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# Evaluation and Management of Drug-Drug Interactions in Patients Hospitalized in Nephrology and Post-Transplant Wards in a Teaching Hospital

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ABSTRACT

***Background:*** Kidney transplant patients usually take a combination of medications after transplantation; hence, medication safety becomes an important issue in order to maintain the new organ working properly. To evaluate the incidence and risk factors associated with potential drug-drug interactions (pDDIs) in hospitalized patients in Nephrology and Post-transplant wards to improve clinical management of pDDIs by a clinical pharmacist.

***Methods:*** In this cross-sectional study, patients in Nephrology and Post-transplant wards were screened for pDDIs, using the interaction screening program Lexi-comp resource®. After evaluating the detected pDDIs for clinical relevance, the intervention was performed through physicians or nurses for type D and X drug interactions. Intervention feedback, implemented recommendations, and any probable adverse drug reactions were documented.

***Results:*** During the study, 399 patients (239 in nephrology and 160 in post-transplant wards) plus 6105 drug orders were evaluated, and a total of 3263 DDIs were identified; of them, 827 (23.5%) were determined to be D and X classifications, and a total of 89.97% of all hospitalized cases had at least 1 pDDIs. Factors that had the greatest influence on pDDI incidence included the number of drugs and the admitted wards. Patients in the post-transplant ward experienced 2.3 times more DDIs than those in the nephrology ward. In total, 78% of class X and D DDIs required intervention, of which 75% were accepted and implemented by the physicians and nurses.

***Conclusion:*** Clinically relevant pDDIs are common in patients in Nephrology and Post-transplant wards, and pharmacists play a critical role in detecting and managing this medical problem in hospitalized patients.

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## Introduction

Medication errors which included adverse drug events (ADEs) and drug-drug interactions (DDIS) have become critical issues in public health (1, 2). It is reported that annually 7000-9000 patients in the United States die from a medication error and this costs the patients and insurance companies $40 billion yearly (3). DDIs are the most preventable common ADEs (4). It is estimated that potential DDIs (pDDIs) occur in about 20% of hospitalized patients (5).

Pharmacokinetic and pharmacodynamic of drugs can severely impair in a patient with renal failure (6). Since chronic kidney disease (CKD) is usually accompanied with diabetes, hypertension, cardiovascular events, anemia, bone and mineral metabolism abnormalities, and fluid and electrolyte abnormalities (6-8), it is necessary to receive multiple medications to treat these comorbidities, known as polypharmacy. Some studies concluded that on average, patients with CKD on dialysis use 10-12 different medications

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simultaneously (9-11). Leendertse et al., indicated that 5.6% of hospitalizations in CKD patients were due to medication related errors, of which 47% were preventable (12).

Kidney transplantation is an established therapeutic option for many patients with end-stage renal disease. Statistics showed that by the end of 2012, 34166 kidney transplantations were performed in Iran (13), and currently 2500 kidney transplants are being performed annually (14). Since most transplant patients take multiple medications for a lengthy period to maintain immunosuppression, ADEs are very common amongst these patients (7, 15).

To the best of our knowledge, this is the first published study to evaluate the pDDIs in nephrology and post-transplant wards by identifying the risk factors for pDDIs and preventing potential them by clinical pharmacist intervention.

## Methods

This cross-sectional study was conducted in 18-bed nephrology and 14-bed post-transplant wards of Namazee hospital, Shiraz, Iran, affiliated to Shiraz University of Medical Sciences (SUMS). This study was conducted after receiving approval from the local Ethics Committee of SUMS from January to June 2016.

In nephrology and post-transplant wards, patients were under the care of 2-7 attending nephrologists and 1-3 internal residents and clinical pharmacist.

All the patients admitted during the study period were eligible to be enrolled in this study. Totally, 441 adult patients were enrolled; however, 42 patients were excluded because they had received no or only one medication during their hospitalization. Patient's demographic data, physicians' orders, laboratory data disease impression, past and current medical history, prescribed medications and dosage, frequencies, and length of consumption were recorded by a pharmacist supervised by a clinical pharmacist. The detected DDIs, clinical pharmacist interventions and the acceptance or rejection of these interventions were recorded. The patients were followed up until the last day of their stay in nephrology or post-transplant wards, and any adverse drug reactions due to drug interactions were recorded.

