T.R.N.C
NEAR EAST UNIVERSITY
INSTITUTE OF HEALTH SCIENCES

Introducing Clinical Pharmacy Services: Pharmaceutical Care Services Provided for Patients in Cardiology and Cardiovascular Surgery Departments at a University Hospital.

A THESIS SUBMITTED TO THE GRADUATE INSTITUTE OF HEALTH SCIENCES

BY:
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In Partial Fulfillment of the Requirements for the Degree of Doctorate of Science in Clinical Pharmacy

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Abstract

Haider Bahaaldeen Mahdi AL-BAGHDADI, Introducing Clinical Pharmacy Services: Pharmaceutical Care Services Provided for Patients in Cardiology and Cardiovascular Surgery Departments at a University Hospital.
Near East University, Institute of Health Sciences, Clinical Pharmacy Doctorate's Thesis', Nicosia, 2017.

Clinical pharmacists are the primary source of scientifically valid information and advice on the safe, rational, and cost-effective use of medications. However, ward-based clinical pharmacy services are not well optimized in Northern Cyprus and Turkey.

This study introduced and evaluated ward based clinical pharmacy services in cardiovascular clinics. The setting was in the cardiology and cardiovascular surgery departments at Near East Tertiary University Hospital. The study is a prospective interventional study introduced and documented clinical pharmacy services for 120 days (January 2015-May 2015). Drug-related problems were classified using the Pharmaceutical Care Network Europe PCNE DRP classification tool V6.2. and the main outcome measures interventions proposed and acceptance rate of recommendations.

A total of 133 patients were reviewed, and, 81 patients experienced drug-related problems. Only 402 (93.1%) of the 432 suggested interventions were accepted and regarded as clinically relevant. Drug-related problems primarily involved antihypertensive, diuretic, and antithrombotic agents. Treatment effectiveness was the major type of drug-related problems (107; 49.3%) followed by adverse drug reactions (74; 34.1%). Drug dose and selection were the most frequent causes of drug-related problems. Add/change/stop medications were the most common types of intervention at the prescriber level. A total of 171 (78.8%) of the identified 217 drug-related problems were solved, 4 (1.8%) of the problems were partially solved, 32 (14.7%) problems were unsolved, and 10 (4.6%) problems had unknown outcomes. Which concluded that clinical pharmacy services have optimized therapy effectiveness and prevent adverse effects. Collaboration with healthcare providers was shown to be a highly effective service that should be further optimized and implemented in other hospitals in Northern Cyprus and Turkey

Keywords: Clinical pharmacy services, Drug-related problems, Pharmaceutical care, Cardiology, PCNE, Cyprus, Turkey

ÖZET

Haider Bahaaldeen Mahdi AL-BAGHDADI, Klinik Eczacılık Hizmetlerinin Tanıtımı: Bir Üniversite Hastanesinde Kardiyoloji ve Kalp-Damar Cerrahisi Bölümlerinde Hastalara Sağlanan İlaç Bakım Hizmetleri. Yakın Doğu Üniversitesi, Sağlık Bilimleri Enstitüsü, Klinik Eczacılık Doktora Tezi, Lefkoşa, 2017.

Klinik eczacılar, ilaçların güvenli, rasyonel ve uygun maliyetli kullanımıyla ilgili bilimsel olarak geçerli bilgi ve tavsiyelerin birincil kaynağıdır. Bununla birlikte, servise dayalı Klinik eczacılık hizmetleri Kuzey Kıbrıs'ta iyi optimize edilmemiştir. Bu çalışma, kardiyovasküler kliniklerdeki servis merkezli klinik eczacılık hizmetlerini tanıtmış ve değerlendirmiştir. Üçüncü basamak üniversite hastanesinde kardiyoloji ve kardiyovasküler cerrahi bölümleri.120 gün boyunca prospektif girişimsel çalışma ile klinik eczacılık hizmetlerini tanıtmış ve belgelemiştir.İlaçla ilgili problemler, İlaç Bakım Ağı Avrupa PCNE DRP sınıflandırma aracı V6.2 kullanılarak sınıflandırılmıştır. Önerilen müdahaleler ve önerilerin kabul oranı.Toplam 133 hasta gözden geçirilmiş ve 81 hastanın ilaca bağlı sorunlar yaşadığı görülmüştür. Önerilen 432 müdahaleden 402 (% 93,1) 'si kabul edilmiş ve klinik olarak anlamlı değerlendirilmiştir. İlaçla ilgili problemlerin başlıca antihipertansif, diüretik ve antitrombotik ajanları içerdiği görülmüştür. Tedavi etkinliği ilaca bağlı problemlerin başında yer alırken (107;% 49.3) ardından advers ilaç reaksiyonları (% 74;% 34.1) gelmiştir. İlaç ile ilgili problemlerin en sık karşılaşılan sebepleri ilaç dozu ve seçimi idi. Reçeteleme aşamasında seviyesinde en yaygın müdahale türleri ilaç eklemek / değiştirmek / durdurmaktı. Belirlenmiş 217 ilaca bağlı sorunların 171'i (% 78.8) çözülmüş; 4'ü (% 1.8) kısmen çözülmüştü, 32'sinde (% 14.7) sorun çözülmemiş ve 10'unda (% 4.6) sorunun çözümü hakkında bilgiye ulaşılmamıştır.
Sonuç: Klinik eczacılık hizmetleri, tedavi etkinliğini optimize edebilir ve yan etkileri önleyebilir. Sağlık hizmeti sunucuları ile yapılan işbirliğinin, Kuzey Kıbrıs'taki ve Türkiye'deki diğer hastanelerde daha da iyileştirilmesi ve uygulanması gereken oldukça etkili bir hizmet olduğunu göstermiştir.

Keywords: Klinik eczane hizmetleri, İlaçla ilgili problemler, farmasötik bakım, Kardiyoloji, PCNE, Kıbrıs, Türkiye.

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LIST OF ABBREVIATIONS:

ACCP: American College of Clinical Pharmacy
ACE/ARB: Angiotensin Converting Enzyme / Angiotensin Receptor Blockers
BMI: Body Mass Index
CHF: Congestive Heart Failure
CP: Clinical Pharmacist
CPS: Clinical Pharmacy Services
CVD: Cardiovascular Disease
DRP: Drug-Related Problem
ESCP: European Society of Clinical Pharmacy
FIP: International Pharmaceutical Federation
GP: General Practitioner
INR: International Normalized Ratio
LDL: Low Density Lipoprotein
MAP: Medication-Related Action Plan
MTM: Medication Therapy Management
MTR: Medication Therapy Review
NSAID: Non-Steroidal Anti Inflammatory Drug
NEU: Near East University
PCNE: Pharmaceutical Care Network Europe
PMR: Personal Medication Record
PPI: Proton Pump Inhibitor
SD: Standard Deviation
TRNC: Turkish Republic of North Cyprus.
WHO: world health organization

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1. Introduction

In the early 1970s, because of concerns about patient safety, the quality of health care and the fast changing in global pharmaceutical markets, Clinical Pharmacy as a new concept was embedded, and in response to the societal need to improve the use of drugs, a clinical role for pharmacists was progressed [1].

In 1980, the concept of pharmaceutical care in its modern sense was introduced by Brodie DC [2]. However, in 1989, Linda Strand and Charles Hepler emphasized the significance of an orientation toward outcomes, which that had been implicit in the definition of Brodie DC. Their definition also addressed responsibility within relationships [3]. The pharmaceutical care concept occurrence was considered as a practice philosophy for pharmacy. Where the concept covers all responsibilities, medication surveillance at both individual and systems level, counseling, and evaluation of care outcomes [4].

As a profession, the pharmacy has gone through rapid changes in last decades, with many of countries orienting for more patient-oriented clinical roles and integrating pharmacists into a multidisciplinary team alongside physicians, nurses and other healthcare providers [5]. Furthermore, in countries such as the UK, Australia, New Zealand, Canada, and the United States, pharmacists are expected to be accessible to patients and to counsel patients about their medications. In the UK, there are pharmacist prescribers and a new role is emerging for pharmacists to work in general practitioner (GP) practices [6].

In Northern Cyprus and Turkey, clinical pharmacy is not well established in hospitals yet. In fact, there is no clinical pharmacist employed by any hospital in this region. In this study, we mark

the first time clinical pharmacy services were introduced and studied in cardiology clinics. Although this step is considered as a challenge for the clinical pharmacy profession, it may open a new gate for clinical pharmacy as an important aspect of pharmacy practice in this region, where hospital-based pharmaceutical care services were not provided for cardiology patients before, and medical doctors had no previous contact with any clinical pharmacist.

In this study, we introduced clinical pharmacy services (CPS) to the cardiovascular clinic and cardio-surgery clinic in a tertiary university hospital at Northern Cyprus. The services were evaluated regarding quantity and quality. Also, according to the study setting, the study is considered as original and first in Northern Cyprus.

In the following sections, we review the definition of clinical pharmacy and responsibilities of clinical pharmacists, also the definition of pharmaceutical care and their effects in cardiovascular clinics before presenting our study findings.

Section one is discussing clinical pharmacy, clinical pharmacist and Pharmaceutical care definition and duties as viewed by different pharmaceutical bodies and organizations; it also explains what is meant by medication therapy managements and its core elements as the most advanced pharmaceutical care tool.

Section two is discussing rational drug use and drug-related problem. Also, it explains drug-related problem classification tool and the role of Pharmaceutical Care Network Europe organization in unifying the tool.

Section three will mention the effect of clinical pharmacy services in different cardiovascular diseases and the role of a clinical pharmacist in cardiovascular clinics.

1.1 Clinical Pharmacy Definitions, Clinical Pharmacist Duties & Roles of Clinical Pharmacist Within the Health Care System, Pharmaceutical Care Definitions, Similarities and Differences Between Clinical Pharmacy and Pharmaceutical Care, And Finally Medication Therapy Management (MTM) Services.

