Department of Social and Clinical Pharmacy[1], Faculty of Pharmacy, Charles University, Hradec Králové; Institute for Clinical and Experimental Medicine[2], Praha; Department of Pharmacology[3], Faculty of Medicine, Masaryk University; Department of Clinical Pharmacy[4], Masaryk Memorial Cancer Institute, Brno; Department of Pharmacology[5], Faculty of Pharmacy, Charles University, Hradec Králové, Czech Republic

Analysis and management of drug related problems on a nephrology ward from a pharmacist´s point of view

E. Dvořáčková[1,2], J. Rychlíčková[3,4], P. Pávek[5], M. Hojný[2], J. Vlček[1]

Received May 14, 2019, accepted June 20, 2019

**Corresponding author: Eliška Dvořáčková, Department of Social and Clinical Pharmacy, Faculty of Pharmacy, Charles University, Heyrovského 1203, Hradec Králové, Czech Republic*
eliskadvorackova@seznam.cz

Pharmazie 74: 625-629 (2019) *doi: 10.1691/ph.2019.9568*

The main goal of the study was to determine the incidence and the character of drug related problems (DRPs) identified in chronic kidney disease patients by the clinical pharmacist at the nephrology department. As secondary objective, the aim was to identify the frequency and character of DRPs of selected high risk drugs in medication reviews. The clinical pharmacist reviewed patients' medication records and made drug therapy-related recommendations to physicians. The clinical pharmacists' interventions were categorized using an adaptation of the Pharmaceutical Care Network Europe. During the study period (January 2016 - June 2018) the clinical pharmacist performed 1192 interventions in 1870 adult patients admitted to the Nephrology Department. The most frequent DRP was untreated indication 324 (27.18%) of all interventions, and incorrect dose 248 (20.81%). Anti-infectives were identified as the drug category with the highest frequency of interventions. Almost 93% of all interventions were accepted by the attending physicians. Still within the second objectives, underdosing was observed as the most frequent problem for renally excreted drugs. It was found that an incorrect dose is a very frequent issue at the nephrology department. Surprisingly, the main problem was underdosing. In the category of renally excreted drugs, underdosing was observed in antithrombotics and antivirals. The above- mentioned results prove the need of a clinical pharmacist, preferably in sense of maximizing of the treatment effect and improving the care of patients.

1. Introduction

Chronic kidney disease (CKD) is a frequent health problem in all industrialized countries. It affects approximately 10% of the adult population, showing increasing incidence with increasing public costs (Levin et al. 2014). CKD is defined as "structural or functional abnormalities of the kidneys for 3 months, as manifested by kidney damage with or without decreased glomerular filtration rate (GFR) under 60 ml/min/1.73m^2" (Levey et al. 2007). A value under 30 ml/min/1.73 m^2 is defined as a moderate-severe reduction of the GFR. On average, patients with reduced renal function take 10-12 medications daily as a result of this disease with around six comorbidities (Castelino et al. 2011; Salgado et al. 2012). Lastly, several physicians participate on medication (Laliberté et al. 2007). Polypharmacy and altered pharmacokinetics of drugs in renal disease create a scope for arising DRPs (drug related problems) that requires therapeutic drug monitoring and comprehensive approach to the medication to stay reasonable. "*A Drug-Related Problem is an event or a circumstance involving drug therapy that actually or potentially* interferes *with desired health outcomes"*(Abstracts 6th working symposium of the Pharmaceutical Care Network Europe (PCNE), 2-3 February 2018, Fuengirola 2018). DRPs are divided into ADRs (adverse drug reactions) and ADEs (adverse drug events). Adverse events, drug interactions and inappropriate doses are frequent in CKD patients (Castelino et al. 2011). Several studies have been published on the topic of DRP frequency in CKD patients. Castelino et al. (2011) found an incidence of approximately 1.06±0.85 DRPs per patient (96 patients were included). Anggriani et al. (2018) identified 0.36 DRPs per patient. In our study, patients at the Nephrology Department often require immunosuppressive drugs after organ transplantation to avoid graft rejection. These drugs have many interactions which can

