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DISSERTATION

„Renal clinical pharmacy services“

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e pensando di lei
mi sopragiunse
uno soave sonno

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in amarissimo pianto

io sono in pace
cor meum
io sono in pace
vide cor meum

Dante Alighieri
La Vita Nuova
~1293

Gewidmet meinen Eltern Annelies und Franz, in aufrichtiger Dankbarkeit und Liebe

Dedicated to my parents Annelies and Franz, in sincere gratitude and love

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1 INTRODUCTION AND FUNDAMENTAL PRINCIPLES

1.1 DEFINITIONS, CONCEPTS, AND TERMINOLOGY

1.1.1 HOSPITAL PHARMACY

According to the definition of the European Association of Hospital Pharmacists (EAHP), hospital pharmacy is “the health care service, which comprises the art, practice, and profession of choosing, preparing, storing, compounding, and dispensing medicines and medical devices, advising healthcare professionals and patients on their safe, effective and efficient use. Hospital pharmacy is a specialised field of pharmacy which forms an integrated part of patient health care in a health facility“ (EAHP 2010).

The centre and overarching goal of hospital pharmacists regarding all medicine-related activities in the hospital is to apply the “seven rights”, which are as follows: the right patient, the right medicine, the right dose, the right route, the right time, and the right information and documentation. The focus lies on optimisation of patient outcomes through the judicious, safe, efficacious, appropriate, and cost-effective use of medicines (EAHP 2010).

Hospital pharmacy originated primarily in response to the needs of hospitals regarding drugs and other pharmacy goods and the structure of their different clinics.
The duties of the hospital pharmacist encompass each step of the medicine use process (Figure 1).

Figure 1: The medicine use process (FIP 2008)

Within this process, several duties and responsibilities are addressed by the hospital pharmacist. These duties can be roughly divided into three main areas (ÖAK 2000):

- Tasks regarding the supply of drugs and other pharmacy goods (e.g., chemicals and reagents) or medicinal products (e.g., dressings, sutures, and diagnostics). This area also includes storage and dispensation of drugs.

- Drug production and individual patient-specific compounding activities. Here, the hospital pharmacist often addresses unmet needs regarding the production of drugs that are not provided by the pharmaceutical industry and of individualised extemporaneous preparations (e.g., patient-specific ointments and capsules for children).
- Other pharmaceutical services, which comprise interdisciplinary activities (e.g., collaboration in working groups, including pain team, wound management team, and others), the provision of drug information to other healthcare providers and patients, and the provision of ward-based services (i.e., clinical pharmacy services).

1.1.2 CLINICAL PHARMACY

Several definitions of clinical pharmacy are published in the medical and pharmaceutical literature, and these definitions describe the concept of clinical pharmacy services as well as their objectives, scope, and contents (Table 1).

American Association of Colleges of Pharmacy	1968	"Clinical Pharmacy is that area within the pharmacy curriculum which deals with patient care with emphasis on drug therapy. Clinical pharmacy seeks to develop a patient-oriented attitude. Acquisition of new knowledge is secondary to attainment of skills in interprofessional and patient communication." (MEYER et al. 2003)
European Society of Clinical Pharmacy (ESCP)	1983	"A Clinical Pharmacist is a health care provider promoting the effective, safe, and rational use of drugs by the individual and by the society." (MEYER et al. 2003)
Bundesvereinigung Deutscher Apothekerverbände (ABDA), Deutsche Pharmazeutische Gesellschaft (DPhG)	1997	„Clinical pharmacy is the discipline of pharmacy, which aims at optimising the use of drugs in and by the patient on the basis of pharmaceutical and natural scientific knowledge." (literally translated from MEYER et al. 2003)
American College of Clinical Pharmacy (ACCP)	2004	"A health science discipline that embodies the application and development, by pharmacists, of scientific principles of pharmacology, toxicology, therapeutics, clinical pharmacokinetics, pharmacoeconomics, pharmacogenomics, and other life sciences for the care of patients." (ACCP 2008)
United Kingdom Clinical Pharmacy Association (UKCPA)	-	"Clinical pharmacy encompasses the knowledge, skills and attitudes required by pharmacists to contribute to patient care." (FRANKLIN and VAN MIL 2005)

Table 1: Definitions of clinical pharmacy

The term 'clinical pharmacy' (Klinische Pharmazie, in German) is not used consistently. In the German language, the term 'Patientenorientierte Pharmazie' (literally translated 'patient-oriented pharmacy') is often used synonymously.

The adjective 'clinical' suggests a narrow scope of clinical pharmacy services that are limited to hospitalised patients. However, clinical pharmacy can also be provided in areas outside of the hospital, e.g., nursing homes, the home of the patient, or in any other institution or area where drugs are prescribed and applied (SCROCCARO et al. 2000). Clinical pharmacy services are one aspect of hospital pharmacy, but they are in no way limited to the hospital area.

The primary objective of clinical pharmacy services is the optimisation of pharmacotherapy. By working with other healthcare professionals, e.g., physicians, nursing staff, dieticians, and others, in an interdisciplinary and interprofessional context, the clinical pharmacist is co-responsible for the rational and effective use of drugs, the application of evidence-based medicine criteria, and economical considerations. The clinical pharmacist provides information regarding all relevant pharmacotherapy issues and the selection and use of drugs.

The occurrence of adverse drug reactions (ADRs) and drug-drug interactions (DDIs), just to name two of common drug-related problems (DRPs) in hospitalised patients with polypharmacy (see 1.1.5), is thought to be decreased by clinical pharmacy services (BOND and RAEHL 2006, KRÄHENBÜHL-MELCHER et al. 2007, VIKTIL and BLIX 2008). Furthermore, the clinical pharmacist addresses adherence issues by providing patient information and counselling.

Taking into account the shortage of financial resources in healthcare systems, the clinical pharmacist plays an important role by providing information on economical drug use and contributes to balancing the increasing cost of drugs and medical services by applying cost reduction strategies (SCHUMOCK et al. 2003).

The optimisation of pharmacotherapy by clinical pharmacists can be addressed in various settings, e.g., during ward round participation, medical chart reviews, interdisciplinary discussions, and any other form of ward-based clinical pharmacy, and at three different levels, i.e., before, during, and after the prescription (Table 2).

Before the prescription	During the prescription	After the prescription
Clinical trials; development, observation, and management of formularies; drug information	Counselling activity on drug selection; pharmacokinetics and therapeutic drug monitoring	Counselling activity; patient-specific compounding; drug use evaluation; outcome research; pharmacoeconomic studies; pharmacovigilance

Table 2: Main levels of clinical pharmacy activities (SCROCCARO et al. 2000)

As a member of the patient care team, the clinical pharmacist is involved in several different time points during the patient journey. All clinical pharmacy activities are performed as shared responsibilities, and they do not diminish the responsibilities of other

healthcare professionals (CLARK 2001). The contact points and possibilities for interaction and contribution by the clinical pharmacist are depicted in Figure 2.

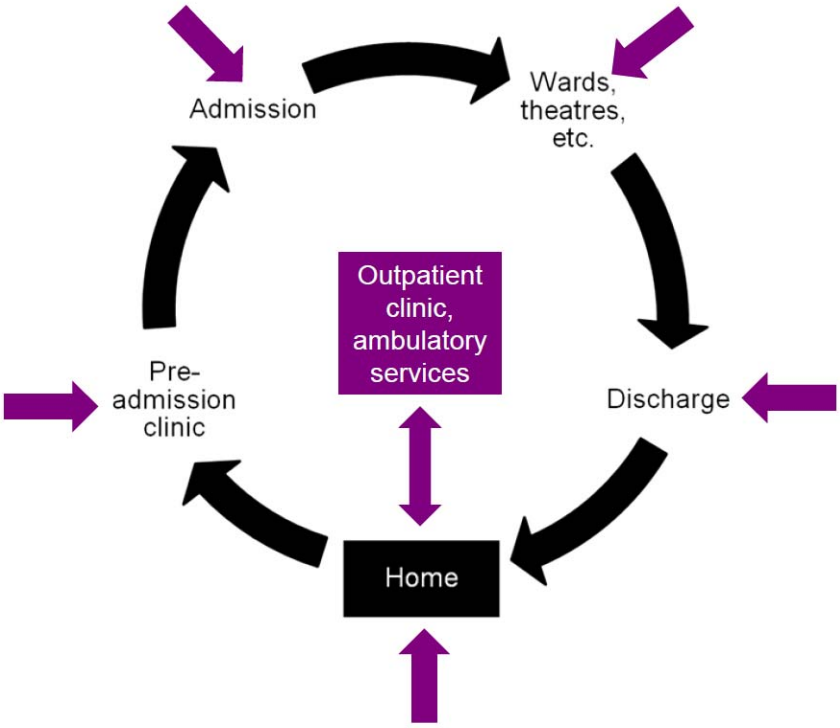

Figure 2: The patient care journey (CLARK 2001)

The complexity within the patient care journey is due to several interfaces that require transitions between primary care (*extramural*) and secondary care (*in-hospital*) as well as the involvement of several healthcare professionals. Several studies report beneficial effects of clinical pharmacy services on humanistic (e.g., quality of life), clinical (e.g., disease control), and economic (e.g., reduced healthcare costs) outcomes (SCROCCARO et al. 2000, KABOLI et al. 2006, VIKTIL and BLIX 2008).

1.1.3 PHARMACEUTICAL CARE

The definition of pharmaceutical care originally dates to the 1980s (BRODIE et al. 1980) and was extended and concretised in 1989 (HEPLER and STRAND 1989) (Table 3). In the German language, pharmaceutical care can be literally translated as ’Pharmazeutische Betreuung’.

1980	"Pharmaceutical care includes the determination of the drug needs for a given individual and the provision not only of the drug required but also 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." (BRODIE et al. 1980)
1989	"The responsible provision of drug therapy for the purpose of achieving definite outcomes that improve patient's quality of life." (HEPLER and STRAND 1989)
1998	"A practice in which the practitioner takes 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." (CIPOLLE et al. 1998)
2005	"…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." (FRANKLIN and VAN MIL 2005)

Table 3: Definitions of pharmaceutical care

The early definitions of this concept are consistent in that 'the pharmacist' is not part of the definition. Although developed by pharmacists, the provision of pharmaceutical care to patients was not thought to be and is still not reserved to pharmacists, and other professionals can deliver pharmaceutical care as well. However, as pharmacists in many countries are well-educated professionals with a solid knowledge of drugs, including their functions and associated problems, they generally have all of the necessary capabilities to deliver pharmaceutical care and address all steps of the pharmaceutical care process (Figure 3). However, in addition to pharmacological knowledge, social and communication skills and a certain patient-oriented attitude is also necessary (VAN MIL et al. 2004).

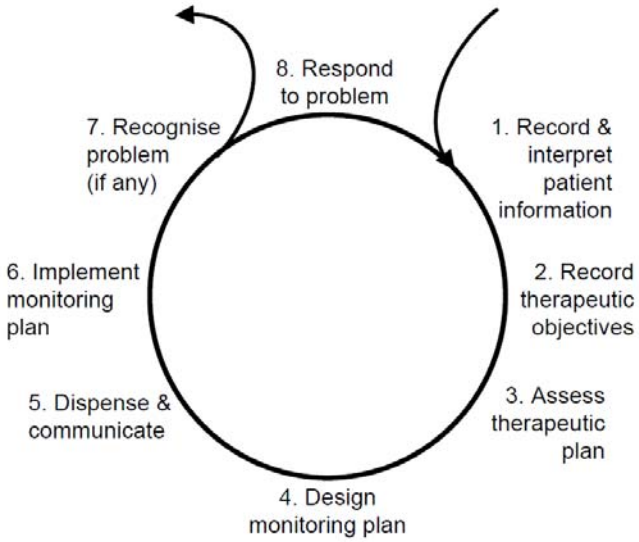

Figure 3: Hepler's pharmaceutical care process (VAN MIL et al. 2004)

Pharmaceutical care describes the process of close interprofessional cooperation and co-working (of a pharmacist) with a patient and other professionals in designing, implementing, and monitoring a therapeutic plan with the goal of producing specific therapeutic outcomes for the patient that are beyond the boundaries of in-hospital patient care, ambulatory patient care, and extramural patient care (HEPLER and STRAND 1989). For the first time, the accountability of the pharmacist for patient specific outcomes was defined and included in the definition of pharmaceutical care.

The patient, with his or her medical and pharmacotherapy-related needs, is in the centre of the pharmaceutical care process. Pharmaceutical care has been described as a philosophy on which clinical pharmacy should be based, relating to the morality of the relationship between the pharmacist and patient and encompassing both clinical pharmacy and social pharmacy. All interventions are performed with focus on positive patient outcomes and an ultimate improvement of the individual's quality of life.

1.1.4 CLINICAL PHARMACY AND PHARMACEUTICAL CARE

Clinical pharmacy and pharmaceutical care are closely related, intertwined, complementary concepts (FRANKLIN and VAN MIL 2005). Clinical pharmacy is an essential component in the delivery of pharmaceutical care (Figure 4), and the two disciplines possess similar goals.

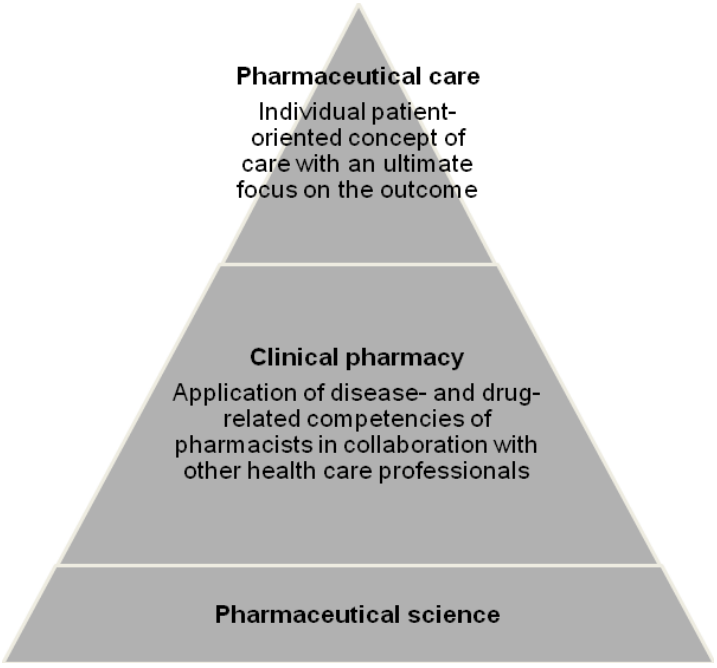

Figure 4: The concept of pharmaceutical care in relation to clinical pharmacy (HERSBERGER 2005)

The discipline of clinical pharmacy contributes to the greater concept of pharmaceutical care by achieving pharmacotherapy-related goals and increasing health-related quality of life (HEPLER 2004). The ACCP states that “clinical pharmacy embraces the philosophy of pharmaceutical care and blends a caring orientation with specialized therapeutic knowledge, experience and judgment for the purpose of ensuring optimal patient outcomes” (ACCP 2008).

This new aspect rendered the pharmacist responsible for the outcomes of drug therapy by refocusing the clinical pharmacy practice from process to outcome (CALVERT 1998). It is evident that both disciplines (either taken individually or as one comprehensive integrative system) are truly interdisciplinary and that cooperation with all involved groups of healthcare professionals and the patients is, therefore, necessary.

For the purpose of the underlying scientific thesis, the term clinical pharmacy will be used consistently throughout as defined by the ESCP (ESCP 2010).

1.1.5 DRUG-RELATED PROBLEMS

Pharmacotherapy not only may have beneficial effects for the patient but also may be associated with problems or even cause harm. Conventional definitions and illustrating examples are given in Table 4.

Drug-related problem (DRP)	"A circumstance that involves a patient's drug treatment that actually, or potentially, interferes with the achievement of an optimal outcome" (JOHNSON and BOOTMAN 1995).	i.e., drug over- or under-dosage; drugs used that are not indicated; indications, but no drug
Medication error (ME)	"Any error in the process of prescribing, dispensing or administering a drug, whether there are adverse consequences or not" (LEAPE 1995)	i.e., unreadable writing leads to drug over-dosage; infusion to be administered centrally is accidentally administered peripherally
Adverse drug reaction (ADR)	"Any response to a drug which is noxious and unintended and which occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function, given that this noxious response is not due to a medication error" (ANONYMOUS 1995)	
Adverse drug event (ADE)	"An injury related to the use of a drug, although the causality of this relationship may not be proven" (LEAPE 1995)	

Table 4: Definitions and examples of problems associated with pharmacotherapy

Because of the different types of DRPs, definitions overlap and are linked to each other. The relationship between various types of DRPs is depicted in Figure 5.

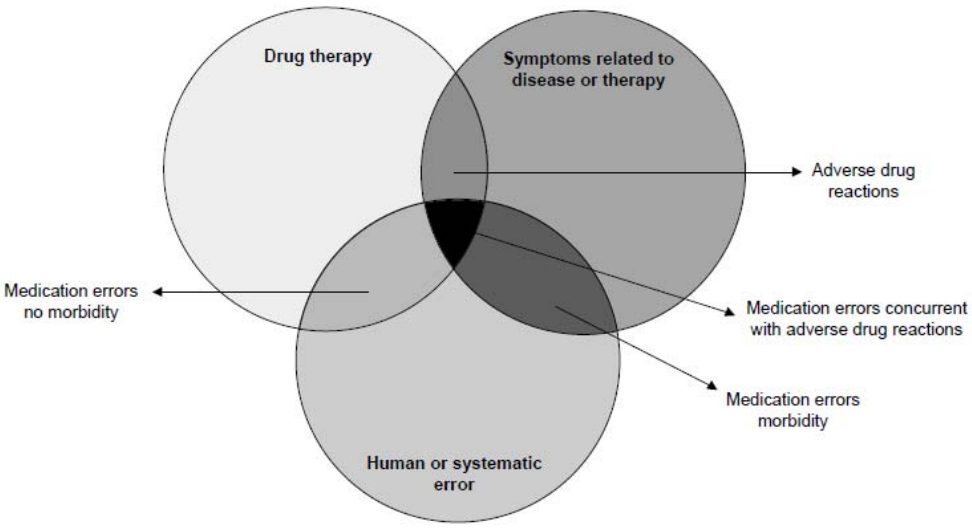

Figure 5: Relationship between types of DRPs (VAN DEN BEMT et al. 2000)

DRPs are common in the hospital setting. In a prospective study among 830 medical patients, 81% of the patients had at least one DRP, and an average of 2.1 clinically relevant DRPs per patient was observed (BLIX et al. 2004). Risk factors for DRPs include age, number of drugs, number of co-morbidities, and female gender (KRÄHENBÜHL-MELCHER et al. 2007).

The occurrence of DRPs is closely linked to increased patient morbidity, and if not adequately addressed and resolved by any healthcare professional, it can lead to drug-related mortality. Furthermore, DRPs can lead to a decreased health-related quality of life and an increased length of hospital stay and increased costs (PIRMOHAMED et al. 1998). Therefore, any measures addressing the prevention of DRPs deserve great attention.

A study in the United States estimated the costs of drug-related morbidity and mortality in a 700-bed teaching hospital (expressed as costs attributable to all ADEs and preventable ADEs) to be approximately $5.6 million and $2.8 million, respectively (BATES et al. 1997). The overall costs of drug-related morbidity and mortality in the US exceeded $177.4 billion in 2000 (ERNST and GRIZZLE 2001). However, data from other countries or healthcare settings are scarce. The Austrian Chamber of Pharmacists estimated that the costs related to misused medical products and the associated morbidity and mortality would account for €3.77 billion in Austria (ÖAK 2010).

ME rates published in the literature range from 1.7% to 59%, but generally assumed rates report 15% for floor stock distribution systems and 2-5% for unit-dose distribution. In Austrian hospitals, the floor/ward stock system is the predominant distribution system. Prescribing errors, which are not included in the aforementioned numbers, are reported to be between 0.3-2.6% (VAN DEN BEMT et al. 2000). Almost 1% of MEs result in an ADE (BATES et al. 1995).

The incidence of ADRs, additional commonly encountered problems in hospitalised patients, ranges between 1.9 and 37.3%. This wide range can be explained by differences in detection and reporting methods of ADRs (VAN DEN BEMT et al. 2000). A meta-analysis reports a fatality rate of 0.32% (LAZAROU et al. 1998).

ADEs occur with a frequency of 0.7 to 6.5%, depending on the strictness of their definition. Between 28 and 56% of ADEs are reported to be preventable (VAN DEN BEMT et al. 2000). Incidence rates from American hospitals report a range from 2 to 7 ADEs per 100 admissions (AHRQ 2001).

The exact magnitude of DRPs is, however, unclear. Prevention strategies that have been shown to be beneficial involve mainly technical interventions at the level of distribution and prescription, e.g., unit-dose systems, computerised physicians order entry systems (CPOEs), automated dispensing systems, and the use of bar coding. Further measures address gaps in education and knowledge and tackle early detection of ADEs (VAN DEN BEMT et al. 2000).

Clinical pharmacists on the ward also significantly contribute to a reduction in MEs (KRÄHENBÜHL-MELCHER et al. 2007) and ADEs (AHRQ, 2001).

1.1.6 EVOLUTION OF CLINICAL PHARMACY SERVICES

Clinical pharmacy services first evolved in the 1960s and 1970s in the United States and around ten years later in the UK. The emergence of clinical pharmacy services as an element of hospital pharmacy reflected similar changes worldwide, especially in North America, Australia, and New Zealand (HUDSON et al. 2007).
For the first time, an analysis of risks and errors associated with drugs and pharmacotherapy was performed, and areas with an urgent need for improvement and optimisation were highlighted. During this time, the process of prescribing, dispensing, and applying drugs was commonly performed without any coordination of or communication between the healthcare professionals involved (MEYER et al. 2003). The awareness of this far-from-ideal situation and the realisation that pharmacists could intervene and contribute by applying their knowledge and experience in this specialised field initiated a shift from the traditional roles of the pharmacists at that time («focus on the drug itself») to a more patient-oriented approach («focus on the patient»). Through this concept, pharmacists could evolve into patient-focused healthcare providers (UKCPA 2010) and expand their traditional roles.
The presence of the pharmacist on the ward and his or her active participation in patient care as a member of the healthcare team was revolutionary (CALVERT 1998). A shift from a reactive role towards a more proactive role was initiated.

The development of the discipline of clinical pharmacy in the US and the awareness of drug-associated morbidity and mortality and its costs were the basic stimuli for the implementation of such services in other countries. However, differences between national healthcare systems and implicit roles and responsibilities of healthcare professionals as well as the lack of human and technical resources significantly influenced this progress and set limitations to the development of the discipline. Another main influencing factor was the lack of clinical orientation during pharmacy education, which is still a major and continuing barrier to professional advancement in several European countries (HUDSON et al. 2007).

1.1.7 CLINICAL PHARMACY SERVICES IN AUSTRIA

In Austria, the emphasis of pharmacy services within the hospital still rests on non-clinical services offered by hospital pharmacists (see 1.1.1). However, the practice of clinical pharmacy services and a more regular clinical role of hospital pharmacists began with the implementation of the compounding of patient-specific ready-to-use cytotoxics and total parenteral nutrition.

Clinical pharmacy was first defined in the Regulation on the Operation of Pharmacies 2005, an ordinance to the Austrian Medicines Act, as adjunctive terminology for patient-oriented services (ABO 2005). For the first time, a legal definition of the function of pharmaceutical services was given. Among others, these services consist of the provision of patient-oriented services (i.e., clinical pharmacy), assistance in optimising pharmacotherapy, and the provision of information and counselling of physicians, other healthcare professionals, and patients regarding all aspects of drugs and pharmacotherapy. Furthermore, this new ordinance authorised the pharmacist to be granted access to patient medical records in order to fulfil the legal requirements of his profession. However, an official and legal job title of “clinical pharmacist” does not exist in Austria as of 2011, and an explicit framework of competencies, duties, and responsibilities in relation to other professions for clinical pharmacists is lacking.

The provision of regular and continuous clinical pharmacy services is influenced, among other factors, by the availability of adequately trained (hospital) pharmacy staff.
In Austria, there are a total of 266 hospitals with a capacity of 64.267 beds. Only 17.3% (n=46) of all hospitals operate their own hospital pharmacy, with a total of 280 hospital pharmacists employed (ÖAK 2010), resulting in a ratio of 0.44 hospital pharmacists per 100 beds. Data from the EAHP Survey in 2005 indicate a lower ratio of 0.31 hospital

pharmacists per 100 beds, taking into account that not all of the 280 hospital pharmacists are working full time (SURUGE and VULTO 2006).
In other words, there is one hospital pharmacist responsible for the care of 300 patients. Compared with data from other European countries (data available from 23 countries), e.g., 1.91, 1.75, and 1.69 hospital pharmacists per 100 beds in Estonia, Norway, and Portugal, respectively, Austria ranks antepenultimate regarding hospital pharmacist staffing.

Systematic data on clinical pharmacy services and their extent and characteristics in Austria are lacking. An unofficial survey of the Austrian Association of Hospital Pharmacists (AAHP) among all Austrian hospitals pharmacy shows that taking together the complete time of hospital pharmacists on the ward, there are 8 full-time clinical pharmacists within a group of 148 full-time hospital pharmacists. The average Austrian hospital pharmacist spends 55 hours per year as a clinical pharmacist on the ward (HETZ 2008).

Further data from 2010 report that 68% of Austrian hospitals have implemented regular clinical pharmacy services. Regular clinical pharmacy services were defined as participation in ward rounds, provision of drug information, and examination of medication profiles. Regarding the extent of clinical pharmacy service implementation, the average Austrian hospital has two clinically active hospital pharmacists in charge of one to two wards, with a median frequency of ward attendance of once per week (FRIEDL 2010).

Hence, data are scarce, and the overall number of clinical active pharmacists varies with the definition of services implemented and the frequency that they are offered. When interpreting the aforementioned data and when making comparisons with other countries, these limitations must be considered. Data on the number of patients receiving clinical pharmacy services and those receiving patient education from clinical pharmacists during their inpatient stay are lacking.

Apart from lacking an adequate number of hospital pharmacy staff, educational programmes in clinical pharmacy are lacking compared with the US or the UK, where there are postgraduate education programmes, e.g., PGYs and MSc-programmes in clinical pharmacy. Advanced training for clinical pharmacists is essential for the promotion of the profession (HUDSON et al. 2007).

Only the minority of Austrian hospital pharmacists attending wards and providing clinical pharmacy services have received specified clinical pharmacy education and if so, then mainly abroad (FRIEDL 2010). Practicing clinical pharmacists in Austria are often autodidactic and have to develop necessary skills and specific knowledge on their own. However, plans for implementation of a postgraduate clinical pharmacy education do exist (LEMMENS-GRUBER 2011).

Some training and continuing education are currently available in Austria implemented, but a career structure that facilitates the development and specialisation within the clinical pharmacy area is absent. Some skills necessary for the practice of clinical pharmacy are currently being taught in the "Krankenhausapothekerweiterbildung" (literally translated 'continuing education for hospital pharmacists'), which was implemented by the Austrian Chamber of Pharmacists. At the university level, no systematic specialisation exists. However, with the implementation of the new pharmacy curriculum in 2007, the old curriculum was amended by the introduction of a mandatory seminar in patient-oriented pharmacy, which focuses on pharmacokinetics and further clinical pharmacy activities, and a combined lecture and practical course on chemical diagnostics and clinical pharmacy. However, clinical pharmacy research and the measurement of efficacy of clinical pharmacy services are still lacking.

Clinical pharmacy services are growing in Austria, although they are still in their early phases. On the basis of international comparisons, the development of these services in the German-speaking countries of Germany and Austria started ten to fifteen years later than in the US (MEYER et al. 2003). Main obstacles to the routine implementation of clinical pharmacy services are the low number of hospital pharmacists (lack of human resources), a lack of a systematic clinical pharmacist education programme, which would ideally begin at the university level (lack of educational measures), and a lack of research within this area to prove the need for and benefit of clinical pharmacy services at a national level in Austria, which has already been published for other healthcare settings and countries.

1.2 RENAL CLINICAL PHARMACY SERVICES

1.2.1 DEVELOPMENT AND CONCEPT OF RENAL CLINICAL PHARMACY SERVICES

Renal clinical pharmacy services (or *nephrology pharmacy*) began in the US in the 1970s, after the overall benefits of general clinical pharmacy had been demonstrated (JOY and MATZKE 2007). In the mid-1980s in the UK, clinical pharmacists dedicated to renal pharmacy founded the UK Renal Pharmacy Group (UKRPG 2011). In 1996, the Renal Pharmacists Network was founded in Canada (RENAL PHARMACISTS NETWORK 2011).

At that time, there was an ever-increasing knowledge of drug behaviour and pharmacotherapy in patients with renal impairment. The need for dose individualisation for primary renally excreted drugs was determined. Nephrology education programmes were developed to educate pharmacists on renal diseases, drug prescribing in renal impairment, and further specifics. Special needs of different nephrology patient groups, e.g., haemodialysis or peritoneal dialysis patients, were described, and the pharmacists' role in their care was defined and investigated. Special interest groups, as mentioned at the beginning of this section, were formed to address these needs (JOY and MATZKE 2007).

The first services implemented were steadily amended by optimising pharmacotherapy with the goal of improving associated outcomes and the highly prevalent co-morbidities of renal patients, e.g., hypertension, anaemia, and hyperparathyroidism.
The role of the clinical pharmacist expanded. With the beginning of the 21st century, several renal clinical services were provided by renal clinical pharmacists, including outpatient CKD or dialysis patient management, supervision of the specific pharmacotherapy-related needs of renal patients, contributions to the understanding of drugs and their removal during different types of renal replacement therapy, and outcome research in the nephrology patient population (JOY and MATZKE 2007). Development of specialised renal services occurred as a result of the growing number of CKD patients and, consequently, different renal replacement therapies (e.g., any form of dialysis or kidney transplantation) (see 1.2.3). Significant contributions to the literature regarding the efficacious and safe utilisation of drugs in transplant and dialysis patients have been made (MANLEY and CAROLL 2002, MANLEY et al. 2003).

Suboptimal management of risk and progression factors of renal impairment and CKD complications, such as anaemia, malnutrition, renal osteodystrophy, and metabolic disorders, have been commonly reported (JOY et al. 2005). One strategy that addressed this gap in care was the introduction of clinical pharmacists as pharmacotherapy experts in multidisciplinary care teams. A possible framework for the multidisciplinary care of CKD patients is depicted in Figure 6.

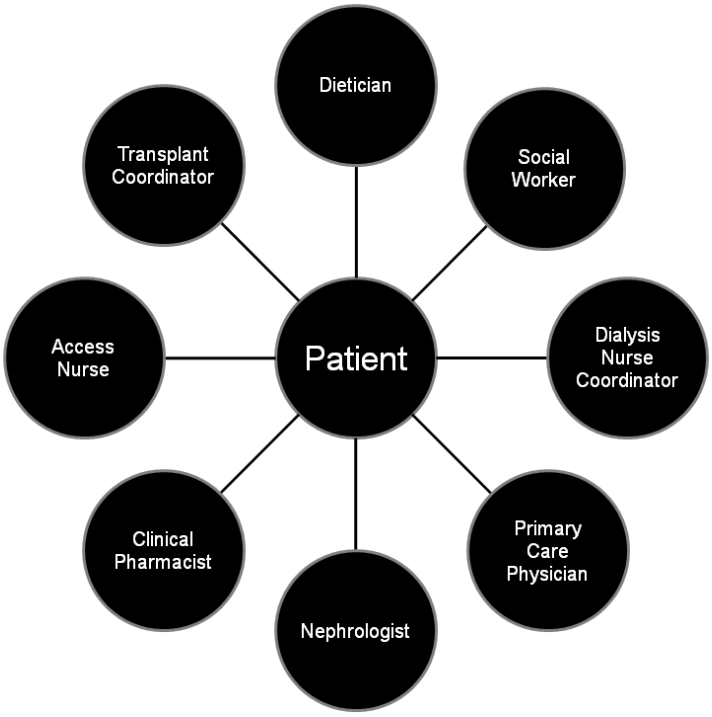

Figure 6: The multidisciplinary approach to CKD care (JOY et al. 2005)

Several opportunities for the clinical pharmacist to contribute to complex patient care and to assume responsibility for drug therapy monitoring and management are described in the literature (ZILLICH et al. 2005).

Within multidisciplinary patient care teams, the clinical pharmacist addresses multiple tasks and fulfils many roles (JOY et al. 2005):

- Blood pressure management
- Glycemic management
- Screening for microalbuminuria/proteinuria and initiation of pharmacologic therapy with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)

- Anaemia management
- Screening and management of metabolic bone disease
- Hyperlipidemia management
- Drug dosage adjustments and avoidance of nephrotoxic agents
- Medication education

A survey among Canadian nephrologists reported that only 65% had access to a clinical pharmacist in a multidisciplinary care team environment, whereas access to nurses, social workers, and dieticians was available for over 90% of all nephrologists (MENDELSSOHN et al. 2006). Data from the US show that pharmacists are not routinely involved in the monitoring of common CKD complications, i.e., anaemia and bone metabolism problems (BENNETT et al. 2006). In Austria, there is no routine involvement of clinical pharmacists in renal clinical pharmacy services.

Standards for the provision of renal clinical pharmacy services have been developed, e.g., those by the UK Renal Pharmacy Group (UKRPG), with the goal of not only guiding clinicians and defining audit measures and outcome parameters but also standardising the education of clinical pharmacists.
These standards involve the following: regular prescription reviews for defined patient groups, e.g., in-hospital patients, kidney transplant recipients, and dialysis outpatients; medication counselling due to complicated prescriptions with multiple drugs in order to maximise their effects; patient discharge planning; the provision of renal medicine information; and protocol and guideline development (UKRPG 2004).
To avoid overlapping responsibilities among healthcare providers, a framework of competencies and responsibilities must be developed, defined, and mutually agreed upon by the multidisciplinary team to reduce overlap, increase efficiency, and optimise patient care.

1.2.2 RENAL FUNCTION AND ITS IMPAIRMENT

1.2.2.1 The kidney and its function

The kidney is mainly responsible for three functions (BRIGGS et al. 2005):

- Maintenance of body fluid composition by regulating fluid volume, osmolarity, electrolyte (e.g., sodium, potassium, chloride, calcium, magnesium, and phosphate) content and concentration, and acidity by correcting perturbations caused by food intake, metabolism, environmental factors, and exercise,
- Excretion of metabolic end products and foreign substances (e.g., drugs, toxins), and
- Production and secretion of enzymes and hormones (e.g., renin, erythropoietin, 1,25-dihydroxyvitamin D_2).

1.2.2.2 Evaluation of kidney function

Knowledge of kidney function is essential for disease staging and influences all aspects of drug and non-drug therapy. The most important parameter to be clinically evaluated is the glomerular filtration rate (GFR). Estimates of GFR, which are based on a 24-hour creatinine clearance (CrCL), require timed urine collections, a time consuming and error-prone process. The measurement of inulin clearance is the gold standard of GFR evaluation. Inulin is an ideal filtration marker that is simply filtered in the glomeruli and neither reabsorbed nor secreted. More sophisticated methods, especially in clinical research, involve the measurement of clearance of radiolabeled markers, such as iothalamate (a radiographic contrast agent), diethylenetriamine pentaacetate (DTPA), and ethylenediamine tetraacetate (EDTA) (HSU 2005). However, in clinical practice, these methods are not feasible. Serum creatinine, which is endogenously produced by the muscle and excreted by the kidney, is a commonly used parameter to judge kidney function. However, serum creatinine alone is not an ideal marker of GFR because it is both filtered in the glomeruli and secreted by the proximal tubule in the kidney.

In clinical practice, the evaluation of kidney function is generally performed by estimating the CrCL and GFR, using the Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) equations, respectively. Generally, these equations are based on serum creatinine values, but are corrected for numerous variables such as age, sex, race, and body size (Table 5). Creatinine clearance approximates GFR, but tends to overestimate kidney function by around 20% in healthy individuals and even more in CKD patients.

Cockcroft-Gault Equation

$$Cl_{Cr} = \frac{(140 - age)\ x\ bodyweight\ (kg)}{72\ x\ S_{Cr}\ (mg/dL)}\ x\ (0.85\ if\ female)$$

Modification of Diet in Renal Disease (MDRD) Equation (simplified)

$$GFR\ (mL/min/1.73m^2) = 186\ \ x\ S_{Cr}\ (mg/dL)^{-1.154}\ x\ age^{-0.203}\ [x\ 0.742\ if\ female]\ [x\ 1.21\ if\ black]$$

Table 5: Equations for the prediction of creatinine clearance or GFR in adults with kidney disease (S_{Cr} serum creatinine)

The accuracy of such equations is limited if serum creatinine levels fluctuate. The MDRD equation yields more accurate results of kidney function in patients with known renal disease. Compared with the Cockcroft-Gault equation, the MDRD equation is superior in patients with a GFR lower than 60 mL/min/1.73m^2.
Especially in extreme deviations of normal body size (e.g., malnutrition, overweight, extremes of age and size), the presence of muscular disease or paralysis, a vegetarian diet, undulating kidney function, and pregnancy, the performance of a 24-hour urine collection and the measurement of creatinine clearance may, nevertheless, be valuable and provide a more accurate estimate of kidney function.

1.2.2.3 Types of kidney failure

Acute renal failure describes a medical condition that is accompanied by a sudden and generally reversible decrease in GFR that occurs over hours to days and the need for renal replacement therapy (FAUBEL et al. 2009).

Chronic kidney disease (CKD) is a progressive condition that is marked by deterioration of kidney function over time. It is defined as either kidney damage or GFR < 60 ml/min/1.73m^2 for over three months (NKF 2002).
The most common staging criteria used for CKD are those given by the US National Kidney Foundation KDOQI, which are based on GFR (Table 6). Staging of kidney function is necessary for the application of guidelines, measurement of clinical performance, and other evaluations of CKD patients, but does not necessarily reflect the extent of residual kidney function, the presence of comorbidities or complications, or other disease issues (NKF 2002).

Stage	GFR (mL/min/1.73m^2)	Description
1	≥90	Normal or increased GFR, with other evidence of kidney damage*
2	60-89	Slight decrease in GFR, with other evidence of kidney damage*
3	30-59	Moderate decrease in GFR, with or without other evidence of kidney damage*
4	15-29	Severe decrease in GFR, with or without other evidence of kidney damage*
5	<15	Established renal failure

* Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

Table 6: Classification of chronic kidney disease

Impaired renal function (defined as decreased GFR) is associated with several complications that are secondary to the progression of kidney disease, including hypertension, anaemia, secondary hyperparathyroidism, and malnutrition. The severity of symptoms generally worsens with a decline in renal function.

Kidney failure (or end-stage renal disease, ESRD) is defined as either a level of GFR < 15 mL/min/1.73m^2 that is most commonly accompanied by signs and symptoms of uraemia or the need for initiation of kidney replacement therapy, which can either be any mode of dialysis (e.g., haemodialysis or peritoneal dialysis) or kidney transplantation. ESRD is associated with a high morbidity and mortality (NKF 2002).

1.2.2.4 Risk factors

Risk factors associated with CKD include *susceptibility factors*, *initiation factors*, and *progression factors* (NKF 2002, JOY et al. 2008; Figure 7).

Susceptibility factors to CKD consist of advanced age, low income or education, racial/ethnic minority status, reduced kidney mass, low birth weight, and a family history of CKD. These factors have not been proven to cause kidney damage themselves, but they may be useful for identifying patients at a high risk for CKD (JOY et al. 2008).

Initiation factors directly initiate kidney damage and can be treated with pharmacologic therapy. Impaired kidney function is also a major risk factor for patients with cardiovascular disease. Examples of initiation factors are diabetes mellitus,

hypertension, autoimmune diseases, polycystic kidney disease, systemic infections, urinary tract infections, urinary stones, and drug toxicity. Diabetes, hypertension, and glomerular diseases are the most common causes of CKD (JOY et al. 2008).

Progression risk factors are those associated with the worsening of kidney function. Underlying initiation factors (e.g., diabetes, hypertension, and glomerulonephritis) may persist and predict the progression of CKD. The presence of albuminuria is a predictor of not only CKD but also cardiovascular morbidity and mortality. Obesity and smoking are also progression factors (JOY et al. 2008).

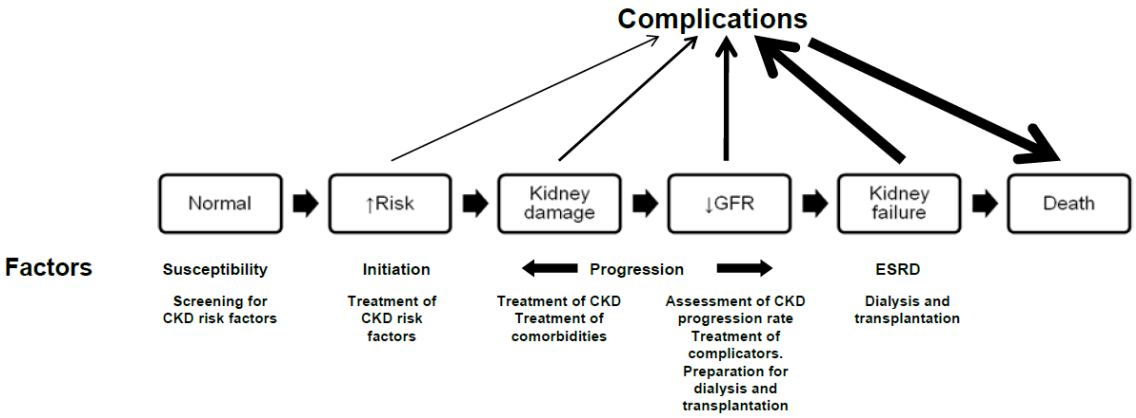

Figure 7: Development and progression of CKD (NKF 2002)

1.2.2.5 Clinical presentation of CKD and management of comorbidities

Symptoms are generally absent in CKD stages 1 and 2 and may be minimal during stages 3 and 4. General symptoms associated with stages 1 to 4 include oedema, cold intolerance, shortness of breath, palpitations, cramping and muscle pain, depression, anxiety, fatigue, and sexual dysfunction.
Signs include evidence of left ventricular hypertrophy, weight loss, arrhythmias, secondary hyperparathyroidism, anaemia of CKD, iron deficiency, bleeding, and several electrolyte disorders (JOY et al. 2008).

The goal of therapy at early stages is to delay disease progression and minimise the development or severity of associated complications, including cardiovascular disease. Generally, the patient benefits from modest dietary protein restriction (non-pharmacological therapy) and a multimodality pharmacological treatment approach, which targets the optimal control of underlying conditions, such as diabetes mellitus and hypertension. ACEIs and/or ARBs to control proteinuria are key elements

in this pharmacological management. Other interventions may include the addition of lipid-lowering agents, smoking cessation, and anaemia management.