1.1.1 Clinical Pharmacy

Clinical Pharmacy is defined by the American College of Clinical Pharmacy (ACCP) as "that area of pharmacy concerned with the science and practice of rational medication use.". Where, the un-shortened definition of clinical pharmacy is "a health science discipline in which pharmacists provide patient care that optimizes medication therapy and promotes health, wellness, and disease prevention." [7]. However, the practice of clinical pharmacy covers the philosophy of pharmaceutical care; it combines a caring orientation with specialized therapeutic knowledge, experience, and verdict for the purpose of ensuring optimal patient outcomes. As a discipline, the clinical pharmacy also has a commitment to contribute to the generation of latest knowledge that improves health and quality of life.

On the other hand, Clinical Pharmacy is defined by the European Society of Clinical Pharmacy (ESCP) as, "a health specialty, which describes the activities and services of the clinical pharmacist to develop and promote the rational and appropriate use of medicinal products and devices" [8]. While, Clinical Pharmacy includes all the services performed by pharmacist practicing in a hospital, community pharmacy, nursing home, home-based care services, clinic and any other setting where drugs are prescribed and used.

1.1.2 Clinical Pharmacist

The clinical pharmacist stating that the clinical pharmacist cares for patients in all health care settings assures two points: that clinical pharmacist provides care to patients (i.e., the clinical pharmacist does not just provide clinical services), and that clinical pharmacist`s practice can occur in any practice setting. However, as a term “clinical” does not necessarily imply an activity implemented only in a hospital setting. A clinical pharmacist as community pharmacist may perform clinical activities in pharmacy. Where, the application of evidence and evolving Sciences of the clinical pharmacist points out that clinical pharmacy is a scientifically discipline; the application of legal, ethical, social, cultural, and economic principles provides to explain that clinical pharmacy as a practice extends beyond science also to take into account societal factors [7].

Clinical pharmacist assumes responsibility and accountability for achieving therapeutic goals; the definition makes it clear that clinical pharmacist is called upon to be more than consultants. Furthermore, the mention of managing therapy in direct patient care settings is of particular importance because it reinforces presenting explanations of the term “clinical.” The term “clinical” is defined by the American Heritage College Dictionary as “involving or based on direct observation of the patient” [9]; on the other hand, clinical medicine is defined by Dorland’s Medical Dictionary as “the study of disease by direct examination of the living patient.” [10]. That is, clinical pharmacists are involved in direct interaction with, and observation of, the patient.

Also, it is observed that clinical pharmacist cares for patients in all health care settings. Clinical pharmacist possesses in-depth knowledge of medications that is integrated with a foundational understanding of the biomedical, pharmaceutical, socio-behavioral, and clinical sciences.

Clinical pharmacists apply evidence-based medicine guidelines, evolving sciences, emerging technologies, and relevant legal, ethical, social, cultural, economic, and professional principles, to achieve required therapeutic goals.

Moreover, to manage medication therapy in direct patient care settings, whether practicing independently or in consultation or collaboration with other health care providers, clinical pharmacist assumes responsibility and accountability.

Clinical pharmacist researcher generates, disseminates, and applies new knowledge that contributes to improved health and quality of life. Within the system of health care, the clinical pharmacist is the expert in the therapeutic use of medications. They routinely provide drug therapy evaluations and recommendations to patients and health care professionals. The clinical pharmacist is the primary source of scientifically valid information and advice regarding safety, rational, and cost-effective use of medications.

1.1.3 Clinical Pharmacist Roles Within the Health Care System

Clinical pharmacist, due consideration as an expert in the therapeutic use of the drug, the clinical pharmacist provides unique knowledge and skills sets to the health care system, and thus, it is sufficient to assume the role of specialists in drug therapy.

Moreover, this expertise is used proactively to ensure and advance rational drug therapy use, thereby averting many of the drug therapy misadventures that ensure following inappropriate therapeutic decisions made at the point of prescribing.

Stating that the clinical pharmacists are the primary source of scientifically valid information and advice regarding safety, rational, and cost-effective use of medications emphasize that the clinical pharmacists serve as objectives, evidence-based sources of therapeutic information and recommendations.

This expertise also covers non-traditional treatments outside of conventional medicine. Finally, it indicates that clinical pharmacist provides therapeutic assessment suggestions, recommendations, and it underscores the fact that there are regular consultations between the evaluation of drug treatment in daily practice with patients and health care professionals [7].

1.1.4 Pharmaceutical Care

Pharmaceutical Care as a term is widely used as a keyword in health care articles, as a performance in patient care, or as a module within a teaching curriculum. In general, people most of the time refer to pharmaceutical care as the definition that given by Hepler and Strand

in 1989: “Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes which improve a patient's quality of life.” [3].

In 1997, a more patient-centered approach was recognized by Linda Strand et al., who stated that Pharmaceutical Care is a philosophy of practice not only a theory [11].

Thenceforward, new concepts and terms of medicines-related patient care have developed, like Disease Management [12], Medicines Management [13], and Medication Therapy Management (MTM) [14]. Twenty-three years after Hepler and Strand published the definition, substantial confusion remains about what Pharmaceutical Care includes and how to differentiate Pharmaceutical Care from such other terms.

According to McGivney et al. [15], for example, MTM integrates both the practice and philosophy of Pharmaceutical Care and elements of Disease Management.

Some authorities and authors consider Pharmaceutical Care as a responsibility shared by all health providers, while others restrict it to the pharmacy profession.

The difficulties with definitions were lately addressed in a joint editorial from the Journal Pharmacy Practice and the International Journal of Clinical Pharmacy [16].

Pharmaceutical Care has been defined many times differently over the last forty-seven years; the first definition was in 1970, by Mikeal, R. L.; Brown, T. R.; Lazarus, H. L.; and Vinson, M. C. which stated that “Pharmaceutical Care is the care that a given patient requires and receives which assures safe and rational drug usage” [17].

In 1980, Brodie, D. C.; Parish, P. A.; and Poston, J. W.; had defined “Pharmaceutical Care” with more expansion as “Pharmaceutical care includes the determination of the drug needs for a given individual and the provision not only of the drugs required but also of the necessary services (before, during or after treatment) to assure optimally safe and effective therapy. It includes a feedback mechanism as a means of facilitating continuity of care by those who provide it” [2].

Hepler, C. D; in 1987 gave his first description of pharmaceutical care as “A covenantial relationship between a patient and a pharmacist in which the pharmacist performs drug-use-control functions (with appropriate knowledge and skill) governed by awareness of and commitment to the patients' interest” [18].

The most famous definition of pharmaceutical care was defined by Hepler, C. D.; and Strand, L. M.; in 1989, which stated that “Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes which improve a patient's Quality of Life” [3].

Strand, Linda M.; in 1992 tried to add more deepness to her first definition by stating that “Pharmaceutical Care is that component of pharmacy practice which entails the direct interaction of the pharmacist with the patient for the purpose of caring for that patient's drug-related needs” [19].

American Society of Hospital Pharmacists was the first organization which defined in 1993 pharmaceutical care as “The direct, responsible provision of medication-related care for the purpose of the achieving definite outcomes that improve a patient's quality of life” [20].

In the same year, Van Mil and J. W. F. defined pharmaceutical care as “The structured, intensive care of the pharmacist for an optimal pharmacotherapy in which the patient and his condition are the primary concern. The aim is to obtain optimal Health Related Quality of Life” [21].

Hepler, C. D.; in 1996, gave a new addition to his last definition stating that “The purpose of pharmaceutical care (in all practice settings) is to provide drug therapy intended to achieve definite outcomes that will improve a patient's quality of life.” [22].

In 1997, a more patient-centered approach was recognized by Linda Strand et al., who stated that “practice for which the practitioner takes responsibility for a patient's drug therapy needs and is held accountable for this commitment.” [11].

Munroe, WP; and Dalmady-Israel, C.; in 1998, were explained the care from anyone for a patient in the field of pharmacotherapy is Pharmaceutical care “Pharmaceutical care as a service which systematically and continuously monitors the clinical and psychosocial effects of drug therapy on a patient.” [23].

International Pharmaceutical Federation (FIP) in 1998 declared as Statement about Pharmaceutical care notify that Pharmaceutical care is “The responsible provision of pharmacotherapy for the purpose of achieving definite outcomes that improve or maintain a patient’s quality of life.” [24].

In the same year, Cipolle, R. J.; Strand, L.; and Morley, P.; were defined Pharmaceutical care as “A patient-centered practice in which the practitioner assumes responsibility for a patient's drug-related needs and is held accountable for this commitment. In the course of this practice,

responsible drug therapy is provided for the purpose of achieving positive patient outcomes." [25].

One year later, Granada Consensus, the detection, prevention, and resolution of drug-related problems are considered as pharmaceutical care [26].

Van Mil, J. W.; Schulz, M.; and Tromp, T. F.; in 2004, had developed their definition by stating that "Pharmaceutical care is a practice philosophy for pharmacy. It is the way of pharmacists to coach the individual patients with their medication. The concept deals with the way a patient should receive and use medication and should receive education on the use of medicines. The concept also deals with responsibilities, medication surveillance, counseling and the evaluation of all the outcomes of care." [27].

In the same year, Berenguer, B.; La Casa, C.; de la Matta, M. J.; and Martin-Calero, M. J.; were stated that "The pharmacists' compromise to obtain the maximum benefit from the pharmacological treatments of the patients, being, therefore, responsible of monitoring their pharmacotherapy." [28].

One year later, Franklin, B. D.; and Van Mil, J. W.; were stated that "The person-focused care relating to medication, which is provided by a pharmacist and the pharmacy team with the aim of improving the outcomes of therapy." [29].