Table 1: Patient demographic data and distribution of eGFR among patients

Patient characteristics	Percentage (Number of patients)
Gender	
Male	63.2 (1169)
Female	36.8 (681)
Age (years)	
< 30	6.92 (128)
31-50	30.76 (569)
51-65	37.14 (687)
66-75	20.38 (377)
76-80	3.40 (63)
> 81	1.40 (26)
eGFR (ml/min)	
≥ 60	31.0 (573)
60-30	24.0 (444)
29-15	32.0 (592)
< 15	13.0 (241)
Number of medications	
0-5	43.03 (796)
6-8	6.38 (118)
9-12	17.13 (317)
> 12	33.46 (619)

increase the risk of developing ADRs. Because many of the indicated drugs have narrow therapeutic ranges, DRP management is extremely important (Chisholm et al. 2000). Clinical pharmacists work directly with physicians, as well as with patients, in order to ensure that the prescribed medications deliver the best possible therapeutic effect to the patients. One of pharmacists' roles is to monitor drug therapy and make recommendations to physicians about dose and dosage interval (Anggriani et al. 2018). This is the general definition of clinical pharmacists' role as specialists who contribute to reducing and solving DRPs and participate in developing of different preventive strategies. Therefore, pharmacists play an important role in DRPs identification and management (Blix et al. 2006).

In the Czech Republic, approximately 40 clinical pharmacy departments are in operation. Vlček et al. have conducted research on clinical pharmacists and their activities, benefiting the health system in the Czech Republic (Dosedel et al. 2014; Vlcek et al. 2009). This collective has published research papers on DRPs, however their focus is DRP in general, not DRP specifically in CKD patients. At the same time, only scarce data have been published providing analysis of DRPs in CKD patients (Müllerová et al. 1997).

The main aim of the present study was to evaluate the incidence and the character of DRPs in patients at the Nephrology Department. As secondary objective, the aim was to identify the frequency and character of DRPs of selected high risk drugs in medication reviews.

2. Investigations and results

2.1. Patient demographics and characteristics

A total of 1850 patients were analyzed and included in the study (approximately 99% of the 1870 admitted patients), out of which 63.2% (1169) were men. Geriatric patients aged ≥ 66 years accounted for 25.19%. Table 1 summarizes all the patient demographic data and distribution of eGFR in the study population. At the first day of their hospital stay, 13% of inpatients met the criteria for end-stage renal failure and 32% of inpatients were classified with severe renal failure. Most patients received between 0 and 5 drugs. This study showed that there is a significant positive correlation between the number of medications used and age ($p<0.01$), and negative correlation with eGFR ($p<0.01$).

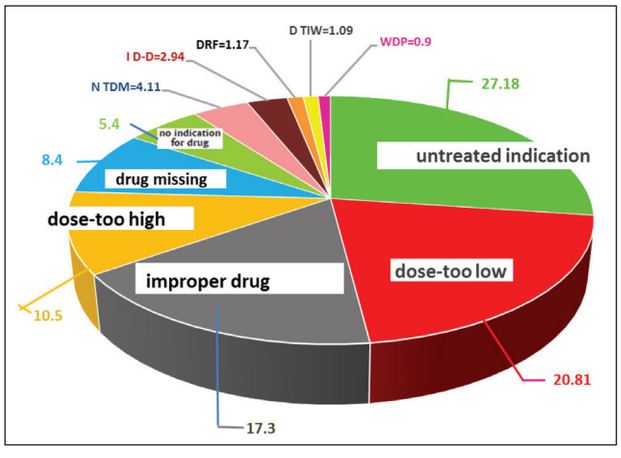

Fig.: Nature and the extent of DRPs (%) by PCNE: N TDM – no therapeutic drug monitoring; I D-D – interaction drug-drug; DRF – dosage regiment too frequent; D TIW – dose timing instruction wrong, unclear or missing; WDP – wrong drug prescription.

