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A Critical Analysis of the Specific Pharmacist Interventions and Risk Assessments During the 12-Month TRANSAFE Rx Randomized Controlled Trial

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Abstract

Background: Medication safety issues have detrimental implications on long-term outcomes in the high-risk kidney transplant (KTX) population. Medication errors, adverse drug events, and medication nonadherence are important and modifiable mechanisms of graft loss. **Objective:** To describe the frequency and types of interventions made during a pharmacist-led, mobile health–based intervention in KTX recipients and the impact on patient risk levels. **Methods:** This was a secondary analysis of data collected during a 12-month, parallel-arm, 1:1 randomized clinical controlled trial including 136 KTX recipients. Participants were randomized to receive either usual care or supplemental, pharmacist-driven medication therapy monitoring and management using a smartphone-enabled app integrated with telemonitoring of blood pressure and glucose (when applicable) and risk-based televisits. The primary outcome was pharmacist intervention type. Secondary outcomes included frequency of interventions and changes in risk levels. **Results:** A total of 68 patients were randomized to the intervention and included in this analysis. The mean age at baseline was 50.2 years; 51.5% of participants were male, and 58.8% were black. Primary pharmacist intervention types were medication reconciliation and patient education, followed by medication changes. Medication reconciliation remained high throughout the study period, whereas education and medication changes trended downward. From baseline to month 12, we observed an approximately 15% decrease in high-risk patients and a corresponding 15% increase in medium- or low-risk patients. **Conclusion and Relevance:** A pharmacist-led mHealth intervention may enhance opportunities for pharmacological and nonpharmacological interventions and mitigate risk levels in KTX recipients.

Keywords
kidney transplantation, pharmacists, medication reconciliation, patient education

Introduction

Medication safety issues are a predominant driver of poor long-term health outcomes, particularly within the high-risk kidney transplant (KTX) population. The era of modern immunosuppression has produced significant advancements in short-term graft outcomes, but these improvements have been slow to translate to long-term survival. Although contemporary immunosuppressive therapies are highly effective at preventing rejection, the increasing complexity and considerable toxicity burden of these regimens makes patients vulnerable to medication safety issues.[1] Medication safety issues, encompassing adverse drug events, medication errors, and medication nonadherence, are among the chief contributors to graft loss.[2-4] Assessing patient risk of developing medication safety issues that could lead to hospitalizations, increased health care costs, and potentially graft loss may be a useful tool for transplant teams. Early identification and mitigation of medication safety issues may be key to preventing downstream consequences.

Clinical pharmacists are uniquely positioned to recognize and attenuate medication safety issues. In the kidney

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transplant population, research demonstrates that the integration of clinical pharmacists into the multidisciplinary transplant care team can lead to improvements in medication reconciliation and patient adherence.[5-8] As the role of the clinical pharmacist in transplant continues to evolve, they will likely play a key role in the search for new approaches to reducing medication safety issues.

In this secondary analysis of data generated during the TRANSAFE Rx study, a prospective randomized clinical trial investigating the impact of a pharmacist-led, mHealth-based intervention, we summarize clinical pharmacist intervention types and trends as well as changes in patient risk level over time.

Methods

Study Design

We conducted a secondary analysis of data generated during a 12-month, parallel arm, 1:1 randomized controlled clinical trial including 136 adult kidney transplant recipients (68 in each arm; NCT03247322). Full details regarding the study rationale and design have been published elsewhere.[9] The primary aim was to summarize the types of interventions made by the clinical pharmacist in the treatment arm. We also sought to examine trends in these interventions over time and describe the impact on patient risk level. This work was conducted in compliance with the institutional review board requirements.

Intervention

All patients received usual posttransplant care, including routine clinic visits and laboratory monitoring. As part of usual care, pharmacists follow kidney patients while in the hospital and during clinic visits during the first 6 months posttransplant. Beyond this early posttransplant period, pharmacists only see patients at the request of the provider, typically concerning medication-related issues. No intervention data were collected on study participants in the control cohort. In addition to usual care, patients randomized to intervention received supplemental clinical pharmacist–led medication therapy monitoring and management via an mHealth-based smartphone app, coupled with risk-based televisits and at-home blood glucose and blood pressure monitoring. The app alerted the clinical pharmacist to significant self-reported medication nonadherence, concerning trends in or singularly concerning blood pressure/glucose values, and patient-reported medication changes made by outside providers and empowered the pharmacist to be engaged in transitions of care. The pharmacist responded to alerts by identifying medication issues and collaborating with providers to develop and integrate management plans.