In 2011, Sanchez, A. M.; published an article at Madrid, Spain, stating that "Pharmaceutical care addresses the patient's drug-related needs comprehensively through a scheduled outline of tasks, in which the practitioner makes sure that the drug therapy is appropriately indicated, effective, safe, and convenient." [30].

Blackburn, D. F.; Yakiwchuk, E. M.; Jorgenson, D. J.; and Mansell, K. D.; in 2012, published an article at Canada, stating that “A patient-centered practice in which the practitioner would be accountable for the drug-related needs of specific individuals as well as groups of patients within a defined practice setting who are at high risk for drug- or disease-induced morbidity.” [31].

On the same year, Carollo, A.; Rieutord, A.; and Launay-Vacher, V.; published an article of European Association of Clinical Pharmacy at Europe as a guideline for pharmaceutical care, stating that “The pharmaceutical contribution to patient care in identifying pharmaceutical care issues (medications-related issues) and establishing and administering a pharmaceutical care plan.” [32].

The latest definition was formulated by The Pharmaceutical Care Network Europe (PCNE) in 2013 “Pharmaceutical Care is the pharmacist’s contribution to the care of individuals in order to optimize medicines use and improve health outcomes.” [33].

1.1.5 Similarities and Differences Between Clinical Pharmacy and Pharmaceutical Care

The comparisons show that clinical pharmacy, as well as pharmaceutical care, are compatible, mutually complementary ideas. Where, clinical pharmacy and pharmaceutical care seem to have similar objectives; however, these targets are expressed in various language frameworks and emphasize different aspects of practice.

One-way to sort clinical pharmacy and pharmaceutical care out would be to identify that to achieving pharmacotherapeutics and quality-of-life therapeutic objectives; clinical pharmacy describes a practice of pharmacy that would contribute, within a larger pharmaceutical care system.

Pharmaceutical care is not “about” pharmacists. However, the idea of pharmaceutical care was developed fundamentally by pharmacists; it is principally an idea about a system for the delivery of patient care. It requires collaboration by a set of hospital and community pharmacists, physicians, nurses, and other healthcare providers. While, clinical pharmacy is an essential component in the delivery of pharmaceutical care. When clinical pharmacy knowledge can upgrade the technical quality of pharmaceutical care. While, pharmaceutical care experience can enrich and expand the philosophy and practice of clinical pharmacy. However, according to these explanations, clinical pharmacy apparently, comprises processes executed by pharmacists without appropriate linkage to outcomes.

The pharmacist is unable to provide drug therapy without collaboration from prescriber and patient. Moreover, Pharmaceutical care is often debated as a system. However, none of the definitions of clinical pharmacy points out systems.

The two concepts seem to have different philosophic essences. Likewise, clinical pharmacy definition of The ACCP notes that it is a health science and enumerates academic disciplines [7]. None of clinical pharmacy's definitions specifically points out values or responsibilities.

Two definitions of pharmaceutical care point out responsibility, but none of them mentions academic disciplines. Apparently, the essence for clinical pharmacy is more in science than in

relationship ethics, whereas the core of pharmaceutical care is more in connection standards than in science.

Clinical Pharmacy and Pharmaceutical care differences are not “black and white” uniqueness. They do not propose that pharmaceutical care, in practice, entirely lacks any element that is existing in the definition of clinical pharmacy or vice versa. Certainly, clinical pharmacy practice is meant to be an ethically mediated method involving responsibility for clinical and quality-of-life outcomes. However, it was not defined as such. Undoubtedly, pharmaceutical care should depend on right processes and should require academic knowledge. However, its definitions do not need these elements. The semantic differentiations show that both concepts are incomplete and that they help and complete each other [34].

1.1.6 Medication Therapy Management (MTM) Services.

Medication Therapy Management is “A distinct service or group of services that optimize therapeutic outcomes for individual patients. Therefore, as part of pharmaceutical care services, they are independent of, but can occur in conjunction with, the provision of a medication product.” [35].

The Medication Therapy Management includes a wide range of professional activities and responsibilities within pharmacists or another qualified provider of medical care, the scope of practice. A program that provides coverage for MTM services should include:

1-Services to particular patients or specific services or sets of services provided directly by a pharmacist to the patient. (These services are different from the focus and use of form, Widespread patient education and other quality assurance measures use of drugs).

2-Face to face interaction between the patient and the pharmacist as the preferred method of delivery. Where specific patient barriers to face-to-face communication exist, patients will have equal access to appropriate alternative methods of administration. The structures that support the maintenance of the patient's pharmacist must be set in MTM programs.

3-Opportunities for pharmacists and other health professionals trained to identify patients who will receive MTM services.

4- Constant Drug Therapy Payment Management Services Suppliers that are based on time, clinical intensity and resources to provide services.

5- Process to improve continuity of care, outcomes and outcome measures [35].

Core Elements of an MTM Service Model in Pharmacy Practice

The MTM service model in pharmacy practice includes the following five core elements:

• Medication therapy review (MTR)

• Personal medication record (PMR)

• Medication-related action plan (MAP)

• Intervention and/or referral

• Documentation and follow-up

Medication Therapy Review: The medication therapy review (MTR) is a systematic process of collecting patient-specific information, assessing medication therapies to identify medication-

related problems, developing a prioritized list of medication-related problems, and creating a plan to resolve them.

Personal Medication Record: The personal medication record (PMR) is a comprehensive record of the patient's medications (prescription and nonprescription medications, herbal products, and other dietary supplements).

Medication-Related Action Plan: The medication-related action plan (MAP) is a patient-centric document containing a list of actions for the patient to use in tracking progress for self-management.

Intervention and/or Referral: The pharmacist provides consultative services and intervenes to address medication-related problems; when necessary, the pharmacist refers the patient to a physician or other healthcare professional.

Documentation and Follow-up: MTM services are documented consistently, and a follow-up MTM visit is scheduled based on the patient's medication-related needs, or the patient is transitioned from one care setting to another [36].

1.2 Rational Drug Use Definition, Core Interventions To Promote Rational Use Of Medicines, The Most Important Points That Must Be Met To Ensure Rational Drug Therapy, Drug-Related Problem, Drug-Related Problem Classification Tool, And Finally Pharmaceutical Care Network Europe Organization's Role In Unifying The Tool

1.2.1 Rational Drug Use Definition

Rational use of medicines requires that “patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community.” [37].

More than 50% of all drugs worldwide are improperly prescribed, dispensed or sold, and 50% of patients do not take it properly. Conversely, about one-third of the world's population lack of access to essential medicines. Treatment Drugs is one of the most cost-effective medical interventions, and the proportion of national health budgets on medicines varies between 10% and 20% in developed countries and between 20% and 40% in developing countries. Therefore, it is extremely serious that so many drugs are used in inadequate and irrational [38].

Common types of irrational use of medicine are:

1-the use of too many medicines per patient (polypharmacy);

2-inappropriate use of antibiotics, often in inadequate dosage, for non-bacterial

infections;

3-over-use of injections when oral formulations would be more appropriate;

4-failure to prescribe by clinical guidelines;

5-inappropriate self-medication, often of prescription-only medicines [39].

1.2.2 Core Interventions To Promote Rational Use Of Medicines

1-A mandated multi-disciplinary national body to coordinate medicine use policies

2-Clinical guidelines

3-Essential medicines lists based on treatments of choice

4-Drugs and therapeutics committees in districts and hospitals

5-Problem-based pharmacotherapy training in undergraduate curricula

6-Continuing in-service medical education as a licensure requirement

7-Supervision, audit, and feedback

8-Independent information on medicines

9-Public education about medicines

10-Avoidance of perverse financial incentives

11-Appropriate and enforced regulation [39].

1.2.3 The Most Important Points That Must Be Met To Ensure Rational Drug Therapy

1-Right patient,

2-Right diagnosis,

3-Appropriate dose,

4-Appropriate dosage form,

5-Appropriate route of administration,

6-Appropriate frequency of administration,

7-Appropriate duration of treatment,

8-Appropriate information to the patient,

9-Adequate follow-up [40,41].

1.2.4 Drug Related Problem

A Drug Related Problem is “an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes” [42]. The identification and resolution of drug-related problems (DRPs) associated with prescriptions errors are the core activities of pharmaceutical care. Where, there is strong evidence linking the negative outcomes of DRPs and

major health issues, and the cost of mortality and morbidity associated with DPRs are very high They account for $76.6 billion in hospital costs, 17 million emergency department visits, and 8.7 million hospital admissions annually in the United States as shown in the probability model used in that study [43].

1.2.5 The Pharmaceutical Care Network Europe

The Pharmaceutical Care Network Europe (PCNE) creates guidelines and classification for DRPs to describe DRPs uniformly and serves as a process indicator in experimental studies. The association was founded in 1994 by several European pharmaceutical care researchers, and it became an official association under Dutch law in 2004 [42,44].

1.3 The Effect Of Clinical Pharmacy Services In Different Cardiovascular Diseases And The Role Of A Clinical Pharmacist In Cardiovascular Clinics

1.3.1 Hypertension

Proper management of hypertension is of prominent importance in patients with CVD. Controlling blood pressure can minimize the incidence of myocardial infarction (20-25%) and heart failure (more than 50%) [45]. The British Heart Foundation Statistics Database determined that only 40% of treated hypertensive patients were controlled [46]. The number was the same for the United States, where 37% of hypertensive patients were at their blood pressure intent [47]. Although it shows that limited access to care might be a common cause for poor blood pressure control [45].Hyman and Pavlik reported that most cases of uncontrolled

hypertension happened in elderly patients who had repeated physician visits [48]. Regular physician visits did not lead to improved control of blood pressure in other studies, as well [49,50].