2.2. Drug related problems and the adapted PCNE classification

In 1850 inpatients 1192 DRPs were identified by the clinical pharmacist. The number of observed DRP incidences was 0.65 per patient (1192/1850). The most frequent DRPs were untreated indication -27.18% (324) and incorrect dose, too low -20.81% (248). Improper drug selection was identified in 17.31% (206) and incorrect dose, too high – in 10.57% (126). Interactions of clinical relevance were noticed only in 2.94% (35). The nature and extent of the ten largest DRPs are summarized in the Fig. According to the hierarchical classification by PCNE V6.2, there are four primary domains for problems and eight primary domains for causes. Problems were mostly related to treatment effectiveness 1134 (95.13%), adverse reaction 18 (1.51%), treatment cost 5 (0.42%), or classified as others 35 (2.94%). In the eight primary domains for causes in the PCNE system, the drug selection (n=677; 56.80%) was the leading cause of DRPs, followed by dose selection (n=459; 38.51%), treatment duration (n=21; 1.76%), inappropriate dosage form (n=16; 1.34%), logistics (n=12; 1.01%), drug administration process (n=6; 0.50%), and patient (n=1; 0.08%).

The majority of all DRPs (1146 DRPs; 96.14%) observed were classified as having minor clinical significance. The moderate level of significance was identified in 43 DRPs (3.60%) and 3 DRPs were classified as having major significance (0.25%).

Out of the total of 1,192 recommendations by the clinical pharmacist, 1,106 (92.79%) were accepted by the physicians. Only 74 (6.20%) DRPs were partially accepted and twelve (1.0%) were rejected by the attending physicians.

2.3. Drugs categorized by the ATC system associated with DRPs

The following four drug classes caused DRPs most frequently: anti-infectives for systemic use (305 DRPs), drugs affecting blood and blood-forming organs (antithrombotic agents) (262 DRPs), drugs affecting the alimentary tract and metabolism (200 DRPs), or the cardiovascular system (167 DRPs). At the second level of ATC classification, the following groups were connected with more than 60 clinical pharmacist's interventions: mineral supplements (63), antithrombotic agents (152), electrolyte solutions (82), serum lipid-reducing agents (77), antibacterials (137) and antivirals (130) for systemic use, as well as immunosuppressive agents (72).

2.4. Subgroup analysis

Table 2 presents an overview of renally eliminated drugs chosen in relation to the second aim of this study; summarized together with the nature of DRPs and the total frequency of these DRPs. At first glance, the biggest problem was underdosing.

2.5. Preventing DRPs

One of pharmacists' roles is the therapeutic drug monitoring (TDM) of antibiotics (vancomycin, amikacin and gentamicin),

Table 2: Therapeutic classes of renal elimination medication as per ATC (anatomical classification system) classification involved in DRPs and the nature of the most common DRPs

ATC	Total intervention	Nature of the most DRPs	Number (%)
N03 Antiepileptics (gabapentin, pregabalin)	8	Treatment effectiveness – dose too low	2 (25)
C07 Beta-blocking agents (atenolol, metoprolol)	13	Treatment effectiveness – untreated indication	7 (54%)
B01 Antithrombotic agents (enoxaparin, nadroparin)	93	Treatment effectiveness – dose too low	33 (36%)
A10 Drugs used in diabetes (metformin)	1	Treatment effectiveness – wrong effect of drug treatment	1 (100%)
J05 Antivirals for systemic use	108	Treatment effectiveness – dose too low	54 (50%)

and giving recommendations to physicians about dosage of the selected antibiotics. These recommendations have gained 100% acceptance. In case of therapeutic drug monitoring, the final decision regarding dosage is not that of the physician, as contrary to other pharmacist interventions. Thus, the pharmacist has full responsiveness of dosing the drugs. The pharmacist interpreted 195-times vancomycin, 39-times amikacin, 16-times gentamicin.

2.6. Conclusion

This study shows that DRPS often occur in patients with renal failure admitted to hospital. The high level of acceptance of recommendations by physicians demonstrates that clinical pharmacists may help to deliver and improve patient care. PCNE classification V6.2 instrument proved the applicability of clinical pharmacy services in the hospital setting.