Interactions were divided into two categories of "administration interactions" which was related to drug-drug interactions on administration performed by nurses, and second "prescription interactions" which was related to the interactions between prescription drugs, by the physicians. DDIs were evaluated, using Lexi-comp resource® (desktop version 2.3.5, 2016) (16). Also, severity, reliability constant, clinical significance and management of the DDIs were evaluated. DDIs were classified into 5 groups: A, B, C, D, and X (Table 1) (16). If DDIs were class D or X that have clinical importance, the clinical pharmacist intervened. All patients were monitored during the course of hospitalization and the proven DDIs outcome was recorded.

The continuous data is shown as mean ± SD and the categorical data is reported as percentages or frequencies. All data were checked for normality of distribution by Kolmogorov-Smirnov test. T-test was used to compare the mean of quantitative variables, and Chi-Square test was utilized to compare qualitative variables. To determine the correlation between the age and potential DDIs, we used Pearson coefficient test. The relationship between the rate of pDDIs with the number of orders, medications and duration of hospitalization was evaluated by Univariate analysis. Finally, DDIs risk factors were investigated using stepwise logistic regression. In this model, odds ratio and 95% confidence interval were determined for the variables. Statistical analysis was performed using SPSS version 18. P-values less than 0.05 were considered statistically significant.

**Table 1.** Lexi-comp drug interaction software classifications definition of drug-drug interactions.

| Classification | Definition |
|---|---|
| **Class** | |
| **A** | Data have not demonstrated either pharmacodynamics or pharmacokinetic interaction between the specified agents |
| **B** | Data demonstrated that the specified agents may interact with each other, but there is little or no evidence of concern resulting from their concomitant use. |
| **C** | Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients. |
| **D** | Data demonstrate that the two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realize the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes, choosing alternative agents |
| **X** | Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated. |
| **Severity** | |
| **Major** | The effects of interaction may result in death, hospitalization, permanent injury or therapeutic failure |
| **Moderate** | The effects of interaction may need medical interventions |
| **Minor** | The effects of interaction would be considered tolerable in most cases and need no medical intervention |
| **Reliability constant** | |
| **Excellent** | Multiple randomized clinical trials or single randomized clinical trial plus more than two case reports |
| **Good** | Single randomized clinical trial plus less than two case reports |
| **Fair** | More than two case reports or less than two case reports plus other supporting data; or a theoretical interaction based on known pharmacology |

## Results

During the study, 399 patients (239 in nephrology and 160 in post-transplant wards) and 6105 drug orders were evaluated, and a total of 3263 DDIs were detected. The most common prescribed medications and their relative frequencies are shown in Figure 1. Pantoprazole, Prednisolone and calcium salts were the most common prescribed drugs in the nephrology ward while Prednisolone, Mycophenolate Mofetil and Pantoprazole were administered more frequently in comparison to other drugs in the Post-transplant ward. Patients' clinical and demographic data are shown in Table 2.

**Table 2**. Demographic and clinical characteristics of hospitalized patients in the nephrology and post-transplant wards of Namazee hospital (N=399).

| Demographic data | Value |
|---|---|
| Sex<br>Male, N (%)<br>Female, N (%) | <br>240 (60.2)<br>159 (39.8) |
| Age in years (mean±SD) | 47± 18 |
| Duration of hospitalization in days (mean±SD) | 8.8 ±7.4 |
| Drug orders per patients (mean±SD) | 15.3± 13.0 |
| Number of patients in wards, N (%)<br>Nephrology<br>Post transplantation | <br>239 (59.9)<br>160 (40.1) |
| Diagnosis, N (%)<br>CKD[1]<br>AKI[2]<br>ESRD[3]<br>Other kidney diseases[4]<br>Liver disease<br>Others[5] | <br>72 (18)<br>49 (12.3)<br>33 (8.3)<br>159 (39.8)<br>38 (9.5)<br>48 (12) |
| Outcome of patients, N (%)<br>Discharge<br>Transfer to another ward<br>Expired | <br>375 (94)<br>11 (2.8)<br>13 (3.3) |
| Medication class prescribed, N (%)<br>Systemic anti-infective agents<br>Gastrointestinal agents<br>Cardiovascular agents<br>Endocrine & metabolic agents<br>Hematologic agents<br>Biologic & immunologic agents<br>Others[6] | 978 (22.6)<br>731 (17)<br>698 (16)<br>455 (10.5)<br>443 (10.2)<br>381 (8.8)<br>641 (15) |