The residence of pharmacists to control Hypertensive patients' usage of drugs, give report about potential adverse effects, and avoid medication interactions is supported by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [51]. Many studies have shown that the association of clinical pharmacists in the management of hypertensive patients produces encouraging outcomes [52-56]. This involvement could have a better value if made in the hospital setting rather than the community (49-53% vs. 96-98%) [57,58]. The difference may be illustrated by the fact that in community pharmacies, close communication between pharmacists and physicians may not be possible. A meaningfully positive influence on physicians' prescription of drugs requires face-to-face academic interviews between pharmacists and physicians in the practice environment [59]. In another study, which was randomized, controlled trial on 95 hypertensive patients having been randomly divided between a control arm of regular medical care and an intervention arm in which a physician and pharmacist worked as a team, the systolic and diastolic blood pressures decreased significantly in the intervention arm as correlated to those in the control arm (23 vs. 11 mmHg and 14 vs. 3 mmHg) [53]. Which led to a higher success rate of blood pressure goal in the intervention arm. In conclusion, the presence of clinical pharmacists as an integral member of a healthcare team could improve the rate of blood pressure control and diminish drug interactions and costs for both patients and health care systems.

The preoccupation of clinical pharmacists in the treatment decision-making process at the time of the prescription of drugs is advantageous to the management of patients, particularly those with chronic diseases. In many hospital settings, physicians' duty is to diagnose the disease; whereas in situations where pharmacotherapy is needed, clinical pharmacists should select the suitable choice and monitor patients for clinical response [52].

1.3.2 Hyperglycemia

Hyperglycemia is linked with poor clinical outcomes in patients with any concomitant diseases [60]. Raised mortality is recognized in hospitalized patients with hyperglycemia in an intensive care unit [61]. patients with hyperglycemia tend to have complications of cardiac surgery, including wound infections, more frequently [62,63]. Acute or stress-induced hyperglycemia preferably than chronic diabetes is a reliable predictor of surgery-associated complications and mortality [64,65]. Irrespective of the cause behind high blood glucose level, hyperglycemic patients with CVD, including those with acute myocardial infarction, arrhythmia, unstable angina, and pulmonary embolism, tend to exhibit increased mortality. The evidence that half of the patients in cardiac care units may have diabetes [66,67] adds to the significance of blood glucose level control in those with CVD. Moreover, some of the medications used in the pharmacotherapy of CVD may provoke new-onset diabetes [68]. Diuretics, beta blockers, and calcium channel blockers are considered to increase the risk of new-onset diabetes [69-75].

Clinical pharmacists' role is also more highlighted in the explanation and implementation of the protocols for glycemic control, estimation of required insulin dose, monitoring of patients' blood glucose level, and adjustment of discharge medication [76]. The active presence of

clinical pharmacists in the insulin regimen management of hospitalized patients was reported to have decreased length of hospital stay, the rate of hyperglycemia, and also hypoglycemic events [77]. Besides, the inappropriate use of sliding-scale insulin regimen without using basal insulin decreased significantly (*p-value < 0.0001*) [77]. Clinical pharmacists should, therefore, be present as a team member in the management of hyperglycemia in an inpatient setting to furnish the necessary information regarding blood glucose monitoring intending to bettering patients' clinical outcome. It is deserving of note that concern of hypoglycemia is one of the obstacles to adequate blood glucose control; clinical pharmacists' input could help in overcoming this problem [77].

1.3.3 Hyperlipidemia

A systematic review of twenty-one randomized clinical trials carried on studies that assessed the influence of clinical pharmacy services on the screening and treatment of patients with dyslipidemia, announced that collaborative care involving clinical pharmacists had attended to improved outcomes in patients with dyslipidemia [78]. This enhanced level of care was revealed by better control of total cholesterol, low-density lipoprotein (LDL), and triglyceride [79].

Such achievement can be justified by the fact that clinical pharmacists play a vital role in making effective drug therapy choice as well as educating patients concerning dyslipidemia and prescribed medications; this can improve control and adherence in the long term [80].

In a prospective study, carried by Bozovich et al., the proportion of patients at their LDL goal at six months' follow-up was higher in those obtained in clinical pharmacist managed lipid disorders clinic than in the ones having taken standard care provided by cardiologists (69% vs.

50%, *p-value = 0.016*) [81]. Geber et al. estimated the level of care provided by clinical pharmacists as opposed to that provided via standard care by physicians in patients with high baseline LDL [82] and reported a significantly large number of patients who attained their LDL goal among those receiving pharmacotherapy care compared to the ones receiving standard care (*p-value < 0.001*). The collaboration between clinical pharmacists and physicians for the superintendence of patients with dyslipidemia can raise the number of individuals who succeed in reaching their target lipid levels. Hence, the establishment of such clinical pharmacy clinics should be established particularly in communities where patients are usually unaware of the role of clinical pharmacists [83].

1.3.4 Heart Failure

Heart failure's patients experience recurrent hospital admissions because of the progressive and chronic aspects of their disease [84]. These repeated hospital admissions may generate changes in patients' drug regimens. Prescription errors or modifications in patients' medications without the requirement of sufficient education can result in readmissions [85,86]. Pharmacotherapy Management is the chief treatment in patients with heart failure; optimizing the pharmacological therapy and supporting patients' adherence are essential for enhancing disease management and decreasing the rate of hospitalization [87].

Pharmaceutical care administered by clinical pharmacists as members of a multidisciplinary team qualified for patients with heart failure can reduce the risk of hospitalization. [88,89]. Not just can pharmacists' interventions improve patients' adherence, but further, they can offer them economic support by lessening health care-associated costs. [90]. Such targets can be

accomplished by counseling clinical pharmacists before patient discharge [91]. Clinical pharmacists can dodge prescription errors and accommodate patients with education concerning the medications requested [87,91]. Furthermore, in the care of patients with heart failure after the implantation of left ventricular support devices, clinical pharmacists are distinguished to have enhanced drug therapy issues significantly [92]. These services rendered by clinical pharmacists can bring about a decrease in patients' readmissions and an increase in their quality of life [93-95]. One of the other strategies that clinical pharmacists can apply to assist patients with heart failure is to decrease the rate of disparities between prescribed medications in each of admissions and those used earlier by reviewing patients' preadmission drug lists [87]. This can be accomplished by taking a prior medical history of patients upon admission and supplying physicians with this data at the time of ordering [96].

In a nutshell, because heart failure is linked to high rates of hospital admissions [97]. and clinical pharmacists' interventions can diminish this rate by one-third, [88] the attendance of clinical pharmacists in the heart failure team is highly recommended [88].

1.3.5 Blood Clotting Disorders

A clinical pharmacist-managed anticoagulation assistance is assumed to increase the control of patients with regard to therapeutic goals and decrease the rate of adverse effects of anticoagulants as well as the episode of thromboembolic events as was attested to by studies that included trained clinical pharmacists in the superintendence of patients on anticoagulants because of a wide diversity of indications and durations using a particular strategy. [98-101].

In the Witt et al. study, the care level administered by clinical pharmacists was correlated to that supplied by experienced physicians: patients in the previous group showed a statistically significant reduction in anticoagulation therapy and thromboembolic complications [102]. This enhanced outcome in those recruited in the pharmacotherapy clinic is because of the greater percentage of time that the patients consumed on their therapeutic goals. Clinical pharmacists conserve protocols for every single anticoagulant appropriated in a hospital setting and set parameters with which they can launch, monitor, and adjust anticoagulation therapy in every written guideline. Drawing upon these guidelines, clinical pharmacists review and manage each patient's treatment and also evaluate the response on a daily basis [103]. Other services that clinical pharmacists can give for patients on anticoagulant therapy involve management of anticoagulants adverse effects, management of anticoagulant treatment in patients prior any surgery, and a shift in the anticoagulant management where necessary. All of these services can be substantial in lessening the complications of anticoagulant management and by expansion, health care expenditure [99,100].

Consequently, the preferred outcome of anticoagulation management forward with a decrease in costs supports the recommendation for a comprehensive implementation of clinical pharmacists' anticoagulation management [83].

2. The Study Objectives, Aims, Rational, And Design

2.1 Objectives Aims And Rationale

Cardiovascular diseases (CVDs) are the highest cause of death globally. An estimated 17.5 million people died from CVDs in 2012, which is 31% of all global deaths [104]. CVDs were the

predominant cause (38%) of non-communicable diseases accounting for the total number of deaths in the Cyprus population in 2014 [105].

Clinical Pharmacy is a frequently used as a term in pharmacy practice and pharmacy literature. It is a health specialization, which describes the activities and services of the clinical pharmacist to develop and improve the rational and proper use of medicinal products and devices.

Clinical Pharmacy covers all the services performed by pharmacists practicing in hospitals wards, community pharmacies, nursing homes, home-based care services, clinics and any other setting where medicines are prescribed and been used.

This study aimed to assess implementation of ward-based clinical pharmacy services in cardiovascular clinics at Near East University hospital and to describe prevalence and nature of encountered DRPs with the associated factors.

Many studies have been performed in cardiology clinics using PCNE DRP tool as a classification tool to detect and characterize DRPs. A total of 265 DRPs were identified in 227 patients in a university hospital study in Gondar, Ethiopia. The most common DRPs were inappropriate drug selection (36.1%) and dose (24.8%) [106]. Another study was performed at teaching hospital in Nitra, Slovakia, and 36 DRPs were identified in 73 patients. The most frequent causes of DRP were dose (n = 13;26%) and use-related [107].

Clinical pharmacy is not well established in hospitals in Northern Cyprus and Turkey, and no hospitals in this region employ a clinical pharmacist. The present study introduced clinical pharmacy services in cardiology clinics for the first time and examined the impact of these services. This step is a challenge for the clinical pharmacy profession, but it may open a new path for clinical pharmacy as an essential aspect of pharmacy practice in this region, where hospital-

based pharmaceutical care services are not provided for cardiology patients, and medical doctors have no previous contact with a clinical pharmacist.