3. Discussion

Based on previously published data from Europe, Asia and the United States, we expected a positive effect of an attending pharmacist on the frequency of DRPs in inpatients (Stemer et al. 2011; Castelino et al. 2011; Quintana-Bárcena et al. 2018). Therefore the aim of this study was to analyze DRPs in CKD patients in a nephrology department and based on these data, to assess the scope for work of a clinical pharmacist. DRPs frequently occur in CKD patients; nevertheless CKD patients are prone to some specific types of DRPs. An adapted PCNE classification was used to identify the most important causes of DRPs. The results were quite surprising to us – the second-most often cause was incorrect dose – too low (20.81%). We consider this result as very important in conjunction with the position of a clinical pharmacist. It is possible to systematically identify overdosing, for example by using computerized physician order entry or by sending some alerts to the prescribing physician if the prescribed dose seems too high according to the laboratory results. On the other hand, underdosing is difficult to identify by the methods mentioned above, and a clinical pharmacist is apparently indispensable. We have a similar pattern of DRPs in the selected renally excreted drugs. The concern of overdose leads to underdosing, which does not exploit the full potential of the particular drugs. The role of a pharmacist is to adjust the medication dosage with the goal of maximizing the patients' benefits, while minimizing the risks of adverse events, with cost benefit of treatments guaranteed. The most frequent DRPs were untreated indication 27.18% (324) and incorrect dose 20.81% (248), which corresponds with the results of Belaiche et al. (2012), who identified problems with untreated indication (30%) and incorrect drug dosing (25.9%). The drug classes of anti-infectives for systemic use (305 DRPs), as well as blood and blood-forming organs (antithrombotic agents) (262 DRPs) caused DRPs most frequently. Similar results were obtained in studies of Castelino et al. (2011). This finding is not surprising, given that patients with renal disease usually have cardiovascular comorbidities. The most common causes of admissions to our hospital are infections and related complications. Furthermore, transplant patients are usually prone to infections, as a result of immunosuppression. Prior to transplantation, the therapy is minimized and subsequently reversed according to the clinical condition and renal function. This is the reason for a frequent DRP of untreated indication. For the same reason, the pharmacist should participate in the prescription the medications before providing orientations to the patient at discharge, by means of medication reconciliation, helping the prescribing physicians with the correct drug therapy (Steeb and Webster 2012).

The majority of all DRPs observed were classified as having a minor level of clinical significance. Clinical pharmacists need to implement specific monitoring and follow-up plans to manage DRPs. In the study of Quintana-Bárcena in patients with CKD, most DRPs presented moderate severity, requiring specific monitoring by pharmacists (such as pharmaceutical opinion issued to the treating physician) (Levin et al. 2014). The moderate severity in their study is minor clinical significance in our study. "Small adjustments and optimizations to therapy, not expected to significantly alter hospital stay, resource or clinical outcome" is defined as our minor significance. In fact, 0.25% of the problems were assessed to have major significance. Examples of major DRPs include the addition of meropenem to a chronic valproate therapy or omitting hepatitis investigation before starting the administration of rituximab. Pharmacotherapy in CKD is complicated, hence clinical pharmacists can play an important role toward safely using of pharmacotherapy. Even Castelino et al. (2011) identified 26% of problems to have important major or moderate significance.

The acceptance rate of the clinical pharmacist's recommendations was around 93%, which is consistent with other studies (Castelino et al. 2011). It has been stated that the highest acceptance rates are obtained when clinical pharmacists are attending the rounds with the physicians and when the proposals are made at the stage of prescribing (Viktil et al. 2008). The reason for non-acceptance was reluctance to make a change in pharmacotherapy because of the inability to monitor the effects of that intervention, due the patient's upcoming discharge.

In our study, 0.65 DRPs per patient were identified. The incidence of DRPs observed previously, 1.8 DRPs per patient, is higher than the data reported in our study (Holm et al. 2015). However, that study was conducted at an internal medicine department, whereas our study was conducted in a specialized nephrology department of transplant medicine. The number of identified DRPs depends on multiple factors, including specialization of the department, the main diagnosis, and the pharmacotherapy, as well as on the education of the attending physician.

