Review Article

The role of the pharmacist in the management of kidney transplant recipients

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ABSTRACT

Pharmacists may play a key role on the multidisciplinary transplant team. This article describes the development and current status of pharmacists in the management of transplant recipients in the United States. Traditionally, pharmacists played an important support role in transplant medicine. This role has been expanded to include direct patient care for the avoidance, detection, and/or treatment of side effects from the polypharmacy necessary in the management of these complex patients. Pharmacists provide pre- and post-transplant education to transplant recipients to enhance adherence to complicated medical regimens and thereby reduce readmission to hospital and unscheduled, costly visits to urgent care centers and/or hospital emergency departments.

Key words: Collaboration, compliance, pharmacist

INTRODUCTION

Because of their extensive knowledge of pharmacology, pharmacists may play key roles on multidisciplinary transplant teams. In the USA, the United Network for Organ Sharing (UNOS) administers the Organ Procurement and Transplantation Network. It is responsible for setting standards for all USA Transplant Programs, and it requires that all transplant programs identify at least one pharmacist to be responsible for providing pharmaceutical care to solid organ transplant recipients.[1] In 2007, the Center for Medicare and Medicaid Services, the government agency responsible for administration of several key federal health-care programs, followed suit and now requires that every transplant center identify an individual trained in pharmacology.[2] Although they do not specifically state that the individual trained in pharmacology must be a pharmacist, it is generally accepted that this role is best filled by a pharmacist.

The role of pharmacists as part of the multidisciplinary transplant team has been well documented for four decades. In 1976, Mitchell described pharmacists as an integral part of the transplant team attending daily rounds, providing medication instruction, following patients, and counseling at discharge.[3] With the increasing recognition of pharmacists as members of the transplant team since the updated UNOS regulations of 2004, the role of pharmacists in transplant has increased significantly. This article describes the development and current status of pharmacists in the management of transplant recipients.

TRANSPLANT PHARMACY PRACTICE

Traditionally, pharmacists played an important supporting role in transplant medicine, with a focus on dispensing medications and providing tools to improve adherence. Today, however, the role of pharmacists has expanded to include responsibilities in the pretransplant, perioperative,

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and posttransplant periods. In daily practice, USA pharmacists are responsible for monitoring and managing complications of immunosuppressive medications. Some of the important components of the job are recognizing drug–drug and drug-disease interactions, monitoring and managing toxicities of immunosuppressants, antimicrobials, and other essential posttransplant medications. Pharmacists provide extensive pre- and post-transplant education to patients to enhance adherence and minimize unscheduled and costly visits to an urgent care center and/or hospital emergency department.

Drug–drug interactions are very important to consider in the posttransplant setting. For example, calcineurin inhibitors (tacrolimus and cyclosporine) and mammalian target of rapamycin inhibitors (sirolimus and everolimus) are substrates of cytochrome P450 (CYP) isoenzyme 3A and p-glycoprotein and are subject to numerous drug interactions with commonly used posttransplant medications. Of particular importance are interactions with anti-infectives, human immunodeficiency virus and hepatitis C virus protease inhibitors, statins, psychiatric medications, antiseizure medications, and some antihypertensives [Tables 1a-c].[4-8] There are also numerous drug-disease interactions that must be monitored closely posttransplant. Mental status changes from immunosuppressants such as prednisone, cyclosporine, and tacrolimus may adversely affect patients with preexisting mental health issues.[9-13] Medication absorption may be altered in patients who have undergone gastric bypass or other gastrointestinal surgeries, patients with short gut syndrome, or patients with gastroparesis from diabetes mellitus.[14-19] More frequent monitoring of immunosuppressant blood levels, dose adjustments, and modification of immunosuppressive regimens to alternative agents with fewer drug-disease interactions may be assessed by a clinical pharmacist to optimize the management of these patients.