2.2 Methods

2.2.1 Setting

The study was performed in the Cardiology and Cardiovascular Surgery Departments from January 2015 to May 2015 at Near East University Hospital, which is the largest and leading medical facility in Nicosia, Northern Cyprus. The services of the hospital are performed within a compound comprising over 56 thousand square meters of indoor space including 209 private, single patient rooms, 8-operating theatres, 30-bed Intensive Care Unit, 17-bed Neonatal Intensive Care Unit, and advanced laboratory. All inpatients admitted by the cardiology and cardiovascular surgery departments were included in the study, whether admitted to intensive care unit or ward patient care clinics. Eight physicians cared for these patients, including: four professor doctors, two assistant professors, and two specialists.

2.2.2 Study Design and Data Collection

This study was a prospective interventional study in which CPSs were provided for inpatients by clinical pharmacist's PhD student and documented over four months. There was no clinical pharmacist employed in these clinics and no interaction with a clinical pharmacist prior to the study.

All patients who were admitted to the hospital for treatment and required at least one overnight stay in cardiology or cardiovascular surgery departments were recruited into the study. A

previously designed data collection form was completed within 24-48 hours of patient admission to the hospital **(Appendix I).** The form included demographics, social history, allergies, patient diagnosis, chief complaint, history of present illness, comorbidities, family history, patient vital signs, laboratory values, past medical history, past medication history and current medications list which were reconciled by the clinical pharmacist. The data were collected from the patient's medical records and a direct patient-pharmacist interview. An advanced medication review was performed for each patient. Also, each patient's medical condition and treatment plan were discussed with physicians. The clinical pharmacist participated in patient visits with physicians during the study period, and patients were reviewed daily. Any change was noted in the medical chart (e.g. patient vital signs, laboratory values, and treatment). Patient services were provided via medication reconciliation/change in drug therapy, monitoring drug therapy, solving DRPs and providing drug information.

The clinical pharmacist used the latest pharmacy guidelines, the European Society of Cardiology guidelines, to detect DRPs and standardized databases such as the British National Formulary (BNF), Medscape, Micromedex, Lexi-Comp Online, and UpToDate, to assist with the calculation of appropriate doses based on creatinine clearance (Cockcroft-Gault equation) and identify current data.

Appropriate interventions for each identified DRP were discussed with the prescriber, and appropriate recommendations were suggested to resolve the problem either during patient-physician visit, or physician-pharmacist meetings. The clinical pharmacist evaluated the outcome of each recommendation, the physicians confirmed the results. The DRPs were categorized using

PCNE DRP classification V6.2. which was; last updated in 2010. **(Appendix II).** The number of DRPs per patient was calculated to estimate the incidence of DRPs.

2.2.3 Data and Statistical Analysis

The identified DRPs, causes, interventions, and outcomes were characterized using the PCNE tool instructions. One Problem (P) may have multiple Causes (C), and lead to more than one Intervention (I), but it leads to only one Outcome (O).

The data were analyzed using GraphPad InStat (version 3.00 for Windows 95, GraphPad Software, San Diego California USA, www.graphpad.com). Individual and problem-level analyses were performed separately because one patient may have exhibited multiple DRPs. Variables were imputed into mean value for continuous variables and the most prevalent categories for categorical variables. Between-group differences were analyzed using the chi-square test with Fisher's exact adjustment where appropriate for categorical variables and the t-test for continuous variables. Normality test was performed. Statistical significance (α) was set at $p < 0.05$. All tests were two-tailed.

2.2.4 Ethical Considerations

Confidentiality was assured during the study with patient's privacy, a Letter of ethical clearance was obtained from the Institutional Review Board (IRB) of Near East University Hospital.

3. Results

A total of 133 patients were admitted to the wards during the 4-month study period. The clinical pharmacist reviewed all the patients, and 81 patients (60.9%) experienced at least one DRP.

A total of 217 DRPs were identified (mean DRP per patient, 1.6 ± 1.7, 95% CI = 1.33–1.93).

Tables 1,2 and 3 provide the baseline characteristics of all patients and DRP status.

The mean patients age was 66.4 ± 10.0 years and 57.1% of the patients were male. The demographic distribution did not vary by DRP status. However, patients varied by body mass index (BMI). Patients with DRPs exhibited a higher mean BMI than patients without DRPs (29.1 ± 5.5 vs. 24.8 ± 7.5, p = 0.0006) (Table 1).

Table 1 Baseline demographic and social history-related characteristics in patients according to DRP status, n (%), mean ± S.D.

	Total	With DRP	Without DRP
Number	133(100%)	81(60.9%)	52(39.1%)
Demographics			
Age, years	66.4±10.0	67.2±10.1	65.2±9.8
Sex, Male	76(57.1)	52(64.2)	24(46.2)
Female	57(42.9)	29(35.8)	28(53.8)
Social History			
Smoke, currently	52(39.1)	37(45.7)	15(28.8)
Alcohol, currently	33(24.8)	20(24.7)	13(25.0)
Caffeine	49(36.8)	29(35.8)	20(38.4)
Exercise	25(18.8)	13(16.0)	12(23.1)
BMI[a]	27.4±6.7	29.1±5.5	24.8±7.5*

S.D. Standard deviation.

a Body mass index(kg/m2).

** p=0.0006.*

Patients with DRPs experienced a greater mean number of medications used than patients without DRPs (10.8 ± 3.6 vs. 8.1 ± 2.8, *p < 0.0001*). The major three medication classes prescribed were beta-blockers (74.4%), proton pump inhibitors (PPIs) (63.2%), and antiplatelet agents

(62.4%). Patients with DRPs exhibited a greater use of medications such as diuretics, anticoagulants, PPIs, antibiotics, and antidepressants than patients without DRPs (Table 2).

Table 2 Baseline medication class and diet supplement-related characteristics in patients according to DRP status, n (%), mean ± S.D.

	Total	With DRP	Without DRP
Number	133(100%)	81(60.9%)	52(39.1%)
Medication related characteristics			
Medication numbers	9.8±3.5	10.8±3.6	8.1±2.8***
Beta-blockers	99(74.4)	65(80.2)	34(65.4)
ACE/ARB inhibitors[a]	76(57.1)	45(55.6)	31(59.6)
Calcium channel blockers	35(26.3)	17(21.0)	18(34.6)
Alpha blockers	11(8.2)	7(8.6)	4(7.7)
Diuretics	74(55.6)	61(75.3)	13(25.0) ***
Digitalis glycosides	12(9.0)	10(12.3)	2(3.8)
Antihyperlipidemic agents	48(36.1)	28(34.6)	20(38.5)
Nitrovasodilators	45(33.8)	23(28.4)	22(42.3)
Anti-arithmetic agents	16(12.0)	12(14.8)	4(7.7)
Anticoagulants	66(49.6)	49(60.5)	17(32.7) **
Antiplatelet agents	83(62.4)	53(65.4)	30(57.7)
Miscellaneous cardiovascular agents [b]	11(8.3)	10(12.3)	1(1.9)
Antidiabetic agents	46(34.6)	29(35.8)	17(32.7)
Proton pump inhibitors	84(63.2)	60(74.1)	24(46.2) **
Thyroid hormones	20(15.0)	13(16.0)	7(13.5)
NSAIDs [c]	13(9.8)	8(9.9)	5(9.6)
Antibiotics	44(33.9)	33(40.7)	11(21.2) *
Anxiolytics	24(18.0)	15(18.5)	9(17.3)
Antidepressants	26(19.5)	21(25.9)	5(9.6) *
Antihyperuricemic agents	24(18.0)	16(19.8)	8(15.4)
Beta agonists	11(8.3)	6(7.4)	5(9.6)
Corticosteroids	13(9.8)	6(7.4)	7(13.5)
Laxatives	36(27.1)	24(29.6)	12(23.1)
Others	30(22.6)	17(21.0)	13(25.0)
Diet supplement-related characteristics			
Diet supplement numbers	0.6±0.8	0.6±0.7	0.7±0.8
Vitamins	20(15.0)	11(13.9)	9(17.3)
Minerals	14(10.5)	12(14.8)	2(3.8)
Polyunsaturated fatty acids	23(17.3)	12(14.8)	11(21.2)
Herbs	15(11.3)	7(8.6)	8(15.4)

a Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers.

b Ivabradine

c Nonsteroidal anti-inflammatory drugs

** p<0.05.*

*** p<0.005.*

**** p<0.0001.*

Simple linear regression analysis showed a positive or direct association between number of medications per patient and DRPs (correlation coefficient (r) = 0.4080, r2 = 0.1665, standard deviation of residuals from line (Sy.x) = 1.601, p < 0.0001).

Patients with DRPs exhibited a greater mean incidence of chronic conditions than patients without DRPs (4.4 ± 1.8 vs. 2.7 ± 0.8, *p < 0.0001*). The most common three conditions noted in patients were systemic arterial hypertension (71.4%), coronary heart disease (45.9%), and congestive heart failure (42.1%). Congestive heart failure, atrial fibrillation, and renal failure were noted more in patients with DRPs than in patients without DRPs. Patients with DRPs also exhibited a lower mean creatinine clearance than patients without DRPs (66.2 ± 41.6 vs. 83.5 ± 31.3, *p < 0.05*) (Table 3).

Table 3 Baseline Disease and creatinine-related characteristics among patients by DRP status, n (%), mean ± S.D.