[1]Chronic kidney disease included stage 1 to 4, [2] Acute kidney injury, [3] End stage renal disease
[4]Other kidney diseases include kidney transplant, rejection of kidney transplant, kidney infection, problems related to kidney transplant, and other problems related to the kidney that are not placed in other cases.
[5]Others include kidney infection, kidney biopsy, encephalitis, pancreas transplant, pancreas disease, nephrotic syndrome, and problems that are not placed in other cases.
[6]Nutrients and nutritional, central neuro-system, respiratory, dermatologic, ophthalmic & otic agents)

A total of 2436 (74.6%) interactions belonged to class C, 759 (23.3%) related to class D, and 68 (2%) as class X. The severity of X and D DDIs were moderate (71%), while 28% and 1% of them were major and minor, respectively. Four hundred and twelve (50%), 279 (34%), 135 (16%), and 1 interaction were considered as good, fair, excellent, and poor, respectively, based on their reliability. Two hundred and fifty-two (63.1%) patients experienced at least one class X or D DDIs. According to Table 3, the incidence of type D and X DDIs in the post-transplant ward was higher than the nephrology ward (P <0.001).

**Table 3.** The incidence of potential DDIs in Nephrology and Post-transplant wards of Namazee hospital.

| Type of DDI | Number of DDIs in each ward (%) | | Total | P-value between two wards |
|---|---|---|---|---|
| | Nephrology ward | Post-transplant ward | | |
| Type C DDI | 1334(45.8%) | 1102(45.2%) | 2436 | 0.051 |
| Type D DDI | 366(48.2%) | 393(51.8%) | 759 | <0.001 |
| Type X DDI | 28(41.2%) | 40(58.8%) | 68 | <0.001 |

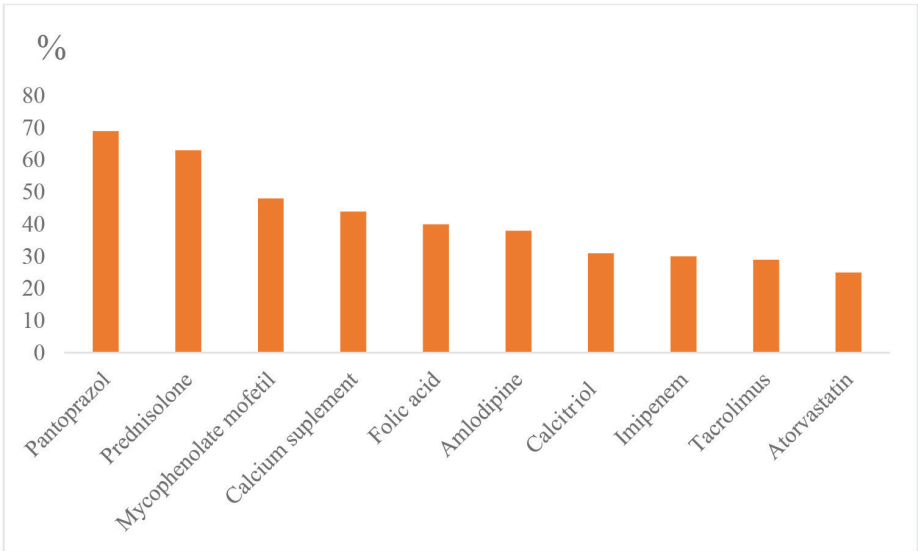
Table 4 shows the most common DDIs, belonging to class C, D and X interactions. Cyclosporine, Imipenem, Ganciclovir, Calcium carbonate and Mycophenolate had the highest interactions with other medications with pDDIs. ADRs were observed in 107 out of 441 patients (26.8%) during the study (Table 5). In total, 827 class X and D DDIs were identified, of which 387 interactions were related to administration interactions and 440 related to prescription interactions, of which 258 interactions required intervention. Interventions were performed by the clinical pharmacist in the case of X and D DDIs, as shown in Table 6.