Outcomes

The primary outcome of this analysis was pharmacist intervention types. The clinical pharmacist recorded both nonpharmacological and pharmacological interventions weekly. For the purpose of this analysis, intervention types were assessed by month based on pharmacist notes and further categorized as patient education, medication changes, medication reconciliation, prescription refills, facilitated medication access, and study technology–related issues. Weekly risk assessments were used to determine risk-based televisits. Patients were identified as high risk if they met 2 or more of the following high-risk criteria: $<80\%$ adherence to medications and/or missed clinic visits, blood pressure outside of 20% of goal, $<80\%$ of blood sugars within goal range, or moderate to severe adverse effects. Patients meeting 1 of the high-risk criteria were deemed moderate risk, whereas those meeting none of the criteria were low risk.

Statistical Analysis

All outcomes reported in this analysis were summarized using descriptive statistics. Continuous data were described using means and SDs. Categorical data were presented as proportions and percentages. Clinical outcomes reported during the TRANSAFE Rx study are briefly reviewed in this article. A detailed overview of the statistical methods used to report these outcomes has been published elsewhere.[10]

Results

Study Population

A total of 68 patients were included in the intervention cohort. Table 1 outlines baseline characteristics of study participants. At baseline, the mean age was 50 years, and participants were predominantly male (51.5%) and Black (58.8%). The primary etiologies of kidney failure were hypertension (92.6%) and diabetes (27.9%); 85.3% of patients were on dialysis at the time of transplant.

Intervention Types and Trends

Table 2 displays the types of pharmacist interventions made during the 12-month study. Predominant pharmacist intervention types included medication reconciliation (n = 213) and patient education (n = 144). Medication changes, encompassing additions, deletions, dose adjustments, schedule changes, interval changes, and dose form changes, were also common. In total, the pharmacist made 141 medication changes, most frequently scheduling changes (n = 41) and deletions (n = 33). Other pharmacist interventions included mitigating study-technology–related issues (n = 45),

Table 1. Baseline Characteristics of Study Participants.

Characteristic	Intervention (n = 68)
Age (years)	50 ± 12.3
Male	35 (51.5%)
Female	33 (48.5%)
White	27 (39.7%)
Black	40 (58.8%)
History of diabetes	19 (27.9%)
History of hypertension	63 (92.6%)
Dialysis at transplant	58 (85.3%)
Years on dialysis	3.9 ± 2.6

facilitating medication access (n = 16), and refilling medications (n = 12).

Patient education, medication reconciliation, and medication changes were the most frequent interventions made during month 1 of the study (Figure 1). Whereas patient education and medication changes trended downward as the study progressed, medication reconciliation remained consistent from month 1 to month 12. The frequency of prescription refills, medication access, and study technology–related interventions was largely stable throughout the study period.

Risk Assessment

At baseline, the dispersion of high-risk and medium-to-low risk patients was nearly equal (Figure 2). From month 1 to month 12, we observed an approximately 15% reduction in those patients deemed high risk and a corresponding increase of approximately 15% in medium-to-low risk patients.

Medication Errors, Adverse Events, Hospitalizations, and Infections

A comprehensive overview of clinical outcomes reported during the TRANSAFE Rx study have been published elsewhere.[10] Patients randomized to the intervention cohort experienced a significant reduction in medication errors (61% reduction in the risk rate; incidence risk ratio = 0.39; 95% CI = 0.28-0.55; $P < 0.001$) as compared with usual care. Administrative errors were primarily a result of omissions, additions, and prescribing errors, whereas clinical errors predominantly encompassed nontreated or undertreated conditions. The intervention also produced significantly lower incidence risk of composite grade 3 or higher adverse events (adjusted IRR = 0.55; 95% CI = 0.30-0.99; $P = 0.05$). Common adverse event classifications included cardiovascular events, metabolism and nutrition disorders, and kidney-related events. Throughout the study period, patients in the intervention group had significantly fewer hospitalizations (1.08 vs 0.65 hospitalizations per patient-year; $P = 0.007$). Primary reasons for hospitalizations were infection, AKI, and cardiovascular- or gastrointestinal-related conditions. Infections rates during the 12-month follow-up were comparable between groups.