Symptoms of CKD stages 4 and 5 are generally related to uraemia and include fatigue, weakness, shortness of breath, nausea, bleeding, and loss of appetite. Itching, peripheral neuropathies, and weight gain may also be common. Oedema and changes in urine output in terms of volume and consistency could be prominent signs of late stage CKD. The most common complications of an aggravation of renal function to CKD stages 4 and 5 involve fluid and electrolyte abnormalities, metabolic acidosis, anaemia of CKD, secondary hyperparathyroidism, and cardiovascular disease (e.g., hypertension, hyperlipidaemia) in dialysis patients (HUDSON 2008).

The general approach to patient care should include frequent medication reviews to reduce the risk of DRPs and exposure to nephrotoxic agents. Adherence to drug dosing guidelines and avoidance of the chronic use of non-steroidal anti-inflammatory drugs (NSAIDs), radiocontrast agents, and nephrotoxic antibiotics are key. As drug regimens of CKD and ESRD patients are often very complex because of a high number of drugs and a high frequency of application, patient education on the characteristics and the correct use of all prescribed drugs is essential (NKF 2002).

Appropriate management of the secondary complications of CKD usually involves a multidisciplinary approach. Recommendations on the management of several complications are published in guidelines, which are systematically collected by the Kidney Disease: Improving global outcomes (KDIGO) initiative (KDIGO, 2011). The following paragraphs include short summaries of therapy goals and descriptions of the main drugs involved in this management. For detailed and more comprehensive information on the management of individual complications and pharmacology, the consecutive guidelines and summary of product characteristics (SPCs) of these drugs should be consulted.

Cardiovascular disease in CKD: The management of hypertension (blood pressure goal in early stage CKD is < 130/80 mm Hg) and hyperlipidaemia (LDL cholesterol < 100 mg/dL) is key in CKD patients as major risk factors for cardiovascular disease. In addition to non-pharmacologic therapy strategies (e.g., sodium and fluid intake restriction, lifestyle modifications including regular exercise and weight loss), blood pressure reduction can often only be achieved through multiple combinations of antihypertensive agents. Thiazides generally lose their

efficacy with lower GFR rates. ACEIs or ARBs are preferred agents in patients with progressive CKD and proteinuria. However, all classes of antihypertensive drugs (also calcium channel blockers, beta blockers, alpha-blockers and central acting antihypertensives) can be used, with regard to concomitant disease states and CKD stage (HUDSON 2008).

Anaemia of CKD: To achieve desired outcomes of anaemia management (e.g., decreasing dyspnoea, orthopnoea, and fatigue, and prevention of left ventricular hypertrophy (LVH) and cardiovascular mortality), iron, folate, vitamin B12, and erythropoiesis stimulating agent (ESA) levels must be sufficient. The target haemoglobin value, the preferred monitoring parameter, is generally set between 11-12 g/dL. Higher levels are associated with increased cardiovascular morbidity. Generally, in addition to iron and vitamin B substitution if necessary, erythropoiesis-stimulating agents (e.g., erythropoietin alpha or beta, darbepoietin) are used to improve haemoglobin levels (HUDSON 2008).

Treatment of secondary hyperparathyroidism and renal osteodystrophy: Important diagnostic criteria for the diagnosis and management of bone disease are levels of calcium, phosphorus, the calcium-phosphorus-product (Ca x P), and intact parathyroid hormone (iPTH). The use of phosphate-binding agents in high quantities (e.g., calcium-containing binders, aluminium salts, lanthanum, and sevelamer) is often necessary to target hyperphosphataemia. Concomitant vitamin D therapy (in its active form, calcitriol) or with vitamin D analogues (e.g., paricalcitol, alfacalcidol) suppresses PTH secretion by stimulating serum calcium absorption. Cinacalcet, a calcimimetic agent, is used for the treatment of secondary hyperparathyroidism in ESRD patients (HUDSON 2008).

1.2.3 ETIOLOGY AND EPIDEMIOLOGY OF RENAL IMPAIRMENT

The leading causes of CKD and, ultimately, of ESRD worldwide shifted from glomerulonephritis to diabetes mellitus and hypertension. These disease states are currently the two major causes worldwide, especially in countries of the developed world.

Chronic kidney disease represents a major public health problem. In the US, around 5% of the adult population is affected by CKD, when defined by a serum creatinine concentration greater than 1.2 to 1.4 mg/dL. Data from the *National health and nutrition*

examination survey (NHANES) study show that nearly 11% (19.2 million) of the US adult population had reduced kidney function, as evidenced by serum creatinine concentrations equal to or higher than 1.5 mg/dL (JONES et al. 1998). Screening surveys from Australia and Japan report that 6-11% of the population have some degree of CKD (EL NAHAS and BELLO 2005).

Few studies have been performed on the epidemiology of CKD in European countries. For Austria, prevalence numbers of CKD are not available. A study conducted by HALLAN et al. 2006 reports a prevalence rate of CKD stages 1-5 of 10.2% in Norway, which is comparable to that in the US. Further data for European countries are available from the EUGLOREH project (EUGLOREH 2007). The prevalence of CKD stages 3-5 in males ranges from 3.6% in Norway to 7.2% in Germany. Prevalence rates were comparable across European countries. In general, females were more often affected than men (Figure 8). The EUGLOREH project reports increasing prevalence rates of CKD stages 3-5 with advanced age.

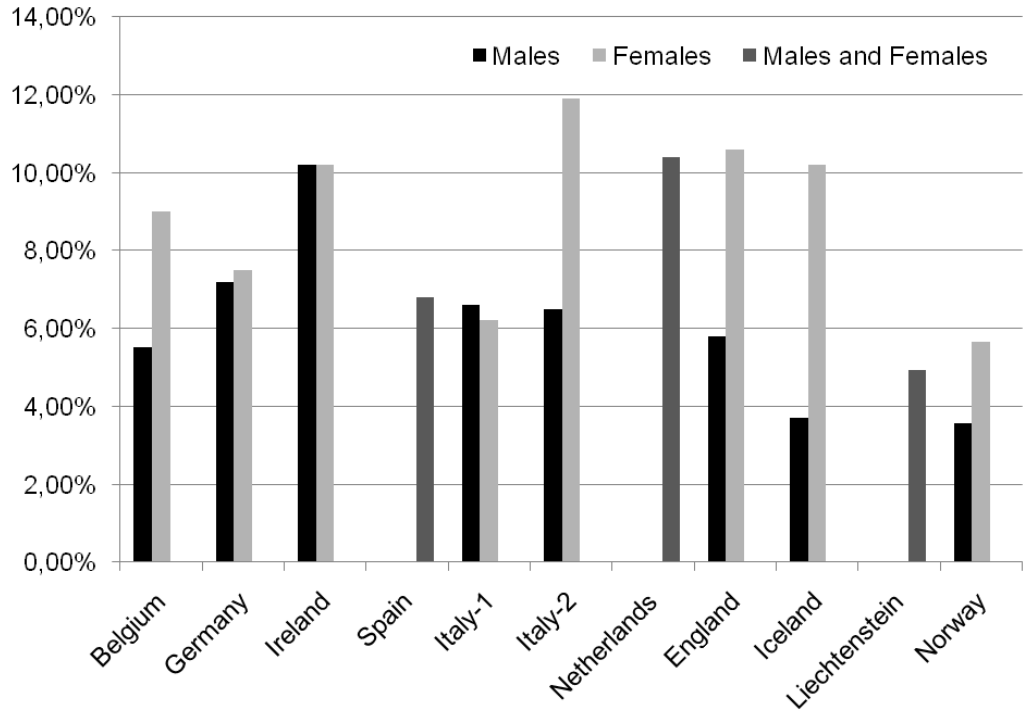

Figure 8: Prevalence rates of CKD stages 3-5 by gender in selected EUGLOREH countries (EUGLOREH 2007)

The incidence and prevalence numbers of ESRD patients are available because of widespread dialysis registries (e.g., the US Renal Data System, the ERA-EDTA-Registry) that provide good quality data.

In the year 2008, the incidence rate of ESRD in the US, the UK, and Austria was 362, 108, and 147 per million people, respectively. Incidence rates of ESRD in the US are 1.5 to 3 times higher than those in Europe. This difference can be partly be explained by a higher incidence rate of diabetic ESRD in the US (EUGLOREH 2007).

In the year 2009 in Austria, 1198 patients with ESRD were initially started on dialysis (1088 on haemodialysis and 110 on peritoneal dialysis). These numbers result in an incidence rate of 143 per million people. Altogether, there have been 4198 patients on dialysis (3819 on haemodialysis and 379 on peritoneal dialysis), which represents a prevalence of 501.3 per million people. The prevalence of patients living with a functioning kidney transplant was 476 per million people (3978 patients). By the end of 2009, a total of 8176 patients were on some form of renal replacement therapy (KRAMAR and OBERBAUER 2009).

The number of patients with ESRD probably does not truly reflect the number of patients with CKD, which may even be higher than those numbers extrapolated from the ESRD numbers. Reasons for this disparity may stem from differences in disease definitions and CKD staging and limitations in the use of single creatinine measurements to estimate kidney function, which is not a valid method. Furthermore, because of a high mortality rate of patients with impaired renal function, which provides a fourfold higher risk of death before reaching the ESRD stage, the ESRD patient population does not necessarily represent the overall CKD population (WALLNER 2006).

The increasing trend in incidence numbers is expected to continue at an annual rate of 5-8%. Underlying reasons for this continuing increase may involve the ageing of the population, increasing life expectancy and longevity, and an increasing number of diabetic people as the major underlying reason for development of CKD (EL NAHAS and BELLO 2005).

1.2.4 SUSCEPTIBILITY FOR DRUG-RELATED PROBLEMS IN PATIENTS WITH RENAL IMPAIRMENT

The incidence of evident and potential ADEs is reported to be 10 and 55.3 per 100 admissions, respectively, in patients with a serum creatinine concentration greater than 1.5 mg/dL (HUG 2009). In this study, most of the adverse events were preventable, but almost none were intercepted. Incorrect dosing in renal insufficiency

leads to most of the preventable adverse events. Accurate assessment of renal function and adaptation of dosing is key to avoid unwanted drug effects and ensure optimal patient outcomes. Only through collaboration of different healthcare providers, can the task of ensuring correct dosing, especially with large numbers of drugs, be achieved.

Patients with impaired renal function are a particularly relevant target population in which the assurance of safety and appropriateness regarding medication use is critical for several reasons:

- the severity of coexistent medical conditions,
- the prevalence of comorbidities that frequently require complex drug therapy regimens, and
- the substantial clinical impact that dialysis procedures have on the pharmacodynamics and pharmacokinetics of the medications taken by ESRD patients.

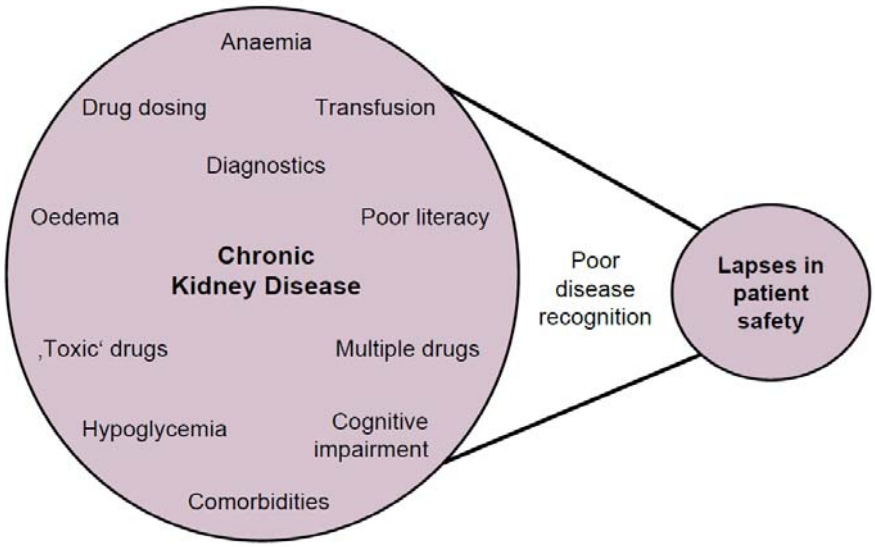

Figure 9: High-risk factors that under circumstances of poor disease recognition, can lead to adverse patient safety events (FINK and CHERTOW 2009)

Patients with impaired renal function are at high risk for developing DRPs, such as drugs without indication, indication without drugs, improper dosages, and incorrect drugs among others. In one study, haemodialysis patients were shown to experience four DRPs at their initial visit on average, decreasing to 0.6 DRPs over a follow-up time of six months (MANLEY et al. 2005).

Drug dosing in renal impairment is particularly complicated by the removal of drugs through haemodialysis and peritoneal dialysis.
Fluctuating renal function, other altered pharmacokinetic factors due to CKD, chronically impaired renal function, and poor medication compliance or adherence are predisposing factors to adverse drug events. Drug absorption, distribution, rate of protein binding, biotransformation, and most importantly, renal excretion may be altered (HASSAN et al. 2009, KUCZYNSKA 2009):

Effects on absorption: Absorption (and, therefore, bioavailability) may be reduced because of nausea, vomiting, or uraemia-associated diarrhoea. The bioavailability of drugs that require an acidic environment for absorption may be decreased because of increased gut pH.

Effects on distribution: Because of changes in states of hydration (e.g., oedema, ascites, general volume overload) and a decreased concentration of serum albumin, the distribution of drugs can be altered.

Effects on metabolism: The rate of drug metabolism, e.g., reduction and hydrolysis, is decreased. Serum concentrations of parent drugs and consequent toxicities may increase if the drug is metabolised to inactive metabolites.

Effects on elimination: The reduction in glomerular filtration and tubular secretion leads to higher plasma drug levels, and the reduction in reabsorption results in higher drug concentrations in the urine. Drugs may accumulate because of impaired elimination capacity.

In addition to these pharmacokinetic changes due to renal impairment, the clinical response of drugs (i.e., the pharmacodynamics) may also be altered, which is caused by concomitant uraemia in most cases. Increased sensitivity to drugs that target the central nervous system, risk of hyperkalaemia with potassium-sparing drugs, and risk of gastrointestinal bleeding or oedema with NSAIDS have been described (KUCZYNSKA 2009).

There is a great rate of incompliance with dosing guidelines in patients with CKD according to the study of LONG et al. 2004, which reports a non-compliance rate of 19-67%. Dose adjustments were necessary in 24% of all patients discharged from the

studied hospital, but were only performed in 59% of these cases (VAN DIJK et al. 2006). These findings show an imminent need for improvement.
In addition to neglected needs for dose adjustments and the resulting drug accumulation, drug-induced renal dysfunction also occurs because of drug nephrotoxicity. The kidney is highly susceptible to nephrotoxic agents, and the kidneys are exposed to circulating drugs to a great extent because of ~25% of cardiac output. Furthermore, nephrotoxic drugs may also alter renal haemodynamics and blood flow, e.g., cyclosporine (VERBEECK and MUSUAMBA 2008).

The involvement of pharmacists at the point of drug prescription is beneficial, as this is the time for decision making regarding dosing. Algorithms and recommendations on how to ensure the effectiveness of the prescription process include (HASSAN et al. 2009):

- Detailed initial assessment: Comprehensive assessment of previous drug exposure, allergies, current medication, clinical status (e.g., fluid volume), etc.
- Evaluation of degree of renal impairment: The most commonly used equations for this evaluation are the Cockroft-Gault and the MDRD equation (see 1.2.2.2).
- Review of medication list: All current drugs should have specific indications. The review is comprised of an evaluation of potential drug interactions and ADRs and correct posology according to renal function.
- Selection of drugs with no or minimal nephrotoxicity: If there is an imminent need for a nephrotoxic drug, the least nephrotoxic drug should be chosen and monitoring of the appropriate therapeutic drug and narrow renal function should be implemented.
- Selection of loading doses and a maintenance regimen: Generally, loading doses are the same as in normal renal function. The maintenance doses should be decided according to well-established dosing guidelines that are derived either from the SPC or other compendia (e.g., Drug prescribing in renal failure, BNF, The Renal Drug Handbook) (ARONOFF et al. 2007, BNF 2009, ASHLEY and CURRIE 2009)
- Monitoring of outcomes and frequent reassessment: Frequent reassessment of renal function and dose appropriateness may be necessary. Certain drugs may also be titrated on the basis of the pharmacodynamic response.

2 AIM OF THE THESIS

To describe renal clinical pharmacy services and the activities of clinical pharmacists involved in the care of CKD, ESRD, and SOT patients and synthesise published evidence.

To describe the roles of clinical pharmacists and areas for possible contributions and interventions, and to evaluate areas with room for improvement in patient care.

To describe and evaluate the characteristics and extent of renal clinical pharmacy services in a large tertiary care hospital.

To describe the extent and characteristics of DRPs and clinical pharmacist interventions and their significance in a large tertiary care hospital.

To describe additional clinical pharmacist activities and possibilities of interdisciplinary functions.

To discuss barriers to and limitations of clinical pharmacy services in general and at the level of the Austrian health system and the Austrian health organisation.

3 SCIENTIFIC WORK

In the introduction, important clinical pharmacy activities are presented and classified into three main levels according to prescription time (SCROCCARO et al. 2000; Table 2). The studies included in this thesis and presented in the following section describe several clinical pharmacy activities that can be categorised within these levels, in order to address the aims of the thesis.

The following literature reviews (STEMER and LEMMENS-GRUBER 2010, STEMER and LEMMENS-GRUBER 2011; see 3.1 and 3.2) on clinical pharmacy services in CKD, ESRD, and SOT patients depict the current status of this field and form a knowledge framework.

The retrospective study on risk factor management (STEMER et al. 2009; see 3.3) investigates the need for specific therapy improvements in patients treated on a highly specialised internal nephrology ward in which renal clinical pharmacy services were implemented. This ward constituted the study setting for all further clinical pharmacy studies.

The clinical pharmacist's impact on the study ward was evaluated in several studies with evolving methodology. Whereas the first study (STEMER and LEMMENS-GRUBER 2010; see 3.4) yielded data on the contributions of the clinical pharmacist who applied a reactive approach to issues and questions raised by members of the ward round team, the following studies (STEMER and LEMMENS-GRUBER 2011, STEMER et al. 2011; see 3.6 and 3.7) deliver results of the proactive interventions relating to DRPs provided by the clinical pharmacist.

The tasks of counselling and providing drug information are both major issues in clinical pharmacy services. The analysis of prescribing patterns on the study ward and the evolution of a synopsis of drug properties that are highly relevant in patients with impaired renal function represented strategies to address the informational needs of the healthcare professionals on the study ward (STEMER and LEMMENS-GRUBER 2010; see 3.5).

The clinical pharmacist, who possesses unique, specialised skills and expertise, also contributes to physician-led interdisciplinary study projects and clinical trials (KAUTZKY-WILLER et al. 2010, HAIDINGER et al. 2010; see 3.8 and 3.9).

3.1 CLINICAL PHARMACY ACTIVITIES IN CHRONIC KIDNEY AND END-STAGE RENAL DISEASE PATIENTS: A SYSTEMATIC LITERATURE REVIEW

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Clinical pharmacy activities in chronic kidney disease and end-stage renal disease patients: A systematic literature review

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Abstract

Background: Chronic kidney disease (CKD) and end-stage renal disease (ESRD) represent worldwide health problems with an epidemic extent. Therefore, attention must be given to the optimisation of patient care, as gaps in the care of CKD and ESRD patients are well documented. As part of a multidisciplinary patient care strategy, clinical pharmacy services have led to improvements in patient care. The purpose of this study was to summarise the available evidence regarding the role and impact of clinical pharmacy services for these patient populations.

Methods: A literature search was conducted using the *Medline*, *Embase* and *International Pharmaceutical Abstracts* databases to identify relevant studies on the impact of clinical pharmacists on CKD and ESRD patients, regarding disease-oriented and patient-oriented outcomes, and clinical pharmacist interventions on drug-related problems.

Results: Among a total of 21 studies, only four (19%) were controlled trials. The majority of studies were descriptive (67%) and before-after studies (14%). Interventions comprised general clinical pharmacy services with a focus on detecting, resolving and preventing drug-related problems, clinical pharmacy services with a focus on disease management, or clinical pharmacy services with a focus on patient education in order to increase medication knowledge. Anaemia was the most common comorbidity managed by clinical pharmacists, and their involvement led to significant improvement in investigated disease-oriented outcomes, for example, haemoglobin levels. Only four of the studies (including three controlled trials) presented data on patient-oriented outcomes, for example, quality of life and length of hospitalisation. Studies investigating the number and type of clinical pharmacist interventions and physician acceptance rates reported a mean acceptance rate of 79%. The most common reported drug-related problems were incorrect dosing, the need for additional pharmacotherapy, and medical record discrepancies.

Conclusions: Few high-quality trials addressing the benefit and impact of clinical pharmacy services in CKD and ESRD patients have been published. However, all available studies reported some positive impact resulting from clinical pharmacist involvement, including various investigated outcome measures that could be improved. Additional randomised controlled trials investigating patient-oriented outcomes are needed to further determine the role of clinical pharmacists and the benefits of clinical pharmacy services to CKD and ESRD patients.

Background

Chronic kidney disease (CKD) represents a major public health problem in developed and developing countries. It is estimated that approximately 5% of the adult U.S. population is affected by CKD, which is defined as serum creatinine concentrations greater than 1.2 to 1.5 mg/dL [1]. The European Kidney Health Alliance (EKHA) reports that approximately 10% of European citizens are affected by some degree of CKD [2].

CKD and end-stage renal disease (ESRD) are associated with an increased risk of mortality, increased rate of hospitalisation, and decreased life expectancy [3]. Progression from early to late stages of CKD generally results in the onset of new symptoms and concomitant complications. Frequent complications and comorbidities of CKD include fluid and electrolyte abnormalities, anaemia, secondary hyperparathyroidism and renal osteodystrophy, hypertension and hyperlipidaemia, metabolic acidosis, and several other comorbidities involving malnutrition, pruritus and uremic bleeding. CKD patients are at increased risk of cardiovascular disease (CVD), which includes coronary heart disease (CHD), cerebrovascular disease, peripheral vascular disease, and heart failure. The management of underlying and evident comorbidities (either as causes or consequences of CKD) and the prevention or delay of its progression to ESRD are complex.

In ESRD patients, the initiation of renal replacement therapies (RRTs), such as long-term dialysis (including haemodialysis (HD) or peritoneal dialysis (PD)) or transplantation, is usually indicated to relieve uremic symptoms and detoxify, whereas kidney transplantation (cadaveric or living donor transplantation) is the therapy of choice for ESRD [4].

Multidisciplinary health care teams of physicians, nurses, dieticians, and clinical pharmacists share the goal of preventing disease progression and managing comorbid conditions in CKD and ESRD patients. As specialists in pharmacotherapy, clinical pharmacists are routinely involved in patient care and interact with other health care professionals, addressing multiple, often unmet needs for pharmacotherapy optimisation. Ideally, this happens through a preventive, rather than a reactive, approach. Evidence from the literature supports the involvement of clinical pharmacists in several disease areas and underlines the positive patient outcomes and improvement of care that result [5, 6]. The medical management of predialysis and dialysis patients involves complex and highly variable pharmacotherapy, including frequent monitoring and evaluation to ensure optimal pharmacotherapy, adherence to medication, and control of comorbidities and other risk factors. A high number of prescribed medications, poor medication adherence, and frequent dosage changes may contribute to drug-related morbidity and related problems [7]. Several studies

report poor quality and gaps in the care of CKD patients with respect to the treatment of comorbidities, referrals to specialists, and the preparation for RRTs [8, 9]. Clinical pharmacists are directly engaged in the care of CKD and ESRD patients in different settings. Various possibilities and opportunities for clinical pharmacists to contribute to this field are described and exemplarily supported by evidence in an American College of Clinical Pharmacy (ACCP) opinion paper [10].

This literature review aims to systematically summarise the published evidence on the role of clinical pharmacists in the care of CKD and ESRD patients across different settings, to synthesise and highlight findings on the impact of clinical pharmacists, their various key activities, and their main areas of involvement, and to describe the different characteristics of clinical pharmacy services for the CKD and ESRD patient population.

Methods

A literature search was conducted using the *Medline* (1970 – Week 46, 2010), *Embase* (1996 – Week 45, 2010) and *International Pharmaceutical Abstracts* (IPA) (1970 – Oct 2010) databases to identify relevant articles. In *Medline*, the following combinations of Medline Medical Subject Headings (Mesh) terms were used as our search strategy: ("pharmacy service, hospital" OR "pharmacists" OR "pharmaceutical services") AND ("renal insufficiency" OR "kidney" OR "renal replacement therapy"). In *Embase* and *IPA*, the search strategy combined the terms ("clinical pharmacy" OR "pharmaceutical care" OR "pharmacist" OR "hospital pharmacy") AND ("renal insufficiency" OR "kidney" OR "renal replacement therapy"). The references sections of the returned publications and review articles were further screened for additional hits. Data were extracted and reviewed by the first study author (GS) and independently reviewed by the second author (RLG). Discrepancies were solved by discussion among the study authors.

All studies addressing the impact of clinical pharmacy services (either at the patient or the physician level) on the care of CKD and ESRD patients for both HD and PD were included. Therefore all studies reporting on disease-oriented and patient-oriented outcomes, and clinical pharmacist interventions on drug-related problems (DRPs) together with the physician acceptance rate, were assessed. Studies addressing the impact of clinical pharmacy services in kidney transplantation were excluded. A detailed review of these kinds of services was recently published [11]. Detailed inclusion and exclusion criteria are described in Table 1. The weakest study design included was observational and solely descriptive, as a high number of randomised controlled trials could not be anticipated. Results published in abstract form (e.g., congress abstracts) were included only if they provided numerically assessable data, such as outcome data, the number of resolved DRPs, or physician acceptance rates.

Predefined data parameters (namely, the study design, duration and setting, the number of included patients, the types of interventions, the relevant outcomes, the results, and available statistical values) were extracted from the literature, summarised in an Excel spreadsheet, and reviewed.

Results

The initial *Medline*, *Embase* and *IPA* searches yielded 339, 199, and 323 citations, respectively. The detailed search results are described in Figure 1.

A total of 861 citations were initially screened for inclusion criteria, and after removing duplicates, a total of 21 citations remained for full review and analysis. The predominant reason for exclusion was a lack of interventional and/or assessable data. Several initial citations had to be excluded because they provided data only on the impact of screening on appropriate renal dosing, with or without computerised support, or they provided only economic data.

General study characteristics

Detailed descriptions on the included studies of CKD and ESRD patients are shown in Tables 2 and 3, respectively. Three study types were identified, including 14 descriptive studies (DSs) (66.7%), four (randomised) controlled (R)CTs (19%), and 3 before-after studies (BASs) (14.3%). A total of seven (33.3%) of the published studies were only available as abstracts. The earliest included study was published in 1993. The study sites were predominantly located in the United States (n=16, 76.2%). The majority of the studies investigated the impact of the clinical pharmacist on the HD patient population only (n=15, 71.4%). Six studies (28.6%) addressed care issues in CKD patients. Only two studies (9.5%) [12,13] included PD patients. Most of the studies were performed in an ambulatory HD or CKD patient care setting (n=17, 81%), whereas only four studies contained data on in-hospital clinical pharmacist activities. Using data from 18 reported studies, the median (range) number of study participants was 60 (10-408), and the median (range) study duration was six (1-32) months.

Scope of clinical pharmacy activities

The interventions performed in the included studies could be roughly grouped into the following categories: (1) general clinical pharmacy services (n = 12, 57.1%) [12-15, 19-22, 29-32], (2) clinical pharmacy services focusing on disease management (n = 7, 33.3%) [17, 18, 23-27] and (3) clinical pharmacy services with a focus on educational activities (n = 2, 9.5%) [16, 28]. A listing of reported clinical pharmacist activities is provided in Table 4.

Outcomes

In 47.6% (n=10) of the included studies [13, 16-19, 23-27], disease-oriented outcomes were reported, whereas patient-oriented outcome data were only available in four studies (19%) [16, 28, 31, 32]. A synthesis of the disease- and patient-oriented outcome data is shown in Table 5. Four controlled trials (three of which were randomised) revealed that clinical pharmacy interventions had a positive impact on patient-oriented outcomes in the intervention group as compared to the available standard of care.

The third type of outcome parameter in the included studies was the total number of clinical pharmacist interventions performed or recommendations given together with the physician acceptance rate. These were considered primary (n=7) or additional secondary (n=3) outcome parameters in 10 out of 21 (47.6%) studies.

In the subanalysis of DSs, a weighted mean acceptance rate (±SD) based on study size of 78.7% (±19.5) was calculated. DRPs were mainly classified according to the system presented by Strand et al. [33]. However, in several included studies, information on classification methodology was scarce, or a system developed by the author was used. The DRPs most frequently described in the included studies were untreated indications, super- or supratherapeutic dosages and consequent dose adjustments, and medication record discrepancies. Assessments of the clinical significance of clinical pharmacist interventions were performed and reported in five of 10 included studies. For this purpose, the significance criteria published by Hatoum et al. [34] was used in two studies [12, 22]. Unspecified categorisation systems were used in the other studies. Bias minimisation methods used during clinical significance assessments generally included a review by independent clinical pharmacists or the achievement of consensus among the ratings of clinicians, nephrologists and pharmacists.

Information on the drug classes among which the clinical pharmacists detected the majority of DRPs was reported in four of 10 studies [12, 22, 31, 32]. The most commonly affected drugs were those used for treatment against renal bone disease and renal osteodystrophy together with anaemia and cardiovascular drugs.

The most common comorbidity in CKD or ESRD patients managed by clinical pharmacists was anaemia. Clinical pharmacists were primarily responsible for ordering and checking laboratory values and managing independent dosing and dose modifications of erythropoiesis-stimulating agents (ESAs) and iron within specific prescribing guidelines. Furthermore, comprehensive disease management programmes also included patient education and adherence-enhancing activities. All of the studies reported that a significantly higher proportion of patients managed by a

clinical pharmacist maintained relevant target ranges (e.g., haemoglobin and haematocrit) as compared to patients receiving standard care. Aside from two studies addressing lipid management and cardiovascular risk reduction in HD patients through multiple disease interventions, no studies on diseases common to CKD or ESRD patients (e.g, hypertension or secondary hyperparathyroidism) with applicable inclusion criteria could be identified.

Discussion

Evidence of gaps in the care of patients with renal impairment is published in the literature [8, 9]. For the patient's sake, these gaps must be addressed using all available methods. Enhancing the involvement of clinical pharmacists may be one potential strategy. Our systematic review synthesises evidence on the impact of clinical pharmacist involvement in DRPs in general, with respect to different comorbidities (e.g., anaemia and lipid management), and regarding educational issues in CKD and ESRD patients.

By addressing the issues illustrated in Table 4 in their general and more specified clinical work, clinical pharmacists fulfil the requirements stated in the NKF–K/DOQUI Guidelines "Chronic Kidney Disease: Evaluation, Classification and Stratification" [35], which explicitly highlight the need for regular medication reviews, including dosage adjustment, adverse drug event (ADE) detection, drug interaction detection, and therapeutic drug monitoring (TDM). Given the nature of their major responsibilities and tasks, clinical pharmacists interact with patients, physicians, and other health professionals and share the goal of optimising pharmacotherapy and patient care. This multidisciplinary and multilevel approach is underlined by all included studies. Clinical pharmacists, as pharmacotherapy experts, are engaged in the care of the CKD and ESRD patient population at different stages and with different responsibilities, as further described in the position statement of the Ambulatory Care and Nephrology Practice and Research networks of the American College of Clinical Pharmacy [10].

The CKD and ESRD population can be characterised by its vulnerability and susceptibility to drug-therapy-related morbidity due to many factors. Commonly reported DRPs in CKD or ESRD patients (e.g., dosing problems and medical record discrepancies) are not surprising given the complexity of dosing during either type of renal replacement therapy due to common changes in drug pharmacodynamics and pharmacokinetics [36]. This fact is further aggravated by the high number of concomitant drugs used and comorbidities, as studies report an average number of 10 to 12 drugs per day and five comorbidities for HD patients [7]. Intensified care and additional monitoring are warranted for patients taking more than five drugs, patients

with more than 12 total medication doses, patients with drug regimens prone to frequent changes and three or more concurrent disease states, and patients with a history of non-compliance, and the presence of drugs requiring TDM [37]. CKD and HD patients generally fulfil all of these criteria and therefore warrant increased monitoring. Problems with medical record discrepancies and the accuracy of medication profiles, which are among the most commonly reported DRPs, are further highlighted in a prospective observational study of 63 HD patients, which reports record discrepancies in 60% of all patients . Several clinical pharmacy studies provide insights into the risk factors for DRPs. One study [15] highlights an inverse correlation between residual kidney function (based on creatinine clearance) and the number of DRPs. Another study reports a positive correlation between the number of DRPs, on the one hand, and age and length of time on dialysis, on the other [30]. All of these aspects present opportunities for clinical pharmacist to engage in CKD and ESRD patient care.

Generally, more than three-quarters of clinical pharmacist interventions and suggestions were accepted by physicians. This physician acceptance rate is well within the range of other reported acceptance rates based on a review of clinical pharmacist impact on DRPs and clinical outcomes [6]. Due to the use of different classification systems and the resulting heterogeneity of DRPs, a profound statistical analysis was not performed.

No studies could be identified that explicitly addressed the issue of adherence in CKD or ESRD patients; nonetheless, it presents a major barrier to optimal patient care. Especially among patients taking a high number of prescription drugs, complex medication schemes and long treatment periods cause adherence to wane [38]. Guaranteeing a high level of medication knowledge may be one strategy to increase adherence and to prevent DRPs resulting from incorrect drug use or overall failure to take medications. Clinical pharmacist intervention to improve patient medication knowledge was the study objective in two of the included studies, which could be achieved.

There seems to be a balance in the proportion of studies investigating patient- versus disease-oriented outcomes. Patient-oriented outcomes are those that directly matter to patients, that is, those regarding longer life and improved quality of life. From an evidence-based point of view, studies investigating patient-oriented outcomes contribute more to the overall evidence and therefore have to be weighted more heavily. However, further studies with hard endpoints, as highlighted in Table 5, as well as longer study periods are definitely warranted, as they provide further evidence on the role of pharmacists in the care of CKD and ESRD patients and other patient groups.

Several studies on clinical pharmacist involvement were identified by our search strategy, but only four of them were controlled trials (two by the same authors) with high-quality methodological design and therefore a higher evidence impact. We decided to also include abstracts in our review, because we are convinced that these small studies of the impact of clinical pharmacy on patient care contribute to the overall evidence on this topic. We could not identify any studies that specifically addressed PD patients. However, in the two studies that included PD patients, the authors did not comment on any special issues (e.g., regarding the type of DRPs or adherence). Given the complexity and specifics of drug dosing during PD, the high need for education and patient training, and the high risk of infections (e.g., peritonitis), data specific to this patient population would be interesting and warranted. We hypothesise that clinical pharmacists are routinely integrated into different aspects of PD patient care, but due to irregular clinical attachment (as compared to HD patients, who generally attend clinic three times per week), such studies are more difficult to perform.

Furthermore, regarding CKD patient studies, it was not possible to subdivide different clinical pharmacist activities and further relevant findings (e.g., common DRPs and performed interventions) according to CKD stage.

Our review is subject to publication bias. We could not identify any studies showing that clinical pharmacy interventions had a negative impact on patient care. Furthermore, studies that used DRPs and physician acceptance rates as outcome parameters lacked information about rejected interventions and the reasons for rejection. The reporting of clinical significance assessments for performed interventions increases the scientific value of clinical pharmacy research, primarily by reducing bias. Data on the impact of clinical pharmacists on hospitalised inpatients is also scarce. In addition, the majority of the studies were published in the United States. Interestingly, only one study [16] from Europe could be identified; three of the remaining four studies were from Asia [14, 25, 28], and one was from New Zealand [30]. However, we hypothesise that clinical pharmacists are widely engaged in the care of CKD and ESRD patients. There are, for example, special interest groups dedicated to their care, such as the United Kingdom Renal Pharmacist Group [39]. Further high-quality studies on the impact of clinical pharmacists on key issues such as adherence and disease progression are thus warranted.

Conclusions

All identified studies on the involvement of clinical pharmacists in the care of CKD and ESRD patients showed some benefit. However, high-quality evidence on the impact of clinical pharmacy services is limited to a few studies. Clinical pharmacists address

areas requiring improvement as well as unmet DRPs responsively and preventatively. By doing so, clinical pharmacists positively contribute to the care of patients with impaired renal function and reduce the gaps in current patient care.

List of abbreviations used

ACCP American College of Clinical Pharmacy
ADE adverse drug event
BAS before-after study
CAM complementary and alternative medicines
CHD coronary heart disease
CKD chronic kidney disease
CVD cardiovascular disease
DS descriptive study
DRP drug-related problem
DTP drug-therapy problem
EKHA European Kidney Health Alliance
ESA erythropoiesis stimulating agent
ESRD end-stage renal disease
HD haemodialysis
IPA International Pharmaceutical Abstracts database
RCT randomised controlled trial
RRT renal replacement therapy
PD peritoneal dialysis
TDM therapeutic drug monitoring

Competing interests

The study was performed within a clinical pharmacy project that was funded by Amgen. The authors declare that there are no financial or other conflicts of interests with respect to the contents of the article.

Author contributions

GS was responsible for the study design, data collection and interpretation and preparation of the manuscript. RLG was responsible for the study design, data interpretation and review of the manuscript. All authors read and approved the final manuscript.

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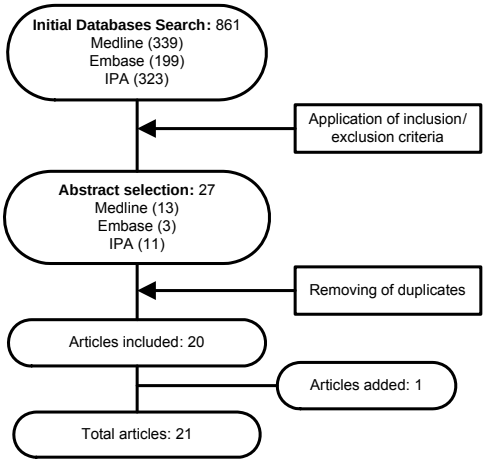
Figures

Figure 1



Tables

Table 1 Inclusion and exclusion criteria for literature search

	Included	Excluded
Study types	Randomized controlled trials (RCTs), descriptive studies (DS), before-after studies (BAS) with interventional data	Case reports, case studies, surveys, cost-effectiveness studies, narrative reviews
Interventions	Any type of clinical pharmacist intervention embedded in comprehensive clinical pharmacy activities if data were assessable numerically and outcomes were reported	Solely screening for inappropriate renal dosing, evaluations of computerised decision support systems
Language	Publications in English and German	Any other language

Table 2 Detailed description of the included publications on CKD patients

First author, (Year), Population	Design	N (INT/CT) [a]	Duration (months)	Interventions	Relevant outcomes [b]	Results	p-Value
Lim SB et al. [14], (2003), CKD inpts *Abstract*	DS	60	2	MR, therapeutic monitoring, feedback to physicians	No./Types of DRPs *Transcription errors* *Renal dosage adjustments* PhAR Significance *Somewhat significant* *Significant* *Very significant*	86 *44%* *10%* 93% *26%* *67%* *4%*	
Patel HR et al. [15], (2005), CKD outpts *Abstract*	DS	119	NR	Review of medical records, evaluations of DRPs, therapeutic recommendations	No. of DRPs Types of Interventions *Change of drugs* *Change of dosage* *Interval adjustments* PhAR	381 (100%) *NR* *NR* *NR* 40.9%	
Allenet B et al. [16], (2007), CKD outpts	BAS	10	3	Pharmacist-managed anaemia educational programmes	Knowledge (% of right answers on a 7-item questionnaire) at baseline vs. follow-up at Month 3 QOL judged on a LAS (0-10) at baseline vs. Month 3 *Energy* *Daily activities* *General well-being*	80±18 / 93±10 *3.3±1.7 / 7.1±1.7* *4.9±2.1 / 7.7±1.9* *4.6±2.2 / 7.5±1.6*	NS <0.05 <0.05 <0.05
Bucaloiu ID et al. [17], (2007), CKD outpts *Abstract*	DS	NR	32	Pharmacist-managed anaemia programmes compared to PCP-managed pts	Weekly erythropoietin dose Time to achieve Hb goal Maintenance of Hb values in target range Maintenance of Tsat values in target range	6.698 / 12.000 units 47.5 / 62.5 days 69.8 / 43.9% 64.8 / 40.4%	0.0001 0.11 0.0001 0.043
Joy MS et al. [18], (2007), CKD outpts	DS	128	28	Clinical pharmacist-managed anaemia programmes with darbopoietin	% of pts achieving Hb target compared to retrospective baseline analysis of data (before clinical implementation)	78 / 41%	

Table 2 Detailed description of the included publications on CKD patients (continued)

First author, (Year), Population	Design	N (INT/CT) [a]	Duration (months)	Interventions	Relevant outcomes [b]	Results	p-Value
Lee J et al. [19], (2009), CKD outpts	CT	18 (9/9)	6	INT: PC CT: SOC	Disease control parameters: Change from baseline to last follow-up visit (INT/CT)		
Abstract					*Blood pressure*	*-6 / +6.8 mmHg*	
					HbA_{1c}	*-0.2 / 0%*	
					Haemoglobin	*1.05 / -1.85 g/dL*	
					Medication adherence (pill count)	97.2 / 88.2%	

BAS before-after study, **CKD** chronic kidney disease, **CT** controlled trial, **DS** descriptive study, **DRP** drug-related problem, **Hb** haemoglobin, **HbA_{1c}** glycosylated haemoglobin, **LAS** linear analogue scale, **MR** medication review, **No.** number, **NR** not reported, **NS** not significant, **PC** pharmaceutical care, **PCP** primary care physician, **PhAR** physician acceptance rate, **pts** patients, **QOL** quality of life, **SOC** standard of care, **Tsat** transferrin saturation

[a] Number of included patients in the intervention (INT) or control (CT) group
[b] For brevity, only the three most commonly performed interventions/drug-related problems are listed.