RESOURCES FOR PHARMACISTS

Pharmacists have many resources available to them through various online and mobile references and clinical decision support (CDS) systems within electronic health records (EHRs) to assist in analyzing drug–drug and drug-disease interactions, therapeutic duplication, and monitoring therapeutic drug levels. Many institutions, especially larger health systems and hospitals associated with a university, purchase drug information resources such as Micromedex, Lexicomp, PubMed, Ovid, DynaMed, and UpToDate for physicians, pharmacists, and nurses to use in their daily practice. Micromedex, Lexicomp, and UpToDate also have mobile applications that can be downloaded and used on smartphones and tablets which can be convenient to use when rounding on patients or in an ambulatory clinic. There are many other drug information resources available via mobile applications including Medscape, Johns Hopkins ABX Guide, and Epocrates; however, a comprehensive list of all available mobile drug information resources is outside of the scope of this review. CDS systems within EHRs utilize multiple tools, including customizable drug databases, to enhance clinical decision-making for pharmacists and other healthcare providers. CDS systems can include alerts, workflow support, and process-based decision support.[20] Alerts can be a helpful tool to assist pharmacists in identifying drug–drug and drug-disease interactions, specific laboratory requirements before initiation of a medication, or need for alternative medication decisions due to drug shortages or formulary restrictions. CDS workflow support may include order sets with preselected medication orders or note templates that are meant to improve efficiency in data entry and documentation. Process-based decision support can enhance the comprehensive care of the patient by identifying follow-up tests that may be needed for a patient such as therapeutic drug levels. These tools do have their limitations: False positive alerts may lead to alert fatigue, note templates may not include all pertinent up-to-date information, and process-based support may lead to ordering unnecessary laboratory tests. The American Society of Health-System Pharmacists has recently published guidelines on the design of database-driven CDS systems which include recommendations on the essential capabilities that all CDS systems should possess.[21] These systems offer tools that pharmacists need in their daily practice to improve quality, safety, and cost of health care.

MEDICATION MANAGEMENT

Pharmacists may provide medication therapy management (MTM) through collaborative drug therapy management (CDTM) agreements under the direction or supervision of a licensed physician or nurse practitioner through a written protocol for patient- and disease-specific medication therapy. MTM activities under CDTMs may include ordering, changing, and/or substituting therapies and/or ordering laboratory tests to monitor drug safety, effectiveness, or therapeutic levels. CDTMs provide pharmacists with increased autonomy and offset some of the work traditionally performed by physicians.

In transplant medicine, compliance plays an important role in allograft survival, especially in younger recipients. Noncompliance to immunosuppressive therapy is a significant cause of graft failures in kidney transplant patients.[22] In a recent study by Gaynor *et al.*, noncompliance to immunosuppressive therapy was found to be the cause of graft failure in approximately 10% of kidney transplant recipients, and as high as one-third of patients in high-risk groups, for example, teenagers.[23] In general, compliance is defined as the extent a patient correctly follows medical advice. In pharmacotherapy, compliance is described as the degree of adherence to a prescribed medication regimen. The implementation of a clinical pharmacy intervention