We have noticed an interesting number of drugs used by patients at the time of hospital admission – the most frequent number was between 0 and 5. It is important to note that the main cause of admission was infection, and the medication is minimized under this condition of an active infectious disease, so that only the vital medication is left. The second most frequent number of medicines was more than 12 systematically used drugs a day. This corresponds to previously published data (Lima et al. 2016). CKD is associated with higher cardiovascular risks, secondary hyperparathyroidism etc. A high number of regularly used drugs could be considered as polypharmacy. In many patients, however, the pharmacotherapy is completely sensible and rational. A similar situation is observed in transplant patients, who are receiving on average 9 drugs per day after transplantation (Flamme-Obry et al. 2018). We found a positive correlation between the number of medications used and age, but a negative one with eGFR, which is consistent with previously published studies (Belaiche et al. 2012; Gheewala et al. 2014). The number and complexity of the medication regimen increases with the progression of CKD, and also with increasing age.

It is important to note that the renal functions were evaluated on the first day of the hospital stay. As we mentioned previously, the most frequent reason for hospital admission was infection, therefore urea and creatinine can be altered due to dehydration, etc. The calculation of glomerular filtration rate using different equations (Cockcroft-Gault, MDRD, etc.) is not accurate. It would be ideal to confirm the glomerular filtration rate during the hospital stay once again; on the other hand it is difficult to standardize the second time of measurement – each patient needs a different amount of time to complete recovery. That is the reason why we decided not to involve these results.

All the results document the systematic approach of screening done by one clinical pharmacist (0.8 FTE) attending 28 beds of the Nephrology Department. The total count of interventions made during the study period was 1,192. The mean time required for performing a medication review was 25 min per patient. TDM was likely to generate more responses to the clinical pharmacist and the pharmacist's recommendations, with significant impact on patient care (Ye et al. 2016). TDM indicates an active approach, used by clinical pharmacists for determination of the initial dose and dosing interval of aminoglycosides, as well as vancomycin for particular patients. In our hospital setting, TDM is carried out by

Table 3: Level of clinical significance of DRPs (Alderman 1997)

Level of significance	
Minor	"Small adjustments and optimizations to therapy, not expected to significantly alter hospital stay, resource or clinical outcome"
Moderate	"Adjustments expected to enhance effectiveness of therapy, producing minor reductions in patient morbidity or treatment costs"
Major	"Interventions expected to prevent or address very serious DRPs, with a minimum estimated effect of reducing hospital stay by no less 24 hours"

clinical pharmacists. The acceptance of their recommendations by the attending physician is 100% due to the transfer of the responsibility for dosing of the selected drugs from the physician to the pharmacist. This is a unique approach in the Czech Republic. However, other hospitals have not yet started to proceed in this way. Usually, the final responsibility is on the attending physician in all pharmacist interventions. The interventions within TDM are not counted in the total count of intervention. TDM is the pharmacist's approach that prevents DRPs; is also contributes to safe pharmacotherapy, potentially reducing treatment costs of adverse events, such as nephrotoxicity.

The significance of this study lies in the description of clinical pharmacy services in a Nephrology Department. It gives an overview of DRPs in CKD patients and documents the need for a clinical pharmacist attending a nephrology department. One clinical pharmacist at one department obtained all the mentioned data, which increases their value by avoiding possible misclassification and bias whenever multiple pharmacists are involved. This study design does not involve a control group. The main reason is that our data were obtained during the daily practice of a clinical pharmacist. In the Czech Republic, clinical pharmacists are not considered a permanent part of healthcare. Hopefully, this study will contribute to the change from a reactive approach to the preventive one.

4. Experimental

4.1. Study population, setting and clinical pharmacy services

This prospective study was conducted over a 2.5-year period from 1 January 2016 – 30 June 2018. During this period, 1870 patients were admitted to the Nephrology Department at the Institute for Clinical and Experimental Medicine (IKEM). This health care center is unique in the Czech Republic due to the close cooperation and interconnection of the clinical and scientific research communities. IKEM is focusing on treatment and research in various fields, such as cardiovascular diseases, organ transplants, and treatment of metabolic disorders, including diabetes mellitus. In total, the institute is provided with 350 beds, out of which 111 are located in intensive care units. There are 28 beds available in the Nephrology Department, offering highly specialized and comprehensive care to patients with renal diseases with special attention to transplant recipients.