Number	Total 133(100%)	With DRP 81(60.9%)	Without DRP 52(39.1%)
Disease-related characteristics			
Chronic conditions	3.7±1.7	4.4±1.8	2.7±0.8***
Systemic arterial hypertension	95(71.4)	63(77.8)	32(61.5)
Diabetes mellitus	44(33.1)	31(38.3)	13(25.0)
Congestive heart failure	56(42.1)	49(60.5)	7(13.5) ***
Renal failure	16(12.0)	16(19.8)	0(0.0) **
Coronary heart disease	61(45.9)	40(49.4)	21(40.4)
Acute coronary syndrome	33(24.8)	23(28.4)	10(19.2)
Atrial fibrillation	22(16.5)	19(23.5)	3(5.8) *
Cerebrovascular accident	12(9.5)	7(8.6)	5(9.6)
Hyperlipidemia	33(24.8)	25(30.9)	8(15.4)
Atherosclerosis	7(5.3)	6(8.6)	1(1.9)

Primary pulmonary hypertension	5(3.7)	4(4.9)	1(1.9)
Aortic stenosis	6(4.5)	4(4.9)	2(3.8)
Asthma	7(5.3)	2(2.5)	5(9.6)
Chronic obstructive pulmonary disease	8(6.0)	4(4.9)	4(7.7)
Benign prostatic hyperplasia	10(7.5)	6(7.4)	4(7.7)
Hypothyroidism	20(15.0)	13(16.0)	7(13.5)
Anemia	18(13.5)	15(18.5)	3(5.8)
Other	39(29.3)	26(32.1)	13(25.0)
Creatinine-related characteristics			
Creatinine clearance (ml/min)	72.9±38.7	66.2±41.6	83.5±31.3*
Creatinine clearance adjustment for height (ml/min)	65.2±33.1	56.4±33.0	78.8±28.6*

** p<0.05.*

*** p<0.005.*

**** p<0.0001.*

Simple linear regression analysis showed a positive or direct association between number of chronic conditions per patient and DRPs (correlation coefficient (r) = 0.4517, r2 = 0.2040, standard deviation of residuals from line (Sy.x) =1.565, $p < 0.0001$).

The four main used medication classes that resulted in DRPs were diuretics (15.0%), PPIs (13.9%), anticoagulants (12.7%), and beta-blockers (10.8%).

Treatment effectiveness was the major type of DRPs (107 of 217 DRPs; 49.3%), followed by adverse drug reactions (74; 34.1%), treatment costs (32; 14.7%) (Table 4).

Table 4 Identified problems according to the PCNE DRP classification tool V6.2.

Code V6.2	Type of Problem	Total number =217(100.0%)
P1	Treatment effectiveness	107(49.3)
P1.1	No effect of drug treatment/therepy failure	5(2.3)
P1.2	Effect of drug treatment not optimal	62(28.6)
P1.3	Wrong effect of drug treatment	13(6.0)
P1.4	Untreated indication	27(12.4)
P2	Adverse reactions	74(34.1)
P2.1	Adverse drug event (non-allergic)	69(31.8)
P2.2	Adverse drug event (allergic)	4(1.8)
P2.3	Toxic adverse drug event	1(0.5)

P3	Treatment costs	32(14.7)
P3.1	Drug treatment more costly than necessary	2(0.9)
P3.2	Unnecessary drug treatment	30(13.8)
P4	Other	4(1.8)
P4.1	Patient dissatisfied with therapy	4(1.8)
P4.2	Unclear problem	0(0.0)

ACE/ARB inhibitors (21; 19.6%) were the primary DRP associated with treatment effectiveness, and beta-blockers (8; 10.8%) were the main DRP in "adverse reactions" category. Antibiotics (5; 15.6%) were the major DRP in the "treatment costs" category. PPIs (4; 100%) were the only drugs in the "other" category, and few PPI patients were dissatisfied with this therapy (Table 5).

Table 5 Baseline medication class and diet supplement-related characteristics according to DRP type using the PCNE DRP classification tool V6.2. code, n (%).

Number	P1 107(49.3%)	P2 74(34.1%)	P3 32(14.7%)	P4 4(1.8%)	Total number =217(100.0%)
Medication numbers	100(93.5)	68(91.9)	30(93.8)	4(100.0)	202(93.1)
Beta-blockers	11(10.3)	8(10.8)	1(3.1)	0(0.0)	20(9.2)
ACE/ARB inhibitors [a]	21(19.6)	6(8.1)	1(3.1)	0(0.0)	28(12.9)
Calcium channel blockers	4(3.7)	4(5.4)	0(0.0)	0(0.0)	8(3.7)
Alpha blockers	0(0.0)	1(1.4)	1(3.1)	0(0.0)	2(0.9)
Diuretics	5(4.7)	21(28.4)	1(3.1)	0(0.0)	27(12.4)
Digitalis glycosides	2(1.9)	1(1.4)	0(0.0)	0(0.0)	3(1.4)
Antihyperlipidemic agents	5(4.7)	0(0.0)	1(3.1)	0(0.0)	6(2.8)
Nitrovasodilators	0(0.0)	2(2.7)	1(3.1)	0(0.0)	3(1.4)
Anti-arithmetic agents	0(0.0)	0(0.0)	2(6.3)	0(0.0)	2(0.9)
Anticoagulants	14(13.1)	7(9.5)	3(9.4)	0(0.0)	24(11.1)
Antiplatelet agents	3(2.8)	4(5.4)	2(6.3)	0(0.0)	9(4.1)
Miscellaneous cardiovascular agents [b]	5(4.7)	0(0.0)	0(0.0)	0(0.0)	5(2.3)
Antidiabetic agents	0(0.0)	7(9.5)	0(0.0)	0(0.0)	7(3.2)
Proton pump inhibitors	20(18.7)	0(0.0)	2(6.3)	4(100.0)	26(12.0)
Thyroid hormones	1(0.9)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
NSAIDs [c]	4(3.7)	1(1.4)	0(0.0)	0(0.0)	5(2.3)
Antibiotics	0(0.0)	3(4.1)	5(15.6)	0(0.0)	8(3.7)
Anxiolytics	1(0.9)	0(0.0)	3(9.4)	0(0.0)	4(1.8)
Antidepressants	1(0.9)	0(0.0)	4(12.5)	0(0.0)	5(2.3)
Antihyperuricemic agents	1(0.9)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Beta agonists	1(0.9)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Corticosteroids	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Laxatives	0(0.0)	1(1.4)	0(0.0)	0(0.0)	1(0.5)
Others	1(0.9)	2(2.7)	3(9.4)	0(0.0)	6(2.8)

Diet supplement numbers	7(6.5)	6(8.1)	2(6.3)	0(0.0)	15(6.9)
Vitamins	1(0.9)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Minerals	6(5.6)	5(6.8)	0(0.0)	0(0.0)	11(5.1)
Polyunsaturated fatty acids	0(0.0)	1(1.4)	0(0.0)	0(0.0)	1(0.5)
Herbs	0(0.0)	0(0.0)	2(6.3)	0(0.0)	2(0.9)

Abbreviations:
P1 Treatment effectiveness.
P2 Adverse reactions.
P3 Treatment costs.
P4 Other.
[a] *Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers.*

[b] *Ivabradine*

[c] *Nonsteroidal anti-inflammatory drugs*

Drug selection was the major cause of DRPs (118; 44.9%) followed by dose selection (76; 22.9%).

A total of 263 DRP causes were identified (Table 6).

Table 6 Identified causes of DRPs according to the PCNE DRP classification tool V6.2.

Code V6.2	Cause of the problem	Total number =263(100.0%)
C1	Drug selection	118(44.9)
C1.1	Inappropriate drug (include contra-indication drug)	20(7.6)
C1.2	No indication for drug	27(10.3)
C1.3	Inappropriate combination of drugs or drug and food	5(1.9)
C1.4	Inappropriate duplication	9(3.4)
C1.5	Unnoticed indication	11(4.2)
C1.6	Too many drugs for indication	3(1.1)
C1.7	More cost-effective drug available	2(0.8)
C1.8	Synergetic or preventive drug available	33(12.5)
C1.9	New indication presented	8(3.0)
C2	Drug form	1(0.4)
C2.1	Inappropriate drug form	1(0.4)
C3	Dose selection	76(28.9)
C3.1	Drug dose too low	16(6.1)
C3.2	Drug dose too high	37(14.1)
C3.3	Dosage regimen not frequent enough	2(0.8)
C3.4	Dosage regimen too frequent	4(1.5)
C3.5	No therapeutic drug monitoring	6(2.3)
C3.6	Pharmacokinetic problem requiring dose adjustment	1(0.4)
C3.7	Deterioration/improvement of disease requiring dose adjustment	10(3.8)
C4	Treatment duration	3(1.1)

C4.2	Duration of treatment too long	3(1.1)
C5	Drug use / administration process	21(8.0)
C5.1	Inappropriate timing of administration / dosing intervals	19(7.2)
C5.2	Drug underused / under administered	2(0.8)
C6	Logistics	0(0)
C7	Patient	1(0.4)
C7.1	Patient forgets to take drug	1(0.4)
C8	Other	43(16.3)
C8.1a	Drug pharmacological side effect	35(13.3)
C8.1b	Patient uncomfortable with drug	8(3.0)

ACE/ARB inhibitor DRP causes were the main DRP in the “Drug selection” category (21; 17.8%), and beta-blocker DRPs were the major DRP in the “Dose selection” category (16; 21.1%), PPI DRP causes were the primary DRP in the “Drug use/administration” category (17; 81.0%) (Table 7).

Table 7 Baseline medication class and diet supplement-related characteristics among DRP causes according to the PCNE DRP classification tool V6.2. code, n (%).