Table 3 Detailed description of the included publications on dialysis patients

First author, (Year), Population	Design	N (INT/CT) [a]	Duration (months)	Interventions	Relevant outcomes [b]	Results	p-Value
Tang I et al. [20], (1993), HD outpts *Abstract*	DS	NR	6	Therapeutic interventions provided by CP	No./Types of interventions *Drug selection* *Drug discontinuation* *Dose selection* Significance of interventions *Preservation of major organ function* *Improvement in quality of care* PhAR	205 (100%) *66 (32.2%)* *39 (19.0%)* *50 (24.4%)* *34.6%* *62.4%* 91.7%	
Kaplan B et al. [21], (1994), HD outpts *Abstract*	DS	24	NR	Focused DT review programmes	No. of recommendations / informative comments PhAR	114 / 85 76% (implemented 70%)	
Grabe DW et al. [22], (1997), HD outpts	DS	45	1	DT reviews by CP Therapeutic recommendations	No./Types of DRPs *Drug interactions* *Dialysis-specific DRPs* PhAR No. of interventions *1 – adverse significance* *2 – no significance* *3 – somewhat significant* *4 – significant* *5 – very significant* *6 – extremely significant*	126 (100%) *35 (27.5%)* *33 (26.5%)* 81% 102 *0%* *6.9%* *0%* *78%* *4.9%* *1%*	
Possidente CJ et al. [12], (1999), HD and PD inpts	DS	37	3.5	CPS (MR, pts interviews, identification and resolution of DRPs)	No./Types of DRPs *Pts did not receive drug* *Overdosage* *Labs needed* PhAR Significance *Somewhat significant* *Significant* *Very significant*	161 More DRPs (77) at admission vs. discharge (41) 95.7% *24.7%* *58.4%* *16.9%*	<0.011
To LL et al. [23], (2001), HD outpts	BAS	49	6	Pharmacist-managed programmes compared to physician-managed pts	Mean HCT (±SD) during physician period vs. pharmacist period Total EPO α dose Total elemental iron dose oral Total elemental iron dose i.v. Mean (±SD) Tsat level	35.36±3.33 / 36.21±3.46% 8.5 / 7.7 million units 85.605 / 95.550 mg 13.600 / 33.025 mg 29.82±14.92 / 30.78±13.17%	0.20 0.37 0.64 <0.001 0.66

Table 3 Detailed description of the included publications on dialysis patients (continued)

First author, (Year), Population	Design	N (INT/CT) [a]	Duration (months)	Interventions	Relevant outcomes [b]	Results	p-Value
Viola RA et al. [24], (2002), HD outpts	DS	26	6	Pharmacist-managed hyperlipidaemia programmes with HD pts (laboratory management, counselling, statin initiation, and adjustments)	% of pts achieving LDL cholesterol target at baseline vs. Month 6	58% / 88%	0.015
					Mean LDL (±SD) cholesterol at baseline vs. Month 6	96±5 / 80±3 mg/dL	<0.01
					Mean total cholesterol (±SD) at baseline vs. Month 6	170±7 / 151±4 mg/dL	<0.01
					No./Types of interventions	15	
					Dose increase	*6*	
					Drug change	*5*	
					Therapy initiation	*2*	
Kimura T et al. [25], (2004), HD outpts	DS	41	9	Pharmacist-managed anaemia programmes	No. pts achieving the HCT target of >30% at baseline vs. Month 9	7 (17.1%) / 32 (78%)	
					No. pts with EPO dose reductions due to intervention	23 (56%)	
Manley HJ et al. [26], (2004), HD outpts *Abstracts*	DS	408	NR	Implementations of treatment algorithms for CV disease in HD pts by a pharmacist, collections of CV medication-related issues and recommendations to nephrologists, pts interview, MR	No. of recommendations	1575	
					PhAR	79.8%	
					Impact of recommendations on pts care		
					Improvement	*89.9%*	
					No impact	*7.6%*	
					Worsened pts care	*2.4%*	
					LDL cholesterol	-31.2 mg/dL	<0.001
					HbA1C	-0.3%	NS
					Adjusted CV mortality hazard ratio	0.48 (CI 0.18, 1.3)	
Walton T et al. [27], (2005), HD outpts	DS	278	26	Pharmacist-managed anaemia programmes	Hb value at baseline and Month 6	9.5 / 11.8 g/dL	
					Mean (±SD) ferritin at baseline and Month 6	280.9±326.4 / 431±232.1 ng/mL	
					Mean (±SD) Tsat at baseline and Month 6	21±7.9 / 33±8%	
Sathvik BS et al. [28], (2007), HD outpts	RCT	90	4	Pharmacist-provided pts education <u>Group 1:</u> Pharmacist pts education (Month 0-2) <u>Group 2:</u> Usual health care w/o pharmacists (Month 0-2) Switch at Month 2	Medication knowledge (MKAQ) at baseline, Month 2 and 4 in Group 1 and 2	Improvement in MKAQ scores in Group 1 compared to baseline and to Group 2 at Month 2	<0.05
						No significant improvement in MKAQ scores in Group 2 compared to baseline at Month 2	>0.05
						Improvement in MKAQ scores in Group 2 at Month 4 compared to baseline and to scores at Month 2	<0.05
						Decrease in MKAQ scores in Group I at Month 4 compared to Month 2	<0.05

Table 3 Detailed description of the included publications on dialysis patients (continued)

First author, (Year), Population	Design	N (INT/CT) [a]	Duration (months)	Interventions	Relevant outcomes [b]	Results	p-Value
Erickson AI et al. [29], (2008) , HD in- and outpts	DS	1184 pts visits	4	Prospective order review by CP and general CPS	Compliance with prospective order review	1059 (89.4%)	
					No./Types of interventions	77 (100%)	
					Therapeutic-related	*11 (14.3%)*	
					Safety-related	*49 (63.6%)*	
					Compliance-related	*17 (22.1%)*	
					PhAR	100%	
Castro R et al. [13], (2009), HD outpts Abstracts	BAS	60	6	MTM	Disease control parameters at baseline vs. follow-up visit at Day 90		
					SBP (MTM)	150±22 / 144±18 mmHg	0.12
					SBP (non-MTM)	143±21 / 145±25 mmHg	NS
					HbA_{1c} (MTM)	9.2±1.6 / 9.0±2.0%	0.58
					HbA_{1c} (non-MTM)	6.2±1.2 / 6.5±1.4%	NS
					Phosphorus (MTM)	6.2 / 5.6 mg/dL	.096
					Calcium/phosphorous product (MTM)	56±19 / 50±16	.03
Mirkov S [30], (2009), HD outpts	DS	64	8	DT reviews by CP	No./types of DRPs	278 (100%)	
					Non-adherence	*61 (22%)*	
					Overdosage	*26 (9.3%)*	
					Untreated indication	*24 (8.6%)*	
Pai AB et al. [31], (2009), HD outpts	RCT	104 (57/47)	24	INT: PC, DT reviews by CP CT: SOC, DT reviews by dialysis nurse	No./Types of DRPs	530 (100%)	
					Drug record discrepancy	*133 (25%)*	
					Untreated indication	*111 (21%)*	
					Subtherapeutic dosage	*74 (14%)*	
					PhAR	100%	
					Reduction in drug use in INT	14%	<0.05
					Reduction of hospitalisations in INT	42%	0.02
					Reduction of LOS in INT	21%	0.06
Pai AB et al. [32], (2009), HD outpts	RCT	107 (61/46)	24	INT: PC, DT reviews by CP CT: SOC, DT reviews by dialysis nurse	Total RQLP scores at Year 1 compared to baseline INT/CT	Worsening in Total RQLP score at Year 1 in CT group (88±31 / 71±34)	0.03
					Total RQLP scores at Year 2 compared to baseline INT/CT	Improvement in INT/CT group, no statistically significant difference	

BAS before-after study, **CP** clinical pharmacist, **CPS** clinical pharmacy services, **CV** cardiovascular diseases, **DRP** drug-related problem, **DS** descriptive study, **DT** drug therapy, **EPO** erythropoietin, **HbA_{1c}** glycosylated haemoglobin, **HCT** haematocrit, **HD** haemodialysis, **Hb** haemoglobin, **LDL** low-density lipoprotein, **LOS** length of stay, **MKAQ** medication knowledge assessment questionnaire, **MR** medication review, **MTM** medication therapy management service, **No.** number, **NR** not reported, **NS** not significant, **PC** pharmaceutical care, **PhAR** physician acceptance rate, **pts** patients, **RCT** randomised controlled trial, **RQLP** renal quality of life profile, **SBP** systolic blood pressure, **SD** standard deviation, **SOC** standard of care

[a] Number of included patients in the intervention (INT) or control (CT) group
[b] For brevity, only the three most commonly performed interventions/drug-related problems are listed.

Table 4 Comprehensive listing of clinical pharmacy activities

- Taking a thorough medication history
- Matching computerised medication profiles with verbally obtained medication history
- Medication review at different time points, such as at admission, during inhospital treatment, during each dialysis session, and at discharge (including OTC drugs, herbal supplements, drugs prescribed by non-nephrologists, and CAM drugs)
- Therapeutic recommendations
- Prevention and resolution of DRPs
- Therapeutic monitoring (treatment, laboratory values, and specific drugs)
- Counselling and provision of drug information for patients and other health care professionals
- Patient and health care provider education
- Compliance assessment
- Compiling of guidelines for proper drug use and implementation of treatment algorithms
- Independent prescribing within the scope of specific guidelines (e.g., anaemia managements or lipid management)
- Medication order review and checking adherence to prescribing guidelines
- Medication use evaluation
- Further audit measures

Table 5 Disease versus patient-oriented outcomes

Disease-oriented outcomes	**Patient-oriented outcomes**
Total cholesterol, LDL, HDL	Rate of hospitalization
HbA1c	Length of stay
Haematocrit, Tsat, ferritin, haemoglobin	Health-related quality of life
SBP, DBP	Medication-related knowledge
Phosphorus, calcium-phosphorus product	Renal quality of life
Drug dosages (e.g., EPO dosage or ferrous dosage)	Patient satisfaction survey

3.2 CLINICAL PHARMACY SERVICES AND SOLID ORGAN TRANSPLANTATION: A LITERATURE REVIEW

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REVIEW ARTICLE

Clinical pharmacy services and solid organ transplantation: a literature review

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Abstract *Aim of the review* Organ transplantation represents the therapy of choice for most types of end-stage organ failure, and post-transplant patient care warrants great attention. The aim of this study was to summarise the available evidence regarding the role and impact of clinical pharmacy services in the care of solid organ transplant patients. *Methods* A search of the literature was conducted using the MEDLINE, EMBASE and IPA databases to identify studies relevant to our investigation of the impact of clinical pharmacists' interventions. *Results* Only five out of nineteen of the included studies were randomised controlled trials; eleven studies were descriptive, and three were before-after studies. Interventions performed in these studies consisted of routine clinical pharmacy services with a focus on identifying, resolving and preventing drug-related problems; clinical pharmacy services with a focus on therapeutic drug monitoring; and those with a focus on compliance enhancement and educational interventions. The number and type of interventions and the physicians' acceptance rates were assessed in the majority of the included studies. Acceptance rates were generally above 95%, and most studies reported that clinical pharmacy services had a positive impact on the care of solid organ transplant patients. Positive perceptions of patients and health care professionals are also reported. In two of the studies, patients' compliance rates and drug knowledge were assessed following counselling by a pharmacist. Dosing-related interventions were the most common interventions proposed. Immunosuppressants, cardiovascular drugs and antimicrobials were the drug classes most affected by the clinical pharmacists' interventions. *Conclusions* High quality evidence that supports the benefit of clinical pharmacy services in the care of solid organ transplant patients is rare. Nevertheless, all of the included studies showed that clinical pharmacy services had a positive impact. Furthermore, all included studies showed that patients and physicians appreciated clinical pharmacists. The various outcome measures used in these studies were improved by interactions with clinical pharmacists. More randomised controlled trials are needed to contribute to the paucity of the existing evidence.

Keywords Clinical pharmacy services · Immunosuppressant medications · Literature review · Solid organ transplantation

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Impact of findings on practice

- Evidence exists regarding the positive impact clinical pharmacy services have on several aspects of the care of solid organ transplant patients.
- This literature review may serve as a basis for further implementation of clinical pharmacy services in the care of solid organ transplant patients.

Introduction

The era of successful clinical organ transplantation began in the middle of the twentieth century when the first

transplantations of the heart, kidney and lung were performed [1]. This coincided with a better understanding of immunological processes, the development and introduction of highly effective immunosuppressive agents, such as azathioprine, corticosteroids and cyclosporine A, and an improvement in organ preservation and surgical techniques, all of which paved the way for solid organ transplantation (SOT) to become the treatment of choice for most types of organ failure. The most frequent SOTs performed are those of the visceral organs (kidney, liver and pancreas) followed by those of the thoracic organs (heart and lung). The most common indications for SOTs are end-stage renal disease of different aetiologies (kidney); cardiomyopathy, myocarditis or heart valve defects (heart); pulmonary hypertension, pulmonary emphysema or cystic fibrosis (lung); end stage of liver cirrhosis of different aetiologies (liver); and diabetes mellitus I (pancreas) [2]. The number of kidney and liver transplantats is increasing, whereas the number of heart, lung and pancreas transplantats is relatively constant or even declining (in the case of pancreas transplants) (Fig. 1).

Immunosuppressant pharmacotherapy is a critically important aspect of post-transplant patient care. Patients must take immunosuppressants for the remainder of their life to prevent episodes of graft rejection and consecutive graft loss and to assure the success of the SOT.

Immunosuppressive maintenance therapy tends to be centre-specific. Maintenance therapies normally consist of a combination of multiple agents, including corticosteroids, calcineurin inhibitors, anti-metabolites and mTor-Inhibitors [3]. The combination therapy approach to the use of immunosuppressive agents is beneficial, because their mechanisms of actions overlap and are potentially synergistic and because combination therapy allows for a reduction in the dose of each individual agent, thereby reducing dose-related drug side effects. The overall therapeutic goal, which is quite challenging, is to maintain a fine balance between over- and under-immunosuppression in these patients. Over-immunosuppression can lead to multiple problems, such as organ toxicity (e.g., calcineurin inhibitor-induced nephrotoxicity) and an increased incidence of adverse drug events (ADEs), as well as an increased risk of life-threatening infections and post-transplantation malignancies. The main risk of under-immunosuppression is that it increases the risk of rejection and graft loss. This goal is generally achieved by careful monitoring of immunosuppressant drug levels and corresponding dose individualisation. It may also be achieved by switching to a different immunosuppressant agent or by adapting the dose according to the time elapsed since transplantation.

In addition to the complexity of immunosuppressive pharmacotherapy itself, there remain multiple other pharmacotherapeutic issues to consider in the transplant recipient. Transplant patients are prone to viral (e.g., cytomegalovirus, herpes simplex virus), bacterial and fungal (e.g., candida, pneumocystiis) infections and therefore, prevention measures are warranted, but antimicrobial treatment is often necessary. Furthermore, immunosuppression-related complications and multiple drug side effects, such as nephrotoxicity,

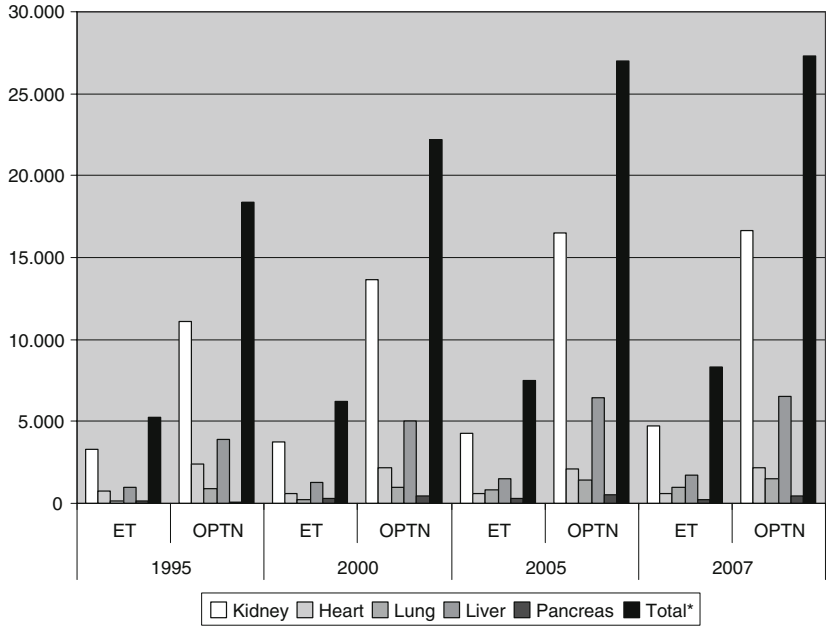

Fig. 1 The total number of single organ transplantations from both deceased and living donors over time. * Adapted from the annual data reports of Eurotransplant (ET) [37] and the Organ Procurement and Transplantation Network (OPTN) [38]

hyperkalemia and other electrolyte disturbances, new-onset diabetes mellitus, hyperlipidemia, hypertension and gastrointestinal problems, among others, must be managed.

Polypharmacy is therefore frequent in the transplant patient population. Patients need to be closely monitored in order to allow medical providers to recognise and consequently manage ADEs. Because the calcineurin inhibitors cyclosporine and tacrolimus and the m-Tor-inhibitors sirolimus and everolimus are metabolised by cytochrome P450 enzymes, drug-drug interactions (DDIs) are likely to occur when these medications are given in combination with inhibitors and inducers of cytochrome P450 enzymes. The recognition and management of DDIs therefore also warrants great attention. Counselling patients on the properties and role of prescribed immunosuppressants in order to raise their awareness of potential drug side effects as well as ensuring patients' compliance with their medical regimen are additional important aspects of post-transplant patient care. Close monitoring is especially critical during the early post-transplantation period, which lasts up to 1 year, and must be continuously pursued, although to a lesser extent, after that [4].

Transplant patients are generally cared for by a multidisciplinary health care team, which includes general practitioners, medical specialists, nurses, psychologists and other health care professionals. Clinical pharmacists who specialise in SOTs are also members of these multidisciplinary teams, and they address drug-related therapeutic issues in this population. Clinical pharmacy services have proven to be beneficial in the management of many diseases and special patient populations and have contributed to patient safety, reductions in drug-associated mortality and hospitalisations, and they have had an overall positive impact on patient care [5–8].

Aim of the review

The aim of this review is to provide an overview of the available literature regarding clinical pharmacists' role in the care of SOT patients. The review summarises and discusses the different concentrations of clinical pharmacy services, the methodological barriers of the studies and further implications for the wider implementation of SOT clinical pharmacy services.

Methods

Search strategy

A literature research was conducted using the MEDLINE (1970—Week 10, 2009), EMBASE (1980—Week 10, 2009) and INTERNATIONAL PHARMACEUTICAL ABSTRACTS (IPA) (1970—Week 10, 2009) databases to identify relevant articles.

In MEDLINE, the following combinations of Mesh (Medline Medical Subject Headings) terms were used as our search strategy: ("*pharmacy service, hospital*" OR "*pharmacists*" OR "*pharmaceutical services*") AND "*transplantation*".

In EMBASE and IPA, the search strategy combined the terms ("*clinical pharmacy*" OR "*pharmaceutical care*" OR "*pharmacist*" OR "*hospital pharmacy*") AND "*transplantation*". We decided to use the umbrella term "*transplantation*", instead of "*organ transplantation*" for our initial search in order to increase the sensitivity of our search.

Inclusion and exclusion criteria

All studies addressing the impact of clinical pharmacy services (either at the patient or physician level) on the care of SOT patients were included. All study types, including randomised controlled trials (RCT), descriptive studies (DS) and before-after studies (BAS) were included if they provided interventional data. Results published in abstract form (e.g., congress abstracts) only were included if they provided numerically assessable data, e.g., the number of interventions, the acceptance rates and the number of resolved drug-therapy problems (DTP). Publications that solely addressed the economic impact and cost reduction associated with pharmacists' interventions, descriptive reviews, surveys of pharmacists' work in the field of transplantation, and single case studies were excluded. All types of study settings, e.g., inpatient care, ambulatory care, etc., were included.

Data collection

The predefined data parameters, namely the study design, the number of included patients, the study duration, the types of interventions, the relevant outcomes and the results were extracted from the literature, summarised and reviewed.

Results

The initial search in MEDLINE, EMBASE and IPA yielded 91, 175 and 174 citations, respectively. The detailed search results are described in Fig. 2. A total of 440 citations were initially screened for inclusion criteria by reviewing the title. A total of 98 abstracts were further screened, and after removing duplicates, a total of 19

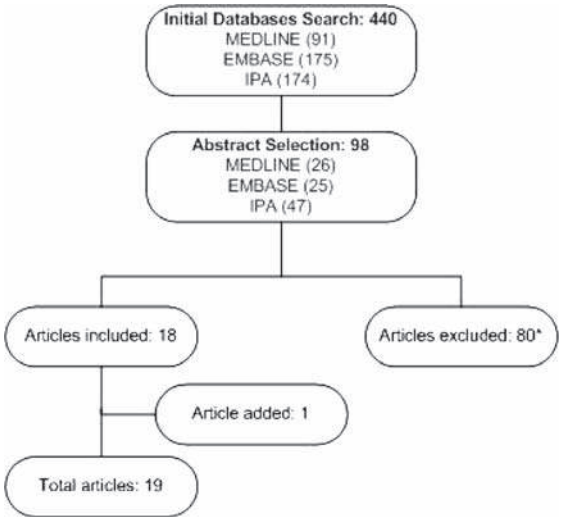

Fig. 2 Flow chart of the search strategy and results. * The predominant reasons for exclusion were the study type, a lack of interventions, non-assessable data and the inclusion of non-SOT patients

citations remained for full review. The predominant reasons for exclusion were publication type (e.g., reviews, letters or commentaries), a lack of interventional data or non-assessable data, and the inclusion of non-SOT patients. Detailed descriptions of the included studies are shown in Table 1.

Three study types were identified, including 11 DSs (58%), 5 RCTs (26%) and 3 BASs (16%). A total of nine of the published studies (47.4%) were only available as abstracts. The earliest included study was published in 1991. The study sites were predominantly located in the US or Canada (13, 68%), three were located in Asia, and three were located in Europe, reflecting the wider implementation and development of clinical pharmacy services in North America. We avoided detailed descriptions of study settings because most of the studies were conducted in the ambulatory care setting.

Interventions

Interventions that were performed in the included studies could be roughly grouped into the following categories: (1) general clinical pharmacy services (13, 68.5%) [9–21], (2) general clinical pharmacy services with a focus on therapeutic drug monitoring (TDM) (2, 10.5%) [22, 23], (3) clinical pharmacy services that predominantly addressed compliance issues (2, 10.5%) [24, 25] and (4) clinical pharmacy services that focused on patient education (2, 10.5%) [26, 27]. The clinical pharmacists' activities that were reported in the 19 included studies are listed in Table 2.

These categories overlap in many cases and this categorisation system was largely chosen in an effort to structure the results. Of the 19 included studies, 15 (78.9%) described the clinical pharmacists' interactions between patients and physicians, and 2 (10.5%) studies described the pharmacists' interactions with physicians or patients, respectively.

Outcomes

The total number of interventions performed or recommendations given, as well as the physicians' acceptance rate, were considered relevant outcome parameters in 13 of the studies (68.4%). Statistically significant findings were only reported in four RCTs. The sample sizes were generally small (mean intervention group size: 17; mean control group size: 15). All RCTs revealed that clinical pharmacy interventions had a positive impact on patients in the intervention group.

Interventions were classified using Strand's classification system in six studies (46.2%) [28]. One study [25] used the PI-Doc System [29]. In six of the studies (46.2%), the type of classification system that was used could not be identified. The clinical significance of the interventions and their impact on patient care were commonly rated using the criteria published by Hatoum et al. [30]. The significance of the interventions was only reported in six of the studies and the assessment was co-reviewed to avoid bias.

The acceptance rates were reported in only seven of the studies and were generally above 95%. Only in the study by Wang and colleagues [21] was there information available regarding rejected pharmacist's recommendations.

Seven of the studies reported on the drug classes that are most affected by clinical pharmacists' interventions (not shown in Table 1). Immunosuppressants, cardiovascular drugs and antimicrobials were involved in the interventions in the majority of studies.

The influence of clinical pharmacists on the optimisation of specific diagnostic parameters, e.g., blood pressure and fasting blood glucose levels, was investigated in two studies[11, 15], both of which showed that clinical pharmacists had a positive impact on these parameters. The impact clinical pharmacists had on drug education was assessed in three of the studies [25–27]. Information regarding the satisfaction of health care professionals and patients with the clinical pharmacist participating as a member of the therapeutic team, as well their appreciation for clinical pharmacy services, were available in six of the studies. In a few of the studies, satisfaction rates were systematically assessed, e.g., by a questionnaire. In most cases, only comments containing positive perceptions of clinical pharmacy services could be found. The study by Lee and colleagues [22] assessed the impact that clinical

Table 1 Detailed description of the included publications

First author, (Year), Organ	Design	N (INT/CT)[a]	Duration (months)	Interventions	Relevant outcomes[b]	Results	*P* value
Burge KL et al. [9], (1992), NR	DS	–	9	Clinical activities of pharmacists in a SOT service (not specified)	No./Types of recommendations	727	–
					Dosage modifications	NR	
					DI	NR	
					Therapeutic recommendations	NR	
					PhAR	97.0%	
					% of patients without complications after discharge	84%	
Chisholm MA et al. [10]., (1998), Kidney Abstract	DS	–	9	MR Identification, resolution and prevention of DRPs Therapeutic recommendations	No./Types of recommendations	385 (100%)	–
					Untreated indications	111 (28.8%)	
					Overdosage	97 (25.3%)	
					Sub-therapeutic dosage	81 (21.1%)	
					PhAR	368 (95.6%)	
					Potential impact on patient care		
					Significant	250 (67.9%)	
					Very significant	108 (29.3%)	
					Extremely significant	NR	
Chisholm MA et al. [11]., (1999), Kidney	RCT	INT: 18 CT: 15	12	INT: Clinical pharmacy services (MR, identification, resolution and prevention of DRPs, therapeutic recommendations) CT: Routine clinic services without clinical pharmacists' interaction	FBG at baseline and mean quarterly change (INT/CT)	1st: 0/+7 mg/dl	NS
						2nd: −21/+13 mg/dl	NS
						3rd: −40/+13 mg/dl	<0.05
						4th: −44/+20 mg/dl	<0.05
Chisholm MA et al. [12]., (1999), Kidney Abstract	DS	–	13	MR Identification, resolution and prevention of DRPs Therapeutic recommendations	No./Types of recommendations	566 (100%)	–
					Untreated indications	154 (27.2%)	
					Overdosage	152 (26.8%)	
					Sub-therapeutic dosage	106 (18.8%)	
					PhAR	541 (95.6%)	
					Potential impact on patient care		
					Significant	422 (78.0%)	
					Very significant	108 (20.0%)	
					Extremely significant	NR	
Chisholm MA et al. [13]., (2000), Kidney Abstract	DS	–	31	MR Identification, resolution and prevention of DRPs Therapeutic recommendations	No./Types of recommendations	1014 (100%)	–
					Untreated indications	270 (26.6%)	
					Overdosage	228 (22.5%)	
					Sub-therapeutic dosage	187 (18.4%)	
					PhAR	976 (96. 3%)	

Table 1 continued

First author, (Year), Organ	Design	N (INT/CT)[a]	Duration (months)	Interventions	Relevant outcomes[b]	Results	*P* value
					Potential impact on patient care		
					Significant	774 (79.3%)	
					Very significant	182 (18.6%)	
					Extremely significant	NR	
Chisholm MA et al. [14]., (2000), Kidney	DS	201	19	MR	No./Types of recommendations	844 (100%)	–
				Identification, resolution and prevention of DRPs	Untreated indications	230 (28.4%)	
					Overdosage	216 (26.6%)	
				Patient interviews	Sub-therapeutic dosage	147 (18.1%)	
				DI	PhAR	811 (96.0%)	
				Therapeutic recommendations			
					Potential impact on patient care		
					Significant	620 (76.4%)	
					Very significant	175 (21.6%)	
					Extremely significant	6 (0.7%)	
Chisholm MA et al. [24]., (2001), Kidney	RCT	INT: 12	12	INT: Clinical pharmacy services (monthly MR, drug therapy optimisation, recommendations to nephrologists, compliance counselling)	Mean Compliance Rate (INT/CT), calculated by refill record data	96.1% ± 4,7%/ 81,6% ± 11,5%	<0.001
					Achievement of target range of SDC	64%/48%	
					Compliance rate at 12 months	75%/33.3%	<0.05
					Duration of compliance	Significantly longer	<0.05
		CT: 12		CT: Routine clinic services without clinical pharmacists' interaction			
Chisholm MA et al. [15]., (2002), Kidney	RCT	INT: 13	12	INT: Clinical Pharmacy Services (MR, identification, resolution, and prevention of DRPs, therapeutic recommendations)	SBP at baseline and quarterly	2nd: 137.8 ± 15.0/ 168.9 ± 15.3	<0.05
						3rd: 135.9 ± 11.7/ 164.6 ± 20.1	
						4th: 145.3 ± 16.8/ 175.8 ± 33.9	
					DBP at baseline and quarterly	2nd: 76.0 ± 11.8/ 84.9 ± 6.1	
						4th: 77.0 ± 10.2/ 91.8 ± 12.0	<0.05
		CT: 10		CT: Routine clinic services without clinical pharmacists' interaction			

Table 1 continued

First author, (Year), Organ	Design	N (INT/CT)[a]	Duration (months)	Interventions	Relevant outcomes[b]	Results	*P* value
Klein A et al. [25]., (2007), Liver	RCT	INT: 20	12	INT: Clinical pharmacy services (patient education: 3–4 interviews prior to discharge, at least quarterly during 12 month study period)	Mean dosing compliance rate (INT/CT), calculated by MEMS-Refill data	90.2 ± 6.2%/80.8 ± 12.4%	<0.015
					Sub-therapeutic SDC	8% (10 of 125)/22% (27 of 121)	
					Patients' knowledge test score (INT/CT)	16.0 ± 1.8/11.0 ± 2.3 points	<0.001
		CT: 21		CT: Routine clinic services without clinical pharmacists' interaction	No. of DRPs identified	162	
					Untreated indications	11%	
				Compliance measurement, patients satisfaction, patients' knowledge about drug therapy, number of DRPs	Duration of drug therapy inadequate	9%	
					SDC problems	8%	
					No. of consecutive interventions	162	
					% of resolved DRPs	96%	
Lee KL et al. [22], (2000), Kidney	RCT	INT: 21	6	INT: TDM service for CsA, identification of DRPs, pharmacotherapy consultation and interventions	No. of DRPs (INT/CT)	182/144	
					No. of identified ADEs	68/35	
					Rejection episodes	2/2	
					Renal transplant clinic visits	160/137	
		CT: 17		CT: no pharmaceutical care	Mean SDC ± SD ng/ml	122.16 ± 24.07/136.44 ± 36.2	
					No. of suggestions to physicians	70	
					CsA dosage regimen	29	
					Increase in dose or frequency	10	
					Alternative drug or therapy	9	
					No. of suggestions to patients	245	
					Hypertension control education	40	
					ADE confirmation or/prevention	34	
					Infection prevention	26	
					Quality of Life Questionnaire SF-36, baseline and final scores	Higher final scores of INT group compared to CT group	
Marek TM et al. [16], (1994), Kidney Abstract	DS	–	1	Medication monitoring	No. of interventions	44	–
				Patients' education sheets	% of patients seen by the clinical pharmacists	55%	
				Medication histories	% of medications discussed	32%	
				DI			
				Therapeutic recommendations			

Table 1 continued

First author, (Year), Organ	Design	N (INT/CT)[a]	Duration (months)	Interventions	Relevant outcomes[b]	Results	*P* value
Mathis AS et al. [17], (2003), Kidney Abstract	DS	–	3	Participation on ward rounds	No./Types of interventions (hours)	317 (130)	–
					DI	62	
					Laboratory monitoring application	46	
					Pharmacokinetic evaluations	43	
Mishima K et al. [23], (2002), Liver	BAS	52	–	Clinical pharmacists' participation in the health care team (dosing, drug interaction checks, monitoring of ADEs, instructions for patient compliance)	Mean SDC-SD (Tacrolimus) before/after participation of the clinical pharmacists	5.9/3.7, significant decrease in variance	NS
					No. of patients with convulsions before/after participation of the clinical pharmacists	20% (5 of 25)/0%	
					Rejection rate before/after participation of the clinical pharmacists	32%/26%	
Monnier G et al. [26], (2003), Liver	BAS	29	9	Pharmacy counselling	Knowledge test score before/after counselling (4 items: name of drug, recognition of drug, indication of drug, dosage of drug)	53.7%/75%	–
				Recommendations/Explanations regarding prescribed drugs			
				Information about self medication			
				Pharmaceutical care plans			
				Information leaflets	Duration of counselling (minutes)	54 ± 15	
Oji VU et al. [18], (1994), Kidney Abstract	DS	–	9	Pharmaceutical care services (drug therapy evaluation; identification, resolution and prevention of DRPs)	No. of clinical interventions	3052	–
Partovi N et al. [27], (1995), NR	BAS	28	–	Medication counselling program for patients	Knowledge test score before/after counselling	25%/66%	–
				Verbal counselling			
				Medication teaching sheets			
				Patient participation in self-medication program			
Prowse A et al. [19], (2004), NR	DS	630	4	MR	No. of patient: pharmacist consultations	972	
				Prescription checks	No./Type of interventions	592	
				Patient counselling	Missing dose on prescription	141 (23.8%)	
				Therapeutic recommendations	Incorrect dose	90 (15.2%)	
				Medication home delivery services	Therapy no longer indicated	67 (11.3%)	
					Significance of interventions		
					Not significant	23%	
					Minor significant	20%	
					Moderate significant	49%	
					Severe	8%	

Table 1 continued

First author, (Year), Organ	Design	N (INT/CT)[a]	Duration (months)	Interventions	Relevant outcomes[b]	Results	*P* value
Ptachcinski RJ [20], (1991), Liver Abstract	DS	287	3	DT evaluation Identification, resolution and prevention of DRPs Therapeutic recommendations Patient instructions	No. of therapy evaluations No. of therapy changes recommended PhAR	930 414 82%	–
Wang HY et al. [21], (2008), Kidney	DS	16	37	MR Identification, resolution and prevention of DRPs Patient interviews DI Therapeutic recommendations	No./Types of recommendations Medication selection Dosage adjustment Improper laboratory PhAR Potential impact on patient care Significant Very significant Extremely significant Patients' outcomes Improvement Maintenance Regression	55 19 (34.5%) 8 (14.5%) 7 (12.7%) 96% (52) 58.2% 21.8% 1.8% 94.2% (49) 5.8% (3) 0% (0)	–

ADE adverse drug event, *BAS* before-after study,*CsA* cyclosporine A, *DBP* diastolic blood pressure, *DI* drug information, *DRP* drug-related problem, *DS* descriptive study, *FBG* fasting blood glucose, *MEMS* medication event monitoring system, *MR* medication review, *NR* not reported, *PhAR* physicians' acceptance rate, *RCT* randomised, controlled trial, *SBP* systolic blood pressure, *SD* standard deviation, *SDC* serum drug concentration, *SOT* solid organ transplant(ation), *TDM* therapeutic drug monitoring

[a] Number of included patients in the intervention (INT) or control (CT) group

[b] For brevity, only the three most commonly performed interventions/drug-related problems are listed

pharmacy services had on patient satisfaction and quality of life using a quality of life questionnaire and found that clinical pharmacists had a positive impact. Due to the use of different satisfaction assessment methodologies, a summary of the overall patient satisfaction with the services provided by clinical pharmacists was not possible. Nevertheless, the rate of satisfaction with the implemented services was high and the study authors generally interpreted these findings as further evidence supporting the implementation of clinical pharmacy services.

Discussion

Compared to other systematic reviews [6, 8] examining the impact of clinical pharmacists on different diseases and different patient populations, very few studies could be identified that addressed the impact of clinical pharmacy services on SOT patients. However, clinical pharmacy services do exist for this specialised patient population, predominantly in the field of kidney and liver transplantation. According to a survey of transplant centres in the U.S. [31], 78 (28 out of 36) had clinical pharmacists' support. We could not identify any published studies regarding the impact of clinical pharmacists that met both our inclusion and exclusion criteria and that addressed the care of heart, lung or pancreas transplant patients. However, descriptive articles regarding pharmacists' impact on patient care and the possible areas in which clinical pharmacists could contribute to patient care have been published [32–36].

Clinical pharmacists' in-depth education in pharmacotherapy empowers them to address the complexity of the issues associated with the care of transplant patients, such as the management of an immunosuppressant regimen, ADEs, DDIs, medication compliance issues and the management of infectious diseases. Other transplant-related roles in which clinical pharmacists participate include education, the development of practice guidelines and quality outcomes monitoring.

By definition, clinical pharmacy services provide a multi-faceted intervention and their role can include multiple different techniques and activities, which are summarised in Table 2. All of the included publications showed that clinical pharmacy services had a positive impact on patient care and, when evaluated, high satisfaction rates regarding the clinical pharmacists' performance were noted. In addition to the relatively small number of RCTs, there exist a larger number of descriptive studies that contribute to the overall evidence regarding the role of clinical pharmacists as part of a multi-disciplinary care team. Descriptive studies can also raise awareness of the impact of clinical pharmacy services and identify areas with further need of clinical pharmacy services. However, studies addressing definitive outcomes, such as hospitalisation time, reduced occurrence of ADEs, disease-related events or mortality, are lacking. Because studies documenting the impact clinical pharmacists have on hard clinical end-points do exist in other patient populations [5, 6], we therefore hypothesise that clinical pharmacy services do positively influence hard clinical end-points in the SOT patient population.

Table 2 The roles of clinical pharmacists in the care of solid organ transplant patients

Acquisition of complete drug histories
Checking dosage, indications and administration modalities
Identification, resolution and prevention of drug-related problems
Providing of therapeutic recommendations to health care professionals and patients
Providing drug information to health-care professionals and patients
Educational activities for health-care professionals (physicians, nurses) and patients
Reporting and management of (suspected) adverse drug events
Management of potential or evident drug-drug and drug-food-interactions
Dosage adjustments of critical drugs based on pharmacokinetic calculations
Counselling patients regarding medication administration and therapy
Follow-up (personal contact, phone calls, etc.)
Compliance-enhancing activities

Most of the interventions addressed dose-related issues, e.g., sub- or supra-therapeutic serum drug concentrations, which highlighted the importance of dosing during the drug prescribing process. It is not surprising that immunosuppressants are one of the classes of drugs that are the most positively affected by the participation of clinical pharmacists. Narrow therapeutic indices, complex dosing regimens and high probabilities of DDIs and ADEs are all properties of immunosuppressants that contribute to the high likelihood of DRPs occurring during therapy. Cardiovascular drugs also represent a drug class that should be closely monitored, largely because of their widespread use due to post-transplant hypertension or post-transplant hyperlipidemia.

Our review is subject to publication bias. We could not identify any studies that showed that clinical pharmacy services had a negative impact on patient care. It is notable that seven of the studies (37%) were performed by Chisholm and colleagues at one centre, which is a highly active research centre regarding this topic. One abstract published by Chisholm and colleagues [13] seems to be a summary of data previously presented at annual congress meetings [10, 12]. Furthermore, we decided to include abstracts in our review because we are convinced that these small

studies regarding the impact of clinical pharmacy on patient care contribute to the overall evidence on the topic. However, due to the small overall number of published studies with a high quality methodological design that have addressed SOT patient care, it is too early to draw a definitive conclusion regarding the impact of clinical pharmacy services on the care of SOT patients.

We hypothesise that clinical pharmacists are involved in the care of SOT patients in many transplant clinics and contribute to their care in many different ways, but there are only a few clinical pharmacists who engage in the publication of their work and scientific research in this area to document and scientifically confirm their everyday clinical work.

However, further studies investigating clinical pharmacy services that involve multiple study sites and larger sample sizes are needed. Additionally, it should be noted that the level of professionalism, personal performance and individual social skills of the involved clinical pharmacists may influence the reproducibility of the study results and remain a confounding factor. This bias could potentially be addressed by investigating the impact of clinical pharmacists at multiple study sites. The standardisation of intervention criteria, the DTPs classification systems and an assessment of significance of the impacts of their interventions would lead to more easily comparable outcomes. Studies addressing the influence of clinical pharmacists on hard clinical-end points are warranted to gain more high quality evidence on this topic.

Conclusion

The participation of clinical pharmacists in multidisciplinary health care teams engaged in the care of SOT patients has previously been shown to be beneficial to patient care. High quality evidence based on randomised clinical trials regarding this topic is scarce, however. Nevertheless, clinical pharmacists address unmet and common drug-therapy problems, focus on disease- and treatment related outcomes, ensure immunosuppressive medication compliance and counsel patients on drug-related issues. Transplant centres with actively involved pharmacists appreciate the presence of their clinical pharmacists.

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Conflicts of interest None declared.

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3.3 EVALUATION OF RISK FACTOR MANAGEMENT OF PATIENTS TREATED ON AN INTERNAL NEPHROLOGY WARD: A PILOT STUDY

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Evaluation of risk factor management of patients treated on an internal nephrology ward: a pilot study

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Abstract

Background: The objectives of this pilot study were to evaluate treatment quality for the risk factors of hypertension, diabetes and hyperlipidemia as well as the overall treatment quality for patients on an internal nephrology ward. This evaluation included the collection of data concerning the quality of therapeutic drug monitoring, drug use and potential drug-drug interactions. Establishing such baseline information highlights areas that have a need for further therapeutic intervention and creates a foundation for improving patient care, a subject that could be addressed in future clinical pharmacy research projects.

Methods: Medical charts of patients treated on a single internal nephrology ward were retrospectively evaluated using a predefined data collection form. Assessment of further need for therapeutic intervention was performed.

Results: For 76.5% (n = 78) of the total study population (n = 102), there was either a possibility (39.2%, n = 40) or a need (37.3%, n = 38) for further intervention based on the overall assessment. For the risk factors of hypertension, diabetes and hyperlipidemia, the proportions of patients that require further intervention were 78.8% (n = 71), 90.6% (n = 58) and 87.9% (n = 58), respectively. Patients with diabetes or hyperlipidemia were less likely to have optimal risk factor control. The number of drugs prescribed and the number of potential drug-drug interactions were significantly higher after in-hospital treatment.

Conclusion: Risk factor treatment needs optimisation. Risk factor management, systematic medication reviews, and screening for and management of potential drug-drug interactions deserve great attention. Clinical pharmacy services could help in the achievement of treatment goals.

Background

Health-care professionals, such as physicians, nurses, and (clinical) pharmacists, in both inpatient and outpatient settings are increasingly confronted with a growing number of patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD)[1]. Medical care for CKD patients is complex due to widespread co-morbidities and major risk factors (RF) for CKD or cardiovascular disease (CVD) [2,3]. The progression of CKD and the deterioration of kidney function from stage 1 CKD [3] to

more severe stages can be slowed by optimal treatment of underlying co-morbidities and RFs, which can be accomplished with lifestyle modifications and/or different pharmacological interventions that address the treatment of hypertension, diabetes mellitus and hyperlipidemia, among others. The slowing down of disease progression is pivotal for prolonging the period before stage 5 CKD or ESRD, which involves the necessary initiation of either dialysis or evaluation of suitability for kidney transplantation. Several initiation and progression factors have been shown to influence disease onset and progression [3,4]. Large-scale efforts that target these RFs have been initiated to improve outcomes in the CKD population [5].

The involvement of clinical pharmacists as members of the interdisciplinary patient care team responsible for the management of many different diseases has proven to be beneficial and has been associated with positive patient outcomes [6-8]. Clinical pharmacists have also been influential in the field of nephrology and have provided valuable support for the achievement of defined goals in the treatment of different RFs and management of drug-related problems in the ESRD population [9-12].