One person (0.8 FTE), who was in the process of acquiring the necessary certification during the study period. Her recommendations to patients were checked by a certified clinical pharmacist with 5 years' experience at the Nephrology Department. In the Czech Republic, this process takes 5 years of postgraduate education. She obtained this certification in November 2018. She had previously worked on medication review at the Nephrology Department for 5 years. The clinical pharmacist attends the Nephrology Department daily, but the services were provided neither during weekends, nor on night shifts or holidays. This study did not require any special approach; all data were obtained in the course of regular clinical pharmacy practice.

The clinical pharmacist proceeded according to the methodology as it had been published (Gregorová et al. 2017). Each patient admitted to the Nephrology Department was evaluated by the clinical pharmacist (referred to a screening for drug interaction, duplicates, incorrect drug dosing, non-reasonable drugs, presence of renally excreted drugs etc.). Consequently, comprehensive and systematic clinical pharmacy care was provided to each patient. The review on admission was done at the beginning of each hospitalization; i.e. it was repeated for each admission of a patient. This activity should always include the review of all available healthcare records. For example, drug dosing by renal failure was checked by KDIGO (Kidney disease improving global outcomes) guidelines for dosing drug, according to the available literature on the pharmacokinetics of these drugs (Matzke et al. 2011; Kasiske et al. 2014). The pharmacist observed the impact of her recommendation: whether it had actually led to the intended goal of therapy. Her responsibilities were established according to the published methodology (Gregorová et al. 2017).

Therapeutic drug monitoring (TDM) represents a specialized, separate activity of the clinical pharmacist. The clinical pharmacist's role is to interpret each measured concentration of antibiotics (vancomycin, amikacin, gentamicin) at the Nephrology Department. TDM involves an estimation of an initial dosage regimen appropriate both for the clinical condition and for the patient's individual characteristics, such as age, weight, renal function, and the concomitant drugs. The primary goal of TDM is to manage medications and to optimize the clinical outcomes of the therapy in various clinical conditions by using the appropriate concentrations of a drug. The specific interpretation is processed into the hospital information system for each the treating physician. TDM service was started in our hospital in 2008. The interpretation contains recommendation of dose, dosing intervals and the measurement of control concentrations. The clinical pharmacist used a pharmacokinetics software (MEDIWARE, Prague, Czech Republic, version 4.0) for the interpretation. The pharmacists developed structured pharmacist-based pharmacokinetic service.

4.2. Classification of DRPs, high risk drugs

Each clinical pharmacist intervention was defined using three different points of view: 1) PCNE (Pharmaceutical Care Network Europe) classification; 2) the level of acceptance by the physician; and 3) the ATC classification of the drug related to the intervention. The total number of interventions was documented as well.

An adapted version of the PCNE classification (V6.2) for drug related problems was used – adapted specifically to the needs of clinical pharmacists (Horvat et al. 2016). This classification has four primary domains for problems, namely (treatment effectiveness, adverse reactions, treatment cost, etc.), and eight primary domains for causes, namely (drug selection, drug form, dose selection, treatment duration, drug use/administration process, logistics, patient, etc.). Each primary domain includes several sub-domains. The identified DRPs were also evaluated in terms of their potential clinical significance. There are three levels of significance according to their having minor, moderate or major clinical significance (see Table 3 for a detailed description) (Alderman 1997).

All the identified DRPs were discussed with the attending physicians. After each discussion, which included additional information for the physicians, a pharmacist's written recommendation was provided to the physician to make the final decision. The acceptance of any change was also documented, including the reason of rejection in case of such a decision.