Number	C1 118(44.9%)	C2 1(0.4%)	C3 76(28.9%)	C4 3(1.1%)	C5 21(8.0%)	C7 1(0.4%)	C8 43(16.3%)	Total number =263(100.0%)
Medication numbers	103(87.3)	1(100.0)	76(100.0)	3(100.0)	21(100.0)	1(100.0)	42(97.7)	247(93.9)
Beta-blockers	4(3.4)	0(0.0)	16(21.1)	0(0.0)	0(0.0)	1(100)	6(14)	27(10.3)
ACE/ARB inhibitors	21(17.8)	0(0.0)	3(3.9)	0(0.0)	0(0.0)	0(0.0)	6(14)	30(11.4)
Calcium channel blockers	4(3.4)	0(0.0)	5(6.6)	0(0.0)	0(0.0)	0(0.0)	2(4.7)	11(4.2)
Alpha blockers	1(0.8)	0(0.0)	1(1.3)	0(0.0)	0(0.0)	0(0.0)	1(2.3)	3(1.1)
Diuretics	4(3.4)	1(100.0)	15(19.7)	0(0.0)	3(14.3)	0(0.0)	16(97.2)	39(14.9)
Digitalis glycosides	4(3.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	4(1.5)
Antihyperlipidemic agents	4(3.4)	0(0.0)	3(3.9)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	7(2.7)
Nitrovasodilators	1(0.8)	0(0.0)	1(1.3)	0(0.0)	0(0.0)	0(0.0)	1(2.3)	3(1.1)
Anti-arithmetic agents	2(1.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(0.8)
Anticoagulants	8(6.8)	0(0.0)	15(19.7)	0(0.0)	0(0.0)	0(0.0)	2(4.7)	25(9.5)
Antiplatelet agents	7(5.9)	0(0.0)	1(1.3)	0(0.0)	0(0.0)	0(0.0)	3(7.0)	11(4.2)
Miscellaneous cardiovascular agents	4(3.4)	0(0.0)	1(1.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	5(1.9)
Antidiabetic agents	7(5.9)	0(0.0)	13(17.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	20(7.6)
Proton pump inhibitors	6(5.1)	0(0.0)	1(1.3)	0(0.0)	17(81.0)	0(0.0)	4(9.3)	28(10.6)
Thyroid hormones	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(4.8)	0(0.0)	0(0.0)	1(0.4)
NSAIDs	4(3.4)	0(0.0)	1(1.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	5(1.9)
Antibiotics	5(4.2)	0(0.0)	0(0.0)	3(100.0)	0(0.0)	0(0.0)	0(0.0)	8(3.0)
Anxiolytics	4(3.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	4(1.5)
Antidepressants	5(4.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	5(1.9)
Antihyperuricemic agents	1(0.8)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.4)
Beta agonists	1(0.8)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.4)
Corticosteroids	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Laxatives	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(2.3)	1(0.4)

Others	6(5.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	6(2.3)
Diet supplement numbers	15(12.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(2.3)	16(6.1)
Vitamins	1(0.8)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.4)
Minerals	10(8.5)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(2.3)	11(4.2)
Polyunsaturated fatty acids	2(1.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(0.8)
Herbs	2(1.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(0.8)

Abbreviations:
C1 Drug selection.
C2 Drug form.
C3 Dose selection.
C4 Treatment duration.
C5 Drug use / administration process.
C6 Logistics.
C7 Patient.
C8 Other.
[a] *Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers.*

[b] *Ivabradine*

[c] *Nonsteroidal anti-inflammatory drugs*

**None of the causes of the DRPs were related to the logistics of the prescribing or dispensing process. Therefore, C6 is not mentioned in the table.*

A total of 432 interventions were suggested (mean number of interventions per patient, 3.2 ± 0.3, 95% CI = 2.65–3.84), and 402 (93.1%) interventions were accepted and regarded as clinically relevant. While 24 (5.6%) interventions were not accepted by prescribing physicians, and 6 (1.4%) interventions were not accepted by patients. Most interventions occurred at the prescriber level (220; 50.9%) (Table 8).

Table 8 Proposed interventions according to the PCNE DRP classification tool V6.2.

Code V6.2	Type of intervention	Total number =432(100.0%)
I0	No intervention	0(0)
I1	At prescriber level	220(50.9)
I1.2	Prescriber asked for information	3(0.7)
I1.3	Intervention proposed approved by prescriber	193(44.7)
I1.4	Intervention proposed not approved by prescriber	24(5.6)
I2	At patient / care level	21(4.9)
I2.1	Patient (medication) counselling	21(4.9)
I3	At drug level	191(44.2)

I3.1	Drug changed	7(1.6)
I3.2	Dosage changed	63(14.6)
I3.3	Formulation changed	2(0.5)
I3.4	Instructions for use changed	23(5.3)
I3.5	Drug stopped	50(11.6)
I3.6	New drug started	46(10.6)
I4	Other	0(0)

The clinical pharmacist suggested the addition of 51 drugs to the treatment plan as part of intervention. However, physicians accepted 46 (90.2%) drugs as clinically relevant interventions. The major suggested medication classes were ACE/ARB inhibitors (39.2%), minerals (11.8%), anticoagulants (7.8%), beta-blockers (5.9%), antihyperlipidemic agents (5.9%), and PPIs (5.9%). The main medication classes that were stopped by physicians based on the clinical pharmacist's suggestions were antibiotics (14.0%), diuretics (12.0%), and NSAIDs (10.0%).

A total of 217 DRPs were identified, and 171 (78.8%) DRPs were solved, while 4 (1.8%) DRPs were partially solved, 32 (14.7%) DRPs were unsolved, and 10 DRPs (4.6%) had unknown outcomes (Table 9).

Table 9: Outcomes according to the PCNE DRP classification tool V6.2.

Code V6.2	Outcome of intervention	Total number =217(100.0%)
O0	Outcome of intervention unknown	10(4.6)
O1	Problem totally solved	171(78.8)
O2	Problem partially solved	4(1.8)
O3	Problem not solved	32(14.7)
O3.1	Lack of cooperation of patient	6(2.8)
O3.2	Lack of cooperation of prescriber	24(11.1)
O3.3	Intervention not effective	2(0.9)
O3.4	No need or possibility to solve problem	0(0)

PPIs 5 (15.6%), anticoagulants 3(9.4%), anti-depressants 3(9.4%), anxiolytics 3(9.4%), beta-blockers 3(9.4%), ACE/ARB inhibitors 3(9.4%) were the most medication classes that associated with unsolved DRPs.

4.Discussion

Several studies in cardiology clinics showed different mean number of DRPs per patient. For example, an 8-month study in the general medicine and cardiology departments in a tertiary care hospital in Coimbatore, India, reported a mean of 4.9 DRPs per patient. Also, 394 DRPs were identified in 80 patients [108]. While a 5-week study in a cardiology clinic at a teaching hospital in Nitra, Slovakia, reported a mean of 1.3 DRPs per patient. Also, 73 medication records were analyzed where minimally one DRP was found in 27 (37%) medication records, and 36 DRPs were identified [107]. However, this study reviewed 133 patients, and 81 (60.9%) patients experienced at least one DRP. The total number of DRPs identified was 217 (mean number of DRPs per patient, 1.6 ± 1.7, 95% CI = 1.33–1.93). These studies varied between countries by patient number, study duration, presence of a clinical pharmacist prior to the study, physician collaboration and many other factors.

Age and gender may not be as important as the number of drugs prescribed as predictors of experiencing a DRP in patients with polypharmacy [109]. The number of drugs used by the patient was a risk predictors for developing DRPs in patients with CVDs in a cardiology ward [110]. However, the average patient age was 66.4 years in this study, which indicates that most patients were geriatric. Polypharmacy was obvious because the average number of medicines prescribed per patient was 9.8 ± 3.5. The number of chronic conditions per patient was 3.7 ± 1.7, which corresponds to obvious multiple morbidities. Also, In the present study, DRPs increased with

increasing numbers of medications per patient, and with increasing number of chronic conditions per patient.

Patients with DRPs used diuretics, anticoagulants, PPIs, antibiotics, and antidepressants more often than patients without DRPs. The four primary medication classes associated with DRPs were diuretics (15.0%), PPIs (13.9%), anticoagulants (12.7%), and beta-blockers (10.8%). The main problem with the prescribing diuretics was ADRs because of the high dose prescribed. PPIs, anticoagulants, and beta-blockers shared the same type of problem, which was decreased treatment effect despite the difference in causes. In contrast, the wrong time of administration was the major PPI-related problem, and the uncontrolled international normalized ratio (INR) was the major anticoagulant-related problem. The low dose of prescribed beta-blockers was the major cause of the noted problems associated with this drug class. Antibiotics and antidepressants shared the same type and cause of DRPs, which were given as unnecessary treatment with no specific indication. The duration of some antibiotic treatment plans was too long, which led to a higher cost for the patient.

ACE/ARB inhibitors are the first-line of treatment for CHF [111]. These drugs were the major medication class (39.2%) that the clinical pharmacist suggested be added to patients' treatment plans because of the failure of physicians to consider these drugs. The failure of consideration increased the incidence of DRPs in patients with CHF ($p < 0.0001$). Uncontrolled INR increased the susceptibility to DRPs in patients with atrial fibrillation ($p < 0.05$). All patients with renal failure exhibited at least one DRP ($p < 0.005$), and patients with DRPs were more susceptible to lower creatinine clearance values ($p < 0.05$).

Another study used the same tool as that in the present study to classify DRPs. This study was performed in the cardiology clinic at a teaching hospital and showed that ADRs were a major type of DRPs (77.8%) [107]. However, the present study revealed treatment effectiveness as a major type of DRPs (107; 49.3%) and adverse drug events (non-allergic) as the most common DRP subtype (69; 31.8%).

Drug pharmacological side effect was one of the major sub-causes of DRPs (35; 13.3%), which was not classified as a choice in the PCNE DRP classification tool V6.2. Therefore, these effects were included in a the “Other” category. This mandatory inclusion of one of the major sub-causes of DRPs in the “Other” category is a major defect in the PCNE DRP classification tool V6.2, because it is not necessary to have any other cause of DRP other than pharmacological side effects.

The interventions in this study were highly accepted (93.1%), which is comparable to the finding in previous studies of the implementation of clinical pharmacy services in different wards and clinics in the United States (95%) [112]. Studies in Europe also reported CPS acceptance rate between 69% and 89%, which is considered high [113-116]. However, the acceptance rate in Jordan was reported to be 69.4% [117].