Table 1a: Cyclosporine and tacrolimus drug-drug interactions

Drug	Mechanism	Effects	Severity*	Comments
Acetazolamide	Decreased clearance	Increase CNI levels	3	May cause acidosis
Acyclovir	Crystallization in renal tubules	Nephrotoxicity	4	Avoid dehydration. Infuse over 1 h
Amikacin	Synergistic nephrotoxicity	Nephrotoxicity	3	Monitor aminoglycoside levels very close. Target amikacin peak 30-40 and trough <10
Amiloride	Decrease K^+ secretion	Hyperkalemia	3	Avoid in transplant recipients
Amiodarone	Decrease clearance	Nephrotoxicity	3	Very slow onset and offset
Amlodipine	Decrease clearance	Increase CNI levels	4	10-15% increase in CNI levels
Amphotericin B	Synergistic nephrotoxicity	Nephrotoxicity	3	Recommend hydration and close electrolyte monitoring
Atorvastatin	CSA decreases clearance of statins	Myopathy, rhabdomyolysis	3	Monitor CPK closely
Carbamazepine	Increase clearance	Decrease CNI levels	3	Slow onset (may take up to 7 days) Monitoring of CNI levels
Carvedilol	Decrease clearance	Increase CNI levels	3	Can cause toxicity
Chloroquine	Decrease clearance	Increase CNI levels	3	Can cause toxicity
Cholestyramine	Increase clearance	Decrease CNI levels	4	Separate doses by 3 h
Cimetidine	Inhibit creatinine secretion	Increase serum creatinine	4	Use other H2RAs (ranitidine, famotidine, nizatidine)
Clarithromycin	Decrease clearance	Increase CNI levels	2	Azithromycin is the preferred agent
Colchicine		Increase neurotoxicity	3	Gastrointestinal dysfunction and neuromyopathy
Co-trimoxazole	Inhibit creatinine secretion	Increase serum creatinine Hyperkalemia	4	Preferred agent for PJP
Digoxin	CSA may decrease clearance of digoxin	Increase digoxin levels	3	Monitor digoxin levels closely
Diltiazem	Decrease clearance	Increase CNI levels	3	Monitor CNI levels closely
Enalapril	Renal dysfunction in	Increase serum creatinine	3	Use for treatment of posttransplant erythrocytosis
Erythromycin	Decrease clearance	Increase CNI levels	2	Azithromycin is the preferred agent
Fluconazole	Decrease clearance	Increase CNI levels	3	Increase LFTs, monitor levels carefully
Fluvoxamine	Decrease clearance	Increase CNI levels	2	Monitor CNI levels closely
Fosinopril	Renal dysfunction in RAS	Nephrotoxicity	3	Can cause elevation of serum creatinine
Fosphenytoin	Increase clearance	Decrease CNI levels	3	Monitor CNI levels closely
Gentamicin	Synergistic nephrotoxicity	Nephrotoxicity	3	Monitor blood concentrations very closely
Griseofulvin	Unknown	Decrease CNI levels	3	Monitor CNI levels closely
Itraconazole	Decrease clearance	Increase CNI levels	3	Monitor CNI levels closely, decrease dosage 50-85%
Ketoconazole	Decrease clearance	Increase CNI levels	3	Monitor CNI levels closely, decrease dosage 25-75%
Lovastatin	CSA decreases clearance of statins	Myopathy, rhabdomyolysis	3	Require close CPK monitoring
Methyl-prednisolone	Decrease clearance	Increase CNI levels	3	Only high doses
Methyl-testosterone	Decreased cyclosporine metabolism	Increase CNI levels	3	Can cause toxicity
Metoclopramide	Decrease gastric emptying time	Increase CNI levels	3	Increase peak and AUC by 25-50%
Metronidazole	Decrease clearance	Increase CNI levels	4	Monitor CNI levels
Mibefradil	Decrease CNI clearance	Increase CNI levels	3	Monitor CNI levels
Nafcillin	Increase CNI clearance	Decrease CNI levels	3	Monitor CNI levels
Nefazodone	Decrease CNI clearance	Increase CNI levels	3	Monitor CNI levels
Nicardipine	Decrease CNI clearance	Increase CNI levels	3	Monitor CNI levels
NSAIDs	Synergistic nephrotoxicity	Nephrotoxicity	3	CNI-induced vasoconstriction
Octreotide	Decrease intestinal absorption of CNI	Decrease CNI levels	3	Monitor CNI levels
Phenobarbital	Increase CNI clearance	Decrease CNI levels	3	Slow onset, slow offset

Contd...

Table 1a: Contd...

Drug	Mechanism	Effects	Severity*	Comments
Phenytoin	Increase CNI clearance	Decrease CNI levels	3	Monitor cyclosporine/FK levels
Pravastatin	CSA decreases clearance of statins	Myopathy, rhabdomyolysis	3	Monitor CPK carefully
Rifabutin	Increase CNI clearance	Decrease CNI levels	3	Monitor CNI levels, rifabutin is a less potent hepatic enzyme inducer than rifampin
Rifampin	Increase CNI clearance	Decrease CNI levels	2	Monitor cyclosporine/FK levels
Sildenafil	Increase FK levels	Decrease CNI levels	4	
Simvastatin	CSA decreases clearance of statins	Myopathy, rhabdomyolysis	4	Monitor CPK carefully
Spironolactone	Decrease K^+secretion	Hyperkalemia	3	Avoid
Terbinafine	Decrease CNI clearance	Increase CNI levels	3	Monitor CNI levels
Ticlopidine	Increase CNI clearance	Decrease CNI levels	3	Monitor CNI levels
Tretinoin	Inhibit tretinoin metabolism	Increase tretinoin toxicity	3	
Triamterene	Decrease K^+secretion	Hyperkalemia	3	Avoid
Troglitazone	Increase CNI clearance	Decrease CNI levels	3	Hepatotoxicity
Valacyclovir	Hemolytic anemic syndrome	Renal dysfunction	3	Acyclovir or famciclovir is preferred agents for treatment of HSV and VZV
Voriconazole	Decrease clearance	Increase CNI levels	3	Monitor levels carefully, decrease dosage 25-75%