The ATC classification (anatomic-therapeutic-chemical classification) was used to determine the character of identified DRPs. According to the first objective of this study, we only used differentiation at the second level of the ATC system. Nevertheless, it was necessary to use the full ATC classification for the second objective of this study. In order to accomplish the second objective, we considered drugs as having high risk in case of significant – i.e. over 80 percent – unchanged portion renal excretion. For this analysis, the following drugs were chosen: pregabalin and gabapentin (together), metoprolol and atenolol (together), low molecular weight heparins (enoxaparin and nadroparin together), metformin, and antiviral drugs (ganciclovir, valganciclovir).

4.3. Data extraction

All the information necessary for the evaluation of each therapy was obtained from medical records, as well as through patients care inquiry (PCI) system (current medication, chronic medication, allergies, medical history, laboratory results etc.), completed by the clinical pharmacist.

Similarly, all the basic demographic and medical data, such as gender, age, serum creatinine, medical history, were collected. The renal function was assessed by calculating the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation at the time the patients was admitted to the hospital (Levey et al. 2007). The number of drugs was calculated from medical records at the time the patient was admitted to hospital. Only systemically administered drugs were calculated, including those used only once a week. The prescription of the same drugs, yet in different dosages, were counted as one drug. Identified DRPs were classified into categories and sub-categories, respectively, as described above. The clinical pharmacist's recommendations related to the high risk medication were selected in the second step. DRP's frequency was then calculated for each group.

4.4. Statistical analysis

The relevant data were analyzed descriptively to characterize the patient population using Microsoft Excel 2013 and IBM SPSS statistics 20 for Windows. Background data are presented as averages and prevalence, while classification of DRPs and actions in relation to these are presented as incidence. The Pearson correlation was used to investigate the association between different factors and the number of medications used. The factors included were eGFR, age and the number of drugs. The tests were considered as significant in cases where $p < 0.01$. Analyses were performed using JASP version 0.9.0.1.

Acknowledgements: The authors sincerely thank IKEM, Nephrology Department for their support and David Hackajlo, for creating the software application used in this analysis.

Conflicts of interest: None declared.

References

Abstracts 6th working symposium of the Pharmaceutical Care Network Europe (PCNE), Fuengirola (2018). Int J Clin Pharm 40: 488–508.

Alderman CP (1997) A prospective analysis of clinical pharmacy interventions on an acute psychiatric inpatient unit. J Clin Pharm Ther 22: 27–31.

Anggriani Y, Ramadaniati HU, Pramularsih ED (2018) Analysis of pharmacists' recommendations to address drug-related problems in chronic kidney disease patients as a basis to develop therapeutic drug monitoring form in an Indonesian hospital. J Appl Pharm Sci 24: 25-27.

Belaiche S, Romanet T, Bell R, Calop J, Allenet B, Zaoui P (2012) Pharmaceutical care in chronic kidney disease: experience at Grenoble University Hospital from 2006 to 2010. J Nephrol 25: 558–565.

Blix HS, Viktil KK Moger, Reikvam A (2006) Characteristics of drug-related problems discussed by hospital pharmacists in multidisciplinary teams. Pharm World Sci 28: 152–158.

Castelino RL, Sathvik BS, Parthasarathi G, Gurudev KC, Shetty MS, Narahari MG (2011) Prevalence of medication-related problems among patients with renal compromise in an Indian hospital. J Clin Pharm Ther 36: 481–487.

Chisholm MA, Vollenweider LJ, Mulloy LL, Jagadeesan M, Wade WE, DiPiro JT (2000) Direct patient care services provided by a pharmacist on a multidisciplinary renal transplant team. Am J Health-Syst Pharm 57: 1599–1601.

Dosedel M, Hendrychova T, Maly J, Kubena A, Byma S, Vlcek J (2014) Prescription of evidence-based medicine drugs by general practitioners to patients after myocardial infarction: outcomes from the Czech Republic. Acta Pol Pharm 71:189–195.

Flamme-Obry F, Belaiche S, Hazzan M, Ramdan N, Noël C, Odou P, Décaudin B (2018) Clinical pharmacist and medication reconciliation in kidney transplantation. Nephrol Ther 14: 91–98.

Gheewala PA, Peterson GM, Curtain CM, Nishtala PS, Hannan PJ, Castelino RL (2014) Impact of the pharmacist medication review services on drug-related problems and potentially inappropriate prescribing of renally cleared medications in residents of aged care facilities. Drugs Aging 31: 825–835.