This pilot study was performed to establish baseline data that address (1) the quality of RF management, (2) overall treatment quality, (3) quality of therapeutic drug monitoring (TDM), (4) quantitative drug use at admission and discharge and (5) the frequency of potential drug-drug interactions (pDDIs) in the studied patient population as well as in the predefined subgroup of kidney transplant patients (TX subgroup). The retrospective evaluation of these parameters should identify areas with the need for further intervention and possibilities for the improvement of patient care that could be addressed in future clinical pharmacy research.

Methods

Study design, group and setting

A retrospective review was conducted of 102 randomly selected medical histories of patients receiving treatment between August 2006 and April 2008 on an internal nephrology ward of General Hospital in Vienna. Data were collected between January and May 2008. There were no direct interventions performed on patients. This descriptive study was approved by the local ethics committee of the Medical University of Vienna and the Vienna General Hospital.

Data sources and collection

Medical charts, physicians' admission and discharge letters and cumulative laboratory findings were the only data sources used. Data were collected according to a predefined data collection form, which was divided into six categories: (1) sociodemographic criteria; (2) cause of hospitalisation, further medical conditions (co-morbidities) and underlying renal disease; (3) treatment of the predefined RFs of hypertension, diabetes mellitus and hyperlipidemia in the total population and quality of TDM in the TX subgroup; (4) drug regimen at the time of admission and discharge; (5) number and severity of pDDIs and (6) overall quality of RF treatment. Furthermore, glomerular filtration rates (GFRs) at discharge and at admission were estimated using the Modification of Diet in Renal Disease (MDRD) study equation. Stages of CKD (based on GFR at discharge) were assigned according to the National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) classification [3].

Assessment of RF treatment quality and overall assessment

Treatment quality during hospitalisation was assessed according to established guidelines for each RF, for quality of TDM in the TX subgroup and for overall treatment quality (see Table 1). The quality of RF and TDM management as well as overall treatment quality was assessed numerically on a scale from one to four (see Table 2). Patient treatment histories that were assessed as being a two or three on this quality scale were compiled and categorised as patients for whom further therapeutic intervention would have been either beneficial (2) or necessary (3) and therefore would represent potential domains for intervention by a clinical pharmacist.

Screening for pDDIs

Admission drug histories and discharge drug histories were electronically screened for pDDIs using Medis®.

Table 1: Risk factor reference values

Risk factor	Reference Values
Hypertension [23,34]	Non-diabetic patients <140/90 mm/Hg Diabetic patients <130/80 mm/Hg Patients with diabetic nephropathy <125/75 mm/Hg
Diabetes mellitus [34]	Fasting plasma blood glucose <110 mg/dl Glycosylated haemoglobin HbA1c 4-6%
Hyperlipidemia [25]	Low density cholesterol <130 mg/dl Total cholesterol <200 mg/dl Triglycerides <200 mg/dl

Table 2: Categories for assessment of individual risk factors, therapeutic drug monitoring and overall assessment

	Individual RF[a] and TDM[b]		Assessment of overall treatment quality	
	Assessment	**Explanation**	**Assessment**	**Explanation**
1	No need for intervention	Values[d] according to references in more than 2/3 of available values; Values better at discharge than at admission; Disease/RF[a] is treated; no severe pDDIs[c]	Very good RF[a] management	No improvements necessary
2	Improvement possible	Values[d] outside of reference range in more than 1/3 of available values; Values worse at discharge; severe pDDIs[c]; RF is treated	Good RF[a] management	Up to two individual RFs[a] being assessed as "improvement possible" (category 2); no untreated RFs[a] (category 3)
3	Disease untreated	No drug therapy for RF[a] treatment; no TDM performed, although appropriate	Improvement in RF[a] management needed	More than two individual RFs[a] or TDMs[b] being assessed as "improvement possible" (category 2) or untreated RF[a] (category 3)
4	No conclusion possible	Missing data; inconclusive data	No conclusion possible	Missing data; inconclusive data

[a] RF = risk factor
[b] TDM = therapeutic drug monitoring
[c] pDDI = potential drug-drug interaction
[d] e.g., blood pressure, fasting blood glucose, lipid levels, plasma levels of immunosuppressants

pDDIs were classified into four categories of relevance given by the database, namely *severe, moderate, minor* and *unknown relevance* (see Appendix for detailed explanations). Only pDDIs classified as *severe* and *moderate* were included in the statistical analysis. Individual drug dosages were not taken into account when assessing pDDIs.

Statistical analysis

Absolute and relative frequencies as well as 95% confidence intervals (lower CI and upper CI) are reported for the four categories of overall assessment for each RF and for overall RF management. Statistical analyses were conducted on the total study population and for the TX subgroup. To analyse the influence of the RFs (hypertension, diabetes mellitus and hyperlipidemia) on assessment category, an ordinal logistic regression analysis of assessment categories one, two or three (see Table 2) was calculated (category 4 is omitted). The probability of the patient being in a higher category was also modelled. P-values, odds ratios and the corresponding 95% confidence inter-

Table 3: Sociodemographic characteristics, stages of CKD and length of stay

	Total population n = 102		TX[a] subgroup n = 49	
	n	**%**	**n**	**%**
Men/Women	67/35	65.7/34.3	37/12	75.5/24.5
Age, years				
Mean ± SD[b]	55.5 ± 13.4		55.4 ± 11.4	
Range	24-86		29-73	
BMI[c], kg/m^2				
Mean ± SD[b]	26.3 ± 5.1		26 ± 4.8	
Range	15-40.2		16-40.2	
Stages of CKD	n = 80		n = 44	
2	3	3.8	2	2.3
3	39	48.8	32	72.7
4	15	18.8	7	15.9
5	23	28.8	3	6.8
Length of stay, days				
Mean ± SD[b]	14.8 ± 10.5		17.06 ± 9.9	
Range	2-47		2-41	

[a] TX = transplantation
[b] SD = standard deviation
[c] BMI = body mass index

vals are given. For the analysis, the RFs of diabetes and hyperlipidemia were both classified into "no diabetes mellitus" or "no hyperlipidemia" versus "diabetes mellitus" or "hyperlipidemia". The analysis was performed using SAS 9. Means will be presented as mean (range, standard deviation).

Results

Sociodemographic and patient characteristics

Sociodemographic characteristics and stages of CKD for the total study population and TX subgroup are shown in Table 3. Major causes of hospitalisation in the study population and the underlying renal diseases are shown in Figures 1 and 2, respectively.

RF: hypertension

A diagnosis of hypertension was seen in 88.2% (90) of patients. The absolute and relative frequencies as well as the corresponding confidence intervals for hypertension are given in Table 4 for the four different categories of overall assessment of the total study population. In 78.8% (71) of patient cases, there was a possibility or need for further therapeutic interventions. Hypertensive patients were treated on the ward for a mean time of 15.2 days (d) (range 2-47, standard deviation 10.84), with an average of 7.7 d (0-45, 9.87) of blood pressure values out of the individual reference range. Estimation of renal function at admission and discharge showed a mean GFR of 23.1 and 30.1 mL/min/1.73 m^2, respectively. Stages 2 to 5 CKD were present in 4.1, 50.7, 17.8 and 27.4% of hypertensive patients, respectively.

RF: diabetes mellitus and elevated fasting blood glucose

A total of 62.8% (64) of patients in this RF group had either a definitive diagnosis of diabetes (diabetes mellitus type I (3.9%, n = 4) or diabetes mellitus type II (30.39%, n = 31)) or continuously elevated fasting blood glucose (FBG) out of reference range (28.4%, n = 29). Absolute and relative frequencies as well as corresponding confidence intervals for the four different categories of overall assessment for the total study population are given in Table 4. The majority (90.6%, 58) of patients had a need for further therapeutic intervention. Patients with diabetes mellitus type I were treated on the ward for an average of 11.3 d (4-22, 8.14), with FBG levels out of reference range on 5.5 d (1-10, 4.65). Patients with diabetes mellitus type II were treated for an average of 30.0 d (2-45, 11.9), with FBG levels out of reference on 6.9 d (1-24, 6.36). Patients with continuously elevated FBG levels were treated for 16.4 d (2-39, 9.89), with elevated FBG for 6.7 d (2-19, 4.6) on average. Glycosylated haemoglobin ($HbA1_c$) levels were evaluated and analysed as a marker of long-term treatment quality. In 43.8% (n = 28) of patients in the diabetes RF group, there was no information available about $HbA1_c$ values. In 25% (n = 16) of patients, reported $HbA1_c$ levels were in accordance with the reference range (see Table 1), and in 25% (n = 16) of patients $HbA1_c$ levels were outside of the reference range. Of patients with $HbA1_c$values outside of the reference range, 68.8% (n = 11) had diabetes type II. Estimation of renal function at admission and discharge showed a mean GFR of 23.2 and 30.2 mL/min/1.73 m^2, respectively. Stages 2 to 5 CKD were present in 3.9, 49.0, 21.6 and 25.5% of patients with the RF of diabetes, respectively.

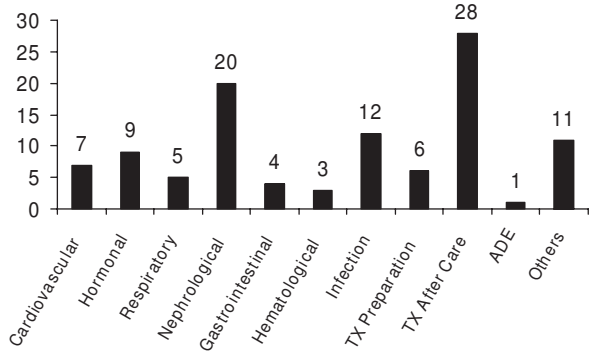

Figure 1
Major causes of hospitalization, classified. TX transplantation. ADE adverse drug event.

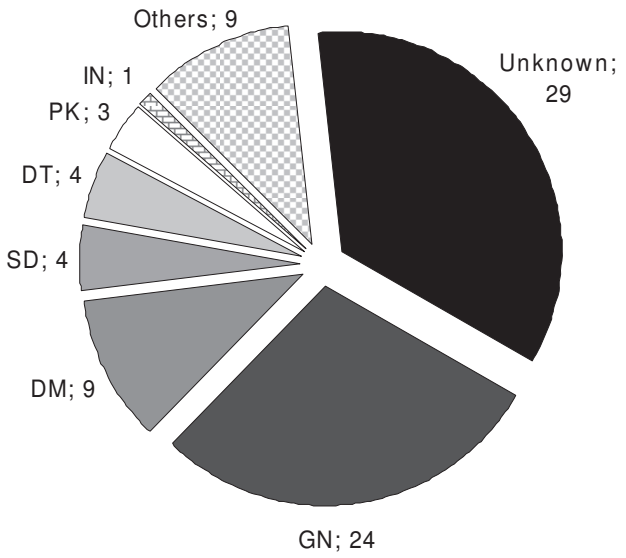

Figure 2
Underlying nephrologic disease (where available). GN glomerulonephritis. DM diabetes mellitus. SD systemic diseases. DT drug toxicity. PK polycystic kidney. IN interstitial nephritis.

Table 4: Assessment of individual risk factors and quality of therapeutic drug monitoring

	No need for intervention		Improvement possible		Disease untreated/ No TDM[a]		No conclusion possible	
	% (n)	95% CI[b]	% (n)	95% CI[b]	% (n)	95% CI[b]	% (n)	95% CI[b]
Hypertension n = 90	17.8 (16)	*0.10-0.26*	37.8 (34)	*0.28-0.48*	41.1 (37)	*0.31-0.51*	3.3 (3)	*0.00-0.07*
Diabetes mellitus n = 64	7.8 (5)	*0.01-0.14*	42.2 (27)	*0.30-0.54*	48.4 (31)	*0.36-0.61*	1.6 (1)	*0.00-0.05*
Hyperlipidemia n = 66	9.1 (6)	*0.02-0.16*	42.4 (28)	*0.31-0.54*	45.5 (30)	*0.33-0.57*	3.0 (2)	*0.00-0.07*
TDM[a] n = 44	29.6 (13)	*0.17-0.45*	34.1 (15)	*0.20-0.50*	0.0 (0)	-	36.4 (16)	*0.22-0.52*

For explanations of assessment categories see table 2.
[a] TDM = therapeutic drug monitoring
[b] CI = confidence interval

RF: Hyperlipidemia

Of the patients reviewed, 64.7% (n = 66) were diagnosed with hyperlipidemia, while 41.2% (n = 42) showed continuously elevated cholesterol-levels and 5.9% (n = 6) showed elevated triglyceride-levels. HMG-Co-enzyme-A-inhibitors (statins) were used in 17.7% (18) of patients for cardiovascular event prophylaxis. Absolute and relative frequencies as well as corresponding confidence intervals of the hyperlipidemia RFs for the four different categories of overall assessment for the total study population are given in Table 4. A possible need for further therapeutic intervention was found in 87.9% (58) of the patients in the study. Estimation of renal function at admission and discharge showed a mean GFR of 21.7 and 28.4 mL/min/1.73 m^2, respectively. Stages 2 to 5 CKD were present in 1.9, 49.1, 20.8 and 28.3% of patients with the RF of hyperlipidemia, respectively.

Characteristics and quality of TDM

The plasma drug levels of immunosuppressant medications were determined and the dosages were adjusted in 89.8% (44) of the TX subgroup patients. Immunosuppressive medications primarily consisted of a three-way combination of calcineurin inhibitors (tacrolimus (79.6%, 35) or ciclosporin (20.5%, 8)), anti-metabolites (mycophenolate mofetil (70.5%, 35), mycophenolic acid (18.2%, 8) or azathioprine (4.5%, 2)) and corticosteroids. In 25% (11) of the TX subgroup patients, a switch in immunosuppressant medication was necessary due to adverse drug events (ADEs). For example, tacrolimus induced tremors and mycophenolate mofetil induced diarrhoea. The quality of TDM was only assessable if a defined therapeutic range was available in the medical chart (61.4%, 27). The number of days with sub-therapeutic and supra-therapeutic concentrations was evaluated based on these defined ranges. Absolute and relative frequencies of TDM for the four different categories of overall assessment in the TX subgroup are given in Table 4.

Overall assessment of treatment quality

Absolute and relative frequencies and corresponding confidence intervals for overall assessment of treatment quality in the total study population and TX subgroup are shown in Table 5. A need for further optimisation of RF treatment was observed in 76.5% (78) of the total study population and 81.6% (40) of the TX subgroup.

Influence of individual RFs on overall treatment quality

Regression analysis showed that the diabetes mellitus and hyperlipidemia RFs had a significant impact on assessment outcome. Patients with diabetes (p = 0.001, OR 4.309, 95%CI: 1.81-10.25) or hyperlipidemia (p = 0.0085, OR 3.146, 95%CI: 1.34-7.39) had a higher overall

Table 5: Overall assessment of treatment quality

	Very good RF[a] management		Good RF[a] management		Improvement needed		No conclusion possible	
	% (n)	95% CI[b]	% (n)	95% CI[b]	% (n)	95% CI[b]	% (n)	95% CI[b]
Total n = 102	19.6 (20)	*0.12-0.27*	39.2 (40)	*0.30-0.49*	37.3 (38)	*0.28-0.47*	3.9 (4)	*0.00-0.08*
TX[c] subgroup n = 49	16.3 (8)	*0.06-0.27*	32.7 (16)	*0.20-0.46*	49.0 (24)	*0.35-0.63*	2.0 (1)	*0.00-0.06*

For explanations of assessment categories see table 2.
[a] RF = risk factor
[b] CI = confidence interval
[c] TX = transplantation

risk of being assessed in category 2 (*good risk factor management, but improvement possible*) or category 3 (*improvement needed*). This correlation was not shown for the hypertension RF (p = 0.2704, OR 2.056, 95%CI: 0.57-7.40).

Quantitative drug use and pDDIs in the total study population

The total sum of prescribed drugs in the total study population was 1110 at admission and 1220 at discharge. Table 6 shows the number of drugs prescribed, number of pDDIs and number of pDDIs per drug prescribed.

All three parameters showed significantly higher values at discharge compared to admission. Treatment on the ward was significantly associated with an elevated number of drugs prescribed and an elevated number of pDDIs.

In the total study population, 45.1% (46) of patients had an increase in the number of pDDIs during treatment on the ward, 41.2% (42) had no change in the number of pDDIs and 13.7% (14) had a decrease in the number of pDDIs. In 43.2% (44) of all evaluated patients, at least one pDDI was associated with an increased probability for nephrotoxicity, thus increasing the risk of acute renal failure and aggravation of renal function.

Quantitative drug use and pDDIs in the TX subgroup

The sum of drugs prescribed to the TX subgroup patients was 619 at admission, compared with 650 at time of discharge. The number of drugs prescribed, number of pDDIs and number of pDDIs per drug prescribed are shown in Table 6.

In-hospital treatment was associated with a significantly elevated number of pDDIs per patient and pDDIs per drug prescribed. When the number of drugs prescribed per patient was compared, there was no statistically significant difference. In 44.9% (22) of the TX subgroup patients, the number of pDDIs increased during treatment on the ward, 38.8% (19) of patients had no change in the number of pDDIs and 16.3% (8) of patients had a decreased incidence of pDDIs during treatment on the ward. In 83.7% (41) of evaluated patients, at least one pDDI was associated with an increased probability of nephrotoxicity, which increased those patients' risk of developing acute renal failure and having an aggravation of renal function.

Discussion

The study results show that the management of the individual RFs of hypertension, diabetes and hyperlipidemia requires improvement. In the overall assessment of treatment quality, more than three-quarters of the patients showed a possibility or evident need for further intervention to reach the treatment goals. Very good RF management was evident in less than 20% of patients for each of the investigated RFs. For diabetes and hyperlipidemia, this proportion was even under the 10% threshold. Based on regression analysis, patients with diabetes or hyperlipidemia were four and three times less likely, respectively, to have optimal RF control. Our results are consistent with published studies and reviews that address treatment quality and adherence to treatment guidelines for hypertension [13-19], diabetes mellitus [15,20,21] and hyperlipidemia [15,19] in CKD patients.

The apparent need for improvement in RF control in our study population must be discussed in light of the special features of the nephrological patient population.

Hypertension, either as a cause or a complication of CKD, is prevalent in up to 75% of patients with CKD stage 3-5, in up to 80% of kidney transplant patients and in up to

Table 6: Quantitative drug use and potential drug-drug interactions at hospital admission and discharge

Total study population n = 102	Admission Mean ± SD[a]	Range	Discharge Mean ± SD[a]	Range	P-value[b]
Number of drugs per patient	10.9 ± 4.2	0-20	12.1 ± 4.3	2-21	<0.0001*
Number of pDDIs[c] per patient	1.9 ± 1.9	0-8	2.7 ± 2.5	0-11	<0.0001*
Number of pDDIs[c] per drug prescribed	0.2 ± 0.2	0-0.83	0.2 ± 0.2	0-0.64	0.0016*
TX[d] subgroup n = 49					
Number of drugs per patient	12.6 ± 3.1	4-20	13.3 ± 3.2	5-20	0.055
Number of pDDIs[c] per patient	1.8 ± 2.4	0-8	2.7 ± 2.8	0-11	0.014*
Number of pDDIs[c] per drug prescribed	0.1 ± 0.1	0-0.53	0.2 ± 0.2	0-0,64	0.014*

Only pDDIs classified as moderate or severe were included in the analysis.
[a] SD = standard deviation
[b] p = statistical significance according to the t-test
[c] pDDIs = potential drug-drug interactions
[d] TX = transplantation
* Statistically significant

90% of maintenance haemodialysis patients [22,23]. Virtually all patients in the study population had kidney function of CKD stage 3 or worse, nearly 50% had one or more kidney transplantations performed, and 27% were dependent on renal replacement therapy (e.g., haemo- or peritoneal dialysis). The very high prevalence and the multifactorial pathogenesis of hypertension in renal disease (e.g., sodium retention and fluid overload and structural kidney changes) and the steady decline in renal function make it difficult *per se* to reach tight treatment goals. Antihypertensive polypharmacotherapy was therefore almost necessary in our study population to even approximate treatment goals. Our study findings stress the importance of drawing attention to tight blood pressure control, as in about the half of the treatment period, blood pressure control was suboptimal. Second, control of diabetes and hyperlipidemia management was also suboptimal. The relevance of these findings is emphasised by the fact that diabetes is not only the leading cause of CKD in developed countries [24], but diabetes and hyperlipidemia are also two of the most important RFs for cardiovascular disease. Of note, CKD patients represent *a priori* the highest risk group for CVD [3]. Therefore, guidelines [24,25] recommend strict glycemic and lipidemic control. Besides patients with a confirmed diagnosis of diabetes mellitus, we also included patients with continuously elevated FBG in the diabetes RF group. Continuously elevated FBG represents, in itself, a RF for the development of diabetes mellitus II, and therefore, clarification and management deserves attention. One fourth of patients in the diabetes RF group had glycosylated haemoglobin values outside of the reference range, confirming the need for improvement of long-term glycemic control, especially for diabetes mellitus II where around 68% of patients had $HbA1_c$ levels outside of the reference range. In nearly 50% of patients in the diabetic subgroup, glycosylated haemoglobin values were totally lacking, and therefore, no information was available concerning the long-term control of their diabetes. Furthermore, the proportion of untreated hyperlipidemia of around 45% also stresses the need for intervention and improvement. Nearly half of our study population was kidney transplant patients. Thus, concomitant immunosuppressive therapy may have also negatively biased RF control, as hypertension, diabetes and hyperlipidemia are all well-described side effects of calcineurin inhibitors. However, our study was not designed to assess a potential correlation. Finally, the main focus during hospitalisation often lies in curing acute disease and in necessary treatment, and consequently, optimisation of RF treatment often takes a back seat. Simple negligence and unintended oversight may also be considered as reasons for suboptimal RF control. In summary, there seems to be vast room for improvement in the control of the investigated RFs in our study population. Clinical pharmacists' activities have proved beneficial for the achievement of treatment goals [10-12].

Our study also examined the quality of TDM in patients receiving immunosuppressants. For the quality analysis, the number of TDM drug levels outside of the reference range was used as a surrogate parameter. For approximately 40% of patients, written information regarding the desired drug concentration range, depending on time since transplantation, was missing in the medical charts and therefore could not be assessed. It was found that only approximately one third of patients with kidney transplants were without need of further intervention. This assessment emphasises the fact that immunosuppressant dose adjustments are common and optimal dosing regimens are difficult to determine, especially in the early postoperative phase [26,27]. Furthermore, frequent medication changes, namely drug additions and discontinuations, complicate dosing regimen optimisation. Widely-used immunosuppressives have great inter- and intra-individual pharmacokinetic variability and many confounding factors (e.g., race, time since transplantation, sex and metabolic profile) that have to be taken into account when adapting dosages on the basis of plasma drug concentration [28]. Constant plasma drug levels corresponding to time since transplantation should be the goal. ADEs are also common in the kidney transplant patient population. Common ADEs seen with immunosuppressives are as follows: new-onset diabetes mellitus, tremors (tacrolimus), hyperlipidemia, hypertension, hypertrichosis (ciclosporin), and gastrointestinal side effects, such as diarrhoea (mycophenolate mofetil) [27]. Typical management of ADEs considers dose reduction of the offending drug or switching to another immunosuppressant medication. All these properties impair dose adjustments and tight drug-level control of immunosuppressant medications. There is evidence that clinical pharmacists can contribute to the vigilant supervision and management of kidney transplant patients [9,29,30].

Evaluation of drug use on the nephrology ward shows that in-hospital treatment is associated with a significant increase in the number of prescribed drugs and pDDIs. Poly-morbidity is frequent, and multiple medications are almost always necessary to meet treatment goals. Our study illustrates that poly-medication, which is almost inevitable in nephrology patients, leads to an increasing number of pDDIs. Other authors report similar findings in other patient populations [31,32]. It must be noted that the number of drugs administered to the patient during the active in-hospital treatment period is even higher compared to the number at admission or discharge due to temporary therapeutic treatments, such as anti-infectives or anticoagulation drugs. Reviewing drug-drug interac-

tions at admission and discharge provides only a fractional view of all pDDIs that by definition can never be complete. According to a published study by Glintborg and colleagues, the clinical relevance of computerised screening of pDDIs, as done in our study, tends to be low [33]. However, in daily practice, this tool proves to be useful for gaining a quick overview and raising awareness of potential medication-related events. Considering the sensitivity of patients with renal impairment and drug-related needs, especially for pDDIs leading to increased nephrotoxicity or aggravation of kidney function, these interactions must be intensely and carefully monitored. Recognition, avoidance and management of drug-drug interactions and medication reviews should be done vigilantly [3] as these procedures also represent markers of treatment quality.

This pilot study was retrospective and was primarily designed to identify different areas with intervention needs (e.g., RFs, TDM) and possibilities for improvement of drug therapy-related aspects (e.g., management of pDDIs, medication reviews). Evidence from the literature shows that these tasks are already performed by clinical pharmacists as a part of their clinical routine. However, the extent of clinical pharmacists' involvement varies considerably. We are aware that this pilot study itself does not contribute to the overall evidence on clinical pharmacy services. However, we hypothesise that clinical pharmacists could play an important part in improving treatment quality, as there is evidence supporting the benefit of clinical pharmacy services in this area [7-11]. Since the process of delivering drug therapy to in-hospital patients is a complex, time-consuming, multi-step and therefore error-prone process, clinical pharmacy services could enforce drug-therapy safety and address therapeutic needs that are being insufficiently met by other health care professionals in the care delivery process.

As with all studies, our current investigations had limitations. The assessment was done by a single pharmacist and included only patients from one internal nephrology ward. Data from other wards were not available. Therefore, the possibility of data extrapolation is limited.

Conclusion

Our pilot study identifies possibilities and needs for improvements in the management of hypertension, diabetes and hyperlipidemia, which are three major RFs for renal and/or CV disease. In the subgroup of TX patients, tight control of immunosuppressant blood levels according to the reference range could be optimised. Medication regimens are complex, and the frequency of pDDIs increased during in-hospital treatment. Detected pDDIs were frequently associated with a potential aggravation of already impaired kidney function. Clinical pharmacy services could positively influence RF management, TDM and the management of pDDIs. However, this hypothesis must be confirmed in future research. Based on our study findings, the impact of clinical pharmacy services on drug-therapy related problems and RF management should be addressed using a prospective study design in a nephrology patient population and a kidney transplant population, respectively.

Competing interests

The study was performed as part of a clinical pharmacy project that was funded by Amgen. The authors declare that there are no financial or other conflicts of interests with respect to the contents of the article.

Authors' contributions

GS was responsible for the study design, data collection and interpretation and preparation of the manuscript. SZ was responsible for the study design, statistical analysis of collected data and reviewing the manuscript. RLG was responsible for study design, data interpretation and reviewing the manuscript. All authors read and approved the final manuscript.

Appendix

Medis® is an Austrian general drug information tool with a pDDIs screening function. The data used originates from Mikropharm - Arzneimittelinteraktionen provided by a collaboration of the Bundesvereinigung Deutscher Apothekerverbände (ABDA), Österreichische Apothekerkammer (ÖAK) and Schweizer Apothekerverein (SAV).

The four categories of relevance were:

Severe interaction: combination may be life threatening; possibility of intoxication; permanent damage may be induced.

Moderate interaction: combination may lead to therapeutic difficulties and may even be harmful; close patient monitoring is needed.

Minor interaction: interaction is to be taken into account but normally causes no harm to the patient.

Unknown relevance: no proven clinical relevance of described interaction.

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3.4 INTERIM RESULTS OF NEWLY IMPLEMENTED CLINICAL PHARMACY SERVICES ON AN INTERN NEPHROLOGY WARD

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Presented as scientific poster at the Symposium of the European Society of Clinical Pharmacy (ESCP), 2009, Geneva
Final Poster, see Appendix 8.1

ABSTRACT

Background and Objective

Routine clinical pharmacy services have newly been implemented on an intern nephrology ward in an effort to further expand these services. The clinical pharmacist participates in ward rounds at least three times per week. The objective is to evaluate the contribution of clinical pharmacy services by documentation of the consultations made during the ward rounds, classified by type, frequency and complexity.

Design

Descriptive, prospective study

Setting

Intern nephrology ward of the Vienna General Hospital – University Clinics

Main Outcome Measures

Type and frequency of drug- or pharmacotherapy-related questions raised by health care professionals during the ward rounds and subsequently answered by the clinical pharmacist

Complexity of questions defined by the total time needed to answer each question

Problems and barriers identified during the initial period of the clinical pharmacy project

Results

From January 2008 to May 2009 (17 months) the clinical pharmacist was asked a total of 174 drug- or pharmacotherapy-related questions during participation in the ward rounds. Questions mainly derived from physicians (n=154; 88.5%), nurses (14; 8%) or medical students (6; 3.5%).

Based on the total time needed to answer, each question was either categorised into group A (up to 15 minutes: 133; 76.4%), group B (up to one hour: 24; 13.8%) or group C (more than one hour, extensive and complex literature research: 17; 9.8%).

The absolute and relative frequency of each type of consultation were: drug therapy selection (40; 23%), general drug information (35; 20.1%), dosage and pharmacokinetics (31; 17.8%), availability of drugs (19; 10.9%), drug interactions (17; 9.8%), adverse drug events (13; 7.5%), application of drugs (8; 4.6%), organisation and logistics (7; 4.0%), pregnancy and breastfeeding (2; 1.1%) and pharmaeconomics (2; 1.1%).

The main problems and barriers identified were: (1) continuity of collaboration due to changes in medical ward staff each semester, (2) bridging psychological borders between physicians and pharmacists, and (3) different levels of professionalism of clinical pharmacists due to a lack of systematic clinical pharmacy education programmes.

Conclusion

Interim results of newly implemented clinical pharmacy services are encouraging and participation in ward rounds will continue. A prospective study to evaluate pharmaceutical care issues in the renal transplant population is ongoing.

3.5 PRESCRIBING PATTERNS ANALYSIS ON AN INTERN NEPHROLOGY WARD: THE “RENAL” FOCUS!

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Presented as scientific poster at the Symposium of the European Society of Clinical Pharmacy (ESCP), 2009, Geneva
Final Poster, see Appendix 8.2

ABSTRACT

Background and Objective

Knowledge of relevant pharmacokinetic parameters, e.g. protein binding, non-renal excretion rate (Q_0-value), eliminiation half-life and the presence of active metabolites, of commonly prescribed drugs is essential for drug therapy individualisation in patients with renal impairment. The objective is to analyse qualitative prescribing patterns on an intern nephrology ward and subsequently develop a synopsis of important pharmaco-therapy relevant parameters.

Design

Retrospective analysis of drug prescriptions of 100 randomly selected patients

Synthesis of a synopsis of drug properties relevant for drug therapy individualisation by searching drug information databases and handbooks of clinical drug data

Setting

Intern nephrology ward of the Vienna General Hospital – University Clinics

Main Outcome Measures

Frequency of the most prescribed drugs

Frequency of drugs identified with pharmacokinetic properties requiring attention

Results

A total of 195 different drugs were identified, adressing typical nephrological pharmaco-therapy questions, e.g. hypertension, diabetes, electrolyte disturbances, secondary hypoparathyreoidism and cardiovascular disease. The ten most prescribed drugs were prednisolone (53%), pantoprazole and esomeprazole (88.2%), aspirin (39.2%), carvedilol (35.3%), tacrolimus (34.3%), candesartan (30.4%), mycophenolate mofetil (29.4%), amlodipine (28.4%) and furosemide (27.45%). Around 50% of the patients had kidney transplantation.

124 drugs were included in the synopsis. Frequency of drugs with pharmacokinetic properties to consider (among others) when prescribing in renal impairment were: highly (>80%) protein bound drugs (52.1%), Q_0-values <0.5 (32.4%), prolonged elimination half-life in renal impairment (47.6%) and the presence of active metabolites (45.2%). Further parameters investigated were frequency of drugs with the need for dose adjustments (49.2%) and the need for therapeutic drug monitoring (10.5%). 44.4% of the drugs are substrates, inhibitors (18.5%) or inducers (4.0%) of CYP450 liver enzymes. The synopsis also comprises dosing guidelines for normal and impaired renal function and further pharmacokinetic drug parameters.

Conclusion

Knowledge of altered pharmacokinetic parameters affecting action, efficacy and toxicity of drugs, is essential when prescribing drugs to patients with renal impairment. The synopsis highlights common drugs requiring special attention. It can be used as a teaching tool for health care professionals beginning in nephrology or as a quick eference guide at the point of care.

THE "RENAL" FOCUS – SYNOPSIS OF DRUG PROPERTIES

POPULAR DRUGS IN NEPHROLOGY - DOSING AND PHARMACOKINETICS

Disclaimer - About the tables

The drugs included are based on a retrospective review of medication regimens of patients treated on an intern nephrology ward. Drugs are classified by the Anatomical-Therapeutical-Chemical (ATC) classification system, which is recommended by the WHO for drug utilisation research. The international non-proprietary names (INN) for the active agents are reported. The brand name refers to drugs licensed in Austria.

Information about average drug dosages for adults is reported for normal renal function (NRF) and renal impairment (RI), on the basis of the summary of product characteristics (SPC). These dosages are meant only as a guide. The dosage of drug depends on indication, different patient factors, and disease state. In the dosing section for RI, glomerular filtration rate (GFR) is reported in mL/min/1.73m^2.

The pharmacokinetic data section contains information on relevant pharmacokinetic drug properties that are necessary for drug therapy individualisation and prescribing in RI. Only major cytochrome enzymes (CYP) and drug-drug interactions (DDI) are reported. For detailed information, refer to other drug information compendia and to the SPC.

<u>Literature</u>

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Abbreviations used in the tables and legend

Drug Name	Consider dose reduction in RI! Sensitive parameter in RI
↑	Increase, increased
↓	Decrease, decreased
Q_0	Non-renal excretion rate
Ø	No need for dose reduction in renal impairment
#	Drug has active metabolite(s)
$\%Ex_{un}$	Fraction of drug excreted as unchanged drug in the urine in normal renal function
AC	Taken before meals (ante cibum)
ADE	Adverse drug event
BB	Beta blockers
BID	Taken twice a day
BUN	Blood urea nitrogen
CHF	Chronic heart failure
CI	Contraindication
CL	Clearance
CyA	Cyclosporine A
CYP	Drug is a substrate of CYP P450 enzymes
CYP	Drug is an inhibitor of CYP P450 enzymes
CYP	Drug is an inducer of CYP P450 enzymes
d	Days
DR	Dose reduction
ESRD	End-stage renal disease
GI	Gastrointestinal
HL	Drug elimination half life
im	Intramuscular administration
iv	Intravenous administration
M	Metabolite(s)
MAO	Monoaminoxidase
N	None
ND	No data available
PB	Protein binding (%)
PL	Drug elimination half life prolonged
po	Peroral
PPI	Proton pump inhibitor
PR	Prolonged release form
Q…h	Taken every …hour
QHS	Taken every night at bedtime
QD	Taken once a day
QOD	Taken every other day
QID	Taken four times a day
sc	Subcutaneous administration
SCr	Serum creatinine
$T_{1/2}$	Drug elimination half life in NRF (mean)
$T_{1/2}^{ESRD}$	Drug elimination half life in ESRD (mean)
TDM	Therapeutic drug monitoring recommended or needed
TE	Thromboembolism
TID	Taken three times a day
TTS	Transdermal therapeutic system
UC	Drug elimination half life unchanged
Vd	Volume of distribution (L/kg), based on an average body weight of 70 kg

ATC: A02	Drugs for acid related disorders										
Drug		Dosing		Pharmacokinetic Data						Miscellaneous	
Active Agent	Brand	NRF	RI (given GFR)	Q_0	% Ex_{un}	$T_{1/2}$	$T_{1/2}^{ESRD}$	PB%	Vd L/kg	CYP / DDI	(Renal) focus
Pantoprazole	Pantoloc®	20-40mg QD 20mg QD (severe hepatic impairment)	Ø	≥0.7	0	1	2-3	98	0.15	2C19	PPI use associated with acute interstitial nephritis
Esomeprazole	Nexium®	20-40mg QD 20mg QD (severe hepatic impairment)	Ø	≥0.9	<1	1.3	ND	97	0.22	2C19	PPI use associated with acute interstitial nephritis
Ranitidine #	Ulsal®, Zantac®	150mg BID 300mg QD in the evening	<50: 150mg QD	0.25	70-80	2.5	**5-10**	15	1.2-1.8	2D6 Antacids!	↑ in SCr reported
ATC: A03	**Drugs for functional gastrointestinal disorders**										
Drug		Dosing		Pharmacokinetic Data						Miscellaneous	
Active Agent	Brand	NRF	RI (given GFR)	Q_0	% Ex_{un}	$T_{1/2}$	$T_{1/2}^{ESRD}$	PB%	Vd L/kg	CYP / DDI	(Renal) focus
Butylscopolamine	Buscopan®	10-20mg TID-QID	Ø	0.55	po:2 iv: 45	5.1	ND	3-11	3.5		
Metoclopramide	Paspertin®	10mg TID	<60: 15mg QD <10: 10mg QD	0.7	10-22	4.5	**14**	35	2-4	2D6, 2D6	↑ in extrapyramidal ADE in RI; increased drug absorption rate; decreased CL in uraemia
ATC: A04	**Antiemetics**										
Drug		Dosing		Pharmacokinetic Data						Miscellaneous	
Active Agent	Brand	NRF	RI (given GFR)	Q_0	% Ex_{un}	$T_{1/2}$	$T_{1/2}^{ESRD}$	PB%	Vd L/kg	CYP / DDI	(Renal) focus
Tropisetron	Navoban®	po 5mg QD	Ø	0.9	10	8	ND	71	7	2D6	2D6 Poor Metabolizer
Ondansetron	Zofran®	po 8mg BID –TID po 16mg 1h prior to surgery	Ø	≥0.8	<5	4	UC	75	2	1A2, 2D6, 3A4	
ATC: A10	**Drugs used in diabetes**										
Drug		Dosing		Pharmacokinetic Data						Miscellaneous	
Active Agent	Brand	NRF	RI (given GFR)	Q_0	% Ex_{un}	$T_{1/2}$	$T_{1/2}^{ESRD}$	PB%	Vd L/kg	CYP / DDI	(Renal) focus
Metformin	Glucophage®, Diabetex®	500-850mg BID, max 3g per day	<60: CAVE CI!	0.1	90-100	1-6	PL	0	10		Risk of lactate acidosis, CAVE: iodine-containing contrast agents
Glimepiride #	Amaryl®	1-4mg QD, with the first main meal	SLOW Titration	1	1	9	ND	99	0.41	2C9	Increased clearance in decreased renal function, more unbound drug in hypoalbuminemia
Gliclazide	Diamicron® MR	30-120mg QD, with the first main meal	AVOID in severe RI	0.8	1-20	12	PL	95	0.24	2C9	
Repaglinide	Novonorm®	0.5-4mg AC, up to 16mg per day	SLOW Titration	ND	0.1	1	ND	98	0.4	3A4, 2C8	

Pioglitazone #	Actos®	15-30mg QD	Ø	ND	ND	16-24 (+M)	UC	99	0.25	2C8, 3A4	Hematuria, anaemia, CAVE: Liver enzymes!
ATC: B01	**Antithrombotic agents**										
Drug		**Dosing**		**Pharmacokinetic Data**						**Miscellaneous**	
Active Agent	**Brand**	**NRF**	**RI (given GFR)**	**Q_0**	**% Ex_{un}**	**$T_{1/2}$**	**$T_{1/2}^{ESRD}$**	**PB%**	**Vd L/kg**	**CYP / DDI**	**(Renal) focus**
Enoxaparin	Lovenox®	according to indication and thromboembolic risk 40mg QD sc for TE prophylaxis	<30: increased exposition to enoxaparin	0.23	10	7	4-10	ND	0.06-0.13		Monitoring of anti Xa-activity, long terminal half-life in RI **TDM**
Nadroparin	Fraxiparin®	according to indication and thromboembolic risk 0,3ml QD (3225IE) sc for TE prophylaxis	<30: increased exposition to nadroparin	0.5	ND	2-5	4-10	ND	0.06-0.13		Monitoring of anti Xa-activity, long terminal half-life in RI **TDM**
Danaparoid	Orgaran®	according to indication and thromboembolic risk		0.5		18-28	PL	ND	0.11		Monitoring of anti Xa-activity, long terminal half-life in RI **TDM**
ASS	Generics	30-300 QD	CI in severe RI	1	1.4	2-3	UC	50-80	0.15		higher unbound drug levels in hypoalbuminemia and uraemia; Potential for Nephrotoxicity and GI-bleeding
Phenprocoumon	Marcoumar®	Loading 9/6/3mg, maintenance according to INR	Ø	1	2	160	UC	99		1A2, **2C9**, 2C19	Decreased protein binding in uraemia, may require lower doses in RI, Drug interactions! **TDM**
Clopidogrel #	Plavix®	75mg QD	Ø	ND	ND	7-8	UC	98	ND	2C19, 2B6, 3A4	Prodrug, Activation via 2C19
ATC: C01	**Cardiac therapy**										
Drug		**Dosing**		**Pharmacokinetic Data**						**Miscellaneous**	
Active Agent	**Brand**	**NRF**	**RI (given GFR)**	**Q_0**	**% Ex_{un}**	**$T_{1/2}$**	**$T_{1/2}^{ESRD}$**	**PB%**	**Vd L/kg**	**CYP / DDI**	**(Renal) focus**
Amiodarone #	Sedacoron®	Saturation for 8-14d: 200mg TID-QID, Maintenance: 100-400mg QD	Ø	1	5	26-107**d**	UC	96	1-66	2D6, **2C9**, 3A4	Potential increase in serum creatinine and BUN, Drug interactions! Drug toxicity! High interpatient variability **TDM**
Digitoxin #	Digimerck®	Middle saturation velocity: 0.15-0.3mg QD for 3d Maintenance: 0.05-0.1mg/d	may require decreased maintenance doses	0.7	20-25	4-6**d**	-9**d**	90-97	0.4-1	3A4	Increased conversion to digoxin, prolonged half-life; Drug interactions! Hypokalemia/Hypomagnesemia predispose to toxicity **TDM**
Isosorbide mononitrate	Isomonat®	20-40mg BID	Ø	0.8	1	6.6	UC	4	0.62		