*Severity: (1) Avoid combination, (2) usually avoid (use only no other alternative agents available), (3) monitor closely, (4) no action needed (the risk of ADR is small). HSV=Herpes-simplex virus, VZV=Varicella-zoster virus, CNI=Calcineurin inhibitor, CSA=Cyclosporine A, CPK=Creatine phosphokinase, FK=Tacrolimus, AUC=Area under the curve, LFTs=Liver function tests, PJP=*Pneumocystis jiroveci* pneumonia, RAS=Renal artery stenosis, H2RAs=Histamine-2 receptor antagonists, ADR=Adverse drug reaction, K^+=Potassium

service in an outpatient transplant clinic for postrenal transplant patients is an essential part of pharmacist activities to improve pharmacotherapy compliance. The clinical pharmacist reviews and optimizes medication therapy, encourages adherence, provides instructions on how to take the medications, assists with enrollment into medication assistance programs, and provides recommendations to the health-care team. In a study by Chisholm-Burns *et al.*, patients were randomized to receive traditional care from the interdisciplinary group (control group) or traditional care in combination with clinical pharmacy services (the intervention group) ($N = 12$ for each group).[24] The majority of patients (66.7%) received kidney transplants from a deceased donor, and approximately 88% were prescribed cyclosporine. The intervention group had a higher overall adherence rate (mean 96.1% vs. 81.6%, $P < 0.001$) and a longer period of adherence time until the 1st nonadherent month, defined as ≤80% adherence (mean 11 months vs. 9 months, $P < 0.05$). There were fewer adverse drug reactions, lower costs, increased patient satisfaction, and improved health outcomes in patients that had a clinical pharmacist as part of their team.[25-30]

Pharmacists are well educated about therapy unrelated to transplantation. Maldonado *et al.* reported that pharmacologic and nonpharmacologic risks are important when evaluating patients on the transplantation waitlist.[31] Their study reviewed the pertinent literature regarding pharmacologic and nonpharmacologic risks that need to be mitigated before receiving a transplant including anticoagulation concerns, mental health medications, chronic pain medication use, allergies, hormonal contraception, history of immunosuppressant use, medication absorption issues, alcohol and tobacco use, illicit substance use, herbal substance use, vaccine delivery, infection prophylaxis and treatment, medication compliance issues, communication barriers, and financial, insurance, or transportation challenges. After reviewing the literature, the authors concluded, based on practitioner consensus, that all of the above-mentioned pharmacologic and nonpharmacologic factors influence outcomes in kidney transplant patients and should be assessed before transplantation. This can be done by the clinical pharmacist.

Taber *et al.* demonstrated that medication use and safety are believed to be the core issues causing delayed discharge and early readmissions of kidney transplant recipients.[32] To improve these common issues, a multidisciplinary quality improvement program was initiated to improve clinical outcomes. These services included improved medication reconciliation, development of a diabetes management service, and improved discharge medication dispensing, delivery, education, and scrutiny. The results showed a reduction in medication discrepancies by >2 per patient and 100% adherence with reconciliation. A 40% reduction in medication safety issues was documented as a result of pharmacists reviewing discharge medications. Short length of stay, a 14% reduction in delayed discharges, and a 50% reduction in 7-day readmission rates were noticeable outcomes. In this study, pharmacists provided

Table 1b: Sirolimus and everolimus drug-drug interactions

Drug	Mechanism	Effects	Severity*	Comments
ACE-inhibitors	Synergistic myelosuppression	Anemia, neutropenia	3	Increase bone marrow toxicity
Amprenavir	Increase plasma levels	Hyperlipidemia, anemia, neutropenia	3	Monitor sirolimus levels
Bromocriptine	Increase plasma levels	Hyperlipidemia, anemia, neutropenia	3	Monitor sirolimus levels
Carbamazepine	Decrease intestinal absorption	Decrease sirolimus levels	2	Monitor sirolimus levels
Cholestyramine	Decrease intestinal absorption	Decrease sirolimus levels	3	Monitor sirolimus levels
Clarithromycin	Increased plasma levels	Hyperlipidemia, anemia, neutropenia	2	Monitor sirolimus levels Azithromycin is the preferred agent
Cyclosporine	Increase plasma levels when taken at the same	Hyperlipidemia, anemia, neutropenia	3	Monitor sirolimus levels, give 4 h after the dose
Danazol	Decrease intestinal absorption	Decrease sirolimus levels	3	Monitor sirolimus levels
Diltiazem	Increase plasma levels	Hyperlipidemia, anemia, neutropenia	2	Monitor sirolimus levels Amlodipine is the preferred agent
Erythromycin	Increase plasma levels	Hyperlipidemia, anemia, neutropenia	2	Monitor sirolimus levels Azithromycin is the preferred agent
Fluconazole	Increase plasma levels	Hyperlipidemia, anemia, neutropenia	2	Monitor sirolimus levels
Ganciclovir	Synergistic myelosuppression	Anemia, neutropenia	3	
Indinavir	Increase plasma levels	Hyperlipidemia, anemia, neutropenia	2	Monitor sirolimus levels
Itraconazole	Increase plasma levels	Hyperlipidemia, anemia, neutropenia	2	Monitor sirolimus levels
Metoclopramide	Increase plasma levels	Hyperlipidemia, anemia, neutropenia	3	Monitor sirolimus levels
Nicardipine	Increase plasma levels	Hyperlipidemia, anemia, neutropenia	2	Monitor sirolimus levels Amlodipine is the preferred agent
Phenobarbital	Increase metabolism	Decrease sirolimus levels	2	Monitor sirolimus levels
Phenytoin	Increase metabolism	Decrease sirolimus levels	2	Monitor sirolimus levels
Rifabutin	Increase metabolism	Decrease sirolimus levels	2	Monitor sirolimus levels
Rifampin	Increase metabolism	Decrease sirolimus levels	2	Monitor sirolimus levels
Ritonavir	Increase plasma levels	Hyperlipidemia, anemia, neutropenia	2	Monitor sirolimus levels
TMP/SMX	Synergistic myelosuppression	Anemia, neutropenia	3	
Verapamil	Increase plasma levels	Hyperlipidemia, anemia, neutropenia	2	Monitor sirolimus levels
Voriconazole	Increase plasma levels	Hyperlipidemia, anemia, neutropenia	2	Monitor sirolimus levels