The high rate of acceptance indicates that the interventions were relevant and highly effective for physicians, especially in determining the treatment plan for patients. This high acceptance rate also supports the strong trust and professional relationship between physicians and the clinical pharmacist.

This study findings have the following Impacts on practice; First, Show the importance and effectiveness of clinical pharmacy services in cardiovascular clinics and the role of these

services in minimizing and resolving drug-related problems. Also, Alert healthcare providers in cardiovascular clinics to drugs that are more associated with drug-related problems and the types and causes of these problems. Finally, encourage other physicians to cooperate with clinical pharmacists to resolve drug-related problems by showing the highly successful rate of resolved problems due to the collaboration of physicians and the clinical pharmacist.

The present study has the following limitations; First, the lack of a control group for comparisons. Also, a major limitation is being unable to evaluate the effect of interventions based on hard clinical end-points (e.g., disease events) due to timing limitation, and difficulty of obtaining patient information post discharge, since there are no national unified patient records in Cyprus. Finally, being a single centered study also limits generalizing its findings. Thus, I recommend further controlled multicenter studies, where interventions are evaluated regarding both updated therapy guidelines and clinical end point, to further characterize DRPs incidence and the role of clinical pharmacist's interventions.

5. Conclusion

A high prevalence of DRPs was been noticed in cardiovascular patients. However, CPS may have optimized therapy effectiveness and prevented of adverse effects. These effects were especially noted in patients with altered renal function. The clinical pharmacist interventions were highly accepted by cardiologists, which showed the trust and professional relationship between physicians and the clinical pharmacist. The successful cooperation between medical professionals highlights a great opportunity to optimize and implement CPS in other hospitals in Northern Cyprus and Turkey. The results of this study provide baseline information on the most common medication classes that tend to produce DRPs in a cardiology clinic.

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Appendix I: Patient's data form.

Name: M/F Admit Date: Room: Unit:

File #:

Age: Wt: BMI: Ht: CrCl(ml/min): | | | | | | |

Allergies:

SH: smoker (y/p): Alcohol: Caffeine: Diet: Exercise:

CC:

HPI:

DX:

PMH:

PHM:

FH:

Admission medications: _____ _____

_____ _____ _____

_____ _____ _____

_____ _____ _____

_____ _____ _____

_____ _____ _____

_____ _____ _____

Current medications:

date	Generic (Brand)	Dose & sig	changes

Pertinent labs:						
Lab	Value/date	Date/value	Date/value	Date/value	Date/value	Ref value
Cr						0.5-1.5 mg/dl
BUN						8-25 mg/dl
Na+						135-145 meq/l
K+						3.5-5.1 meq/l
Cl-						92-109 meq/l
HCO3-						24-31 meq/l
PT/INR						11-13 sec /2.0-3.0
PTT						25-35 sec
INR						
WBC						4.5-10 103/μl
Hgb						14-18/12-16 g/dl
Hct						40-52/37-47%
MCV						80-95 μm^3
Plt						150-400 103/μl
Diff						
Smear						
Glc						80-110 mg/dl
Ca++						8.0-10.5 mg/dl
Glc						80-110 mg/dl
Ca++						8.0-10.5 mg/dl
P						2.5-5 mg/dl
Mg++						1.5-2.4 mg/dl
TPr						6-8 g/dl
Alb						4-6g/dl

Alk P						30-120 U/L
AST/						0-35 IU/L
ALT/						0-35 U/L
Tbili						0-1 mg/dl
Others						

Vital Signs:

Date	Temperature	Pulse	Respiratory Rate	Blood Pressure	Pain	Oxygen saturation

Patient story:

Patient problems:

Medications problems:

Drug -Drug interactions:

Cause of these interactions:

How to avoid these interactions:

Treatment strategy for short period:

Treatment strategy for long period:

Appendix II: PCNE Classification scheme for Drug-Related Problems V6.2

The basic classification

	Code V6.2	Primary domains
Problems	P1	**Treatment effectiveness** There is a (potential) problem with the (lack of) effect of the pharmacotherapy
	P2	**Adverse reactions** Patient suffers, or will possibly suffer, from an adverse drug event
	P3	**Treatment costs** The drug treatment is more expensive than necessary
	P4	**Others**
Causes	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 therapy
	C5	**Drug use/administration process** The cause of the DRP can be related to the way the patient uses the drug or gets the drug administered, in spite of proper instructions (on the label, package or leaflet)
	C6	**Logistics** The cause of the DRP can be related to the logistics of the prescribing and dispensing process
	C7	**Patient** The cause of the DRP can be related to the personality or behaviour of the patient.
	C8	**Other**
Interventions	I0	**No intervention**
	I1	**At prescriber level**
	I2	**At patient (or carer) level**
	I3	**At drug level**
	I4	**Other**
Outcome of intervention	O0	**Outcome intervention unknown**
	O1	**Problem totally solved**
	O2	**Problem partially solved**
	O3	**Problem not solved**

The Problems

Primary Domain	Code V6.2	Problem
1.Treatment effectiveness There is a (potential) problem with the (lack of) effect of the pharmacotherapy	**P1.1** **P1.2** **P1.3** **P1.4**	No effect of drug treatment/ therapy failure Effect of drug treatment not optimal Wrong effect of drug treatment Untreated indication
2. Adverse reactions Patient suffers, or will possibly suffer, from an adverse drug event	**P2.1** **P2.2** **P2.3**	Adverse drug event (non-allergic) Adverse drug event (allergic) Toxic adverse drug-event
3. Treatment costs The drug treatment is more expensive than necessary	**P3.1** **P3.2**	Drug treatment more costly than necessary Unnecessary drug-treatment
4. Others	**P4.1** **P4.2**	Patient dissatisfied with therapy despite optimal clinical and economic treatment outcomes *Unclear problem/complaint. Further clarification necessary (please use as escape only)*

The Causes

N.B. One problem can have more causes

Primary Domain	Code V6.2	Cause
1. Drug selection The cause of the DRP is related to the selection of the drug	C1.1	Inappropriate drug (incl. contra-indicated)
	C1.2	No indication for drug
	C1.3	Inappropriate combination of drugs, or drugs and food
	C1.4	Inappropriate duplication of therapeutic group or active ingredient
	C1.5	Indication for drug-treatment not noticed
	C1.6	Too many drugs prescribed for indication
	C1.7	More cost-effective drug available
	C1.8	Synergistic/preventive drug required and not given
	C1.9	New indication for drug treatment presented
2. Drug form The cause of the DRP is related to the selection of the drug form	C2.1	Inappropriate drug form
3. Dose selection The cause of the DRP is related to the selection of the dosage schedule	C3.1	Drug dose too low
	C3.2	Drug dose too high
	C3.3	Dosage regimen not frequent enough
	C3.4	Dosage regimen too frequent
	C3.5	No therapeutic drug monitoring
	C3.6	Pharmacokinetic problem requiring dose adjustment
	C3.7	Deterioration/improvement of disease state requiring dose adjustment
4. Treatment duration The cause of the DRP is related to the duration of therapy	C4.1	Duration of treatment too short
	C4.2	Duration of treatment too long
5. Drug use process The cause of the DRP can be related to the way the patient uses the drug, in spite of proper dosage instructions (on the label)	C5.1	Inappropriate timing of administration and/or dosing intervals
	C5.2	Drug underused/ under-administered (deliberately)
	C5.3	Drug overused/ over-administered (deliberately)
	C5.4	Drug not taken/administered at all
	C5.5	Wrong drug taken/administered
	C5.6	Drug abused (unregulated overuse)
	C5.7	Patient unable to use drug/form as directed
6. Logistics The cause of the DRP can be related to the logistics of the prescribing and dispensing process	C6.1	Prescribed drug not available
	C6.2	Prescribing error (necessary information missing)
	C6.3	Dispensing error (wrong drug or dose dispensed)
7. Patient The cause of the DRP can be related to the personality or behaviour of the patient.	C7.1	Patient forgets to use/take drug
	C7.2	Patient uses unnecessary drug
	C7.3	Patient takes food that interacts
	C7.4	Patient stored drug inappropriately
8. Other	C8.1	Other cause; specify
	C8.2	No obvious cause

The Interventions

N.B. One problem can lead to more interventions

Primary Domain	Code V6.2	Intervention
No intervention	**I0.0**	No Intervention
1. At prescriber level	**I1.1**	Prescriber informed only
	I1.2	Prescriber asked for information
	I1.3	Intervention proposed, **approved** by Prescriber
	I1.4	Intervention proposed, **not approved** by Prescriber
	I1.5	Intervention proposed, outcome unknown
2. At patient/carer level	**I2.1**	Patient (medication) counselling
	I2.2	Written information provided only
	I2.3	Patient referred to prescriber
	I2.4	Spoken to family member/caregiver
3. At drug level	**I3.1**	Drug changed to ….
	I3.2	Dosage changed to ….
	I3.3	Formulation changed to …..
	I3.4	Instructions for use changed to …..
	I3.5	Drug stopped
	I3.6	New drug started
4. Other intervention or activity	**I4.1**	Other intervention (specify)
	I4.2	Side effect reported to authorities

The Outcome of the Interventions

N.B. One problem (or the combination of interventions) can only lead to one level of solving the problem

Primary Domain	Code V6.2	Outcome of intervention
0. Not known	**O0.0**	Outcome intervention not known
1. Solved	**O1.0**	Problem totally solved
2. Partially solved	**O2.0**	Problem partially solved
3. Not solved	**O3.1**	Problem not solved, lack of cooperation of patient
	O3.2	Problem not solved, lack of cooperation of prescriber
	O3.3	Problem not solved, intervention not effective
	O3.4	No need or possibility to solve problem