Our results indicated that on average, 11.75±4.3 and 10.6±5.2 drugs were administered per patient in the post-transplant and nephrology wards, and this difference was significant (P<0.05). Ninety percent of the patients who were taking more than 13 drugs experienced at least one D or X DDI. Also, the patients in the post-transplant ward experienced 2.3 times more DDIs than those in the nephrology ward. Univariate analysis showed that there was a close relationship between the rate of class X or D DDI and the number of prescribed medications, duration of hospitalization, number of day orders, and the type of ward (P<0.001 in all of them). Stepwise logistic regression showed that there was a significant relationship between the presence of at least one class X or D interaction and the number of drugs being used (OR=1.37, CI 95%=1.27-1.47), and also the type of ward (OR=2.3 CI 95%=1.39-1.86). Analysis of the results showed that there was no significant relationship between the occurrence of pDDIs and gender (P:0.57), age (P:0.39) and underlying kidney diseases (P:0.13).

Table 4. The most common potential drug-drug interactions among the patients in Nephrology and Post-transplant wards of Namazee hospital.

| Type of interactions | Drug pairs | Mechanism of interaction | Number (%) |
|---|---|---|---|
| C | Mycophenolate – Pantoprazole | Proton Pump Inhibitors may decrease the serum concentration of Mycophenolate. | 148 (6.1) |
| | Calcitriol- Calcium salts | Calcium salts may enhance the adverse/toxic effect of Vitamin D analogs. | 76 (3.1) |
| | Prednisolone – Ciprofloxacin | Corticosteroids (Systemic) may enhance the adverse/toxic effect of Quinolones. | 61 (2.5) |
| | Prednisolone – Insulin | Hyperglycemia-Associated Agents may diminish the therapeutic effect of Antidiabetic Agents | 60 (2.5) |
| | Mycophenolate - Ciprofloxacin | Quinolones may decrease the serum concentration of Mycophenolate. | 51(2.1) |
| D | Prednisolone - Calcium salts | Calcium Salts may decrease the bioavailability of Corticosteroids (Oral). | 117 (15.4) |
| | Mycophenolate - Calcium salts | Calcium Salts may decrease the absorption of Mycophenolate. | 93 (12.2) |
| | Mycophenolate – Cyclosporine | Cyclosporine (Systemic) may decrease the serum concentration of Mycophenolate. | 39 (5.1) |
| | Ciprofloxacin - Calcium salts | Calcium Salts may decrease the absorption of Quinolones. | 30 (4) |
| | Cotrimoxazole – Fluconazole | CYP¹2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk with Inhibitors). | 25 (3.3) |
| X | Ganciclovir – Imipenem | Ganciclovir may enhance the adverse/toxic effect of Imipenem. | 16 (23.5) |
| | Cyclosporine – Atorvastatin | Cyclosporine (Systemic) may increase the serum concentration of Atorvastatin. | 15 (22) |
| | Tacrolimus – Sirolimus | Sirolimus may enhance the adverse/toxic effect of Tacrolimus (Systemic). Tacrolimus (Systemic) may enhance the adverse/toxic effect of Sirolimus. Sirolimus may decrease the serum concentration of Tacrolimus (Systemic). | 7 (10.3) |
| | Calcitriol– Aluminum salts | Vitamin D Analogs may increase the serum concentration of Aluminum salts. | 5 (7.3) |
| | Tacrolimus – Spironolactone | Potassium-Sparing Diuretics may enhance the hyperkalemic effect of Tacrolimus (Systemic). | 3 (4.4) |

**Figure 1**. The most common prescribed medications among the patients admitted to Nephrology and Post-transplant wards, Namazee hospital.



## Discussion

Detecting and resolving DDIs can help to improve the patients' care and their quality of life and reduce the recurrent hospitalizations and costs to the healthcare system.