Table 2. PharmD Interventions.

PharmD interventions	Number of interventions
Patient education	144
Additions	29
Deletions	33
Dose adjustments	27
Schedule changes	41
Interval changes	5
Dosage form changes	6
Medication reconciliation	213
Prescription refills	14
Facilitating medication access	16
Study technology–related issues	45

Discussion

In this secondary analysis of data gathered during the TRANSAFE Rx study, we described the frequency and types of interventions made during a pharmacist-led, mHealth-based initiative. The primary interventions made by clinical pharmacists encompassed medication reconciliation and patient education. The intervention also produced a reduction in the number of KTX recipients deemed high risk. To our knowledge, this is the first study describing the frequency and trends in pharmacist intervention and risk assessments using a mHealth-based intervention in transplant recipients.

As the role of the pharmacist continues to evolve, research has demonstrated that engaging pharmacy services within the transplant team can improve patient medication management, including medication reconciliation and patient education. In a systematic review of 12 studies, representing 1837 transplant patients, Sam et al[11] found that pivotal pharmacist activities included medication counseling and medication reconciliation. Patient education and counseling was a pillar of pharmacist intervention in 9 of these studies. The provision of education mainly occurred during face-to-face encounters within the inpatient setting prior to discharge and at follow-up clinic visits. In another study, Musgrave et al[12] determined that pharmacists prevented 1.9 errors per patient on discharge medication reconciliations in a prospective cohort of patients. Of the errors not identified at the time of discharge, all were identified by the pharmacist at the patient's first clinic visit. In a retrospective cohort of patients, an average of 3.4 errors per patient made at discharge were not corrected until at least the time of the first clinic visit.[12] In a recent study, a pharmacist-driven intervention was designed to improve medication accuracy in KTX recipients in the outpatient setting. In this study, a pharmacist performed medication

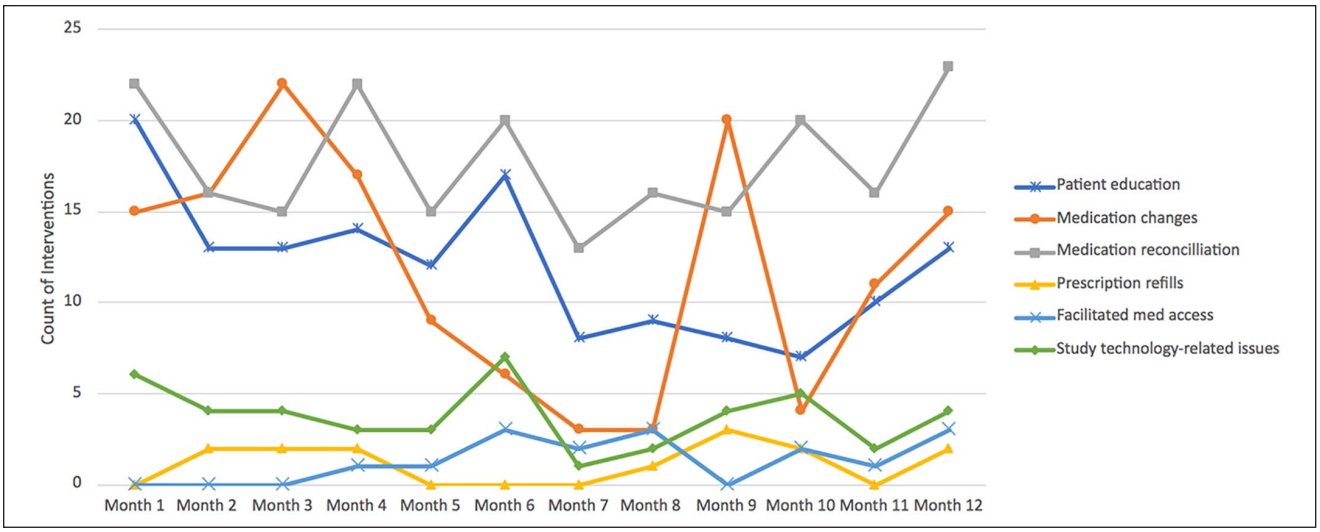

Figure 1. PharmD interventions by month.