Molsidomin #	Molsidolat®	2-4mg BID-TID	lower initial dosage, based on tolerability and response	0.9	2	1.6	UC	11	1-1.9		
Nicorandil	Dancor®	10-20mg BID	Ø	1	1	1.5	UC	24	1-1.4		
ATC: C02	**Antihypertensives**										
Drug		**Dosing**		**Pharmacokinetic Data**						**Miscellaneous**	
Active Agent	**Brand**	**NRF**	**RI (given GFR)**	**Q_0**	**% Ex_{un}**	**$T_{1/2}$**	**$T_{1/2}^{ESRD}$**	**PB%**	**Vd $_{L/kg}$**	**CYP / DDI**	**(Renal) focus**
Clonidine	Catapresan®	0.075-0.15mg BID, max 0.6mg per day	slow titration in RI	**0.4**	45	12-16	**41**	20-40	2		
Moxonidine #	Moxonibene®	0.2-0.4mg QD, max 0.6mg per day	30-60: max 0.4mg QD, single dose max 0.2mg	0.4	51	2-3	3.5-7	6-8	2.2-2.4		Accumulation in RI, higher doses combined with diuretics
Rilmenidin	Iterium®	1mg QD in the morning – 1mg BID	15-80: 1mg QD <15: 1mg QOD	ND	65	8,5	**18-45**	10	5		
Terazosin	Vicard®	1-5mg QHS	slow titration in RI	0.95	10	9-12	UC	90-94	0.4-0.9		
Doxazosin	Supressin®, Ascalan®	1-16mg QD	slow titration in RI	0.95	0.6-9	16-22	UC	98-99	3.4		First dose Hypertension
Urapidil #	Ebrantil®	60mg QD – 60mg BID, evening dose not after 5 pm	Ø	0.7	10-15	3	10	75-80	0.4-0.8		reduced CL and prolonged HL in RI
Minoxidil #	Loniten®	5mg QD, up to 20-40mg QD in 1-2 doses	Ø	0.9	15-20	3.5	PL	0	2-3		Combination-Therapy with BB and/or diuretics; prolonged HL, pericardial effusion, fluid retention;
Dihydralazine	Nepresol®	25-100mg in 2 to 3 doses	prolongation of dosing interval up to 16h	ND	ND	2-4	PL	88-90	ND		drug induced lupus erythematosus
ATC: C03	**Diuretics**										
Drug		**Dosing**		**Pharmacokinetic Data**						**Miscellaneous**	
Active Agent	**Brand**	**NRF**	**RI (given GFR)**	**Q_0**	**% Ex_{un}**	**$T_{1/2}$**	**$T_{1/2}^{ESRD}$**	**PB%**	**Vd $_{L/kg}$**	**CYP / DDI**	**(Renal) focus**
Hydrochlorothiazide	Generics, combined	12.5-25mg QD, up to 100mg QD	Ø Not effective in GFR<30	0.05	50-70	6-8	12-20	40	3-4		Hyperuricemia
Xipamide	Aquaphoril®	20-40mg QD	Up to 60mg in RI	ND	88	7	9	99	0.1-0.3		
Torasemide #	Generics	2.5-20mg QD	Ø	0.75	21	3-6	UC	99	0.16-0.2	2C8,9	risk of ototoxicity in RI; high ceiling effect in high doses
Bumetanide	Burinex®	0.5-1mg QD, up to 2mg BID-TID	Ø	0.35	45-60	1-1.5	UC	90-99	0.2-0.5		risk of ototoxicity increased in RI, high doses effective in ESRD
Furosemide	Lasix®	40-80mg QD-BID	Ø	0.3	67	0.5-2	4-6	91-99	0.2		risk of ototoxicity increased in RI, high doses effective in ESRD

Spironolactone #	Aldactone®	25mg BID-TID, up to 200mg	increase dose interval	1	20-30	1.3	**9-23**	98	ND		Hyperkalemia, gynecomastia
ATC: C07	**Beta-blocking agents**										
Drug		**Dosing***		**Pharmacokinetic Data**						**Miscellaneous**	
Active Agent	**Brand**	**NRF**	**RI (given GFR)**	**Q_0**	**% Ex_{un}**	**$T_{1/2}$**	**$T_{1/2}^{ESRD}$**	**PB%**	**Vd L/kg**	**CYP / DDI**	**(Renal) focus**
Metoprolol-succinat # Metoprolol-tartart #	Seloken® Beloc®	47,5-95mg QD 50-100 BID	Ø	0.8	5	3-7	UC	12	5.6	2D6	hyperglycaemia, hyperkalemia
Atenolol	Tenormin®	50-100mg QD	15-35: 25-50mg QD <15: 12.5-25mg QD OR increase dose interval QOD	0.12	90	6	**15-35**	3	0.7-1.02		Accumulation in ESRD
Bisoprolol	Concor®	1.25-10mg QD	Ø	0.48	50	11	**18-24**	30-35	3	2D6, 3A4	hyperglycaemia, hyperkalemia
Nebivolol #	Nomexor®	1.25-5mg QD	Ø	0.95	1	12-19	ND	98	10-40	2D6	prolonged HL (27h) in poor 2D6 metabolizer
Carvedilol #	Dilatrend®	3.125-25mg BID	Ø	1	2	5-8	UC	95	1.6	2D6, 2C8/9, 3A4	hyperglycaemia, hyperkalemia; decrease in renal function possible; increased toxic-ity/response in poor 2D6 me-tabolizer
Propranolol #	Inderal®	40mg BID-TID	Ø	1	5	1-6	UC	93	6	1A2, 2D6	decreased renal plasma flow, increased bioavailability in ESRD
***According to indication, 2D6 poor metabolizer**											
ATC: C08	**Calcium channel blockers**										
Drug		**Dosing**		**Pharmacokinetic Data**						**Miscellaneous**	
Active Agent	**Brand**	**NRF**	**RI (given GFR)**	**Q_0**	**% Ex_{un}**	**$T_{1/2}$**	**$T_{1/2}^{ESRD}$**	**PB%**	**Vd L/kg**	**CYP / DDI**	**(Renal) focus**
Nitrendipine	Baypress®	10-20mg BID	Ø	1	0.1	12	UC	97-99	6	3A4	
Amlodipine	Norvasc®	5-10mg QD	Ø	0.85	10	35-50	UC	93-98	21	3A4	Oedema, flush
Lercanidipine	Zanidip®	10-20mg QD	Ø	ND	ND	8-10	ND	98	ND	3A4, 2D6	elevated plasma levels in ESRD
Verapamil #	Isoptin®	80mg TID-QID or 240-480mg in 3-4 doses	Ø	0.8	3-4	5	ND	83-93	3.8	3A4	May increase digoxin / CyA levels, worsening of hyper-kalemia, acute renal failure
Diltiazem #	Generics	60mg TID (normal release) 180-360 mg daily dose (extended re-lease)	Ø	0.9	10	2-11	UC	98	5.3	3A4	May increase digoxin / CyA levels, worsening of hyper-kalemia, acute renal failure

ATC: C09	Agents acting on renin-angiotensin system											
Drug		*Dosing		Pharmacokinetic Data						Miscellaneous	
Active Agent	Brand	NRF	RI (given GFR)	Q_0	% Ex_{un}	$T_{1/2}$	$T_{1/2}^{ESRD}$	PB%	Vd $_{L/kg}$	CYP / DDI	(Renal) focus
Enalapril # Enalaprilat	Renitec®, Generics	5-20mg QD	10-30: 2.5mg QD <10: 2.5mg on days with dialysis	0.1	88	11	35	50-60	1-2.4		CAVE: renal artery stenosis; hyperkalemia; parameters of active metabolite enalaprilate
Lisinopril	Acemin®	10-20mg QD	10-30: 2.5-5mg QD <10: 2.5mg	0.2	80-90	12	40-50	0	1.8		CAVE: renal artery stenosis; hyperkalemia
Ramipril # Ramiprilat	Tritace®	2.5-10mg QD	<60: max 5mg QD <10: max 2.5mg QD	0.15	35	15	40	55-70	7.1		CAVE: renal artery stenosis; hyperkalemia; parameters of active metabolite
Fosinopril # Fosinoprilat	Fositens®	10-40mg QD	Ø	0.5	9-16	12	32	90-100	0.15		ACEI least likely to accumulate in RI CAVE: renal artery stenosis; hyperkalemia; parameters of active metabolite
Losartan #	Cosaar®	12.5-50mg QD	Ø	0.95	3-5	2	4-6	99	0.5	2C8/9, 3A4	CAVE: renal artery stenosis; hyperkalemia
Valsartan	Diovan®	80-160mg QD-BID	Ø	0.7	7-13	7	7	95	0.24		CAVE: renal artery stenosis; hyperkalemia
Candesartan #	Atacand®, Blopress®	4-32mg QD	Ø, lower maintenance doses	0.4	26	9	16	99	0.13	2C9	CAVE: renal artery stenosis; hyperkalemia
Telmisartan	Micardis®	20-80mg QD	Ø	1	1	24	UC	99	7.1		CAVE: renal artery stenosis; hyperkalemia
*According to indication (hypertension or CHF)											

ATC: C10	Lipid-modifying agents										
Drug		Dosing		Pharmacokinetic Data						Miscellaneous	
Active Agent	Brand	NRF	RI (given GFR)	Q_0	% Ex_{un}	$T_{1/2}$	$T_{1/2}^{ESRD}$	PB%	Vd $_{L/kg}$	CYP / DDI	(Renal) focus
Simvastatin #	Generics	20-80mg QD	Ø, 5mg initial dose	1	0.5	2	ND	95	ND	3A4	risk of rhabdomyolysis, drug interactions
Fluvastatin	Lescol®	40-80mg QD	Ø	ND	6	3	ND	98	0.42	2C9, 3A4, 2D6, 2C8	risk of rhabdomyolysis, drug interactions
Atorvastatin#	Sortis®	10-80mg QD	Ø	0.7	ND	16	32	98	5.4	3A4	risk of rhabdomyolysis, drug interactions
Gemfibrozil #	Gevilon®	900mg QD in the evening, up to 1200mg QD in 2 doses	<30: CI	1	6	2	ND	97	0.2	1A2, 2C8/9, 2C19	risk of rhabdomyolysis, in combination with statins, taken 30 minutes before meals
Fenofibrat#	Lipsin®	200mg in the morning, 100mg in the evening, 250mg QD (extended release)	1,6-2,6mg/dl: 100mg BID; 2,6-6mg/dl: 100mg QD	0.2	ND	20-22	15d	99	0.9	2C9, 3A4	Increase in serum creatinine and BUN possible

Ezetimibe #	Ezetrol®	10mg QD	Ø	1	ND	19-30	ND	90	1.5		
Statins taken as single doses in the evening, risk for DDI potentially lower with pravastatin or fluvastatin. Dose depends on lipid levels and on cardiovascular risk. Lower initial doses and titration based on response.											
ATC: G04	**Urologicals**										
Drug		**Dosing**		**Pharmacokinetic Data**						**Miscellaneous**	
Active Agent	**Brand**	**NRF**	**RI (given GFR)**	**Q_0**	**% Ex_{un}**	**$T_{1/2}$**	**$T_{1/2}^{ESRD}$**	**PB%**	**Vd $_{L/kg}$**	**CYP / DDI**	**(Renal) focus**
Tamsulosin	Alna®	0.4mg extended release QD in the morning	Ø	0.9	10	12	UC	99	0.2	2D6, 3A4	
Trospium	Inkontan®	15mg TID / 20mg BID	<30: 15mg BID	ND	60	18	33	50-85	5.6		prolonged HL in ESRD
ATC: H02	**Systemic corticosteroids**										
Drug		**Dosing**		**Pharmacokinetic Data**						**Miscellaneous**	
Active Agent	**Brand**	**NRF**	**RI (given GFR)**	**Q_0**	**% Ex_{un}**	**$T_{1/2}$**	**$T_{1/2}^{ESRD}$**	**PB%**	**Vd $_{L/kg}$**	**CYP / DDI**	**(Renal) focus**
Dexamethasone	Fortecortin®	po: 4-24mg QD iv: 40-100mg QD according to indication	Ø	0.9	8	3	ND	70	2	2D6	hyperglycaemia
Prednisolone #	Aprednislon®	15-75mg QD	Ø	0.7	34	3	UC	70-90	1.5	3A4, 3A4, 3A4	hyperglycaemia, steroid toxicity in uremic patients, increased fraction of unbound drug in hypoalbuminemia
ATC: H05	**Calcium homeostasis**										
Drug		**Dosing**		**Pharmacokinetic Data**						**Miscellaneous**	
Active Agent	**Brand**	**NRF**	**RI (given GFR)**	**Q_0**	**% Ex_{un}**	**$T_{1/2}$**	**$T_{1/2}^{ESRD}$**	**PB%**	**Vd $_{L/kg}$**	**CYP / DDI**	**(Renal) focus**
Cinacalcet	Mimpara®	30-180mg QD	Ø	ND	ND	30-40	ND	93-97	14	1A2, 2D6, 3A4	
Dosing regime in addition with phosphate binders, vitamin D analogues											

ATC: J01	Antibacterials, systemic											
Drug		Dosing		Pharmacokinetic Data						Miscellaneous	
Active Agent	Brand	NRF	RI (given GFR)	Q_0	% Ex_{un}	$T_{1/2}$	$T_{1/2}^{ESRD}$	PB%	Vd $_{L/kg}$	CYP / DDI	(Renal) focus
Doxycycline	Vibramycin®, Generics	po/iv: 200(-300)mg QD	Ø	ND	35-45	16	18-25	80-90	0.75		Decreased absorption due to polyvalent cations (Al, Mg, Ca); Sunlight!;
Amoxicillin Clavulanic acid	Augmentin®, Generics	po: 1g BID-QID iv: 2.2-4.4g TID	10-30: po: 625mg BID iv: 550mg BID <10: po: 625mg QD iv: 550mg QD	0.12 0.5	50-70 40	1 1	5-20 3-4	15-25 30	0.26 0.3		Acute interstitial nephritis, hepatotoxicity
Piperacillin Tazobactam	Tazonam®, Generics	iv: 4.0/0.5g TID-QID	20-40: 4.0/0.5g TID <20: 4.0/0.5g BID	0.3 0.17	60-80 80	1 1	2-6	30 30	0.3 0.2		Interstitial nephritis, acute renal failure
Cefuroxime	Curocef®, Zinnat®, Generics	po: 500mg BID iv: 1.5-3g TID	<20: po: 1000mg max iv: 0.75-1.5g BID	0.1	90	1.5	17	50	0.13-1.8		
Ceftazidime	Fortum®, Generics	1-3g TID	31-50: 1g BID 30-16: 1g QD <16: 0.5g QD	0.05	90-96	1.8	25-34	17	0.28-0.4		increase in serum creatinine, azotemia
Cefpirom	Cefrom®	1-2g BID-TID	1-2g QD	0.2	80-90	2	5-15	10	0.2-0.37		
Meropenem	Optinem®	0.5-2g TID	26-50: 0.5-1g BID, 10-25: 0.5g BID, <10: 0.5 QD	0.24	70	1	4-20	2	0.17-0.28		oliguria, deterioration of kidney function, elevation of serum creatinine
Sulfamethoxazole Trimethoprim	Bactrim® forte	0.8/0.16g BID-TID	15-30: 0.4/0.08g BID-TID <15: CI	0.8 0.5	70 40-70	10 10	20-50 30	50 30-70	0.28-0.38 1-2.2	2C9 2C8, 3A4	decreased PB in CKD, elevation of serum creatinine and BUN, interstitial nephritis, acute renal failure
Clarithromycin #	Klacid®, Generics	po: 250-500mg BID iv: 0.5g BID	<30: 250mg BID	0.6	15-20	5	10	70	3.5-3.8	**3A4,** 3A4	elevation of serum creatinine
Clindamycin #	Dalacin®, Generics	po: 0.3-0.6g TID iv: 0.6-1.2g TID	Ø po: 0.3g TID iv: 0.3-0.6g TID	0.8	10	3	UC	60-95	0.6-1.2		
Gentamicin	Refobacin®	3-5mg/kg QD C_0 <2mg/L (<4.32µmol/L)	1.5mg/kg QD, C_0<2mg/L	0.02	95	3	20-60	5	0.26		Ototoxicity and nephrotoxicity;
Ciprofloxacin #	Ciproxin®, Generics	po: 250-500mg BID-TID iv: 200-400mg BID-TID	po: <30: 250mg BID iv: 31-60: 400mg BID <30: 400mg QD	0.5	50-70	4	6-9	20-40	1.2-2.7	**1A2**	interstitial nephritis, interactions with polyvalent cations

Levofloxacin	Tavanic®	po: 250-500mg BID iv: 500-1000mg QD	Loading 500-250mg, 10-50: 125-250mg QD-BID	0.23	67-87	6-8	76	34-38	1.25	1A2	prolonged HL, acute interstitial nephritis
Moxifloxacin	Avelox®	400mg QD	Ø	0.8	15-21	12	UC	30-50	1.7-3.5		acute renal failure, acute interstitial nephritis
Vancomycin	Generics	1.0-2.0g BID	Initial dose 15mg/kg 10-50: 1g Q24-96h, <10: 1g Q4-7d trough level 5-10µg/mL (<7µmol/L)	0.05	90-100	5	10d	30-55	0.2-1.25		decreased protein binding in renal impairment, deterioration of renal function; CAVE: infusion velocity!
Teicoplanin	Targocid®	Initial dose 12mg/kg followed by 3-6mg/kg	15-25µg/ml therapeutic level 30-80: 400mg QOD <30 400mg Q72h	0.3	40-60	90-157	102-347	60-90	1.13		potential for nephrotoxicity
Fusidic acid #	Fucidin®	po: 0.5g TID-QID iv: 0.5g TID	Ø	1	ND	6	UC	98	ND		
Fosfomycin	Generics	4.0-8.0g BID-TID	2.0-4.0g QD	0.1	90	2	PL	0	ND		
Linezolid #	Zyvoxid®	po/iv: 600mg BID	Ø	0.65	30	6-8	6-8	31	0.57-0.7		metabolites may accumulate, MAO Inhibition
ATC: J02	**Antimycotics, systemic**										
Drug		**Dosing**		**Pharmacokinetic Data**						**Miscellaneous**	
Active Agent	**Brand**	**NRF**	**RI (given GFR)**	**Q_0**	**% Ex_{un}**	**$T_{1/2}$**	**$T_{1/2}^{ESRD}$**	**PB%**	**Vd $_{L/kg}$**	**CYP / DDI**	**(Renal) focus**
Fluconazole	Diflucan®	200-800mg QD or 6-12mg/kg, according to indication	10-50: DR 50%	0.2	80	30	125	12	0.56-0.82	2C19, 2C9, **3A4**	drug interactions
Voriconazole	Vfend®	po: 200-400mg loading, 100-200mg BID maintenance iv: 6mg/kg BID loading, 4mg/kg BID maintenance	Ø (for oral dosing) iv: avoid if <50	0.98	2	6	ND	58	4.6	2C19, 2C9, 3A4	Accumulation of solubilising agent when given iv; switch to oral therapy in RI; drug interactions

ATC: J04	Antimycobacterials											
Drug		Dosing		Pharmacokinetic Data							Miscellaneous	
Active Agent	Brand	NRF	RI (given GFR)	Q_0	% Ex_{un}	$T_{1/2}$	$T_{1/2}^{ESRD}$	PB%	Vd $_{L/kg}$	CYP / DDI	(Renal) focus	
Isoniazid #	Generics	5mg/kg or 300mgQD	Ø	0.6	5-30	1.2	8-17	4-30	0.6-0.75	2C9, 2E1	CAVE: slow acetylators - metabolites may accumulate in RI	
Rifampicin #	Rifoldin®	450-600mg QD	<50: 5mg/kg	0.85	15-30	2.8	2-11	60-90	0.9	2B6, 2C8, 2C19, 2C9, 2D6, 3A4	discolouration of urine, acute renal failure	
Ethambutol	Etibi®, Myambutol®	25mg/kg QD	10-50: 25mg/kg Q24-36h, <10: 25mg/kg QOD	0.2	75-90	4	7-15	10-30	1.6-3.9			
ATC: J05	**Antivirals, systematic**											
Drug		Dosing		Pharmacokinetic Data						Miscellaneous		
Active Agent	Brand	NRF	RI (given GFR)	Q_0	% Ex_{un}	$T_{1/2}$	$T_{1/2}^{ESRD}$	PB%	Vd $_{L/kg}$	CYP / DDI	(Renal) focus	
Acyclovir	Zovirax®	po: 200-800mg Q4h iv: 5-20mg/kg TID	10-50: 5mg/kg BID-QD <10: 2.5mg/kg QD	0.25	40-71	3	20	10-30	0.8		neurotoxicity, acute renal failure if injected to rapidly	
Valaciclovir #	Valtrex®	500-1000mg TID	250-500mg TID <10: 250-500mg QD	ND	ND	0.5	ND	ND	ND		see active metabolite aciclovir for pharmacokinetic properties	
Ganciclovir	Cymevene®	5mg/kg BID	2.5mg/kg BID-QD <10: 1.25mg/kg QD	0.05	90-100	3	9-29	1-2	0.74		bone marrow toxicity	
Valganciclovir#	Valcyte®	Induction: 900mg BID Maintenance: 900mg QD	40-59: 450mg BID/QD 25-39: 450mg QD/QOD 10-24: 450mg QOD/twice per week	ND	ND	0.4-0.6	ND	ND	ND		see active metabolite ganciclovir for pharmacokinetic properties	
ATC: L01	**Antineoplastics**											
Drug		Dosing		Pharmacokinetic Data						Miscellaneous		
Active Agent	Brand	NRF	RI (given GFR)	Q_0	% Ex_{un}	$T_{1/2}$	$T_{1/2}^{ESRD}$	PB%	Vd $_{L/kg}$	CYP / DDI	(Renal) focus	
Cyclophosphamide #	Endoxan®	1-2mg/kg QD	10-50: DR 75%, <10: DR 50%	0.5	5-25	7	10	24	0.3-1.2	2B6, 2C19, 3A4		

ATC: L04	Immunosuppressants										
Drug		Dosing		Pharmacokinetic Data						Miscellaneous	
Active Agent	Brand	NRF	RI (given GFR)	Q_0	% Ex_{un}	$T_{1/2}$	$T_{1/2}^{ESRD}$	PB%	Vd $_{L/kg}$	CYP / DDI	(Renal) focus
Azathioprine #	Imurek®	3-5mg/kg QD	10-50: 75% <10: 50%	1	10	4.5	PL	30	0.5-0.8		CAVE: combination with allopurinol; increased bioavailability in uremic patients, hematologic toxicity
Mycophenolate-mofetil #	Cellcept®	1g BID (kidney TX)	Ø	0.7	1	16-18	UC	97	3.6-4		diarrhoea, leucopoenia, thrombocytopenia
Mycophenolic acid	Myfortic®	720mg BID	Ø	0.7	1	8-16	UC	97	3.6-4		diarrhoea, leucopoenia, thrombocytopenia
Cyclosporine A #	Sandimmun®	10-15mg/kg QD in 2 doses initially Maintenance : 3-6mg/kg °Therapeutic range: 100-350µg/L	Ø	1	0.1	10-27	UC	90	3.9-4.5	3A4	nephrotoxicity, elevation of serum creatinine level, hypertension
Tacrolimus #	Prograf®	0.2-0.3mg/kg QD in 2 doses °Therapeutic range: 5-20µg/L	Ø	1	1	14	ND	99	0.85-1.91	3A4, 2D6	tremor, hyperkalemia and nephrotoxicity
Consistent schedule relative to meals and day time ° Therapeutic range, depends on organ (for CyA, given for kidney), depends on protocol, co-immunosuppression (corticoids, antimetabolites), risk of rejection, time since transplantation											
ATC: M04	Antigout										
Drug		Dosing		Pharmacokinetic Data						Miscellaneous	
Active Agent	Brand	NRF	RI (given GFR)	Q_0	% Ex_{un}	$T_{1/2}$	$T_{1/2}^{ESRD}$	PB%	Vd $_{L/kg}$	CYP / DDI	(Renal) focus
Allopurinol #	Urosin®	300mg QD	>50: 200mg QD 10-50: 150mg QD <10: 100mg QOD	0.1	8-12	2-8	1 week (M)	5	1.6-2.4		active metabolite oxypurinol, interstitial nephritis, hypersensitivity CAVE: CI combination with azathioprine

ATC: N02A	Analgesics: Opioids			
Drugs		**Dosing**		
Active Agent	**Brand**	**NRF**	**RI (given GFR)**	**Miscellaneous**
Buprenorphine	Temgesic® Sublingual Tbl. 0.2mg	0.2-0.4mg TID-QID	Ø	Max. 5mg per day, duration 6-8h, ceiling effect
Buprenorphine TTS	Transtec® TTS 35, 52.5, 70µg/h	Start with TTS 35µg/h, individual titration, change every 4th day	Ø	
Hydromorphoen #	Hydal® Caps.. 1.3, 2.6mg Hydal® Caps. PR 2, 4, 8, 16, 24mg	Normal release: Up to six times per day 1.3-2.6mg PR: 2-24mg BID	Ø	Duration normal release: 2-5h Duration PR: 12-13h
Fentanyl TTS	Durogesic® TTS	Start with TTS 25µg/h, individual titration, change every 3rd day	Ø	
Oxycodone #	Oxynorm® Caps. 5, 10, 20mg Oxycontin® Tbl. PR 5, 10, 20, 40, 80mg	Normal release: Up to 4-6 times per day 5-20mg PR: 10-80mg BID	Ø	Duration normal release: 4-6h Duration PR: 12h
Morphine hydrochloride #	Vendal® Amp. 10mg 1ml Vendal® Amp. 100mg 10ml Vendal® Tbl. PR. 10, 30, 60, 100, 200mg	Single dose sc / im: 5-10mg, max 30mg, every 4-6 hour Single dose iv: 2-10mg, continuous infusion 1-2mg/h PR: 10-30mg BID	10-50: DR 75% <10: DR 50%	Morphine-6-glucuronide as metaboli tends to accumulate Slowly inject i.v. over 4-5min Duration parenteral: 4h Increase in dosing possible
Morphine sulfate #	Morapid® 10, 20mg Mundidol® Tbl. PR 10, 30, 60, 100, 200mg	Normal release: Up to six times per day 10-20mg PR: 10-30mg BID	10-50: DR 75% <10: DR 50%	Morphine-6-glucuronide as metaboli tends to accumulate Duration normal release: 4h Duration PR: 12h Increase in dosing possible
Piritramid	Dipidolor® Amp. 15mg 2ml	im / sc: 15mg TID-QID iv: 7.5-22.5mg (1-3ml)	Ø	If given i.v. slowly inject.
Tramadol #	Tradolan® Amp. 50mg 1ml, 100mg 2ml Adamon® Tbl. 50mg Tradolan® Tbl. PR 100, 150, 200mg Adamon® long PR 150, 300mg Noax® Uno PR 100, 200mg	Single dose iv, im, sc: 50(-100mg), TID – QID Normal release: Up to 4-6 times per day 50-100mg PR: 100(150)-200mg BID	<30: dosing interval every 12th hour <10: max 50mg BID	Avoid PR forms in GFR < 30

ATC: N02B	Other analgesics and antipyretics			
Drugs		**Dosing**		
Active Agent	**Brand**	**NRF**	**RI (given GFR)**	**Miscellaneous**
Acetylsalicylic acid, ASS	Aspirin Tbl. 500mg	500-1000mg BID - TID	CI in severe RI	Max 3000mg per day
Paracetamol	Perfalgan 1g, 500mg Mexalen Tbl. 500mg	iv 1000mg up to QID oral single dose 500mg, up to 2g per day	10-50: 500mg QID <10: 500mg TID	Max 4000mg, give post dialysis
Metamizol #	Novalgin Amp. 1g 2ml Novalgin Amp. 2.5g 5ml Novalgin Tbl. 500mg	Single dose iv / im: 500-1000mg, up to QID Single dose oral: 500-1000mg, up to TID	Use lowest possible dosage, reduced elimination velocity	Inject slowly, risk of anaphylaxis

Titration of pain medication according to intensity, indication and prior pain medication use, slow titration in severe RI, consider accumulation of active metabolites. Monitor liver function as well.

ATC: N03	Antiepileptics											
Drug		**Dosing**		**Pharmacokinetic Data**						**Miscellaneous**	
Active Agent	**Brand**	**NRF**	**RI (given GFR)**	**Q_0**	**% Ex_{un}**	**$T_{1/2}$**	**$T_{1/2}^{ESRD}$**	**PB%**	**Vd L/kg**	**CYP / DDI**	**(Renal) focus**
Gabapentin	Neurontin®	300-600mg TID	In 3 daily doses: 50-79: 600-1800mg/d, 30-49: 300-900mg/d, 15-29: 150-600mg, <15: 150-300mg in 3 daily doses	0.08	76-80	5-7	132	3	0.8-0.87		HL proportional to CL
Pregabalin	Lyrica®	50-100mg TID or 75-150mg BID	30-60: 75-300 in 3 doses 15-30: 25-150 in 1-2 doses <15: 25-75 QD	0.01	90-99	6.3	ND	0	0.5		Supplemental dose after 4h of dialysis (50% removal)

ATC: N05	Psycholeptics										
Drug		**Dosing**		**Pharmacokinetic Data**						**Miscellaneous**	
Active Agent	**Brand**	**NRF**	**RI (given GFR)**	**Q_0**	**% Ex_{un}**	**$T_{1/2}$**	**$T_{1/2}^{ESRD}$**	**PB%**	**Vd L/kg**	**CYP / DDI**	**(Renal) focus**
Zolpidem	Generics	5-10mg	Ø	1	1	2.5	UC	93	0.54	3A4	
Oxazepam	Praxiten®	15-50mg BID-TID	Ø	1	50	3-9	25-90	86-99	0.67	3A4	
Bromazepam	Lexotanil®	1.5-3mg QD-TID	Ø	1	2-3	16	ND	70	0.96	3A4	
Flunitrazepam #	Somnubene®	0.5-1mg	Ø	1	2	29	ND	80	3.3-5.5	3A4	Long elimination HL
Alprazolam #	Xanor®	0.5-4mg TID	Ø	0.7	ND	13	ND	80	1.1-1.2	3A4	
Lormetazepam #	Noctamid®	0.5-1mg	Ø	0.85	ND	11-16	ND	85	4.6	3A4	
Risperidone #	Risperdal®	1-6mg QD	lower initial dose and slower titration	ND	ND	3	ND	90	1-2	2D6, 3A4	Accumulation in RI

ATC: N06	Psychoanaleptics										
Drug		**Dosing**		**Pharmacokinetic Data**						**Miscellaneous**	
Active Agent	**Brand**	**NRF**	**RI (given GFR)**	**Q_0**	**% Ex_{un}**	**$T_{1/2}$**	**$T_{1/2}^{ESRD}$**	**PB%**	**Vd $_{L/kg}$**	**CYP / DDI**	**(Renal) focus**
Amitriptyline #	Saroten®	75-150mg QD in divided doses	Ø	0.9	ND	9-25	ND	96	22	1A2, 2C19, 2C9, 2D6	
Sertraline #	Gladem®	50-200mg QD	Ø	1	1	24	ND	99	20	2C9, 2C19, 2D6, 3A4	acute renal failure, drug interactions
Paroxetine	Seroxat®	20-60mg QD	10-50: 50-75%, <10: 50%	0.95	2	15-22	30	95	8.7	2D6	HL increased in RI
Citalopram #	Seropram®	10-60mg QD	Ø	0.7	8	22-32	ND	56	12-15	2D6, 2C19, 3A4	
Duloxetine	Cymbalta®	60-120mg QD in 1-2 divided doses	lower initial dose and slower titration	ND	1	12	ND	90	23.4	2D6, 2D6	
Mirtazapine #	Generics	15-45mg QD	lower initial dose and slower titration	ND	ND	33	PL	85	1.5	2D6, 3A4	
Trazodone #	Trittico®	150-300mg QD in divided doses	Ø	1	ND	7.1	ND	90-95	0.47-0.84	2D6, 3A4	
Slow titration											
ATC: N06	**Antiprotozoals**										
Drug		**Dosing**		**Pharmacokinetic Data**						**Miscellaneous**	
Active Agent	**Brand**	**NRF**	**RI (given GFR)**	**Q_0**	**% Ex_{un}**	**$T_{1/2}$**	**$T_{1/2}^{ESRD}$**	**PB%**	**Vd $_{L/kg}$**	**CYP / DDI**	**(Renal) focus**
Metronidazole #	Anaerobex®	po: 500mg TID iv: 500mg TID	<10: 50%	0.85	6-18	7	7-21	20	0.2-0.85	2C9, 3A4	accumulation of metabolites
Atovaquone	Wellvone®	1500mg QD	Ø	ND	0.6	50-84	ND	100	0.6		
ATC: R03	**Drugs for obstructive airway disease**										
Drug		**Dosing**		**Pharmacokinetic Data**						**Miscellaneous**	
Active Agent	**Brand**	**NRF**	**RI (given GFR)**	**Q_0**	**% Ex_{un}**	**$T_{1/2}$**	**$T_{1/2}^{ESRD}$**	**PB%**	**Vd $_{L/kg}$**	**CYP / DDI**	**(Renal) focus**
Theophylline	Theospirex®	individual dose titration according to symptom control: ~ 8-12mg/kg/d in 2 divided doses	Ø	0.8	10	4-12	ND	40	0.45	1A2, 2E1, 3A4	drug interactions, increased diuresis, high pharmacokinetic variability

3.6 THE CLINICAL PHARMACIST'S CONTRIBUTIONS WITHIN THE MULTIDISCIPLINARY PATIENT CARE TEAM OF AN INTERN NEPHROLGY WARD

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The clinical pharmacist's contributions within the multidisciplinary patient care team of an intern nephrology ward

Abstract

Objective: To describe and evaluate newly implemented clinical pharmacy services and ward round participation on a specialized nephrology ward in a large tertiary care hospital.

Method: All issues addressed by the clinical pharmacist were systematically collected, and the contributions were classified by type. Where applicable, physicians' acceptance rates were recorded. The drugs most commonly affected by the clinical pharmacist's contributions are described.

Results: A total of 158 clinical pharmacist's contributions were recorded. Approximately 90% (n=104) of applicable suggestions (117 out of 158; 74%) were accepted by the treating physicians. Most issues were discussed with physicians (85%); the remaining issues were discussed with nurses and medical students. Antimicrobials, drugs affecting the alimentary system and metabolism, and cardiovascular drugs were among the most commonly affected drugs. Issues concerning dosage and drug-therapy selection were common. The clinical pharmacist was also involved in developing dosing guidelines and performing literature searches.

Conclusion: The observed effects of a newly implemented clinical pharmacy service on an internal nephrology ward are encouraging; acceptance rates of suggestions and the multidisciplinary appreciation of clinical pharmacy services are high.

Keywords: clinical pharmacy services, nephrology, kidney, Austria

Impact of findings on practice:

The clinical pharmacist addresses drug therapy selection and dosing as the most common issues during ward round participation on an internal nephrology ward.

The clinical pharmacist's contributions and suggestions are being appreciated, and even if rejected, increase awareness of pharmacotherapy-related problems among other health care professionals.

Introduction

Clinical pharmacists are experts in pharmacotherapy who routinely provide patient care and interact with patients and other health care professionals with the goal of optimizing pharmacotherapy[1]. The primary responsibilities of clinical pharmacy services include the identification, resolution and prevention of drug-related problems (DRPs) during the continuous patient care process. A DRP is defined as an "event or circumstance involving a patient's drug treatment that actually, or potentially, interferes with the achievement of an optimal therapeutic outcome"[2], and comprises medication errors (MEs) and adverse drug events (ADEs). MEs subsume any errors in the process of prescribing, dispensing or administering a drug, independent of occuring harm or not. An ADE is defined as any injury related to the use of a drug[3].

A review of DRPs in hospitals reported average ME rates of 6% in hospitalized patients and 1.07 MEs per 100 patient-days. Important risk factors contributing to the occurrence of MEs include a lack of information about drugs, errors in patient charts and/or documentation and inadequate or decentralized pharmacy services, among others[3]. Due to the avoidable nature of MEs, their management warrants great attention. Furthermore, DRPs contribute substantially to drug-associated morbidity and mortality, leading to prolonged hospitalization and increased overall health care costs[2].

Clinical pharmacy services have evolved over time, and the involvement of clinical pharmacists in multidisciplinary patient care is proven to be influential and has been associated with positive patient outcomes[4]. Several studies have shown that the presence of clinical pharmacists on inpatient wards leads to a reduction in the occurrence of MEs[3] and ADEs[5]. Clinical pharmacy services have also been shown to be beneficial in the care of patients with acute or chronic kidney failure, patients undergoing different renal replacement therapies and patients after kidney transplantation[6,7]. In these settings, specialized clinical pharmacists contribute to the management of important issues, such as the increased susceptibility to drug toxicity due to impaired renal function, common polypharmacy, altered drug pharmacokinetics, and complex underlying comorbidities (e.g., hypertension, diabetes, anemia), in this patient population. The prevalence of DRPs is particularly high in patients with impaired renal function, whose management is complex[6,8]. The overall awareness of DRPs has increased and ME rates, as one subgroup of DRPs, have decreased secondary to the integration of clinical pharmacists in multidisciplinary therapeutic teams[3].

Aim

The aim of the study was to describe, for the first time, the clinical pharmacist's contributions and areas of intervention in the nephrology setting in a large Austrian tertiary care hospital.

Methods

This descriptive single clinical pharmacist study was designed to prospectively analyze and evaluate newly implemented clinical pharmacy services on an intern nephrology ward. The highly specialized ward comprises 28 beds, occupied primarily by chronic or acute kidney failure patients, those on renal replacement therapies, kidney transplant recipients immediately after discharge from the surgical department and those recipients receiving continuous post-transplant care. Clinical pharmacy services have been added to routine patient care, i.e. the clinical pharmacist joined the ward round team, which then included a senior physician, several assistant physicians, nursing staff, and the clinical pharmacist. The clinical pharmacist did not receive any formal training.

The clinical pharmacist participated in the ward round thrice weekly between June 2009 and March 2010 (10 months). During the ward rounds, the current medication regimen of admitted patients were discussed and the clinical pharmacist made contributions.

Contributions comprised interventions to DRPs initiated by the clinical pharmacist (proactive) and the provision of, by members of the ward round team requested, information and support (reactive). All contributions made by the specially assigned clinical pharmacist were systematically collected, recorded, and classified according to categories, derived from the Guideline for Quality Control of Drug Information in the Hospital Pharmacy, provided by the German Society of Hospital Pharmacists[9]. Issues were subdivided into eight topical categories (five and three categories for pro- and reactive contributions, respectively; see Table 1 for description of categories) and immediately documented in writing after the ward round using an Microsoft® Excel spreadsheet. For proactively performed interventions to DRPs, the physicians' acceptance rate of the clinical pharmacist's interventions was recorded, immediately afterwards or later, but not later than during the next ward round. Drugs that were subject to the clinical pharmacist's contributions were recorded based on the WHO-ATC-Code[10].

Results

A total of 158 clinical pharmacist's contributions were recorded. Frequencies of different categories and illustrative examples are given in Table 1. Among all contributions, 74% (n=117) were applicable for documentation of acceptance rates; 88.9% (n=104) of

contributions were accepted by physicians. Predominant reasons for the rejection of pharmacist suggestions included missing laboratory data and lack of other relevant information for immediate decision-making. The vast majority of contributions (95%) were discussed during ward rounds at the point of care. Remaining issues required additional time to be addressed, resulting in extensive literature searches, including searches for dosing guidelines (e.g., for analgesics in impaired renal function) and teaching aids (e.g., comparison chart of total parenteral nutrition solutions). The clinical pharmacist discussed most issues with physicians (85,4%), nurses (7%) and students (7.6%). The primary drug classes subject to the clinical pharmacist's contributions were systemic antimicrobials (ATC code group J - 26,7%), drugs affecting the alimentary system and metabolism (ATC code group A - 17,4%), those affecting the cardiovascular system (ATC code group C - 17,4%), those affecting the nervous system (ATC code N - 11,2%), and antineoplastics and immunomodulatory agents (ATC Code L - 8,7%) (Table 1).

Table

Table 1.

Frequency of clinical pharmacist's contributions per category

Category	N (%)	Drugs or drug classes primarily affected	Examples
*Drug administration and application	8 (5.1)	Tacrolimus	
*Drug therapy selection and discussion	61 (38.6)	Antimicrobials, low molecular weight heparins, antihypertensives, electrolytes	Hypomagnesemia and hypokalemia – need for supplementation; unindicated use of proton pump inhibitors; stop of unnecessary antimicrobials (therapy duration too long), optimisation of antimicrobial combination therapy
*Drug dosage and pharmacokinetics	38 (24.1)	Valganciclovir, trimethoprim/sulfamethoxazole, amlodipine	Amlodipin overdosage (>10mg per day) and incorrect dosing frequency; overdosage of antimicrobials for cytomegalovirus or pneumocystis infection prophylaxis
*Adverse drug events	4 (2.5)	-	
*Drug interactions	6 (3.8)	Tacrolimus	Anticipating increased tacrolimus blood level due to start of clarithromycin; anticipating increased tacrolimus blood level due to start of fluconazole; risk of QT interval prologantion due to combination of ciprofloxacin and tacrolimus
Drug availability	9 (5.7)	-	
Organization and logistics	9 (5.7)	Monoclonal antibodies and cytotoxics	
General drug information	23 (14.6)	Antihypertensives	Switch of drugs according to hospital formulary guidelines

* Categories with acceptance rates recorded

Discussion

We report encouraging results regarding the clinical pharmacist's contributions on an internal nephrology ward, including high acceptance rates of recommendations and appreciation of implemented services by multidisciplinary team members. Clinical pharmacy services in Austrian hospitals are just beginning to grow, and the systematic and widespread implementation of such services, as seen in the U.S. and U.K., in Austrian hospitals is still lacking. However, small and limited clinical pharmacy efforts are emerging in an increasing number of Austrian hospitals.

Our data analysis demonstrated that the clinical pharmacist's primary areas of contribution include selection and discussion of drug therapy and handling of dosing issues. Regarding the type of the clinical pharmacist's contributions, our results are comparable to those described in literature[6]. Selection of presumptive antimicrobial therapy, adaptation to microbial sensitivity results and discontinuation of antimicrobial treatment were among the most common issues addressed by the clinical pharmacist. Overdosing of antivirals, such as valganciclovir for cytomegalovirus infection prophylaxis in kidney transplant recipients, was common. In particular, patients in the early post-transplant period, when renal function is prone to fluctuations, required frequent dose adaptations. Over- and under-dosing predominantly occurred with antiviral, antibacterial and antihypertensive drugs. Immunosuppressants and other routinely prescribed drugs in renal transplant recipients were among the top five drug groups affected by the clinical pharmacist's contributions. Immunosuppressant pharmacotherapy is a critically important aspect of post-transplant patient care. Due to the complexity of managing transplant recipients (e.g., infection prophylaxis, metabolic complications), clinical pharmacists are becoming increasingly involved in their care[7]. The overall rate of contributions regarding drug interactions was low with only 3.8%. In other clinical pharmacists' intervention studies in end-stage renal disease patients the proportion of drug interactions was higher with around 10-15%[6]. One hypothetical reason, that we can not, however, support by evidence, may be an already high awareness of drug interaction among commonly prescribed drugs by nephrologists.

The high acceptance rate of nearly 90% of contributions during the ward rounds reported here is also encouraging. Our acceptance rates are consistent with acceptance rates that have been previously published in the literature[4]. Reasons for the rejection of initial suggestions were primarily missing laboratory data or other clinical data relevant to decision making. However, the clinical pharmacist's recommendations were considered by the treating physicians. We, therefore, hypothesize that every issue raised and discussed, although rejected, increases the awareness of potential problems and highlights crucial steps

and points to consider. In addition to assisting with pharmacotherapy-related issues, the clinical pharmacist also supported the ward team with organizational and logistic concerns (e.g. assistance in the drug ordering process of preparations for specific patients, advice on stock keeping), which somewhat eased the nurses' workload.