*Severity: (1) Avoid combination, (2) usually avoid (use only no other alternative agents available), (3) monitor closely, (4) no action needed (the risk of ADR is small). ACE=Angiotensin-converting enzyme, ADR=Adverse drug reaction

Table 1c: Azathioprine and mycophenolate drug–drug interactions

Drug	Mechanism	Effects	Severity*	Comments
ACE-inhibitors	Synergistic myelosuppression	Anemia, neutropenia	3	Increase bone marrow toxicity
Acyclovir	Increase AUC of MMF	Not significant	4	
Allopurinol	Inhibit xanthine oxidase	Severe neutropenia	2	Decrease azathioprine dose by 75%
Antacids	Decrease absorption of MMF	Decrease efficacy	3	
Cholestyramine	Decrease absorption of MMF	Decrease efficacy	3	Increase bone marrow toxicity
Ganciclovir	Synergistic myelosuppression	Anemia, neutropenia	3	
TMP/SMX	Synergistic myelosuppression	Anemia, neutropenia	3	

*Severity: (1) Avoid combination, (2) usually avoid (use only no other alternative agents available), (3) monitor closely, (4) no action needed (the risk of ADR is small). ACE=Angiotensin-converting enzyme, ADR=Adverse drug reaction, MMF=Mycophenolate mofetil, TMP/SMX=Trimethoprim-sulfamethoxazole

comprehensive medication reviews to identify drug–drug, drug-lab, and drug-nutrition interactions for a given therapeutic regimen and to design appropriate plans, along with other health-care team members, to minimize the chance of significant medication problems. Clinical improvement in medication safety in kidney transplant patients was the result of having a multidisciplinary quality improvement initiative.

Martin *et al.* assessed the expanding roles of transplant pharmacists across each aspect of the care of transplant recipients.[33] In a survey to 118 transplant centers, 36 out

of 41 responding centers had incorporated pharmacists into the transplant team. These pharmacists were involved in kidney (86%), liver (71%), pancreas (50%), heart (25%), and lung (7%) transplants. Pharmacists were salaried through the department of pharmacy (74%), college of pharmacy (12%), transplant center (8%), and the department of surgery (6%). Posttransplant care was the primary focus of these transplant pharmacists. The average percentage of the pharmacists' time was spent as follows: Inpatient service (43%), outpatient clinic (15%), research (14%), other transplant-related (6%), and nontransplant-related (22%). According to the responding centers, the average number of organs transplanted was 99 kidneys, 45 livers, 28 pancreata, 14 hearts, and 26 lungs. The number of transplants was not correlated with the presence or absence of a clinical pharmacist.

CONCLUSION

Transplant clinical pharmacists have expertise in patient education, detection of major drug adverse events and interactions, and improvement of adherence. Pharmacists play a vital role in patient monitoring to determine whether or not a specific event was caused by a specific medication. In the field of transplantation, pharmacists are integral members of the transplant patient care team as experts in medication-use safety and quality.

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Conflicts of interest
There are no conflicts of interest.

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