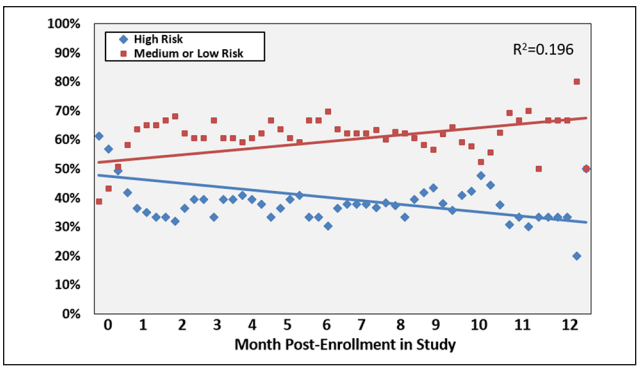

Figure 2. PharmD risk assessment.

reconciliation with patients via telephone 2 weeks after a clinic visit and significantly reduced medication list discrepancies from 95% to 28% ($P < 0.05$).[8]

Research has demonstrated that clinical pharmacist intervention improves outcomes in other disease states outside of transplant. In a study involving 180 patients with heart failure and reduced ejection fraction undergoing evaluation in the ambulatory setting, patients were randomized to receive either clinical pharmacist evaluation or usual care. The intervention included clinical pharmacist–led medication evaluation, therapeutic recommendations, patient education, and telehealth monitoring. For the primary composite end point of all-cause mortality and heart failure clinical events, the intervention produced significantly lower rates as compared with usual care (4 vs 16; $P = 0.005$). Additionally, higher doses of angiotensin-converting enzyme (ACE) inhibitors were seen in the intervention arm. These results demonstrated that engaging clinical pharmacists as members of the multidisciplinary heart failure team can improve clinical outcomes. The authors noted that these improvements may come as a result of increased ACE inhibitor doses and closer follow-up.[13] Another study in the heart failure population showed improved medication compliance following a pharmacy-led intervention in patients with moderate to severe disease.[14] Barker et al[15] found that postdischarge pharmacist direction medication reviews did not offer improvements on mortality or health care utilization and highlighted the need for a multidisciplinary approach versus pharmacist intervention alone.

In diabetes, clinical pharmacist engagement can improve long-term health outcomes. In a review of 25 studies including nearly 3000 patients with diabetes, Iqbal et al[16] concluded that across a variety of pharmacist-led interventions, pharmacists were able to produce significant reductions in hemoglobin A_{1C} levels, improve outcomes, and reduce disease-related complications. In another recent systematic review, Presley et al[17] evaluated 59 studies with pharmacist-driven interventions in patients with diabetes. The authors found that most studies engaged the patient in the decision-making process and aimed to improve medication adherence. Several studies involved other health care professionals (ie, nurses, dietitians, physicians) and highlighted the importance of a multidisciplinary approach to provide comprehensive patient care. Overall, pharmacist interventions enhanced outcomes in patients with diabetes, and education-based initiatives were among the most effective approaches.[17]

The evolution of mHealth technologies has improved access to important health services. However, current research primarily focuses on the provision of medication adherence–enhancing therapies. One study demonstrated that transplant recipients utilizing an mHealth app experienced higher rates of medication reconciliation, although these findings were not significant.[18]

Several barriers to the incorporation of mHealth technologies exist. Although research has shown that technology is an effective strategy to educate patients, willingness and access to mobile devices can be a barrier to implementation. Two surveys conducted in 2012 and 2015 demonstrate increasing trends in smartphone ownership among kidney transplant recipients, with one also showing a high degree of willingness to incorporate mHealth into their care.[19,20] Several other studies report a high satisfaction among patients who have participated in mHealth trials. However, there is evidence to suggest that reported willingness may not translate into sustained utilization over time.[21] Additionally, the cost-effectiveness of mHealth technologies, especially incorporating pharmacists, remains a question. The use of stand-alone mHealth apps versus those embedded within EMR solutions is also a challenge to widespread implementation—one that is beyond the scope of this article but worthy of detailed discussion and analysis.[20]