Nevertheless, obstacles to the further expansion of clinical pharmacy services in our hospital and in Austria in general do exist. The absence of electronic medical records and other technology support tools for prescribing, data collection or analysis in our hospital represent a major barrier to the growth of clinical pharmacy services and clinical pharmacy research in our hospital. The lack of systematic clinical pharmacy education on a national Austrian level and the low staffing of hospital pharmacists (0.36 pharmacists per 100 beds)[10] further complicate the development of systematic clinical pharmacy services for our ongoing projects.

We report the results of a single clinical pharmacist study in a developing area and acknowledge the lack of a control group and significance assessment of the clinical pharmacist's contributions as limitations of our study. Study results may be significantly influenced by characteristics at the level of the pharmacist, e.g., motivation, workload, experience, among others. Further limitations comprise the lack of information on clinical or humanistic outcomes. The absence of sociodemographic patient data limits the generalizability of our results. Our findings show that a clinical pharmacist can contribute to patient care by addressing unmet drug therapy needs. Although limitations exists, our results highlight the need for further impulses to expand clinical pharmacy services.

Conclusion

Based on our encouraging results and appreciation of the contributions of the clinical pharmacist to patient care during ward rounds, clinical pharmacy services will continue. The presence of clinical pharmacists raised the awareness of potential problems or issues and informed the multidisciplinary patient care team. The clinical pharmacist was welcomed during ward rounds as a valuable source of pharmacologic knowledge by the interdisciplinary care team of physicians, nurses and medical students.

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Conflicts of interest

No conflict of interest.

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3.7 COMPREHENSIVE EVALUATION OF CLINICAL PHARMACISTS' INTERVENTIONS IN A LARGE AUSTRIAN TERTIARY CARE HOSPITAL

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Final Poster, see Appendix 8.3

Comprehensive evaluation of clinical pharmacists' interventions in a large Austrian tertiary care hospital

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Abstract

Background and objective: Data on clinical pharmacy activities and their characteristics in Austrian hospitals and the possible impact on patient care are relatively scarce. The objectives were to analyse drug-related problems and the impact of clinical pharmacists' interventions.

Method: Prospective 22-week observational descriptive clinical pharmacists' intervention study on six different wards of a tertiary care university hospital. In-depth analysis of drug-related problems and interventions. Inter- and intra-rater variability analysis of interventions' significance assessment.

Main outcome measures: Type and frequency of DRPs and clinical pharmacists' interventions and the physicians' acceptance rate. Further outcome parameters were the clinical significance of the interventions and the proportion of those with a cost-reducing potential.

Results: A total of 478 drug-related problems were detected during 138 ward rounds. The most common drug-related problems related to specific information (30.1%), organisational advice (14.2%), medical chart errors (7.7%), untreated indications (7.5%) and drug use without indication (6.9%). Clinical pharmacists provided information (42.9%), suggested the addition of new drugs (13.4%) and the adaptation of drug dosages (12.6%). Antibacterials for systemic use, antithrombotics, and drugs for acid related disorders were commonly implicated. Mean acceptance rate of interventions was 54.7%. Three out of four clinical pharmacists' interventions were rated to be significant. The inter-rater reliability analysis of clinical significance immediately and two weeks after study completion showed a fair to moderate agreement (Fleiss's Kappa 0.35, pairwise Spearman correlation coefficients between 0.5 and 0.74, all $p<0.0001$). Every twentieth intervention showed a cost reducing potential.

Conclusions: The results highlight a positive impact of clinical pharmacy services in a continually developing environment. Although, on average every second intervention was immediately accepted, the proportion of significant interventions was high. Clinical pharmacy services are one method of addressing evident drug-related problems in hospitalised patients in Austria.

Article summary

Article focus:

- Clinical pharmacy services are known to improve patient care by addressing drug-related problems.
- The study aimed at evaluating the type and frequencies of drug-related problems, and the impact of clinical pharmacists' interventions in a, regarding clinical pharmacy services, continually developing setting.

Key messages:

- Need for information, organisational advice, medical chart errors, untreated indications, and drugs used without indications were common drug-related problems addressed by the clinical pharmacists.
- Clinical pharmacists valuably contributed to patient care by providing information, suggesting the addition of new drugs and drug dosage adaptations.
- Approximately every second suggested intervention was accepted by physicians, and three out of four interventions were rated to be significant

Strengths and limitations of this study:

- This study provides evidence of a beneficial impact of clinical pharmacy services on drug-related problems in a large tertiary care hospital in Austria.
- Bias related to the assessment of the significance of clinical pharmacists' interventions was addressed by performing inter-rater and intra-rater analysis.
- The lack of reporting on patient-related and clinical outcomes has to be acknowledged as a major weakness of this study.

Introduction

Clinical pharmacy is defined as the part of pharmacy practice 'that contributes directly to patient care and develops and promotes the rational and appropriate use of medicinal products and devices'.[1] In many countries these services have emerged over time, and the involvement of clinical pharmacists in multidisciplinary patient care is beneficial and has been associated with positive patient outcomes [2-4] and economic benefits.[5]

The cornerstones of clinical pharmacy services are the detection, resolution and prevention of drug-related problems (DRPs). A DRP is defined as an 'event or circumstance involving a patient's drug treatment that actually, or potentially, interferes with the achievement of an optimal therapeutic outcome'.[6] Several studies have shown that the presence of clinical pharmacists in inpatient wards leads to a reduction in the occurrence of common DRPs, e.g., medication errors (MEs)[6] and adverse drug events (ADEs)[7], and therefore contributes to overall patient safety.

However, the extent of the development and implementation of clinical pharmacy services vary, primarily when comparing services in Europe to those in the US[4,8], but also among European countries themselves. In 85% of European hospitals, some form of clinical pharmacy services is implemented. Differences regarding centralised (i.e., wards visited at least once daily or less frequently) versus decentralised services (i.e., at least 50% of time on the ward) and the overall time pharmacists spend on the ward exist.[9]

In Austria, there is still a system of hospital pharmacy practice that focuses on traditional tasks, e.g., production and logistics. The Ordinance Regulation on the Operation of 2005 clearly defines and describes, for the first time, the clinical and patient-oriented tasks of the hospital pharmacist in Austria. However, systematic full-time and comprehensive clinical pharmacy services are still non-uniformly implemented across Austrian hospitals. A survey of the Austrian Association of Hospital Pharmacists showed that there are only 8 full-time clinical pharmacists compared to 140 full-time hospital pharmacists, when considering the overall time hospital pharmacists spend on ward-based services.[10] To our knowledge, data on the benefits and extent of clinical pharmacy services in Austria are only available as poster abstracts[11-14] and a narrative report.[15] Further evidence supporting the value of clinical pharmacy services in Austria is urgently needed to pursue the development, implementation and acceptance of clinical pharmacy services, with the ultimate goal of improved patient care.

The *Vienna General Hospital – University clinics* is the largest Austrian tertiary care hospital, with a capacity of 2130 in-hospital beds, 1450 physicians, and 30 pharmacists, 6 of them being involved in the provision of clinical pharmacy services during ward round participation and other ward-based activities (e.g., interdisciplinary rounds). Clinical pharmacy in our hospital mainly evolved from initial small-scale projects of shorter duration that have been adopted into the routine. To date, clinical pharmacy services are implemented on three standard care units (SCUs) and three intensive care units (ICUs). In the ambulatory drug addiction clinic, clinical pharmacy services have been established in close conjunction with the provision of methadone and other opioids, as part of the outpatient treatment for opioid addiction maintenance therapy.

Aim of the study

The aim of this study was to perform a comprehensive evaluation of the implemented clinical pharmacy services across all clinical pharmacist–attended clinics by describing and analysing DRPs and consecutive clinical pharmacists' interventions.

Method

Study design and setting

The study was designed as a prospective 22-week observational and descriptive clinical pharmacists' intervention study. A detailed overview of wards with regular clinical pharmacy services is given in Table 1. In addition to participation in ward rounds, clinical pharmacists are available for consultations on call during the day

Table 1 Overview of wards with regular clinical pharmacy services

Clinic Code	Description of clinics	Ward type and frequency of ward round participation	Years of experience in provision of clinical pharmacy prior to study	Years of hospital pharmacy experience
CS	Department of Surgery, Division of Cardio Surgery	SCU - twice weekly	2	25
GE	Department of Medicine III, Division of Gastroenterology and Hepatology	ICU - once weekly	1.5	2.5
HE	Department of Medicine I, Division of Haematology and Haemostaseology	SCU - twice weekly	0.2	3
ID	Department of Medicine I, Division of Infectious Disease and Tropical Medicine	ICU - once weekly	3	11
NE	Department of Medicine III, Division of Nephrology and Dialysis	SCU - thrice weekly	3	4
NN	Department of Paediatrics and Adolescent Medicine, Division of Neonatology, Intensive Care and Neuropaediatrics	ICU - twice weekly	2	11
PC	Department of Psychiatry and Psychotherapy, Division of Biological Psychiatry	AC - daily	9	9

Description of clinical pharmacy services

A quality management process for clinical pharmacy services has been developed, based on initial experiences with small-scale clinical pharmacy efforts, the results of extensive literature reviews and a focus group meeting among all involved clinical pharmacists. A schematic description of the clinical pharmacy sequence is depicted in Figure 1**.**

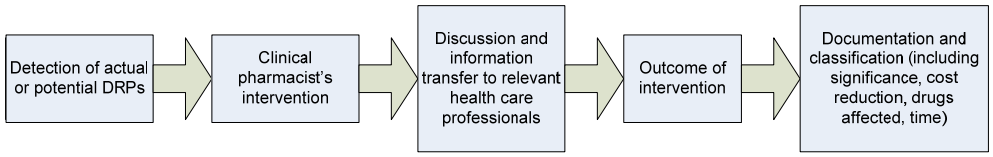

Figure 1: Clinical pharmacy process

On the SCUs, the clinical pharmacists screened paper-based medical charts, discussed incidental DRPs and provided suggestions for their resolution (intervention) during ward rounds. The clinical pharmacists assigned to the ICUs prepared for ward rounds centrally in the pharmacy in advance, by accessing the electronic medical records, including relevant data, e.g., drug therapy, diagnosis, and lab values. However, potential DRPs were also discussed during ICU ward rounds. Ward round teams routinely consisted of a senior physician, several junior physicians, nursing staff, and medical students. All clinical pharmacists educated themselves about the patient cases on their own. The overall time of the individual clinical pharmacist's attachment to the ward prior to study and years of hospital pharmacy experience are also given in Table 1.

Comprehensive documentation system

The type of DRP, the suggested intervention or contribution (a term related to informational or organisational issues), the status of acceptance of interventions, and the drug classification according to World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) Code classification system, therapeutic subgroup level, were recorded. For documentation and categorisation purposes, a published and validated system[16] was used, which was adapted and amended according to the clinical pharmacists' needs, extracted during the focus group meeting. Acceptance rates were assessed using a four-point rating scale comprising the categories 'accepted', 'taken into consideration', 'rejected', and 'non-assessable'. The acceptance rate was not recorded for contributions related to organisation and information. Furthermore, all interventions were judged regarding their cost-reducing potential. A detailed explanation of the several documentation categories is shown in the appendix (web-only). The clinical significance of interventions was assessed using a 6-

point significance-rating scale (adverse significance–extremely significant).[17] Every intervention or any other contribution was rated by the clinical pharmacist immediately at the time of the intervention and again two weeks after the study ended. Upon study completion, all interventions and contributions were co-assessed in random order by each clinical pharmacist who was blinded to the other clinical information. No formal training in documentation or significance assessment was performed prior to the study.

Main outcome measures

The main outcome measures were the type and frequency of DRPs, the type and frequency of clinical pharmacists' interventions and contributions, and the physicians' acceptance rate. Further outcome parameters were the clinical significance of the interventions and the proportion of interventions with a cost-reducing potential. In-depth analysis was performed for all DRPs and for the individual clinical setting. The drugs that were most commonly involved in DRPs are reported descriptively.

Statistical methods

Absolute and relative frequencies of DRPs, interventions, and commonly implicated drugs are provided. To assess the inter-rater and intra-rater variabilities of clinical significance, Cohen's and Fleiss's Kappa and Spearman correlation coefficients are reported. Bowker's symmetry test was calculated to determine whether the first and second assessment were consistently different.

Results

DRPs and interventions

During 138 ward rounds (25 in CS, 16 in GE, 14 in HE, 11 in ID, 38 in NE, 11 in NN, and 23 in PC), a total of 478 DRPs were addressed. A mean (± standard deviation) of 0.3 (± 0.4) and 3.5 (±1.5) DRPs were identified per patient and per ward round, respectively. The most common DRPs were related to specific therapy discussions and the need for information (30.1%), organisational advice (14.2%), medical chart errors (7.7%), untreated indications (7.5%), and drugs used without indication (6.9%). The most frequent clinical pharmacists' interventions and contributions were related to general information (42.9%), the addition of new drugs (13.4%), and dose adjustments (12.6%). The overall frequency of various DRPs and interventions per clinical area are given in Tables 2 and 3, respectively.

Table 2: Type and frequency of drug-related problems, per clinical area and total

	CS	GE	HE	ID	NE	NN	PC	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Non-conformity to guidelines or contraindication				1 (2.4)	13 (6.2)		3 (11.5)	**17 (3.6)**
Untreated indication	11 (11.5)	2 (3.6)			17 (8.1)	1 (3.1)	5 (19.2)	**36 (7.5)**
Subtherapeutic dosage	3 (3.1)	4 (7.1)		2 (4.9)	11 (5.3)			**20 (4.2)**
Supratherapeutic dosage	5 (5.2)	3 (5.4)		2 (4.9)	22 (10.5)			**32 (6.7)**
Drug without indication					33 (15.8)			**33 (6.9)**
Drug interaction: To be taken into account	2 (2.1)	9 (16.1)		6 (14.6)	4 (1.9)			**21 (4.4)**
Drug interaction: Use with caution	1 (1.0)		1 (5.6)	7 (17.1)			7 (26.9)	**16 (3.3)**
Drug interaction: Combination to be avoided	1 (1.0)	3 (5.4)					2 (7.7)	**6 (1.3)**
Drug interaction: Combination contra-indicated								
Adverse drug reaction	2 (2.1)			2 (4.9)	5 (2.4)		1 (3.8)	**10 (2.1)**
Improper administration	3 (3.1)	5 (8.9)		2 (4.9)	5 (2.4)	1 (3.1)		**16 (3.3)**
Failure to receive drug	2 (2.1)				1 (0.5)	1 (3.1)		**4 (0.8)**
Drug monitoring	1 (1.0)			1 (2.4)	2 (1.0)		2 (7.7)	**6 (1.3)**
Medical chart error	5 (5.2)	9 (16.1)		2 (4.9)	21 (10.0)	1 (3.1)		**38 (7.9)**
Specific information and therapy discussion	48 (50.0)	5 (8.9)	8 (44.4)	8 (19.5)	64 (30.6)	10 (31.3)	1 (3.8)	**144 (30.1)**
Literature search	2 (2.1)	1 (1.8)	2 (11.1)		2 (1.0)	4 (12.5)		**11 (2.3)**
Others	10 (10.4)	15 (26.8)	7 (38.9)	8 (19.5)	9 (4.3)	14 (43.8)	5 (19.2)	**68 (14.2)**
Total	**96 (100)**	**56 (100)**	**18 (100)**	**41 (100)**	**209 (100)**	**32 (100)**	**26 (100)**	**478 (100)**

Table 3: Type and frequency of interventions and contributions by the clinical pharmacists, per clinical area and total

	CS	GE	HE	ID	NE	NN	PC	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Addition of a new drug	22 (22.9)	3 (5.4)	6 (33.3)	5 (12.2)	21 (10.0)	3 (9.4)	4 (15.4)	**64 (13.4)**
Drug discontinuation	6 (6.3)	1 (1.8)		2 (4.9)	46 (22.0)	1 (3.1)		**56 (11.7)**
Drug switch	9 (9.4)	5 (8.9)		3 (7.3)	6 (2.9)	1 (3.1)	5 (19.2)	**29 (6.1)**
Change of administration route	4 (4.2)	4 (7.1)		3 (7.3)	2 (1.0)	3 (9.4)		**16 (3.3)**
Drug monitoring		6 (10.7)		10 (24.4)	3 (1.4)		5 (19.2)	**24 (5.0)**
Administration modalities optimisation	8 (8.3)	6 (10.7)		3 (7.3)	4 (1.9)	2 (6.3)	1 (3.8)	**24 (5.0)**
Dose adjustment	10 (10.4)	5 (8.9)	3 (16.7)	2 (4.9)	38 (18.2)	1 (3.1)	1 (3.8)	**60 (12.6)**
Others	37 (38.5)	26 (46.4)	9 (50.0)	13 (31.7)	89 (42.6)	21 (65.5)	10 (38.5)	**205 (42.9)**
Total	**96 (100)**	**56 (100)**	**18 (100)**	**41 (100)**	**209 (100)**	**32 (100)**	**26 (100)**	**478 (100)**

The majority of DRPs (n=413, 86.4%) were addressed and interventions were immediately performed by the clinical pharmacist. In total, 13.6% of DRPs resulted in an increased need for time to address them (n=48, 10% up to one hour; n=17, 3.6% more than one hour).

In 89.1% (n=426) of DRPs, interventions were discussed with physicians and for the other DRPs, interventions were discussed with the nursing staff. Of those interventions discussed with nursing staff, 78% were informational in nature or were related to organisational advice (e.g., advice on ward stock-keeping or the order of patient-specific preparations). Five percent of interventions by the clinical pharmacists were accompanied with a potential cost reduction, with the most commonly applied strategy being the discontinuation of unnecessary drugs (see Figure 2).

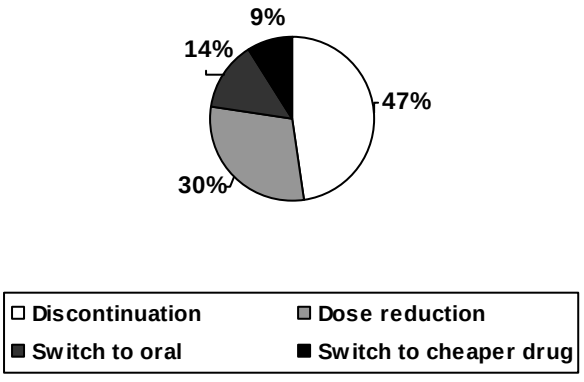

Figure 2: Interventions with a cost-reducing potential

For 71.1% (n=340) of the interventions, an acceptance rate was recorded. The mean (±SD) acceptance rate of the suggested clinical pharmacists' interventions was 54.7% (±22.87) (see Figure 3).

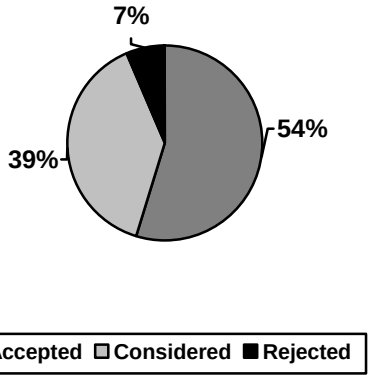

Figure 3: Overall outcome of clinical pharmacists' interventions

Including those interventions that were not immediately accepted but were considered by the physicians, the mean (±SD) overall acceptance rate increased to 93.5% (±5.60). Only 22 suggested interventions were rejected. Crude acceptance rates (%) were 65.8, 25.8, 91.7, 30.6, 60.9, 46.7 and 40.9 for CS, GE, HE, ID, NE, NN, and PC, respectively.

Significance of interventions

Analysis of the clinical pharmacists' self-assessment of the significance of interventions upon first-time detection showed an overall proportion of 75.3% of interventions ranged as significant (subsumed categories 'somewhat significant' to 'very significant'). Compared to the clinical pharmacists' self-assessment of significance of interventions two weeks after the end of the study (68.8% of significant interventions), intra-rater analysis showed a moderate agreement between the two different time points (intra-rater reliability Cohen's Kappa = 0.58, 95% CI 0.48–0.67).

The percentage of significant interventions as first assessed was 86.5, 87.8, 61.1, 64.3, 70.8, 74.0, and 84.6 for CS, GE, HE, ID, NE, NN, and PC, respectively. During the study period, there were no interventions classified as 'extremely significant'. One intervention was judged to have adverse significance. This intervention was related to the provision of false information regarding the stability of a reconstituted drug on the basis of out-dated information. The error was detected shortly after providing the false information, and no subsequent errors or patient harm occurred. Regarding the significance of interventions, there was a trend towards lower significance assessment at the end of the study compared to the initial assessment (symmetry test p=0.006).

The inter-rater reliability analysis of clinical significance immediately and two weeks after study completion showed a fair to moderate agreement (Fleiss's Kappa 0.35, pairwise Spearman correlation coefficients between 0.5 and 0.74, all p<0.0001). The overall frequency of each significance level of interventions is depicted in Figure 4.

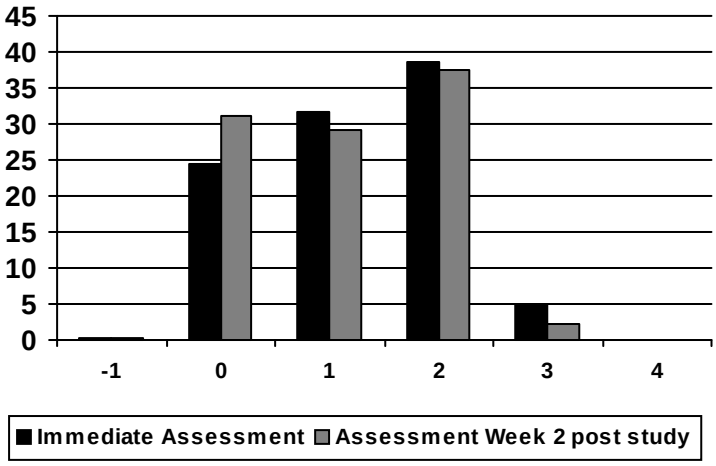

Figure Legend: -1, adverse significance; 0, no significance; 1, somewhat significant; 2, significant; 3, very significant; 4, extremely significant

Figure 4: Percentage of overall significance categories of interventions

Analysis of involved drugs

Anti-infectives for systemic use, drugs affecting the nervous system, and those affecting the alimentary system and metabolism were involved in the majority of DRPs (see Figure 5).

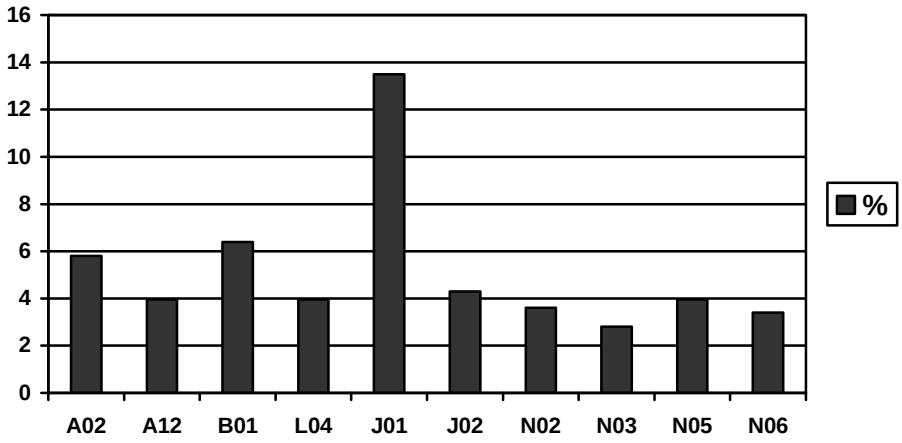

Figure Legend: A02, drugs for acid-related disorders; A12, mineral supplements; B01, antithrombotic agents; L04, immunosuppressants; J01, antibacterials for systemic use; J02, antimycotics for systemic use; N02, analgesics; N03, antiepileptics; N05, psycholeptics; N06, psychoanaleptics

Figure 5: The 10 most affected drugs (ATC Code therapeutic subgroup level)

Half of the DRPs detected in our study were related to a drug from the 10 most prevalent ATC code groups. Drug interactions (all four subcategories) represented a common DRP among drugs affecting the nervous system (ATC Code N), immunosuppressants (ATC Code L04) and anti-infectives for systemic use (ATC Code J). The frequency of drug interactions was significantly higher in immunosuppressants compared to non-immunosuppressants (Fisher's exact test, p=0.004). Furthermore, drugs used without indication and under- and overdosages were more prevalent among systemic anti-infectives compared to other drug classes (chi-square tests p=0.02 and p=0.014, respectively)

Discussion

Our study suggests a valuable contribution of the clinical pharmacist to multidisciplinary patient care during ward rounds, by addressing DRPs, performing interventions, and providing information and organisational support. DRPs are highly prevalent in hospitalised patients[18], and optimisation of drug therapy by preventing DRPs positively influences costs, reduces mortality and improves patients' quality of life.[19,20] Evidence regarding clinical pharmacy services is published for several patient groups and clinical settings, e.g., SCUs[21], ICUs[22,23] and the psychiatric setting[24], comparable to those where clinical pharmacy services are implemented in our hospital.

In our study, 50% of interventions were accepted, with a change happening immediately. This proportion is lower than published average rates, which range between 80 and 90%.[25] However, 39% of interventions were taken into consideration by physicians but did not lead to immediate changes (either because of missing data or because other information was needed for decision making). We believe that these suggestions highlight the problem DRPs and should at least prompt a reconsideration of addressed DRPs by the physicians. Thus, by adding this proportion to the crude acceptance rate, it increases to the aforementioned rates from other studies. Furthermore, the acceptance rates are influenced by several crucial factors, e.g., the clinical pharmacists' knowledge, clinical experience and communication skills, the physicians' confidence in the pharmacists' intervention, and the multidisciplinary working climate. Shortcomings concerning the management of these factors and the low familiarity with clinical pharmacy services among clinicians should be urgently addressed as one method of improving acceptance rates in our setting.

Approximately one-third suggested interventions in our study was lost during the assessment of acceptance rates, as it was related to informational or organisational issues only. Our analysis highlights a need for specific therapy discussions and information across all clinical areas of all involved health care professionals, especially

among nursing staff, as reflected by the high proportion of 78% of information/organisation-related interventions. From our point of view, this and the overall low rate of rejected interventions (6.5%) also emphasise that clinical pharmacists are seen as a valuable source of pharmacotherapy knowledge.

The proportion of drug interactions that were detected as DRPs is comparatively higher on ICUs than on SCUs. The detection of drug interactions in this area is facilitated and therefore enhanced by the availability of an electronic medical record that allows for an electronic pre-check before attending the ward rounds. Drug interactions were, not surprisingly, a prevalent problem among immunosuppressants. Anti-infectives were the drugs that were most affected by interventions, and the clinical pharmacists generally addressed the cessation of anti-infectives that were no longer indicated or that microorganisms were not susceptible to. Anti-infectives were commonly under- or overdosed. In this study, antiviral agents were especially common. Correct dosing is crucial, and multiple dose adaptations are common, especially if renal function is rapidly changing during the clinical course.

Clinical pharmacy services have also proved to be cost-effective[5,22], although the generalisability of economical studies is often limited due to their dependency on local settings and the availability of resources. Our study was not designed to determine the economical benefit of clinical pharmacy services. By determining the proportion of interventions associated with a cost reduction potential, we wanted to highlight the potential cost savings that result when DRPs are addressed. With 5% of interventions in our study resulting in cost savings, our proportion was rather small compared to another clinical pharmacy study, which reported a proportion of 32%.[26] However, our finding of a small cost-reduction potential is difficult to interpret because the four categories used were not meant to be a comprehensive list, but rather a sample choice.

The analysis of clinical significance shows that 75% of interventions were significant to some extent when self-assessed immediately at the time of documentation. We decided to use independent, blinded and random co-assessment of all performed interventions by all clinical pharmacists at two different time points to reduce assessment bias. Correlation coefficients show a fair to moderate agreement among different raters. Consistency among the same rater was moderate. We believe that the moderate level of agreement was due to new implementation of the concept of significance assessment and consequently a low level of familiarity. Furthermore, the specialisation of each clinical pharmacist in his or her clinic and the body of experience may influence objective assessment abilities. From our point of view, the issue of significance assessment warrants great attention and is important for our further

projected studies. Assessment of the value of services is a critically important step in health-service research, also with regard to potential reimbursement of additional services. This is not yet a matter of broad discussion in Austria, as there is a relative lack of systematic services. The documentation and rating process was described as time-consuming by all clinical pharmacists. The relative simplicity of the system, however, led to a notion of usability and acceptance.

There are several limitations to our clinical pharmacy services based on the way they are currently implemented. The frequency and continuity of ward round participation overall has to be increased, as once weekly ward attendance, for example, complicates the follow-up of addressed DRPs, suggested interventions and patient outcomes and the overall multidisciplinary team work. In particular, the continuous offering of clinical pharmacy services, even when the assigned clinical pharmacist who is normally responsible for the ward is on leave, has to be pursued. Although the clinical pharmacy service process is standardised, the individual characteristics depend on each clinical pharmacist and his or her performance, which is in turn influenced by knowledge and wealth of experience. Furthermore, the monitoring and documentation of patient outcomes, in addition to surrogate parameters, should be the focus of further clinical pharmacy work as a method of efficiency determination in our hospital.

Obstacles to the advancement of clinical pharmacy services and promotion of clinical pharmacy research may include the low staffing in hospital pharmacies. With 0.36 hospital pharmacists per 100 beds, Austria ranks third to last in Europe, compared to the European average of 0.93 hospital pharmacists per 100 beds.[27] The majority of Austrian hospitals (apart from intensive care units) still depend on paper-based medical records. The availability of an electronic patient record and the availability of labs, drug prescriptions and physician’s notes in real time would definitely facilitate the growth of clinical pharmacy services. The lack of any systematic clinical pharmacy education and the relative absence of a promising model for professional advancement in clinical pharmacy on a national level is probably the largest obstacle to overcome, as clinically active pharmacists often gather their knowledge and experience autodidactically within their area. Hence, standardisation is difficult to achieve. Furthermore, psychological barriers and a lack of confidence persist concerning the extension of pharmacists’ traditional roles and the shift from a reactive drug-focused role towards a more pro-active patient-oriented role with new responsibilities. Overcoming these barriers would allow us to better utilise the specific and unique resources and expertise of the pharmacists.

This study shows the beneficial impact of clinical pharmacists’ activities in a continually developing setting by describing DRPs and clinical pharmacists’ interventions and by

using surrogate measures (e.g., acceptance rate, significance), whereas, our critical analysis highlights the weaknesses of implemented services, documentation, and performance as well as the measurement of these services.

Conclusion

To our knowledge, this is the first published study to highlight the beneficial effect of clinical pharmacy services in the Austrian hospital setting. Although only half of interventions were immediately accepted, the proportion of significant interventions was high. Clinical pharmacy services will be one method of addressing evident DRPs in hospitalised patients in Austria. However, the professional advancement of clinical pharmacy services has to be pursued to increase the continuity and professionalism of services, the quality of clinical pharmacy research, and overall patient care.

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Competing interests

All authors declare that there are no financial or other conflicts of interests with respect to the contents of the article.

Contributorship statement

GS was responsible for study design, data collection, analysis, and interpretation, and drafting of the manuscript. GLW, IK, PP, SM, SS were responsible for data collection, analysis, and interpretation, and drafting of the manuscript. SZ was responsible for study design, statistical analysis of data and preparation of the mansucript. ED was responsible for study design, data interpretation and drafting of the manuscript. All authors read and approved the final manuscript.

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3.8 SEX-SPECIFIC DIFFERENCES IN METABOLIC CONTROL, CARDIO-VASCULAR RISK, AND INTERVENTIONS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Sex-Specific Differences in Metabolic Control, Cardiovascular Risk, and Interventions in Patients With Type 2 Diabetes Mellitus

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ABSTRACT

Background: Sex-specific differences appear particularly relevant in the management of type 2 diabetes mellitus (T2DM), with women experiencing greater increases in cardiovascular morbidity and mortality than do men.

Objective: The aim of this article was to investigate the influence of biological sex on clinical care and microvascular and macrovascular complications in patients with T2DM in a Central European university diabetes clinic.

Methods: In a cross-sectional study, sex-specific disparities in metabolic control, cardiovascular risk factors, and diabetic complications, as well as concomitant medication use and adherence to treatment recommendations, were evaluated in 350 consecutive patients who were comparable for age, diabetes duration, and body mass index. Study inclusion criteria included age ≤75 years, T2DM, a documented history of presence or absence of coronary heart disease (CHD), and informed consent. Patients were followed in the diabetes outpatient clinic between November 2007 and March 2008.

Results: Two hundred and one patients with T2DM met inclusion criteria (93 [46.3%] women, 108 [53.7%] men). Women with T2DM had higher mean (SE) systolic blood pressure (155.4 [22.5] vs 141.0 [19.8] mm Hg for men; $P < 0.001$) and total cholesterol (TC) (5.28 [1.34] vs 4.86 [1.29] mmol/L for men; $P < 0.05$), but a lower TC:HDL-C ratio (4.1 [1.19] vs 4.5 [1.2] for men; $P < 0.05$). Slightly more men (32.4%) than women (26.9%) reached the therapeutic goal of <7.0% for glycosylated hemoglobin. Women with shorter diabetes duration (<10 years) received oral antihyperglycemic therapy less frequently ($P < 0.05$). Women with longer disease duration had hypertension more frequently than did their male counterparts (100% vs 86.0%, respectively; $P < 0.01$). Despite a similar rate of CHD, men were twice as likely as women to have had coronary interventions (percutaneous transluminal coronary angioplasty/coronary artery bypass graft, 25.0% vs 12.9%, respectively; $P < 0.05$). Women with CHD also had a higher rate of cerebral ischemia than did men (27.6% vs 5.4%, respectively; $P < 0.05$) and received aspirin less frequently for secondary prevention ($P < 0.001$). Men had greater overall adherence to diabetes and cardiovascular risk guidelines than did women (66.4% vs 58.9%, respectively; $P < 0.01$).

Conclusions: In this study of diabetes clinic outpatients, women with T2DM had a worse cardiovascular risk profile and achieved therapeutic goals less frequently than did men. Treatment strategies should be improved in both sexes, but women with diabetes may be in need of more aggressive treatment, especially when cardio-

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vascular disease is present. (*Gend Med*. 2010;7:571–583) © 2010 Elsevier HS Journals, Inc.

Key words: type 2 diabetes mellitus, gender, diabetic complications, cardiovascular risk, blood pressure, lipid profile.

INTRODUCTION

Women with impaired glucose metabolism have a much greater increased risk of coronary artery disease than do men with impaired glucose control. Women aged ≥48 years and men aged ≥41 years have a 20% attributed increase in the 10-year risk of myocardial infarction (MI), cerebral ischemia, or death. These events occur ~15 years earlier in patients with diabetes than in those without diabetes.[1] In contrast to the pattern of reduced cardiovascular mortality in the nondiabetic population and in men with diabetes, the rate of cardiovascular death has increased in women with diabetes in the past decade. The reason for this difference is unknown, but it may, in part, be ascribed to poorer achievement of common treatment goals.[2–5]

Two studies in different countries have reported that women achieved therapeutic metabolic goals less frequently and also had a more adverse cardiovascular risk-factor profile. It is unclear whether the underlying causes are predominantly biological or psychosocial mechanisms. Thus, the observed sex disparities might be explained by more conservative prescribing of aspirin, lipid-lowering agents, and angiotensin-converting enzyme (ACE) inhibitors[2,5] or, alternatively, by differences in patient compliance.

To further describe sex-specific differences in cardiometabolic risk factors in patients with type 2 diabetes mellitus (T2DM), we studied sex disparities in blood pressure (BP), metabolic control (glycosylated hemoglobin [HbA_{1c}], fasting glucose, and lipid levels), diabetic complications, prescribed medication, and achievement of therapeutic goals at an outpatient department in a Central European university clinic.

PATIENTS AND METHODS

Consecutive patients with T2DM attending the diabetes outpatient clinic at the Medical University of Vienna, Austria, between November 2007 and March 2008, who fulfilled the inclusion criteria (age ≤75 years, T2DM, a documented history of presence or absence of coronary heart disease, and having given informed consent) were included in the study. The required sample size was calculated using standard formulae for sampling for a survey to produce percentage frequency rates of nominal data within conventionally acceptable error rates (margin of error 5%) and 95% CIs. Sampling was carried out using standard data collection.

A previously described questionnaire was used to obtain information about age, known duration of DM, height, weight, adherence to drug treatment, smoking habits, alcohol consumption, parental history of diabetes, BP, glycemic control, lipid profile, and parameters of liver and kidney function.[6] In addition, the presence of diabetic microvascular and macrovascular complications and a history of previous percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass surgery (CABG) were assessed. The information derived from the questionnaire was self-reported, but all data concerning medical history and clinical characteristics were immediately checked and completed using the clinical records. All patients maintained stable weight, and moderate physical activity and nutrition therapy were recommended for all.

Subgroup analyses were performed to compare the above-mentioned criteria, to determine whether primary prevention or secondary prevention therapy was indicated. Patients with *cardiovascular disease* (CVD), defined as ischemic heart disease, MI, and/or angina pectoris, were considered as requiring secondary prevention. The *metabolic syndrome* was defined according to World Health Organization criteria by the presence of DM/insulin resistance plus ≥2 of the following parameters: obesity (body mass index [BMI] ≥30 kg/m^2), hypertension (BP ≥140/90 mm Hg or use of antihypertensive drugs), and dyslipidemia (triglycerides [TG] ≥1.71 mmol/L and/or HDL-C <0.9 mmol/L for men and <1.03 mmol/L for women).[7]

To test the adherence of patient populations to evidence-based clinical prescribing recommendations, a medication assessment tool was employed.[6,8]

This 23-item instrument is based on the guidelines established by the Scottish Intercollegiate Guidelines Network (SIGN),[9] which is in accordance with the guidelines of the American Diabetes Association[10] and the European Society of Cardiology.[11] For every patient, each criterion of the item was judged as "applicable," "insufficient data" (lack of information), "not applicable" (criterion relevant for patient but patient's data did not meet the qualifying statement), or "justified nonadherence" (explanation for a patient's treatment not meeting a quality criterion). Adherence to the guideline recommendations was calculated as previously described in detail.[6,8] Levels of adherence were compared using the χ^2 test and $P < 0.05$ as the threshold for statistical significance. A Microsoft Access (Microsoft Corporation, Redmond, Washington) database was created, from which data from the specific subgroups were extracted. These data were statistically evaluated using SPSS 16.0 (SPSS Inc., Chicago, Illinois).

For metric and ordinal characteristics, the number of patients and arithmetic means with standard errors are given. For evaluation of statistically significant sex-dependent differences within the whole sample and specific subgroups, the Student *t* test, Welch *t* test, and Mann-Whitney *U* test were used, depending on the sample size and test criteria. For nominal characteristics, the number of patients and percentage are given. Statistically significant sex-dependent differences for the whole sample and specific subgroups were calculated using the χ^2 and Fisher exact tests. Statistical significance was determined at levels of $P < 0.05$, $P < 0.01$, and $P < 0.001$.

RESULTS

Metabolic Syndrome and Patient Profile

Of 350 consecutive patients with T2DM attending the diabetes outpatient clinic, 201 patients (93 [46.3%] women, 108 [53.7%] men) met the inclusion criteria. Eighty-six women (92.5%) were postmenopausal. Only one of these women was taking hormone replacement therapy (estradiol and norethisterone). The metabolic syndrome affected 68.7% of the entire study sample, with a significantly higher rate in women than in men (79.6% vs 59.3%, respectively; $P < 0.05$) (**Table I**). Women with T2DM had higher mean (SE) systolic BP (SBP) (155.4 [22.5] vs 141.0 [19.8] mm Hg for men; $P < 0.001$ by Student *t* test) and total cholesterol (TC) (5.28 [1.34] vs 4.86 [1.29] mmol/L for men; $P < 0.05$ by Student *t* test), but a lower TC:HDL-C ratio (4.1 [1.1] vs 4.5 [1.2] for men; $P < 0.05$ by Student *t* test). Slightly more men (32.4%) than women (26.9%) reached the therapeutic goal of HbA_{1c} <7.0%. In patients with mean (SE) HbA_{1c} ≥7% (67 women: 8.6% [1.8%] vs 71 men: 8.5% [1.4%]), both SBP (159.3 [21.8] vs 140.6 [19.0] mm Hg; $P < 0.001$ by Student *t* test) and diastolic BP (88.4 [12.9] vs 83.7 [12.9] mm Hg; $P < 0.05$ by Student *t* test) were significantly higher in women than in men, respectively. Women with longer disease duration had hypertension more frequently than did their male counterparts (100% vs 86.0%, respectively; $P < 0.01$ by Student *t* test). In women compared with men, significantly higher SBP levels were observed in most subgroups, including the overweight (152.7 [21.2] vs 135.8 [23.7] mm Hg; $P < 0.01$ by Student *t* test) and obese (156.9 [23.9] vs 143.2 [17.1] mm Hg; $P < 0.001$ by Welch *t* test) patients. Even in patients without hypertension, women had notably higher SBP values than did men (135.3 [7.5] vs 127.2 [13.1] mm Hg, respectively; $P < 0.05$) by Mann-Whitney *U* test.

TC was also significantly higher in women than in men (**Table I**), including the subgroup (87 women, 97 men) of hypertensive patients (204.3 [52.6] vs 188.1 [50.1] mg/dL; $P < 0.001$ by Student *t* test). In the group requiring secondary prevention, fewer women (n = 29) reached the LDL-C goal and, consistently, they had higher mean LDL-C levels than did men (n = 37) (2.94 [1.11] vs 2.37 [0.93] mmol/L, respectively; $P < 0.05$ by Student *t* test). In all subgroups, women were characterized by higher HDL-C levels, resulting in a lower mean TC:HDL-C ratio compared with men. In the subgroups of patients with diabetes duration <10 years or a BMI ≥30 kg/m^2, TG levels were significantly lower in women than in men ($P < 0.05$ by Student *t* test).

Diabetic Complications

Some differences in diabetic macrovascular complications, but no differences in diabetic microvas-

Table I. Clinical characteristics and cardiovascular risk of patients attending a diabetes outpatient clinic. Data are shown as mean (SE), unless otherwise indicated.