Gregorová J, Rychlíčková J, Šaloun J (2017) Standardization of clinical pharmacist's activities: Methodology. Saudi Pharm J 25: 927–933.

Holm H, Bjerke K, Holst L, Mathiesen L (2015) Use of renal risk drugs in patients with renal impairment. Int J Clin Pharm 37; 1136–1142.

Horvat N, Kos M (2016) Development and validation of the Slovenian drug-related problem classification system based on the PCNE classification V 6.2. Int J Clin Pharm 38: 950–959.

Kasiske BL, Wheeler DC (2014) Kidney disease: improving global outcomes--an update. Nephrol Dial Transplant 29: 763–769.

Laliberté MC, Normandeau M, Lord A, Lamarre D, Cantin I, Berbiche D, Corneille L, Prud'homme, L, Lalonde L (2007) Use of over-the-counter medications and natural products in patients with moderate and severe chronic renal insufficiency. Am J Kidney Dis Off J Natl Kidney Found. 49: 245–256.

Levey AS, Atkins R, Coresh J, Cohen EP, Collins AJ, Eckardt KU, Nahas ME, Jaber BL, Jadoul M, Levin A, Powe NR, Rossert J, Wheeler DC, Lameire N, Eknoyan G (2007) Chronic kidney disease as a global public health problem: Approaches and initiatives – a position statement from Kidney Disease Improving Global Outcomes. Kidney Int 72: 247–259.

Levin A, Stevens PE (2014) Summary of KDIGO 2012 CKD Guideline: behind the scenes, need for guidance, and a framework for moving forward. Kidney Int 85:49–61.

Lima LF, Martins BCC, Oliveira FRP, Cavalcante RM, Magalhães VP, Firmino PYM, Adriano LS, Silva AM, Flor MJN, Néri EDR (2016) Pharmaceutical orientation at hospital discharge of transplant patients: strategy for patient safety. Einstein Sao Paulo Braz 14: 359–365.

Matzke GR, Aronoff GR, Atkinson AJ, Bennett WM, Decker BS, Eckardt KU, Golper T, Grabe DW, Kasiske B, Keller F, Kielstein JT, Mehta R, Mueller BA, Pasko DA, Schaefer F, Sica DA, Inker LA, Umans JG, Murray P (2011) Drug dosing consideration in patients with acute and chronic kidney disease a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 80: 1122–1137.

Müllerová H, Vlcek J (1997) Drug information centre--analysis of activities of a regional centre. Int J Med Inf 45: 53–58.

Quintana-Bárcena P, Lord A, Lizotte A, Berbiche D, Lalonde L (2018) Prevalence and Management of Drug-Related Problems in Chronic Kidney Disease Patients by Severity Level: A Subanalysis of a Cluster Randomized Controlled Trial in Community Pharmacies. J Manag Care Spec Pharm 24: 173–181.

Salgado TM, Moles R, Benrimoj SI, Fernandez-Llimos F (2012) Pharmacists' interventions in the management of patients with chronic kidney disease: a systematic review. Nephrol Dial Transplant 27: 276–292.

Steeb D, Webster L (2012) Improving care transitions: optimizing medication reconciliation. J Am Pharm Assoc 52: 43-52

Stemer G, Lemmens-Gruber R (2011) Clinical pharmacy activities in chronic kidney disease and end-stage renal disease patients: a systematic literature review. BMC Nephrol 12: 35.

Viktil KK, Blix HS (2008) The impact of clinical pharmacists on drug-related problems and clinical outcomes. Basic Clin Pharmacol Toxicol 102: 275–280.

Vlcek J, Malý J, Dosedel M (2009) Pharmaceutical care of patients with diabetes mellitus and its relationship to clinical pharmacy. Vnitr Lek 55: 384–388.

Ye ZK, Chen K, Chen YL, Zhai S (2016) A protocol for developing a clinical practice guideline for therapeutic drug monitoring of vancomycin. J Huazhong Univ Sci Technol Med Sci 36: 469–472.