There are several strengths of this study. First, all interventions were made by 1 clinical pharmacist, establishing greater consistency among patients. Additionally, this analysis provided greater insight into the frequency of pharmacist interventions utilizing mHealth technologies. Other reports are mainly limited to the types of interventions and do not provide further granularity. Moreover, describing trends in intervention types contributes to our understanding of the duration of impact of pharmacist-empowered mHealth technologies.

There are several limitations to this analysis. We only analyzed pharmacist interventions made in the intervention arm. Thus, we did not capture interventions made by the pharmacist during usual posttransplant care. Additionally, we only assessed changes in risk level for patients randomized to intervention. It is possible that decreases in patient risk levels over the study period may be partially attributed to increasing time from transplant. As time from transplant increases, there is typically a corresponding decrease in regimen complexity, which may lead to improved adherence and less-frequent adverse effects. Additionally, risk assessment was based on adherence, blood pressure/glucose trends, and adverse effects. These criteria may have been influenced by a number of pharmacist intervention types that we are unable to delineate between. Finally, we did not use attention control in the control arm because of cost constraints regarding the provision of smartphones. It is possible that increased attention in the intervention arm affected outcomes. However, the favorable return on investment reported for this intervention would support implementation of a similar program in clinical practice—even the increased attention was a primary driver of the results. We are unable to determine which components of the intervention—mHealth app, increased attention, or pharmacist-led medication therapy monitoring and management—affected outcomes, although, it is likely that all 3 contributed. Thus, the application of 1 component of this intervention may not necessarily lead to results similar to those reported here.

Conclusions and Relevance

This intervention represents a promising mechanism to improve medication safety outcomes. A pharmacist-led, mHealth-based intervention may increase opportunities for both pharmacological and nonpharmacological interventions and reduce the number of high-risk patients in the KTX population. Future studies should focus on expanding our understanding of the utility of these interventions and determining sustainability. Further investigation into the cost-effectiveness of this intervention is also warranted.

Authors' Note

Trial registration: ClinicalTrials.gov (NCT03247322). Clinical outcomes reported during the TRANSAFE Rx study were presented as an abstract during the plenary session at the 2020 American Transplant Congress. Results of the secondary analysis described in this article have been presented as an oral abstract at the 2021 American Transplant Congress.

Declaration of Conflicting Interests

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References

1. Samal L, Bates DW. To err is human: lessons from patient safety research for transplant care. *Clin J Am Soc Nephrol*. 2014;9:845-847. doi:10.2215/CJN.02850314
2. Meier-Kriesche H, Schold JD, Srinivas TR, Kaplan B. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. *Am J Transplant*. 2004;4:378-383. doi:10.1111/j.1600-6143.2004.00332.x
3. Meier-Kriesche HU, Schold JD, Kaplan B. Long-term renal allograft survival: have we made significant progress or is it time to rethink our analytic and therapeutic strategies? *Am J Transplant*. 2004;4:1289-1295. doi:10.1111/j.1600-6143.2004.00515.x
4. Parasuraman R, Abouljoud M, Jacobsen G, Reddy G, Koffron A, Venkat KK. Increasing trend in infection-related death-censored graft failure in renal transplantation. *Transplantation*. 2011;91:94-99. doi:10.1097/tp.0b013e3181fdd96c