Characteristic	Women (n = 93)	Men (n = 108)
Age, y	60.5 (8.6)	58.2 (9.6)
Geriatric (>65 y), %	37.6	35.2
Age at diagnosis, y	50.5 (9.4)	49.9 (9.5)
Duration of diabetes, y	10.1 (7.7)	8.4 (7.0)
Smoker, no. (%)	14 (15.1)*	30 (27.8)
Abstain from alcohol, no. (%)	72 (77.4)†	58 (53.7)
Noncompliant to medication, no. (%)	12 (12.9)	14 (13.0)
Family history of CVD, no. (%)	40 (43.0)	36 (33.3)
Metabolic syndrome, no. (%)	74 (79.6)‡	64 (59.3)
Fasting blood glucose, mg/dL	140.8 (65.0)	138.4 (47.1)
HbA_{1c} <7.0%, no. (%)	25 (26.9)	35 (32.4)
HbA_{1c}, %	8.0 (1.8)	7.8 (1.6)
Hypertension, no. (%)	87 (93.5)	97 (89.9)
SBP, mm Hg	155.4 (22.5)§	141.0 (19.8)
DBP, mm Hg	86.5 (12.2)	83.3 (12.5)
BMI, kg/m^2	31.8 (6.2)	31.6 (5.6)
Overweight, no. (%)	36 (38.7)	31 (28.7)
Obese, no. (%)	50 (53.8)	68 (63.0)
Hyperlipidemia, no. (%)	87 (93.6)	93 (86.1)
TC, mmol/L	5.28 (1.34)‡	4.86 (1.29)
LDL-C, mmol/L	3.00 (1.11)	2.73 (1.08)
HDL-C, mmol/L	1.36 (0.36)§	1.13 (0.33)
TC:HDL-C ratio	4.1 (1.1)‡	4.5 (1.2)
Triglycerides, mmol/L	2.34 (1.72)	2.44 (1.40)
Secondary prevention, no. (%)	29 (31.2)	37 (34.3)
FHS risk score, %	24.2 (0.8)	26.0 (0.7)
FHS risk score for primary prevention and age >60 y, %	26.5 (2.3)‡‖	29.9 (0.8)

CVD = cardiovascular disease; HbA_{1c} = glycosylated hemoglobin; SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index; TC = total cholesterol; FHS = Framingham Heart Study.
*$P < 0.05$, by χ^2 test.
†$P < 0.001$, by χ^2 test.
‡$P < 0.05$, by Student *t* test.
§$P < 0.001$, by Student *t* test.
‖$P < 0.01$, by χ^2 test.

cular complications (neuropathy, nephropathy, or retinopathy), were observed between women and men (**Figures 1** and **2**). Despite a similar rate of coronary heart disease, men were twice as likely to have had coronary interventions as were women (PTCA/CABG: 25.0% vs 12.9%, respectively; $P < 0.05$ by χ^2 test) (**Figure 1A**). In the subgroup requiring secondary prevention, women featured a similar rate of angina pectoris compared with men (65.5% vs 56.8%, respectively), but underwent PTCA/CABG less frequently (41.4% vs 73.0%; $P < 0.01$ by χ^2 test). Concerning macrovascular

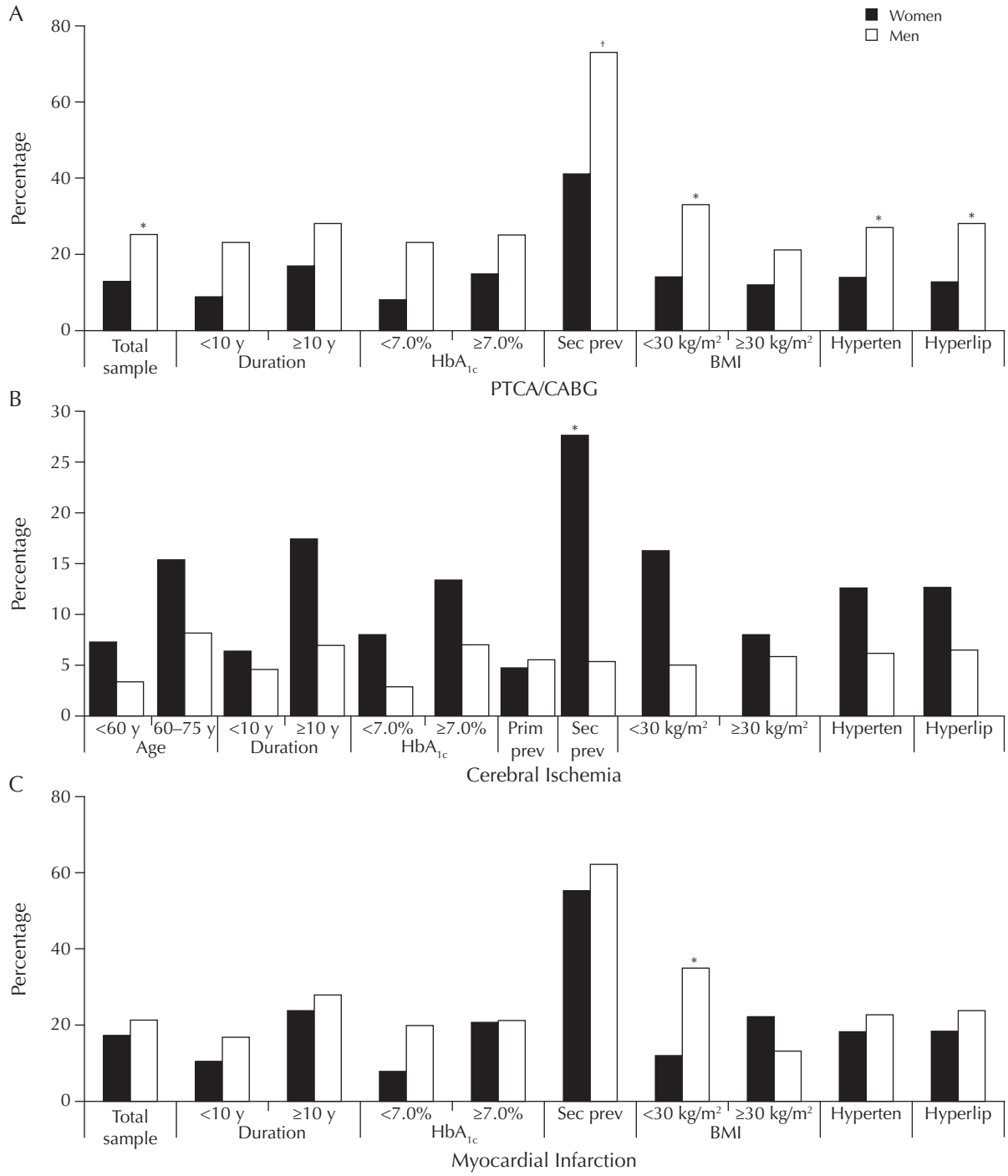

Figure 1. (A) The percentage of women and men with percutaneous transluminal coronary angioplasty/coronary artery bypass graft (PTCA/CABG) is shown for the total sample and in relation to duration of type 2 diabetes mellitus, glycosylated hemoglobin (HbA_{1c}), secondary prevention (sec prev), body mass index (BMI), and for hypertensive (hyperten) and hyperlipidemic (hyperlip) patients. (B) Percentage of women and men with cerebral ischemia is presented for the total sample and all subgroups. Women experienced cerebral ischemia more often than did men, and this difference became significant for secondary prevention. (C) Men had myocardial infarction more frequently than did women; the difference became significant with BMI <30 kg/m^2. This tendency was reversed in the subgroup of obese patients. Symbols indicate significant sex differences within a subgroup: $^*P < 0.05$ and $^\dagger P < 0.01$.

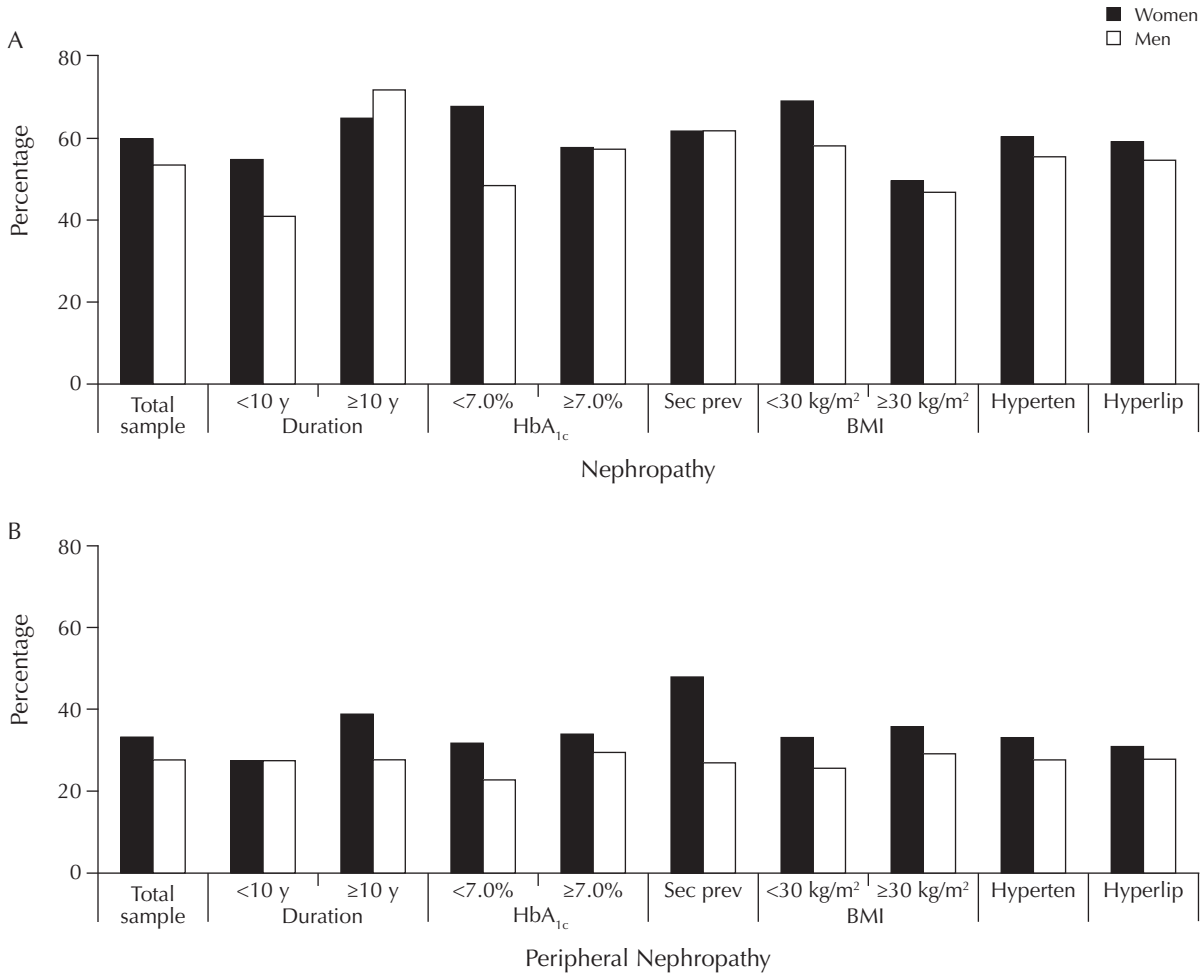

Figure 2. (A) The percentage of women and men with nephropathy is shown for the total sample and for subgroups. There was a tendency toward more women than men having nephropathy, but no significant sex differences were observed. (B) Women experienced peripheral neuropathy more often than did men; however, the differences were not statistically significant. HbA_{1c} = glycosylated hemoglobin; sec prev = secondary prevention; BMI = body mass index; hyperten = hypertensive; hyperlip = hyperlipidemic.

(continued)

complications, significant sex differences were observed in the prevalence of cerebral ischemia (**Figure 1B**) and MI (**Figure 1C**). The rate of cerebral ischemia was markedly higher in women than in men with CVD (secondary prevention group) (27.6% vs 4.7%, respectively; $P < 0.05$ by Fisher exact test).

Pharmacotherapy

For patients with diabetes, most diabetes association guidelines recommend an HbA_{1c} goal of <7.0%, with the exception of an optimal goal of <6.5% if it can be easily and safely achieved. In the present study, HbA_{1c} <6.5% was achieved with diet in patients with short (<10 years) disease duration only (6.4% of women vs 1.5% of men; $P < 0.05$ by χ^2 test). Women with shorter diabetes duration (<10 years) received oral antihyperglycemic therapy less frequently ($P < 0.05$ by χ^2 test). Fewer women were treated with insulin alone (25.8% vs 27.8%; P = NS by χ^2 test), but more women than men tended to take insulin in addition to an oral antidiabetic drug (OAD) (35.5% vs 23.1%; P = NS by χ^2 test). This latter sex difference was more evident in the subgroup of hypertensive patients (37.9% of women vs 23.7% of men; $P < 0.05$ by χ^2 test). A

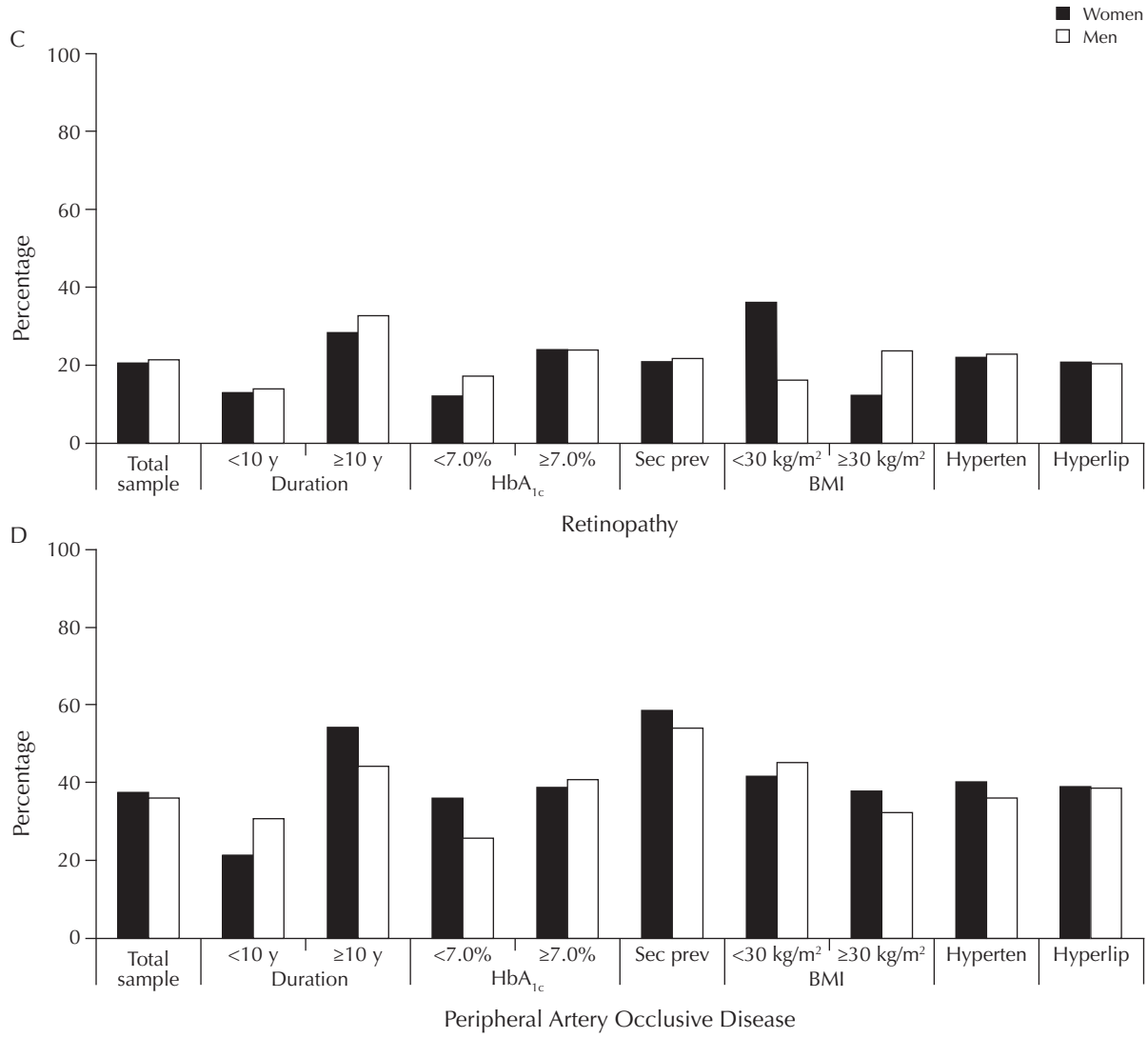

Figure 2 (continued). (C) No significant sex differences were found between women and men with retinopathy. (D) No significant sex differences were found between women and men with peripheral artery occlusive disease.

total of 16.7% of female patients and 22.8% of male patients were treated with ≥1 OAD; P = NS by χ^2 test). No significant sex differences were found in the percentage of patients taking OADs (60% were taking metformin, 37% sulfonylureas, 13% glitazones, 4% gliptins, and 3% both α-glucosidase inhibitors and glinides). Overall, significantly fewer women than men achieved BP values ≤130/80 mm Hg (13.3% vs 36.3%, respectively; $P < 0.001$ by χ^2 test) despite a similar rate of antihypertensive therapy compared with men (86.4% vs 84.7%; P = NS). In the subgroup of patients requiring primary prevention, even fewer patients, especially women, reached the therapeutic target (8.5% women vs 26.1% men; $P < 0.05$ by χ^2 test). In most cases, a combination of antihypertensive drugs was administered, including diuretics, ACE inhibitors, β-adrenoceptor blockers, angiotensin II type 1 receptor blockers, calcium antagonists, α1-blockers, and α2-agonists.

The overall adherence to prescribing guideline criteria (SIGN) was significantly lower in women than in men (59.8% vs 66.4%, respectively; $P < 0.01$ by χ^2 test) (**Table II**), especially in the subgroup requiring secondary prevention (60.0% women vs 74.0% men; $P < 0.001$ by χ^2 test). More men than women received aspirin for secondary

Table II. Adherence to selected criteria of the Scottish Intercollegiate Guidelines Network in primary prevention and secondary prevention, using a medication assessment tool (MAT).*

	Adherence				
	Women		Men		
MAT Criteria	Yes/ Applicable	% (95% CI)	Yes/ Applicable	% (95% CI)	*P*
Patient receives aspirin (75–150 mg/d)	36/86	42 (32–52)	51/90	57 (46–66)	<0.052
Patient with TC ≥5.16 mmol/L receives statin	62/85	72 (63–81)	66/97	68 (58–77)	0.52
Patient receiving statin achieved re-test TC <5.16 mmol/L	33/58	57 (44–69)	43/63	68 (56–79)	0.26
Patient receiving antihypertension therapy	76/88	86 (78–92)	83/98	85 (76–91)	0.84
Patient receiving antihypertension therapy achieved BP ≤130/80 mm Hg	10/75	13 (7–23)	29/80	36 (27–47)	<0.01
Patient appropriately prescribed ACE inhibitor†	45/71	63 (52–74)	50/79	63 (52–73)	1.00
Overweight patient in need of OAD is prescribed metformin	55/58	95 (85–99)	58/63	92 (82–97)	0.72
Overall adherence (1466 criteria)	401/681	59 (55–63)	521/785	66 (63–70)	<0.01

TC = total cholesterol; BP = blood pressure; ACE = angiotensin-converting enzyme; OAD = oral antidiabetic drug.

*Adherence to the guideline recommendations in the patient group was calculated for each criterion and for the MAT overall by summing the "yes" responses to the application of the standard, expressed as the percentage adherence to the standard, using the number of applicable criteria as the denominator.

†Patient with no apparent contraindication/intolerance to an ACE inhibitor who falls into any of the following categories: postmyocardial infarction; left ventricular systolic dysfunction; age >55 years with at least one other known risk factor (smoking, hypertension, TC >5.16 mmol/L or HDL-C ≤1.03 mmol/L, microalbuminuria).

prevention (88.6% men vs 51.9% women; $P < 0.001$ by χ^2 test), whereas no significant sex differences were observed in those without CVD (primary prevention group). If aspirin was contraindicated or not tolerated, men tended to receive clopidogrel more frequently than did women (35.7% vs 16.7%, respectively; *P* = NS by Fisher exact test) and achieved target cholesterol levels more often while taking statins (68.3% vs 56.9%; *P* = NS by χ^2 test).

DISCUSSION

Risk Profile

In contrast to previous analyses, no significant sex differences in age or diabetes duration were observed in our study sample, rendering women and men comparable for the evaluation of cardiovascular risk and complications. There also were no significant sex differences in glycemic control, which is consistent with another study in patients without CVD (primary prevention),[12] but in contrast to previous findings in patients requiring secondary prevention.[2] Overall, only about one third of the patients reached the therapeutic goal of HbA_{1c} <7.0% at our tertiary care center; however, we observed that fewer women than men reached this goal.

We found female gender to be associated with higher SBP levels despite a similar rate of antihypertensive treatment. Interestingly, women achieved the BP treatment goal of <130/80 mm Hg less frequently than did men, which is, in part, consistent with previous reports.[12,13] Of note, women with good metabolic control did not differ from their male counterparts regarding high BP, suggesting that worsening of metabolic control is associated with hypertension, particularly in women. Chu et al,[14] however, reported an association between HbA_{1c} and SBP only in males with diabetes, thus arguing against a prominent gender effect. Causally, various factors might contribute to sex/gender disparities in BP regulation, including not only

sex-related differences in renin–angiotensin system activity, salt sensitivity, and menopause-associated alterations in circulating sex hormone levels, but also gender gaps in hypertension awareness and risk-factor management.[15–19] Furthermore, differences in atherogenic risk-factor clustering with more unfavorable changes in coagulation, endothelial function, and inflammatory processes in women have already been described very early in the development of T2DM, suggesting that "the clock starts ticking earlier" in women.[20,21]

The United Kingdom Prospective Diabetes Study found that a decrease in SBP of 10 mm Hg was associated with an 11% risk reduction of MI and a 13% risk reduction of macrovascular disease.[22] These data underscore the clinical implications of a 14-mm Hg sex difference in mean SBP in our study, because even moderate increases in BP markedly increase the risk of CVD in women with diabetes.

Premenopausal women usually have a less atherogenic lipid profile, which deteriorates after menopause. In accordance with other studies,[2,3,23] we found both TC and HDL-C to be increased in women compared with men. Of note, in our study, distinct sex differences in lipid profile were observed in the subgroup requiring secondary prevention. Women requiring secondary prevention more often failed to achieve their sex-specific treatment goal in HDL-C (40 mg/dL in this study), which was associated with higher LDL-C levels. Consistent with previous results,[12] this finding might be attributable to more conservative use of antihyperlipidemic therapy. In primary prevention in our study, LDL-C tended to be increased in women and has been found to be significantly higher in other studies as well.[2,24] In fact, the age-related loss of female sex hormones is associated with a more pronounced disruption of lipid homeostasis in women, which may be further aggravated by impaired glucose metabolism with concomitant subclinical inflammation and increased oxidative stress.[25,26]

Even slight sex differences in LDL-C might be of relevance, as an increase of 1 mg/dL increases cardiovascular mortality risk by 4%.[27] Although TG levels were not significantly different between the sexes in our study, hypertriglyceridemia appears to represent a greater hazard for women.[28] However, the importance of serum TG as an independent predictor of CVD remains controversial.[29] A recent analysis reported that the combination of fenofibrate with a statin had some gender-dimorphic effects, with benefit in males and potential harm in females.[30]

In the present study, men had a more adverse cardiovascular risk-factor profile in relation to cigarette smoking and alcohol consumption. Nicotine abuse has been associated with a more dramatic increase in the risk of MI in women compared with men.[31]

Diabetic Complications

We did not find significant sex differences regarding microvascular disease or peripheral vascular disease. Although female gender is associated with relative protection with regard to the development and progression of nondiabetic kidney disease, at least in premenopausal women, the current literature is inconclusive as to the presence of diabetes and sex differences in diabetic nephropathy, retinopathy, or neuropathy.[32]

As men were more frequent smokers, other atherogenic risk factors (eg, lipid disorders or changes in oxidative stress) seemed to mainly contribute to peripheral arterial disease (PAD) in women with diabetes. Indeed, except for smoking, age and diabetes have been found to be the most important predictors of PAD, which has also been related to increased mortality in both women and men.[33] In the present study, PAD was associated with CVD in both sexes, in agreement with other published findings.[34] In those findings, the condition showing the strongest association with vascular disease in females was diabetes, but in males it was smoking.

In nondiabetic subjects, CVD tends to become manifest 10 years earlier in men than in women.[1,5] The presence of diabetes, however, seems to limit sex differences and increases the prevalence of CVD and MI at all ages—more prominently in women than in men.[35] In past years, CVD-associated mortality rates have decreased in men both with and without diabetes, irrespective of glucose tolerance, but have remained unchanged in women who have diabetes. Although no significant sex differ-

ence in CVD or MI was observed in our study, women tended to show a higher frequency of CVD in some subgroups (age <60 years, good metabolic control, or secondary prevention). Despite this fact, women notably were less likely to have a history of PTCA or CABG. This finding also applied to the subgroups. Similar results with regard to risk-factor screening, cardiac interventions, and pharmacotherapy have been found in other studies in different populations, but without differentiation between individuals with or without diabetes.[36] Such inequality in treatment strategies might be ascribed, in part, to atypical symptoms and false stress electrocardiogram test results, which are more common in women with CVD. These findings suggest that it might be worthwhile to increase physicians' awareness about sex differences in cardiovascular risk.

In the present study, the difference in MI rates between women and men with diabetes was 18%, and therefore much lower than the 45% reported for the Austrian population in 2007.[37] This discrepancy might be explained by the exclusion of nondiabetic subjects in our study and is consistent with the data reported by Mulnier et al.[35] The observed sex difference in MI rates was smaller in the subgroups with a diabetes duration >10 years and HbA_{1c} ≥7.0%, suggesting that longer duration of the disease and worse metabolic control may be a greater hazard in women.[36]

The prevalence of cerebral ischemia is, in general, similar between the sexes, although the relative risk has been reported to be increased in women with diabetes, particularly at younger ages.[23] In our study, there was a nonsignificant trend for women to have cerebral ischemia in the total cohort as well as in all subgroups, but this was statistically significant in women with CVD (secondary prevention group).

Pharmacotherapy

Women with diabetes, based on these findings and those in other studies, could a priori have a more adverse diabetes-associated cardiovascular risk profile or be subject to differences in prescribing and/or pharmacologic responsiveness. In the present study, we also evaluated medication prescribed in terms of the level of prescribing adherence to evidence-based treatment recommendations. In contrast to other studies reporting on lower frequency of statin use in women,[38] we found no significant sex differences, although there was a trend for target cholesterol to be achieved more often in men. BP targets were achieved in <25% of patients and this was much more of a problem in women. Similar findings have been reported in other studies.[2,12,24] Regarding secondary prevention, women were less likely to receive aspirin ($P < 0.05$) and perhaps ACE inhibitors (nonsignificant trend). Overall, women had lower adherence to pharmacotherapy guidelines, especially in respect to attention to secondary prevention decisions.

Regarding therapeutic antihyperglycemic strategy, we found that, compared with men, women with shorter disease duration more often received only lifestyle therapy. Furthermore, there was a trend for women to be treated more frequently with a combination of oral antihyperglycemic therapy and insulin than were men; this difference became significant in the presence of hypertension, which is in line with previous findings.[12] Despite similar glycemic control in both sexes, we cannot determine whether women more readily accepted insulin injections, were prescribed insulin more often, or more frequently needed insulin to control their metabolism. In any case, careful consideration of diabetic treatment is required—epidemiologic studies have found that metformin is associated with a lower risk for cancer and that exogenous insulin may be associated with an increased risk, although these associations are complex and may be confounded by biological diabetes/obesity-related changes.[39,40] In particular, insulin therapy has been related to increased risk of breast cancer, which could be explained by activation of insulin-like growth factor signaling pathways and increased signaling through the estrogen receptor. On the other hand, women with diabetes and breast cancer who were taking metformin therapy have experienced better chemotherapy response rates, possibly due to reduction of growth factor signaling and induction of cell cycle arrest.[40]

Women with diabetes are at high risk for cardiovascular events, and therefore evidence-based guidelines recommend aspirin for CVD prevention in women.[41] In our study, the use of aspirin was low but comparable between women and men without CVD (primary prevention group), but it was significantly less common in women requiring secondary prevention. This finding is corroborated by previous reports in patients requiring primary or secondary prevention.[38] The benefits of aspirin use in secondary prevention to reduce cardiovascular events have previously been reported in both sexes[42]; however, they are less clear for women who require primary prevention. Evidence supports the superiority of aspirin effects on coagulation and MI risk reduction in men, whereas the preventive effects on cerebral ischemia appear to be higher in women.[43] A recent longitudinal observational study indicated some beneficial effects of aspirin, reporting that its use was associated with a 50% reduction in cardiovascular and all-cause mortality in T2DM in a primary prevention setting.[44] In addition, aspirin use was independently associated with reduction of all-cause mortality in men and in both sexes aged >65 years. On the other hand, a recently published record linkage study revealed increased mortality with aspirin use in patients with diabetes who did not have CVD.[45] Thus, for the time being, aspirin is of uncertain value for primary prevention, especially in women.

Adherence to all recommendations was similar in both sexes without CVD (primary prevention group), but among patients with CVD (secondary prevention group), prescribing was less adherent to guidelines in women than in men, leading to overall lower guideline adherence in women.

CONCLUSIONS

Our data suggest that women with T2DM have a more adverse risk profile, reduced pharmacotherapy, and fewer cardiovascular interventions compared with their male counterparts, despite a comparable rate of both microvascular and macrovascular diabetic complications. Although our findings indicate that clinical recommendations should be followed more carefully in both sexes, they point to the need for more aggressive treatment, in particular for women with T2DM, and they further outline the importance of sex- and gender-specific medical assessment and intervention.

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3.9 A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, PROSPECTIVE TRIAL TO EVALUATE THE EFFECT OF VILDAGLIPTIN IN NEW-ONSET DIABETES MELLITUS AFTER KIDNEY TRANSPLANTATION

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TRIALS

STUDY PROTOCOL Open Access

A randomized, placebo-controlled, double-blind, prospective trial to evaluate the effect of vildagliptin in new-onset diabetes mellitus after kidney transplantation

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Abstract

Background: New-onset diabetes mellitus after transplantation (NODAT), a frequent and serious complication after transplantation, is associated with decreased graft and patient survival. Currently, it is diagnosed and treated primarily according to existing guidelines for type II diabetes. To date, only a few trials have studied antidiabetic drugs in patients with NODAT. Vildagliptin is a novel dipeptidyl peptidase-4 (DPP-4) inhibitor that improves pancreatic islet function by enhancing both α- and β-cell responsiveness to increased blood glucose. Experimental data show potential protective effects of DPP-4 inhibitors on islet function after exogenous stress stimuli including immunosuppressants. Therefore, the therapy of NODAT with this class of compounds seems attractive. At present, vildagliptin is used to treat type II diabetes as monotherapy or in combination with other antidiabetic drugs, since that it efficiently decreases glycated hemoglobin (HbA1c) values. Additionally, vildagliptin has been shown to be safe in patients with moderately impaired kidney function. This study will evaluate the safety and efficacy of vildagliptin monotherapy in renal transplant recipients with recently diagnosed NODAT.

Methods/Design: This study is a randomized, placebo-controlled, double-blind, prospective phase II trial. Using the results of routinely performed oral glucose tolerance tests (OGTT) in stable renal transplant patients at our center, we will recruit patients without a history of diabetes and a 2 h glucose value surpassing 200 mg/dl (11.1 mmol/l). They are randomized to receive either 50 mg vildagliptin or placebo once daily. A total of 32 patients with newly diagnosed NODAT will be included. The primary endpoint is the difference in the 2 h glucose value between baseline and the repeated OGTT performed 3 months after treatment start, compared between the vildagliptin- and the placebo-group. Secondary endpoints include changes in HbA1c and fasting plasma glucose (FPG). The safety of vildagliptin in renal transplant patients will be assessed by the number of symptomatic hypoglycemic episodes (glucose <72 mg/dl or 4 mmol/l), the number of adverse events, and possible medication-associated side-effects.

Discussion: NODAT is a severe complication after kidney transplantation. Few trials have assessed the safety and efficacy of antidiabetic drugs for these patients. The purpose of this study is to assess the safety and efficacy of vildagliptin in renal transplant patients with NODAT.

Trial Registration: ClinicalTrials.gov NCT00980356.

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Background

New-onset diabetes after transplantation (NODAT), also called post-transplant diabetes mellitus (PTDM), remains a severe metabolic complication in patients after organ transplantation. NODAT leads to an increased incidence of cardiovascular disease (CVD) and consequently reduced graft and patient survival [1,2]. In non-transplanted patients, diabetes mellitus (DM) has been identified as a major independent risk factor for CVD [3]. CVD includes atherosclerotic coronary heart disease, heart failure, myocardial infarction, stroke and peripheral vascular disease [4]. Patients with CVD and DM suffer from a worse prognosis for survival than patients without these conditions. In organ transplant recipients, mortality due to CVD remains the most common cause of mortality [1]. In renal transplant recipients NODAT is associated not only with increased cardiovascular morbidity and mortality, but also with impaired long-term graft function and increased risk of graft loss [4,5]. Hence, NODAT needs medical attention and treatment and therefore clinical trials with antidiabetic drugs for the therapy of NODAT remain of high interest.

The reported incidence of NODAT varies between 2 and 53%. This high variability is due the lack of a standard definition in clinical studies [6]. Some reports define NODAT by the requirement for exogenous insulin without further examinations, such as an oral glucose tolerance test (OGTT). Currently, the diagnosis of NODAT is based on guidelines for type II diabetes (T2DM) from the American Diabetes Association (ADA), which include impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) as diagnostic parameters [7]. Development of NODAT has modifiable (e.g. body weight, immunosuppressive drug therapy) and non-modifiable (e.g. age, ethnicity, polycystic kidney disease) risk factors [8]. The role of immunosuppressants (e.g. corticosteroids or calcineurin inhibitors (CNIs)) in the clinical course of diabetes is clearly established, and disease development is probably mediated by an increased beta-cell apoptosis and impaired insulin sensitivity [4,9]. The incidence of steroid-induced diabetes is related to the treatment duration and the dose of corticosteroids [10]. Some authors propose steroid reduction or complete withdrawal as a means to reduce the incidence of NODAT, but steroid withdraw has been associated with an increased risk for graft rejection [4].

Most centers currently follow so-called "step-up" strategies established for the treatment of T2DM starting with non-pharmacological therapies and life-style modification, subsequently followed by oral antidiabetic therapy and finally insulin [4]. Pharmacodynamic and pharmacokinetic drug properties may be altered in patients with renal impairment and new drugs have to be studied regarding safety and effectiveness in patients with impaired renal function. In renal transplant patients, drugs are at additional risk of interacting with immunosuppressive agents as well as with other co-medications [11].

Vildagliptin, a dipeptidyl peptidase IV (DPP-4) inhibitor that, belongs to a new class of oral antidiabetic drugs [12]. DPP-4 inhibitors enhance the activity of incretin hormones in response to a glucose load by blocking the hormones responsible for incretin degradation [13]. Incretins are gut hormones that are secreted from enteroendocrine cells into the blood within minutes after food intake. The incretin hormones *glucose-dependent insulinotropic polypeptide* (GIP) and *glucagon-like peptide-1* (GLP-1) have been reported to exert numerous metabolic effects contributing to the regulation of blood glucose levels [14]. Vildagliptin decreases glycated hemoglobin (HbA1c) in patients with T2DM when given as monotherapy or combined with metformin or glitazones [15-19]. Furthermore, vildagliptin has been shown to be safe in patients with mild to moderately impaired kidney function [20].

This study aims to assess the safety and efficacy of vildagliptin in patients with NODAT.

Methods/Design

Hypothesis

Vildagliptin improves glucose metabolism in patients suffering from newly diagnosed NODAT.

Objectives

This 16-week trial aims to evaluate the safety and efficacy of vildagliptin in stable renal transplant recipients with newly diagnosed NODAT.

The primary outcome parameter will be the difference in 2 h glucose levels obtained during an OGTT between stable renal transplant patients receiving vildagliptin or placebo after 3 months treatment.

The secondary study outcomes will include change in HbA1c and fasting plasma glucose after three months of treatment, the safety of vildagliptin in renal transplant recipients regarding kidney function, liver function and the potential for drug-drug interactions with immunosuppressive medications (Intention to treat (ITT) analysis), the safety of vildagliptin for glycemic control in patients with impaired kidney function, and the long-lasting effects of vildagliptin on β-cell function one month after treatment stop.

Study design and setting

This study is a prospective, single-center, double-blind, randomized, placebo-controlled, phase II trial in patients

with newly diagnosed NODAT. Patient recruitment and follow-up are conducted at the Medical University of Vienna. The study recruitment has started in February 2010.

Study setting

Patients with a stable kidney allograft, more than 6 months after transplantation, without a history of T1DM or T2DM routinely undergo an OGTT at our outpatient department. All patients with a pathological OGTT (serum glucose levels ≥ 200 mg/d (11.1 mmol/L)) are classified as patients suffering from NODAT. 32 Patients eligible for the study are invited to the outpatient clinic and therapeutic options are discussed. Patients who are willing to take part in the study and have signed their informed consent form are randomized in a 1:1 ratio into study arm A (vildagliptin) or study arm B (placebo). The detailed study flow chart and an overview of study procedures are depicted in Figure 1 and 2, respectively.

Study intervention

Patients will receive their study medication (vildagliptin or placebo) with instructions to take it once daily 30 minutes before breakfast. Patients will receive continuous counseling on lifestyle modification (e.g. diet, physical exercise) until the end of the study. Participants in the study have to be on a triple immunosuppressive therapy consisting of a CNI (tacrolimus or cyclosporine A), prednisolone, and mycophenolic acid, either as the prodrug (mycophenolate mofetil) or as delayed-release mycophenolic sodium. All changes in concomitant medication will be recorded. Patients will have a visit at our outpatient clinic during weeks 2, 4, 8, 12, and 16 (Figure 2). At each visit, blood samples are collected to determine blood parameters including complete blood count, serum chemistry, C-reactive protein, creatinine, calculated glomerular filtration rate (cGFR) using the "Modification of Diet in Renal Disease" (MDRD) formula, potassium, sodium, phosphate, chloride, calcium, total bilirubin, ALAT, ASAT, total protein, LDL, HDL, triglycerides. Patients with a cGFR between 30 and 50 mL/min./1.73 m^2 will have weekly blood checks comprising creatinine and ASAT/ALAT during the first month for safety reasons. Each patient is expected to parcipate in the study for 120 days. Unblinding of the study will be performed after the end of the complete trial. Patients whose OGTT did not improve 4 months after study start will be treated by the physicians of our outpatient clinic according to the guidelines.

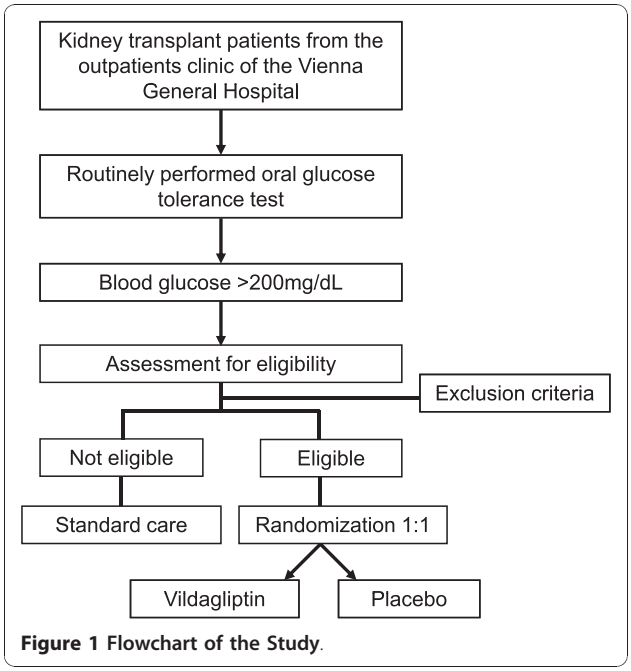

Figure 1 Flowchart of the Study.

Informed consent

The investigator explains the nature of the study, its purpose, procedures, expected duration, and the potential risks and benefits associated with study participation along with any discomfort that may be expected. Patients will be informed about the strict confidentiality of their subject data, but also that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. Each subject will be informed that study participation is voluntary and withdrawal is possible at any time during the study period. Withdrawal will not prejudice the subject's subsequent care. Subjects are given time to read and understand the statements before signing consent and dating the document. Subjects receive a copy of the signed written statement and the original copy of the informed consent is stored in the investigator study files. No subject is entered into the study until informed consent has been obtained.

Safety assessments

Safety assessments will include the monitoring and recording of all adverse events (AE), including serious adverse events (SAE). An AE is any undesirable experience associated with the use of a medical product in a patient. An SAE is defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity. The most probable AEs caused by vildagliptin are consistent with the known side-effects, which are the cause of the previously described exclusion criteria (table 1), such as wound healing disorders or severe renal impairment. The

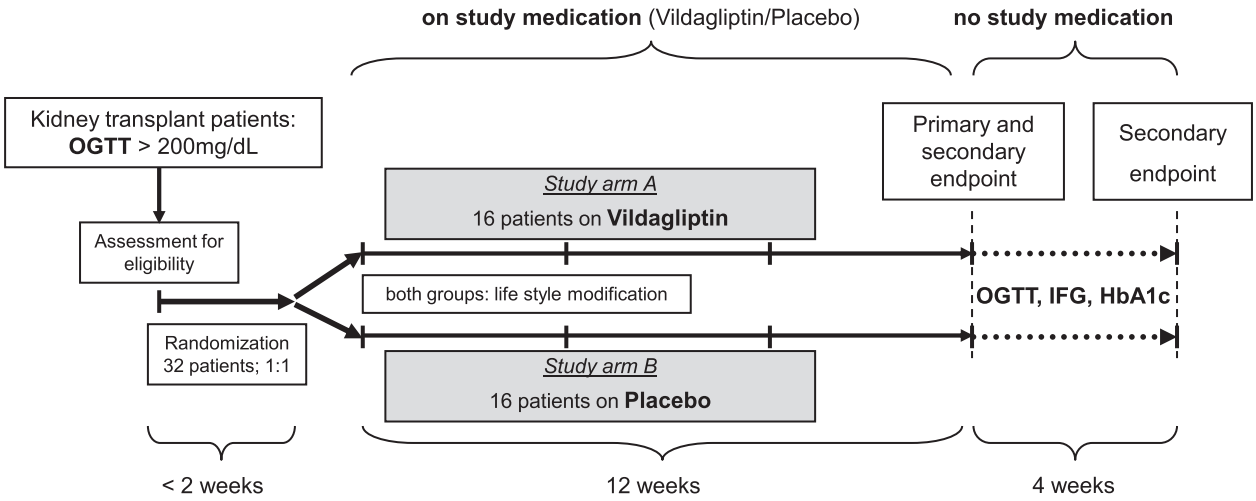

Figure 2 Study procedures. OGTT, oral glucose tolerance test.

interruption or premature discontinuation of the study drugs might be triggered by AE, diagnostic or therapeutic procedures, abnormal laboratory values (e.g. basal ASAT/ALAT 50% elevated or more, serum creatinine 25% elevated or more) and for administrative reasons, in particular the withdrawal of the patient's consent.