Our study showed that 359 (89.97%) patients experienced at least 1 DDIs, and 252 (63%) patients had at least one potential class D or X DDIs; however, in Rama et al. study (17) on 205 patients hospitalized in nephrology ward, 76% of patients experienced potential DDIs. One reason for this difference might be our clinical pharmacist who was in contact and communicated with the nephrologist during his rounds regarding DDIs. Our results showed that nearly 60% of the patients were hospitalized in the nephrology ward and 40% in the post-transplant, but the incidence of pDDIs in the post-transplant ward (55.3%) was more than that in the nephrology ward (44.7%) ($P < 0.05$), which might be because kidney transplant patients must take the number of different classes of medications simultaneously, such as immunosuppressive drugs, prophylactic antimicrobial medications and gastrointestinal related medications; hence, the poly-pharmacy becomes a risk factor for the occurrence of pDDIs. According to other studies, over a period of 1 month to 1 year after kidney transplantation, a common immunosuppressive regimen that a patient should use consists of more than 8 different medications (18-20).

A total of 26.8% of our patients experienced ADR due to DDIs, which was higher than other studies (21, 22). In a study by Joshua et al. (21), conducted in the nephrology ward of a sub-specialty hospital in India over the course of one year, ADR occurred in 17% of patients. It should be noted that this study specifically focused on ADR according to the WHO definition, which is more realistic due to precision, but this study had a limitation. It was a retrospective study and it is possible that the reported ADR was underestimated since careful evaluation of ADR requires close monitoring and patient's follow up. According to Pranabjyoti et al., (22) study results, moon face and allergic reaction were the most reported ADRs among patients with renal disorders, but in our study, rash was the most common ADRs, which might be due to the use of prednisone, but in our study pantoprazole was the most prescribed drug.

Univariate analysis showed that there was a significant relationship between the rate of class X or D DDI and the number of prescribed medications, duration of hospitalization, number of orders, and the type of ward. Further analysis via stepwise logistic regression showed that there was a significant relationship between the presence of at least one class X or D interaction and number of drugs being used, and the ward. In line with our research, many studies found a relationship between the incidence of DDIs and the number of prescribed medications (23, 6, 24-28). In one study evaluating the risk factors for pDDIs in critically ill patients showed that the number of prescribed drugs had the most impact on the occurrence of DDIs in comparison to other risk factors (29).

Based on our findings and previous studies, increased hospitalization is associated with increased incidence of pDDI (30, 31, 27, 32). Sharma et al. showed a significant positive linear relationship between the length of hospital stay and pDDIs ($r=0.63$, $P<0.01$) (32). This relationship can be explained by the increase in the number and type of prescribed medications in long-term hospitalization.

There are many studies that have evaluated DDIs, but only in a few of them interventions were done regarding drug interactions and other medical errors by a clinical pharmacist. In total, in our study 78% of class X and D DDIs required intervention, of which 75% were accepted and implemented by the physicians and nurses. The prime reason for refusing clinical pharmacist recommendations by the physicians was the absence of clinical relevance and/or the rarity of clinical ADRs associated with these pDDI. In Vonbach et al., survey (33), 80.50% of the interventions were accepted by the healthcare team. The difference between the results of this study and ours was their study design. They had five medical wards with 851 patients; also, they used handwritten leaflet with detailed information about the mechanisms of the pDDI, possible ADRs, the clinical management of the pDDI and ADRs, and then these leaflets were sent to the treating physicians. In this method, it seems that physicians have more time to carefully evaluate the interactions and implement the recommendations as compared to when they communicate verbally (34).

Our study had several limitations that have to be considered. First, our study included only one hospital a city, while it would be better to compare hospitals in different cities. Second, it is possible that some pDDIs were missed if they were not considered by Lexi Comp® and it is recommended that we should use different software for detecting more pDDIs. Third, patients in this study were followed only during their hospitalization period at the nephrology and post-transplant wards and if they were transferred to other wards, they were excluded from the study. It seems that the use of decision support systems, such as electronic prescription and computer system for monitoring and reporting DDIs, as well as inclusion of a clinical pharmacist as a member of the multidisciplinary healthcare team can reduce DDIs.

In conclusion, the present study showed that pDDIs were common in the post-transplant and nephrology wards. Patients admitted to the post-transplant ward are at greater risk of drug interactions due to the high number of prescribed drugs. The number of prescribed medications, duration of hospitalization, number of day orders, and type of the ward were identified as risk factors for occurrence of class X or D DDIs. Given these points, more attention should be paid to drug interactions in renal failure patients, especially kidney recipients.

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