5. Reeder TA, Mutnick A. Pharmacist- versus physician-obtained medication histories. *Am J Health Pharm*. 2008;65:857-860. doi:10.2146/ajhp070292
6. McCarthy L, Su X, Crown N, et al. Medication reconciliation interventions in ambulatory care: a scoping review. *Am J Health Syst Pharm*. 2016;73:1845-1857. doi:10.2146/ajhp150916
7. Chisholm MA, Mulloy LL, Jagadeesan M, DiPiro JT. Impact of clinical pharmacy services on renal transplant patients' compliance with immunosuppressive medications. *Clin Transplant*. 2001;15:330-336. doi:10.1034/j.1399-0012.2001.150505.x
8. Cohen EA, McKimmy D, Cerilli A, Kulkarni S. A pharmacist-driven intervention designed to improve medication accuracy in the outpatient kidney transplant setting. *Drug Healthc Patient Saf*. 2020;12:229-235. doi:10.2147/DHPS.S264022
9. Fleming JN, Treiber F, McGillicuddy J, Gebregziabher M, Taber DJ. Improving transplant medication safety through a pharmacist-empowered, patient-centered, mHealth-based intervention: TRANSAFE Rx study protocol. *JMIR Res Protoc*. 2018;7:e59. doi:10.2196/resprot.9078
10. Gonzales HM, Fleming JN, Gebregziabher M, et al. Pharmacist-led mobile health intervention and transplant medication safety: a randomized controlled clinical trial. *Clin J Am Soc Nephrol*. 2021;16:776-784. doi:10.2215/CJN.15911020
11. Sam S, Guerin A, Rieutord A, Belaiche S, Bussières JF. Roles and impacts of the transplant pharmacist: a systematic review. *Can J Hosp Pharm*. 2018;71:324-337.
12. Musgrave CR, Pilch NA, Taber DJ, et al. Improving transplant medication safety through pharmacist discharge medication reconciliation. *Am J Transplant*. 2013;13:796-801. doi:10.1111/ajt.12070
13. Gattis WA, Hasselblad V, Whellam DJ, O'Connor CM. Reduction in heart failure events by the addition of a clinical pharmacist to the heart failure management team: results of the Pharmacist in Heart Failure Assessment Recommendation and Monitoring (PHARM) Study. *Arch Intern Med*. 1999;159:1939-1945. doi:10.1001/archinte.159.16.1939
14. Bouvy ML, Heerdink ER, Urquhart J, Grobbee DE, Hoe AW, Leufkens HG. Effect of a pharmacist-led intervention on diuretic compliance in heart failure patients: a randomized controlled study. *J Card Fail*. 2003;9:404-411. doi:10.1054/s1071-9164(03)00130-1
15. Barker A, Barlis P, Berlowitz D, Page K, Jackson B, Lim WK. Pharmacist directed home medication reviews in patients with chronic heart failure: a randomised clinical trial. *Int J Cardiol*. 2012;159:139-143. doi:10.1016/j.ijcard.2011.02.034
16. Iqbal MZ, Khan AH, Iqbal MS, Syed Sulaiman SA. A review of pharmacist-led interventions on diabetes outcomes: an observational analysis to explore diabetes care opportunities for pharmacists. *J Pharm Bioallied Sci*. 2019;11:299-309. doi:10.4103/jpbs.JPBS_138_19
17. Presley B, Groot W, Pavlova M. Pharmacy-led interventions to improve medication adherence among adults with diabetes: a systematic review and meta-analysis. *Res Social Adm Pharm*. 2019;15:1057-1067. doi:10.1016/j.sapharm.2018.09.021
18. Levine D, Torabi J, Choinski K, Rocca JP, Graham JA. Transplant surgery enters a new era: increasing immunosuppressive medication adherence through mobile apps and smart watches. *Am J Surg*. 2019;218:18-20. doi:10.1016/j.amjsurg.2019.02.018
19. McGillicuddy JW, Weiland AK, Frezel RM, et al. Patient attitudes toward mobile phone-based health monitoring: questionnaire study among kidney transplant recipients. *J Med Internet Res*. 2013;15:e6. doi:10.2196/jmir.2284
20. Browning RS, McGillicuddy JW, Treiber FA, Taber DJ. Kidney transplant recipients' attitudes toward using mobile health technology for managing and monitoring medication therapy. *J Am Pharm Assoc (2003)*. 2016;56:450-454. doi:10.1016/j.japh.2016.03.017
21. Fleming JN, Taber DJ, McElligott J, McGillicuddy JW, Treiber F. Mobile health in solid organ transplant: the time is now. *Am J Transplant*. 2017;17:2263-2276. doi:10.1111/ajt.14225