Statistical analysis plan

The statistical analysis plan (SAP) provides full details regarding the analyses, the data display, and the algorithms to be used for data derivations. The SAP includes the definition of major and minor protocol deviations which will be identified by medically trained staff before the study closure. Safety and tolerability are analyzed descriptively. Safety analysis is performed on the ITT population.

The study sample will consist of 32 patients with newly diagnosed NODAT. For the primary endpoint analysis, we will assess the differences between treatment and control group in the 2 h glucose value obtained during an OGTT (75 g glucose) after 3 months of vildagliptin or placebo treatment. Based on a two-sided testing and a standard deviation of 20% in relative changes of 2 h OGTT glucose values, $\alpha = 0.05$ and ß = 0.2, a sample size of 16 patients per group can detect a minimal difference in serum glucose level of 20 mg/dl at the 2 hour time point of the OGTT when comparing baseline levels to levels on day 90. The "Last observation carried forward" (LOCF) method will be used for missing data.

Two different analysis sets are defined for safety and efficacy, respectively. The efficacy of vildagliptin is assessed in all subjects who received the study drug (at least one dose) and did not violate the protocol in a way that might affect the evaluation of the effect of the study drug(s) on the primary objective, i.e. without major protocol violations. The per-protocol set is employed in the analysis of efficacy variables. A sensitivity analysis will be performed for efficacy with the ITT population.

The safety analysis set includes subjects who were randomized and received at least one dose of the study drug (modified intention to treat). The safety set is employed in the analysis of tolerability and safety variables. Statistical analysis is performed with SPSS.

Approval of the ethics committee and the regulatory authority

The trial is performed in accordance with the Declaration of Helsinki as well as the Austrian drug law. It subscribes to the principles outlined in the most recent version of the International Conference on Harmonization on Good Clinical. Approvals were obtained from the ethics committee of the Medical University of Vienna and the Vienna General Hospital (Reference Number 645/2009) and from the Austrian regulatory authority (Federal Office for Safety in Health Care, Austrian Agency for Health and Food Safety) and was registered to the European Clinical Trials Database (EUDRACT number: 2009-14405-14). The study has also been registered in a public clinical trial database (Identifier Number NCT00980356, http://clinicaltrial.gov).

Discussion

Risk-benefit assessment

We expect all patients participating in this study to benefit because of patient counseling and emphasis placed on life-style modification in both study arms. Counseling is performed according to the guidelines of the

Table 1 Patients inclusion and exclusion criteria of the study.

INCLUSION CRITERIA	EXCLUSION CRITERIA
– ≥18 years	–Patients with prior **history of type 1 or type 2 diabetes**
–Newly diagnosed **NODAT** defined by pathologic OGTT (2 h, 75 mg glucose): glucose ≥200 mg/dL	–**Body mass index** (BMI) **> 40 kg/m^2** –- **Pregnancy**
–**Renal transplantation** (deceased or living donor) and treatment with the standard immunosuppressionat our center, consisting of a triple therapy with tacrolimusor cyclosporine A, mycophenolatemofetil, and prednisone	–**Severe renal impairment** (GFR < 30 mL/min./1.73 m^2)
–**Stable graft function** for more than 6 months post transplant	–**Severe liver impairment** (ASAT/ALAT levels over threefold elevated compared to reference values)
–**Informed consent** of the patient	–Severe blood glucose elevation with the need for **insulin therapy** or

International Diabetes Federation (IDF) [4]. If the hypothesis is true, the vildagliptin group (study arm A) will experience improved glycemic control. Vildagliptin is well tolerated in patients with mild to moderate renal impairment [20]. Patients with severe renal impairment (GFR < 30 mL/min/1.73 m^2) will not be included in our study. Patients with a GFR between 30 and 50 mL/min./1.73 m^2 will have weekly visits at our outpatient clinic during the first 4 weeks (serum-creatinine and ASAT/ALAT) for safety. If renal function declines for any reason to a level below 30 mL/min/1.73 m^2, administration of the study medication will be stopped.

NODAT continues to be a common and serious metabolic complication after organ transplantation. Currently, NODAT is diagnosed and treated like T2DM, but there is only limited evidence about the efficacy and safety of the novel antidiabetic drug vildagliptin in patients with NODAT, although it is already commonly used in T2DM. Based on the differences in pathophysiology between T2DM and NODAT, the complex drug profiles in transplanted patients, and the possible influence of renal impairment on the pharmacokinetic properties of vildagliptin, the antidiabetic efficiency of this drug in NODAT remains to be established. This trial will investigate whether vildagliptin is efficient and safe in patients with NODAT.

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Authors' contributions
MHa made substantial contributions to the conception and design of the study. He was involved in drafting the study protocol and wrote this manuscript. HCV, JW, MHe, WHH, DD, and TW participated in the design of the study and its coordination and helped to draft the manuscript. JP participates in the design of the study by giving advice on statistics and will be involved in the statistical analysis. GS will be in charge of the production, blinding and dispensing of study medication and helped to draft the manuscript. MDS is the principal investigator, responsible for recruitment and trial coordination. He developed the study idea and made substantial contributions to conception and design. Moreover, he was involved in drafting and revising the study protocol as well as this manuscript. All authors will participate in the implementation or analysis of this study and approved the final manuscript. All authors have read and approved this manuscript.

Competing interests
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4 DISCUSSION

This doctoral thesis deals with the implementation and scientific evaluation of renal clinical pharmacy services in the largest Austrian tertiary care hospital, the Vienna General Hospital (VGH). Data on such important patient care services in Austria are completely lacking. The underlying publications forming this scientific work address the possible roles of clinical pharmacists in renal clinical pharmacy services in general, describe areas in which clinical pharmacists can contribute in the inpatient care sector, and provide data on DRPs. Regarding the professional advancement of the clinical pharmacy discipline and the implementation of research and scientific evaluation, the Austrian situation can be called a developing system. This work represents the first comprehensive scientific thesis of applied clinical pharmacy research in Austria.

The introduction concisely highlights the background and concept of clinical pharmacy services in general and that of renal clinical pharmacy services in particular. The few available studies on clinical pharmacy services at a national level in Austria are summarised and discussed within the basic legal and educational framework that they are based on. Furthermore, the introduction illustrates why patients with impaired renal function are especially susceptible to DRPs and focuses on several factors to consider when treating patients with renal insufficiency. A detailed, in-depth description and analysis of the clinical pharmacists' role in renal clinical pharmacy has been provided. This analysis is provided in the two literature reviews on clinical pharmacy services in CKD and dialysis patients, and SOT patients.

Renal clinical pharmacy services are well established in routine patient care in several, especially English-speaking countries. Special care needs of patients with impaired renal function are addressed. No border exists for the provision of renal clinical pharmacy services at the transition of patients from the inpatient to the outpatient setting. Furthermore, evidence for the clinical pharmacist's impact on different aspects of nephrology patient care in the ambulatory care sector is published in the two literature reviews. Even in healthcare systems with advanced renal clinical pharmacy services, such as in the UK or the US, the scope, characteristics, and level of services may vary. One can only hypothesise to what extent services are established and can only extrapolate from the available relevant scientific publications in this field. This may not, however, necessarily reflect the true extent of services, as not all hospitals, especially smaller, non-university affiliated hospitals, may be engaged in hospital pharmacy-based research or research on applied clinical pharmacy services.

Therefore, two goals have been achieved by performing the literature reviews on clinical pharmacy activities in CKD and ESRD patients, and in SOT patients, respectively. First, the literature reviews contribute to the overall understanding of the value of implementing such services. Strengths, weaknesses, and differences among implemented services were identified. Second, various areas in which the hospital or clinical pharmacist can engage in the care of patients with renal impairment are described.

These reviews could be seen as a vital step in setting up services in a new setting by establishing a theoretical knowledge base on renal clinical pharmacy services. In the VGH, there were few practical experiences regarding the concurrent establishment and scientific evaluation of new clinical pharmacy services. Hence, evidence and information of previously published projects were the only sources for orientation, benchmarking, and service comparisons. The description of the pharmacists' work, although often only narrative and out of the explicit context of scientific research, was truly valuable for defining target areas and processes and for the establishment of structural service criteria, e.g., defining the type of co-working during ward round participation and the documentation criteria. Examination of the published literature on renal clinical pharmacy services was essential to define a *modus operandi* and yielded valuable information.

Knowledge of risk factors and their management is essential for the preservation of kidney function, management of established kidney disease, and reduction in disease progression. In our work on risk factor management of patients treated on an internal nephrology ward, we clearly showed the need for further improvement of risk factor treatment in this in-hospital patient population. During a retrospective medical chart review and assessment of treatment quality regarding several risk factors, e.g., hypertension and diabetes, we identified suboptimal control in a majority of patients. Other problems, e.g., potential DDIs, were identified in the study population and in the subgroup of kidney transplant patients. We hypothesised that clinical pharmacy services could be one way to approach these care gaps, as evidence from literature shows that clinical pharmacists positively influence these risk factors (KABOLI et al. 2006, VIKTIL and BLIX 2008). The methodology of this retrospective, descriptive study undoubtedly has its limitations and does not contribute to the evidence of clinical pharmacy services. However, seen as an audit measure, needs for improvement in care were highlighted.

To definitely describe the impact of the clinical pharmacist in the nephrology setting in the VGH, several small- to large-scale studies were conducted. In the analysis of prescribing patterns of patients treated on the ward and the synthesis of a synopsis of highly prevalent drugs, a knowledge framework for the clinical pharmacist and concerned physicians was established. The provision and availability of additional information regarding the pharmacologic properties of commonly used drugs and essential (dosing) information on drug prescribing in patients with impaired kidney function addressed a constant need of the members of the multidisciplinary healthcare team. The high level of clinical pharmacist input related to informational contributions, which was detected across all descriptive studies, further reflects this need.

Out of three clinical pharmacist intervention studies (STEMER and LEMMENS-GRUBER 2010, STEMER and LEMMENS-GRUBER 2011, STEMER et al. 2011), evidence was generated on the clinical pharmacist's contributions during ward rounds, the clinical pharmacist's contributions on DRPs, and the clinical pharmacist's interventions, respectively (see 3.4, 3.6, and 3.7). The type of interventions performed and problems addressed (e.g., sub- and supratherapeutic dosages, need for additional drugs) are comparable to other studies (MANLEY et al. 2005, MANLEY and CAROLL 2002). This similarity is not surprising, as the complexity of patient care and related pitfalls (e.g., the occurrence of ADEs, inaccuracy in patient charts, prescribing errors, and dosing errors) generally do not differ between individual healthcare settings and systems. However, these are the first data to describe this concept in the Austrian setting.

Whereas the methodology of the first study (STEMER and LEMMENS-GRUBER 2010, see 3.4) was descriptive in terms of the clinical pharmacist's contributions to questions raised by other healthcare professionals of the multidisciplinary patient care team, the second study (STEMER and LEMMENS-GRUBER 2011, see 3.6) mainly yielded data on proactively performed interventions by clinical pharmacists. In other words, the influence and work style of the clinical pharmacist during ward rounds evolved from a reactive to a proactive method of addressing evident or potential DRPs. This change was definitely due to the steady evolution of knowledge and increase in professionalism on the clinical pharmacist's side, and overall longer duration of co-working in which the clinical pharmacist was a member of the team for a longer time period and established a good and trustful working climate.

Furthermore, the evolution of the study methodology included the measurement of the physicians' acceptance rates of the clinical pharmacist's interventions as an outcome parameter. Information on the drugs most involved in the clinical pharmacist's interventions and most implied in DRPs, information on the cost reduction potential of interventions, and an assessment of the clinical significance of the interventions were amended in the methodology of further studies. By reviewing data on all DRPs and interventions in the VGH-implemented clinical pharmacy services, a comprehensive evaluation of the clinical pharmacists' contributions in individual settings was undertaken. Thus, the thinness of single results was further enhanced, and the comparison of specific characteristics in the renal setting to other clinical areas was possible. In the in-depth analysis of the results presented for the nephrology area, high proportions of drugs used without indication and supratherapeutic dosages were detected. These two types of DRPs are of great importance, as the overall number of drugs is generally already high in this special patient group, and a high number of drugs is associated with several, well-known potential problems (e.g., weaning compliance, drug-drug interactions, and prescribing cascade). The acceptance rate of the clinical pharmacist's interventions on the nephrology ward was 61%, with 71% of all interventions assessed as significant. Approximately 37% of all proposed interventions were associated with cost reduction potential (STEMER et al. 2011, see 3.7).

The involvement of the clinical pharmacist in other clinical research projects, apart from his or her own clinical pharmacy research agenda, is described as a major task of clinically active pharmacists (SCROCARRO et al. 2000). During this project, the clinical pharmacist was involved in two clinical studies on various levels and (co)-responsible for the planning, data analysis, and the discussion of results in this study. The clinical pharmacist valuably contributes by integrating a unique set of competencies and capabilities (e.g., pharmacological knowledge, knowledge on drug production, and pharmacoepidemiological knowledge) and, therefore, enriches multidisciplinary clinical research groups (ASHP 1991).

As previously illustrated and discussed, the study methodology applied evolved and broadened over the period of this project. The prospectively conducted clinical pharmacy evaluation studies mainly involved a conservative approach of monitoring, describing, and assessing the clinical pharmacist's interventions as an indirect measure of their effects on patients. The monitoring of clinical pharmacists' interventions is a widespread method applied in clinical pharmacy research and is seen here as a valuable tool (CALVERT 1998). However, limitations of intervention monitoring result

from assessment of their value in terms of quality or costs. Monitoring and documentation is a time-consuming and error-prone process (CALVERT 1998). The essential assumption that nothing would have been done without the pharmacists' interventions is made. This assumption, however, represents a paradox, as this assumption further implies the direct correlation between the number of interventions and their impact and value. In an ideal and optimal setting with high quality patient care, the number of interventions should actually approach zero, as no interventions addressing improvement of patient care would be indicated (CALVERT 1998). These considerations must be considered when interpreting data on interventions.

The measurement of outcome parameters according to the ECHO (Economical – Clinical – Humanistic Outcomes) Model remains important in the analysis of pharmaceutical treatments and services (KOZMA et al. 1993). Clinical outcomes are medical events that occur as a result of a disease or treatment. Economic outcomes are direct, indirect, and intangible costs compared with the costs of medical treatment alternatives. Humanistic outcomes consist of consequences of disease or treatment on patient functional status or quality of life (GUNTER 1999).

The studies included in this thesis do not generally report on outcomes according to this model, apart from information on the cost reduction potential that lies within clinical pharmacist interventions (STEMER et al. 2011, see 3.7). DRPs, precursors of the most important outcome variables that have influenced economic, clinical, and humanistic outcomes, have been investigated. The limitation of not being able to establish an association between our observed DRPs and the clinical pharmacist's interventions and the occurrence or avoidance of a definitive final outcome must be acknowledged. However, we know from the literature (VAN DEN BEMT et al. 2000, GASTELURRUTIA et al. 2011) that DRPs are strongly linked to the occurrence of final outcomes. By assessing the clinical significance of performed interventions, the weight of every single intervention and the possible implied impact on patient care could be underlined. In the descriptive clinical pharmacist intervention studies forming this thesis, socio-demographic data on the study population, i.e., patients admitted to an internal nephrology ward of a large tertiary care hospital, is limited. However, we report data on the average patient population of our study ward (an internal nephrology ward), including comorbidities and underlying diseases, in the publication of risk factor management. It must be clearly stated that the lack of socio-demographic data represents a weakness that limits our ability to generalise the study results.

Fundamental difficulties regarding the generation of evidence in clinical pharmacy research from an evidence-based medicine/pharmacy standpoint exemplarily demonstrate the need for large study populations, long follow-up periods, and the involvement of multiple centres and multiple pharmacists. In their comprehensive analysis on the impact of pharmaceutical services in community and ambulatory care, SINGHAL et al. also published recommendations for future research. Although deduced and extrapolated from the ambulatory care setting, these recommendations may similarly apply to clinical pharmacy research in the hospital setting as well (SINGHAL et al. 1999). SINGHAL et al. report, among others, on several concerns on external validity. A single pharmacist and/or a single centre study may be biased in that the observed effects may occur only in this setting. The results may not necessarily be transferable to other settings. Study results may be significantly influenced by characteristics at the level of the pharmacist, e.g., motivation, workload, social interaction skills, and previous experiences. The goal should be uniform and standardised skills of each clinical pharmacist participating in the study. By applying a broad, multi-centre, multi-pharmacist study design, these threats to external validity could be approached (SINGHAL et al. 1999). A comment on the possibility and limitation of extrapolating study results to different settings was published by the German Pharmaceutical Society in reaction to a Swedish clinical pharmacist intervention study by GILLESPIE et al. (2009). The study investigated the effectiveness of interventions by ward-based pharmacists on morbidity reduction and use of hospital care among older patients. The authors state that the addition of a pharmacist to healthcare teams leads to major reductions in morbidity and healthcare costs. The comment clearly states the difficulties in extrapolating data from other settings and underlines the necessity for multi-centre clinical pharmacy studies, external funding of studies, and further enhancement and pursuit of research on patient safety. As research has its main focus in the university setting, the dissolution of old and established conventions, exploration in new research areas, new professorships, and qualified staff are necessary (BERTSCHE et al. 2009).

The implementation of renal clinical pharmacy services and its scientific analysis in the scope of a doctoral thesis approached a completely new area in Austria from both a healthcare system and a scientific standpoint. Difficulties arose because of the relative lack of experience in conceptualising the idea of setting up clinical pharmacy services with a focus on renal clinical pharmacy services and in forming research questions to be answered by the underlying scientific thesis. To summarise, several limitations were encountered that must be mentioned. These limitations significantly contributed to difficulties in further implementing clinical pharmacy services, scientifically evaluating

them, and pursuing the advancement of this profession. These system barriers may also have significantly influenced the results and outcome of this thesis.

First, there is, what could be called, an education gap. Clinical pharmacists working in specialised clinical areas are often autodidactically trained and must develop skills on their own. An education system of clinical pharmacy on a national level is absent. The lack of such a system results in variations of individual knowledge when clinical pharmacy services are performed and makes comparison difficult, even among clinical pharmacists working in the same hospital. Further variations from other publications derive from the fact that the provision of services could not be continuously offered, as there was only one clinical pharmacist providing services, and no substitute was available if he was on leave. The absence of substitutes is one of the major weaknesses in the VGH-implemented clinical pharmacy services. The results reflect the individual performance of a single clinical pharmacist, with his individual capabilities, and, thus, they may not necessarily reflect the true reality. This limitation must be considered when comparing the results of this thesis to other publications.
To address the issue of performance standardisation and variation reduction, a quality management process for clinical pharmacy services, including standard operating procedures (SOPs), was implemented in the VGH. A similar process is underway in other hospitals that provide clinical pharmacy services in Austria as well (WUNDER et al. 2011).
The standardised provision of clinical pharmacy services mainly focuses on comprehensive and standardised documentation criteria for DRPs and respective clinical pharmacist interventions. By self-assessing the intervention significance first followed by co-assessment of all involved clinical pharmacists at two different time points, a measure of the value of the interventions was documented (STEMER et al. 2011). The co-assessment at two different time points aimed at bias reduction in the judgement of significance. Inter- and intra-rater variability of intervention significance assessment is reported, and the correlation coefficients indicate moderate agreement. We attribute this moderate agreement to the fact that the process of significance assessment according to the published categories by HATOUM et al. (HATOUM et al. 1988) was newly implemented and familiarity was low.

A vast amount of literature has been published on the necessity, importance, and prerequisites of documentation of clinical pharmacist interventions (VAN MIL et al. 2004, GRANAS et al. 2010).

In the VGH, a published, validated documentation system (ALLENET et al. 2006) was adapted during the implementation of the quality management process. Practicability and usability was assessed during the prospective comprehensive clinical pharmacist intervention study in all clinical areas where clinical pharmacy services are implemented in the VGH. All involved clinical pharmacists reported a good level of practicability and usability for the system.

Clinical pharmacy services can only be successful if the process of gaining respect and trust as a member of multidisciplinary patient care teams is successful, as a close collaboration is essential. During this process, psychological barriers and “prejudices” of other involved professionals must be addressed and often defeated. In a traditional hierarchy, there may still be prejudices against the role of the clinical pharmacist, the capabilities of the individual pharmacists, and (unjustified) fears of losing competencies and interfering with duties of other professionals. Shared understanding of roles and expertise, transparency in decisions, negotiation, and a non-competitive, non-hierarchical approach to patient and care is needed (SMADU 2008).
A high level of social skills, in addition to professional skills, is needed. Working in a trustful climate allows for addressing sources of errors and areas with a need for improvement with sensibility and professionalism, which will ultimately succeed in the goal of providing the best patient care possible. Mutual trust and respect are essential elements of interprofessional relationships (LIAW and PETERSON 2009).
A model of mentorship, compared with the profession of physicians, or a model of training “junior” clinical pharmacists on the job by “senior” clinical pharmacists is absent, but would definitely facilitate the process. The joint education of pharmacists and physicians with enhanced possibilities to exchange knowledge, experiences, and a professional discourse would also be helpful. The adoption of a more research-oriented attitude, similar to that of physicians, by clinical pharmacists would be a positive development.

As mentioned in the introduction, in addition to a weak educational structure for clinical pharmacists, a gap in legislation also exists. Although the term clinical pharmacist occurs in Austrian law, a detailed description of duties, responsibilities, and qualifications is lacking. The visibility of the discipline of clinical pharmacy, its achievements, and its implied potential to stakeholders in the health system, however, must be pursued and amplified, thus underlining the importance of clinical pharmacy services in addressing the needs of patient care. Furthermore, awareness should be raised on pharmacotherapy-associated problems and the use of drugs as an error-prone

process. Only a few studies on the various aspects of drug safety, medication errors, and DRPs and their consequences (i.e., ADRs) are have been conducted in Austria. A study performed by SCHULER et al. shows that 17.8% of patients admitted to selected internal wards had experienced an ADR. In the majority of these cases, the ADR was the reason for hospital admission (SCHULER et al. 2008).
The data gap regarding these two areas should be addressed by surveying and performing epidemiological research, which will define requirements for additional services on a national healthcare system level. The regulatory bodies and politicians currently handle trials on quality, efficacy, and safety, but do not necessarily devote adequate attention to drug therapy safety (BERTSCHE et al. 2009).

It is important to clearly state the reasons why hospital pharmacy and clinical pharmacy research is vital for the profession, the healthcare system, and the individual patient. Research is an important educational tool for junior hospital pharmacists and an excellent opportunity to build networks with other healthcare professionals, facilitating the development of new service and exploration of new tasks. To establish a sound and reliable research project, specialised problem solving knowledge should be available and the project should involve the development of new activities and collaboration, communication, and education of others (BONABRY, 2011).
Implementation of research and communication of results and achievements could act as stimuli for further projects, especially as the communication of results to stakeholders and healthcare professionals (other pharmacists, physicians, nurses) increases. The discipline of hospital pharmacy and the concepts of clinical pharmacy and pharmaceutical care are applied core disciplines in the overall pharmacy specialty. In the medical area, research represents a key activity and quality indicator, and as the hospital and clinical pharmacist are members of the hospital patient care team, it is time to pursue clinical pharmacy research in addition to basic pharmacy research at a university level (BONABRY, 2011). However, according to the EAHP survey in 2005, only 51% and 27% of hospital pharmacies are engaged in research of inpatients and outpatients, respectively. The majority of hospital pharmacies is involved in clinical drug trials (which deal more with the logistics or production of the study drugs). Clearly, a minority of pharmacists are involved in drug use evaluations (DUEs) or medication use evaluations (MUEs), and only 20% are involved in pharmacoepidemiological research tasks (EAHP, 2005).

The present thesis provides evidence that supports the benefit of renal clinical pharmacy services in the setting of a large tertiary care hospital. In the included

publications, several issues on the roles of the clinical pharmacist (e.g., addressing DRPs, analysing situations and deducting measures or indicators, establishing guidance) are described.
In the discussion of the thesis the overall scientific work has been set in association to its constituting individual pieces, has been discussed in the framework of other clinical pharmacy services in the same setting, and in the framework of published evidence, with the background of clinical pharmacy research. Furthermore, the discussion highlighted the value of advancement, difficulties, barriers, and implementation of clinical pharmacy services in a developing system.

Compared with previously published evidence, this thesis contributes data for the Austrian in-hospital patient care sector for the first time. On a national level, it contributes by describing the evolution of clinical pharmacy services and their scientific evaluation for the first time within the scope of a doctoral thesis in a new applied research area. It aims at serving as a stimulus for further research projects and contributes to the further recognition of clinical pharmacy services within the Austrian healthcare system, by various Austrian healthcare services, by professional bodies, and by schools of pharmacy. The importance of clinical pharmacy services with regard to an overall ageing population, polypharmacy, several comorbidities, increasing complexity in drugs used, and patient care will be enhanced from both an institutional perspective and the perspective of society as a whole.

5 SUMMARY

5.1 ABSTRACT ENGLISH

Renal clinical pharmacy services focus on special drug- and pharmacotherapy-related issues in patients with renal impairment (e.g., CKD patients, ESRD patients, kidney transplantation patients). Patients with renal insufficiency are characterised by several different comorbidities that affect many organ systems.

Opportunities for the clinical pharmacist to contribute to the complex care of these patients at various stages and in the aforementioned patient groups are described. Possible areas in which the clinical pharmacist can contribute are risk factor management (e.g., hypertension, cardiovascular disease, and diabetes), management of comorbidities (e.g., anaemia, metabolic bone disease), and prevention and management of DRPs.

Patients with renal impairment are especially susceptible to DRPs. Non-adherence to dosing guidelines often leads to the occurrence of preventable ADEs. Accurate assessment of kidney function and assurance of dosage adaptation is key to avoid unwanted drug effects and, ultimately, to ensure optimal patient outcomes. Factors including the severity and prevalence of coexistent medical conditions and different procedures (e.g., form of dialysis) may influence the pharmacokinetics and pharmacodynamics of the drugs used and, therefore, contribute to the occurrence of DRPs.

Successful implementation of clinical pharmacy services on an internal nephrology ward was evaluated by describing and evaluating the impact of a clinical pharmacist's participation during ward rounds. Data on commonly detected DRPs (e.g., dosing issues, use of unindicated drugs, inaccuracies in medical records), performed interventions, affected drugs (e.g., antibiotics, proton pump inhibitors, antivirals), the physicians' acceptance rate of the suggested interventions, and the significance assessment of the interventions are reported. Limitations to the results and their impact are mainly due to issues in study methodology.

This thesis represents the first scientific thesis in the area of applied clinical pharmacy research on a national level in Austria and yields data on its implementation in the renal setting and the clinical pharmacist's role in the evolving system of clinical pharmacy services.

5.2 ABSTRACT DEUTSCH

Klinisch-pharmazeutische Dienstleistungen im Bereich Nephrologie befassen sich unter anderem mit speziellen Arzneimittel- und Arzneimitteltherapie-assoziierten Problemen in Patienten mit eingeschränkter Nierenfunktion bei chronischer Niereninsuffizienz, terminalem Nierenversagen oder nach Nierentransplantation. Charakteristische Begleiterkrankungen in dieser Patientenpopulation sind häufig. Für den Klinischen Pharmazeuten bieten sich in diesem komplexen Umfeld viele Möglichkeiten einen Beitrag zu leisten und es gibt umfangreiche wissenschaftliche Literatur hierfür. Möglichkeiten umfassen u.a. das Management von Risikofaktoren (z.B. Hypertonie, kardiovaskuläre Erkrankungen und Diabetes), das Management von Begleiterkrankungen (z.B. Anämie, Störungen im Calcium-, Phosphat- und Vitamin-D-Haushalt), sowie die Prävention und das Management von Arzneimittel-assoziierten Problemen. Patienten mit eingeschränkter Nierenfunktion sind besonders empfindlich für Arzneimittel-assoziierte Probleme. Die fehlende Berücksichtigung von Dosierungsempfehlungen bedingt häufig eigentlich verhinderbare Arzneimittelnebenwirkungen. Die Beurteilung der Nierenfunktion und korrekte, an diese angepasste Arzneimitteldosierungen sind unerlässlich, um unerwünschte Arzneimittelwirkungen zu vermeiden und letztendlich eine optimale Patientenversorung zu gewährleisten. Die Existenz von Begleiterkrankungen, deren Schweregrad und verschiedene Verfahren (z.B. Dialyse) beeinflussen die Pharmakokinetik und die Pharmakodynamik von Arzneimitteln und können so zum Auftreten von Arzneimittel-assoziierten Problemen beitragen. Auf der nephrologischen Normalpflegestation einer großen österreichischen Universitätsklinik wurden erfolgreich klinisch-pharmazeutische Dienstleistungen implementiert und durch Beschreibung und Auswertung der klinisch-pharmazeutischen Interventionen und anderen Beiträgen während der Stationsvisiten evaluiert. Häufige Arzneimittel-assoziierte Probleme (z.B. Dosierungsfehler, Gebrauch nicht indizierter Arzneimittel, Fehler in der Dokumentation), häufig betroffene Arzneistoffe (z.B. Antibiotika, Protonenpumpenhemmer, Virustatika), die Akzeptanzrate der vorgeschlagenen Interventionen seitens des ärztlichen Personals und die Beurteilung der Signifikanz wurden erhoben. Die Ergebnisse müssen unter Berücksichtigung methodischer und systematischer Grenzen interpretiert werden.

Die vorliegende Arbeit stellt die erste wissenschaftliche Arbeit im Bereich angewandter klinisch-pharmazeutischer Forschung auf nationaler österreichischer Ebene dar. Sie liefert Ergebnisse zur Implementierung klinisch-pharmazeutischer Dienstleistungen und unterstreicht den Beitrag des Klinischen Pharmazeuten in einem diesbezüglich noch in den Kinderschuhen steckenden Umfeld.

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7 ABBREVIATIONS

AAHP	Austrian Association of Hospital Pharmacists
ABDA	Bundesvereinigung Deutscher Apothekerverbände – Federal Alliance of German Pharmacy Associations
ABO	Apothekenbetriebsordnung – Regulation on the operation of pharmacies
ACCP	American College of Clinical Pharmacy
ACEI	Angiotensin-converting enzyme inhibitor
ADE	Adverse drug event
ADR	Adverse drug reaction
AHRQ	Agency for Healthcare Research and Quality
ARB	Angiotensin receptor blocker
BNF	British National Formulary
CKD	Chronic kidney disease
CrCL	Creatinine clearance
DDI	Drug-drug interaction
DPhG	Deutsche Pharmazeutische Gesellschaft – German Pharmaceutical Society
DRP	Drug-related problem
DTPA	Diethylenetriamine pentaacetate
DUE	Drug use evaluation
EAHP	European Association of Hospital Pharmacists
EDTA	Ethylenediamine tetraacetate
ERA-EDTA	European Renal Association – European Dialysis and Transplantation Association
ESA	Erythropoiesis stimulating agent
ESCP	European Society of Clinical Pharmacy
ESRD	End-stage renal disease
FIP	International Pharmaceutical Federation
GFR	Glomerular filtration rate
iPTH	Intact parathyroid hormone
KDIQO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
LDL	Low density lipoprotein
LVH	Left ventricular hypertrophy
MDRD	Modification of Diet in Renal Disease
ME	Medication error
MSc	Master of Science
MUE	Medicines use evaluation
NHANES	National Health and Nutrition Examination Survey
NKF	National Kidney Foundation
NSAID	Non-steroidal antiinflammatory drug
PGY	Pre-registration year
ÖAK	Österreichische Apothekerkammer – Austrian Chamber of Pharmacists
SCr	Serum creatinine
SOP	Standard operating procedure

SPC	Summary of product characteristics
SOT	Solid organ transplantation
VGH	Vienna General Hospital
UK	United Kingdom
UKCPA	United Kingdom Clinical Pharmacy Association
UKRPG	United Kingdom Renal Pharmacy Group
US	United States

8 APPENDIX

8.1. INTERIM RESULTS OF NEWLY IMPLEMENTED CLINICAL PHARMACY SERVICES ON AN INTERN NEPHROLOGY WARD

Interim results of newly implemented clinical pharmacy services on an intern nephrology ward

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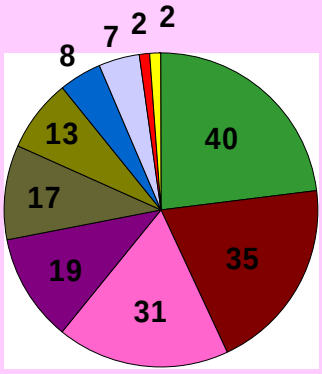
BACKGROUND: Routine clinical pharmacy services have newly been implemented on an intern nephrology ward in an effort to further expand these services. The clinical pharmacist participates in ward rounds at least three times per week.

OBJECTIVES: To evaluate the contribution of clinical pharmacy services by documentation of the consultations made during the ward rounds, classified by
- type and frequency, and
- complexity.

DESIGN AND SETTING: Descriptive, prospective study on an intern nephrology ward of the Vienna General Hospital – University Clinics; January 2008 – May 2009 (17 months)

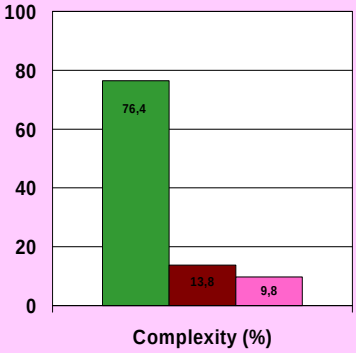
MAIN OUTCOME MEASURES:
- **Type** and **frequency** of drug- or pharmacotherapy-related questions raised by health care professionals during the ward rounds and subsequently answered by the clinical pharmacist
- **Complexity** of questions defined by the total time needed to answer each question
- **Problems** and **barriers** identified during the initial period of the clinical pharmacy project

RESULTS: The clinical pharmacist was asked a total of **174 drug- or pharmacotherapy-related questions** during participation in the ward rounds. Questions mainly derived from physicians (n=154; 88.5%), nurses (14; 8%) or medical students (6; 3.5%).



The absolute and relative **frequency** of each **type of consultation** were: **drug therapy selection** (40; 23%), **general drug information** (35; 20.1%), **dosage and pharmacokinetics** (31; 17.8%), **availability of drugs** (19; 10.9%), **drug interactions** (17; 9.8%), **adverse drug events** (13; 7.5%), **application of drugs** (8; 4.6%), **organisation and logistics** (7; 4.0%), **pregnancy and breastfeeding** (2; 1.1%) and **pharmaeconomics** (2; 1.1%).

Based on the total time needed to answer, each question was either categorised into **group A** (up to 15 minutes: 133; 76.4%), **group B** (up to one hour: 24; 13.8%) or **group C** (more than one hour, extensive and complex literature research: 17; 9.8%).



Problems and **barriers** identified were:
- continuity of collaboration due to changes in medical ward staff each semester,
- bridging psychological borders between physicians and pharmacists, and
- different levels of professionalism of clinical pharmacists due to a lack of systematic clinical pharmacy education programmes.

CONCLUSION: Interim **results** of newly implemented clinical pharmacy services are **encouraging** and **participation** in ward rounds will **continue**.

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8.2 PRESCRIBING PATTERNS ANALYSIS ON AN INTERN NEPHROLOGY WARD: THE “RENAL” FOCUS!

Prescribing patterns on an intern nephrology ward: The „renal“ focus!

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BACKGROUND: Knowledge of relevant pharmacokinetic parameters, e.g. protein binding, non-renal excretion rate (Q_0-value), eliminiation half-life (HL) and the presence of active metabolites, of commonly prescribed drugs is essential for drug therapy individualisation in patients with renal impairment (RI).

OBJECTIVES: To analyse **qualitative prescribing patterns** on an intern nephrology ward and subsequently develop a synopsis of important pharmacotherapy relevant parameters.

DESIGN: Retrospective analysis of drug prescriptions of 100 randomly selected patients;
Synthesis of a synopsis of drug properties relevant for drug therapy individualisation by searching drug information databases and handbooks of clinical drug data

MAIN OUTCOME MEASURES:
- Frequency of the most prescribed drugs
- Frequency of drugs identified with pharmacokinetic properties requiring attention in RI

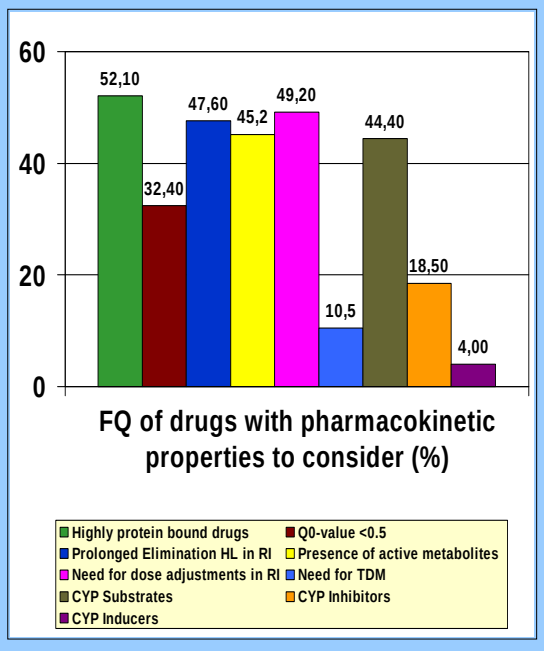
RESULTS: A total of **195 different drugs** were identified, adressing typical nephrological pharmacotherapy questions, e.g. hypertension, diabetes, electrolyte disturbances, secondary hypoparathyreoidism and cardiovascular disease. Around 50% of the patients had kidney transplantation.
124 drugs were included in the synopsis.

The **10 most prescribed drugs** were

- prednisolone (53%),
- the PPIs pantoprazole and esomeprazole (88.2%),
- aspirin (39.2%),
- carvedilol (35.3%),
- tacrolimus (34.3%),
- candesartan (30.4%),
- mycophenolate mofetil (29.4%),
- amlodipine (28.4%) and
- furosemide (27.45%).

Pharmacokinetic properties to consider (among others) when prescribing in RI were:

- **High protein binding rate**
- **Non-renal excretion rate (Q_0-values <0.5)**
- **Prolonged elimination HL in RI**
- **Presence of active metabolites**



Further parameters investigated were frequency (FQ) of **drugs with the need for dose adjustments** and the **need for therapeutic drug monitoring** (TDM).
44.4% of the drugs are substrates, inhibitors (18.5%) or inducers (4.0%) of CYP450 liver enzymes.

The synopsis also comprises dosing guidelines for normal and impaired renal function and further pharmacokinetic drug parameters.

CONCLUSION: Knowledge of altered **pharmacokinetic parameters** affecting action, efficacy and toxicity of drugs, is **essential** when prescribing drugs to patients with **renal impairment**.
The synopsis highlights common drugs requiring special attention. It can be used as a teaching tool for health care professionals beginning in nephrology or as a quick reference guide at the point of care.

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8.3 CLINICAL PHARMACY SERVICES IN THE LARGEST AUSTRIAN TERTIARY CARE HOSPITAL

16th EAHP Congress in Vienna, March 2011

Our systematic evaluation of clinical pharmacy services highlights on areas with needs for improvement of care.
Every second recommendation was accepted.
The proportion of somehow significant contributions was high.

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CLINICAL PHARMACY SERVICES IN THE LARGEST AUSTRIAN TERTIARY CARE HOSPITAL

CPC053

BACKGROUND

Clinical pharmacists (CPs) take part in ward rounds on 3 standard care units: department of nephrology (NE, thrice weekly), cardiac surgery (CS, twice weekly) and hematology (HE, twice weekly), and on 3 intensive care units weekly: department of infectious diseases (ID), gastroenterology (GE) and neonatology (NN). In the psychiatric clinic (PC) a CP is available for consultations daily.

PURPOSE

Detection, analysis, and evaluation of pharmaceutical care issues (PCIs) and the CPs' contributions on attended wards

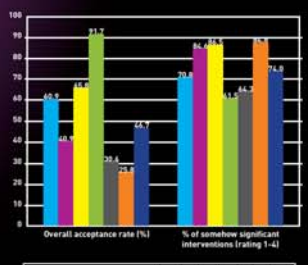
STUDY DESIGN

- Study period: 22 weeks
- Documentation of PCIs, the CP's recommendations, the acceptance rate (excluding solely informational and organisational issues) according to an adapted classification system[1]
- Assessment of significance of the CPs' recommendations on a 6-point-significance rating scale: (-1: adverse significance – 4: extremely significant) [2]

OVERALL RESULTS

- 478 PCIs detected during 138 ward rounds
- Most common PCIs: See pie chart
- Most frequent CPs' recommendations:
  - General information (42.9%)
  - Addition of new drugs (13.4%)
  - Dose adjustments (12.6%)
- Drugs mostly affected:
  - Antibacterials for systemic use (J01)
  - Antithrombotics (B01)
  - Drugs for acid related disorders (A02)
- Proportion of somehow significant recommendations (rating 1-4): 75.3%
- Mean acceptance rate: 54.7%

Results per ward



Average number of PCIs per ward round	NE	PC	CS	HE	ID	GE	NN
	5.5	1.1	3.8	1.3	3.7	3.5	2.9

Most common PCIs

References:
1.Allenet B et al. Validation of an instrument for the documentation of clinical pharmacists' interventions. Pharm World Sci 2006; 28(4):181-188
2.Hatoum HT et al. Evaluation of the contribution of clinical pharmacists: inpatient care and cost reduction. Drug Intell Clin Pharm 1988; 22(3):252-9

9 CURRICULUM VITAE

PERSONAL INFORMATION

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Nationality	Austria
Date of Birth	7, January, 1982

WORK EXPERIENCE

Since Dec. 2007	Pharmacist, Pharmacy Department of the Vienna General Hospital, Drug Information pharmacist and clinical pharmacist
Oct. 2006 – Sept. 2007	Pre-registration year, Pharmacy Department of the Vienna General Hospital
2001 – 2006	Several trainings in community and hospital pharmacies

SECONDARY AND TERTIARY EDUCATION

Since Oct. 2007	Doctoral studies at the Department of Pharmacology and Toxicology, University of Vienna
Sept. 2007	Qualification as pharmacist,Austrian Chamber of Pharmacists
Oct. 2000 – Mar. 2006	Studies of pharmacies, University of Vienna
Sept. 1996 – Jun. 2000	Bundesoberstufenrealgymnasium, Feldkirch, with an emphasis on and additional classes in biology, physics, and chemistry

ALTERNATIVE CIVILIAN SERVICE

Feb. 2003 – Jan. 2004	Multiple Sclerosis Society, Vienna

PERSONAL SKILLS AND COMPETENCES

Mother tongue	German
Other languages	English, excellent; French, basic
Social skills and competences	Flexibility, strong ability to solve problems, capacity for teamwork, high level of self-motivation, high sense of responsiblity
Computer literacy	Comprehensive knowledge in MS-Office programmes, Knowledge in SAP
Additional information	Comprehensive knowledge in literature research using literature databases (e.g., PubMed, EMBASE), Evidence-based-Medicine