption of the legal framework specifically addressing CMM services.

Namely, based on collaboration between pharmacists, general practitioners (GPs), and patients, and aiming to ensure optimal medication use and improve patients' clinical outcomes, this service brings novelty to the Croatian healthcare system. Currently, one of the most prominent obstacles related to the broader implementation of CMM services in the Croatian healthcare system is the lack of a legal framework specifically addressing CMM services. It is expected that such a legal framework will be laid out in the next amendments of the Pharmacy Act and will enable the Croatian Health Insurance Fund to reimburse these pharmacy services.

The results of this study reinforce the growing body of literature indicating that the enhancement of the clinical status of hypertension is attributable to the adequate provision of CMM services within the practice of pharmaceutical care.

Our results revealed that the general practitioners' acceptance rate of pharmacists' interventions was 73.1 %, rendering this acceptance rate considerably higher than the ones previously reported at the primary care level, regardless of the clinical setting where it was carried out. Namely, in a Brazilian study conducted in a public specialty pharmacy and aiming at examining CMM's impact on chronic obstructive pulmonary disease (COPD) patients, an acceptance rate was 55 % (19), while in the American study determining prescriber responses to pharmacist-initiated recommendations in an MTM service, the

acceptance rate was 47 % (18). That much higher acceptance rate registered in our study could be explained by the fact that apart from conveying our recommendations through written communication (e-mail and letters delivered to the patient), we insisted on a 'personal touch' (whenever feasible we would meet in person or call the GP, construct an email in such a fashion that we would personally ask for their feedback, ask patients to provide us with feedback on GP's response with regards to our expert opinion) whereby we managed to engage and involve patients' authorized GPs in patients' medication management. Namely, higher prescriber approval rates (more than 90 %) have been reported for face-to--face interactions and collaborative care agreements in clinic settings (38, 39), whereas lower approval rates (32 to 61 %) have been found when communication is conducted through written communications such as mail and fax (18, 19, 40–42). The mixed-method approach of communication we employed has proven satisfactory, especially considering such a high acceptance rate. Additionally, our results are partly adversely influenced by the lack of collaborative practice agreements permitting pharmacists to make interventions without physician involvement, dissimilar to the United States (US) CMM practice. Had we had a chance to intervene without the GP's approval, the percentage of endorsed interventions would have been even higher.

In our study cohort, most of the patients had multiple comorbidities that were accompanied by complex therapy regimens. Accordingly, the average number of DTPs (3.5 ± 1.8) was similar to or higher than those reported elsewhere (13, 19, 21, 23, 37, 43). An extremely high proportion of patients with at least one DTP (98 %) was superior to the ones detected by other investigators (21, 37) highlighting the omnipresent issue of medication mismanagement and underlining the need for a wider CMM implementation. Furthermore, this could be explained by the fact that the patients who used the CMM services were primarily those with complex therapeutic regimens searching for solutions to their therapeutic problems and those referred by their GPs who were unable to help them with such problems.

Hence, this contributed to the creation of a sample with a higher-than-usual number of comorbidities and, consequently, therapy and a higher number of unresolved DTPs.

Similarly to previous evidence (21, 22), about 37 % of the drug therapy problems were related to indication, 41 % to effectiveness, 18 % to safety concerns, and 3 % to adherence. Around two-thirds (63.5 %) of DTPs involved the need for initiating a new medication or dosage increase, suggesting that when a pharmacist employs a standardized patient care process an increase in medication use usually occurs. These results are in line with those of previous investigators that evaluated the clinical outcomes of CMM services and point to the underutilisation of effective medications leading to worse disease control and increased healthcare usage (41, 44, 45). By repeating the results from the studies conducted elsewhere, we confirmed that pharmacists, that is pharmaceutical care providers, in Croatia followed the standardised, rational decision-making process proposed by Cipolle *et al.*

Standardization of the patient care process is extremely important, especially if we want to be recognized as health care professionals equal to other health professions contributing and adding value to a multidisciplinary health care team.

Several limitations of our study should be mentioned. Firstly, physician's reasons for not accepting pharmacists' interventions were not further explored nor documented. Nevertheless, we empirically 'knew' that one of the main reasons for the non-acceptance of our interventions was due to patients' lack of willingness to communicate our expert opinion with their authorised general practitioner, mainly out of fear that this report could

jeopardize their relationship. Additionally, some patients simply came for a second opinion and were reluctant to proceed with our recommendations. Assuredly, in a smaller proportion of cases general practitioners received our report and simply declined to endorse the proposed interventions. In the future it might be prudent to analyse general practitioners' reasons for non-acceptance, thus gaining further insights into this discontinuity of GP--pharmacist communication and patient care. Even more, to examine this notion a qualitative study should be put in place. Namely, if we are to change this alienated behaviour and create a more supporting and stimulating environment, we need 'rich data' that will inform us of GPs' true motives for their absence of collaboration with other healthcare providers (*e.g.* clinical pharmacists).

Second, this research was conducted in the largest provider of primary health care services in the Republic of Croatia, HCZC, operating in 64 locations of the City of Zagreb through coordinated activities of 315 contracted teams from 19 different industries. Hence, the results might be difficult to generalize to other primary health care services in Zagreb and the rest of Croatia.

Third, the lack of a control group in this study makes it difficult to ascribe outcomes to the CMM intervention. Namely, patients seeking medication management services were highly motivated and as such were incomparable to the remaining patients receiving standard care.

CONCLUSIONS

This study provided evidence that pharmacists working in collaboration with general practitioners identified and resolved a high number of drug therapy problems thereby improving patients' hypertension clinical status. The high overall prescriber approval rate of pharmacist-initiated interventions corroborates and reinforces the need to incorporate pharmaceutical care services at the primary care level, hence improving the clinical outcomes of chronic patients.

Supplementary data are available upon request.

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Authors contributions. – Conceptualization, I.M. and A.B.; methodology, I.M., A.B. and D.R.O.; analysis L.A.B., I.M. and A.B.; investigation, L.A.B., H.O., A.B. and I.M.; writing, original draft preparation, I.M., A.B., L.A.B., H.O.; writing, review and editing, I.M. and A.B. All authors have read and agreed to the published version of the manuscript.

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