REVIEW

Roles and Impacts of the Transplant Pharmacist: A Systematic Review

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ABSTRACT

Background: Pharmacists have been involved in the care of transplant recipients for several decades, and a growing body of literature shows the beneficial effects of clinical pharmacist care on important outcomes for these patients.

Objectives: The primary objective was to describe the roles and impacts of pharmacists in a solid organ transplant setting. The secondary objective was to describe and rate the pharmacists' interventions.

Data Sources: Three databases —PubMed, Embase, and Evidence-Based Medicine Reviews —were searched from January 1, 1990, to June 16, 2015.

Study Selection and Data Extraction: All studies addressing the roles of pharmacists and the impacts of clinical pharmacy services on the care of solid organ transplant recipients were considered. Only studies providing a statistical analysis were included. Design, setting, sample size, patient characteristics, pharmacists' interventions, study bias, and outcomes were extracted for analysis.

Data Synthesis: Four randomized controlled trials, 4 cohort studies, 3 pre–post studies, and 1 quasi-randomized controlled trial were included in the review, representing a total of 1837 patients. Of the 12 studies included, 8 specifically focused on renal transplant, and 1 each focused on liver, lung, abdominal organ, and general solid organ transplant. The pivotal pharmacist activities leading to the main patient outcomes were medication counselling (n = 8 studies), medication reconciliation (n = 5), and reviewing and optimizing drug therapy (n = 3). Improvements to medication adherence (n = 6 studies), morbidity (n = 4), costs (n = 2), and medication errors (n = 2) were reported.

Conclusion: Currently available evidence suggests that pharmacists can improve patient outcomes in the solid organ transplant setting. Adherence, morbidity, costs, and medication errors were identified as the main outcomes that were improved by pharmaceutical interventions. Transplant programs need to invest more in this resource.

Keywords: pharmacist, organ transplantation, impact, clinical pharmacy, outcome-based research

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RÉSUMÉ

Contexte : Les pharmaciens participent aux soins des greffés depuis plusieurs décennies et un nombre croissant de publications révèlent les effets bénéfiques des soins prodigués par les pharmaciens cliniciens quant aux résultats thérapeutiques importants pour ces patients.

Objectifs : L'objectif principal était de décrire les rôles des pharmaciens et leurs influences par rapport aux greffes d'organes solides. L'objectif secondaire était de décrire et d'évaluer les interventions des pharmaciens.

Sources des données : Les bases de données PubMed, Embase et Evidence-Based Medicine Reviews ont été interrogées pour la période allant du 1er janvier 1990 au 16 juin 2015.

Sélection des études et extraction des données : Toutes les études abordant les rôles des pharmaciens et l'influence des services de pharmacie clinique sur les soins des receveurs d'organes solides ont été prises en considération. Seules les études présentant des analyses statistiques ont été retenues. Le plan d'étude, le contexte, la taille de l'échantillon, les caractéristiques des patients, les interventions des pharmaciens, les biais et les résultats thérapeutiques ont servi à l'analyse.

Synthèse des données : Quatre études contrôlées à répartition aléatoire, 4 études de cohorte, 3 études avant-après et 1 essai comparatif à répartition quasi-aléatoire ont été retenus pour l'analyse, ce qui représentait au total 1837 patients. Parmi les 12 études retenues, 8 abordaient spécifiquement la greffe rénale et chacune des 4 autres concernait respectivement une greffe hépatique, une greffe pulmonaire, une greffe d'organe abdominal et une greffe d'organe solide. Les activités clés des pharmaciens menant aux principaux résultats thérapeutiques étaient les conseils sur les médicaments (n = 8 études), l'établissement du bilan comparatif des médicaments (n = 5) ainsi que l'examen et l'optimisation de la pharmacothérapie (n = 3). On a constaté des améliorations des taux d'observance pharmacothérapeutique (n = 6 études), des taux de morbidité (n = 4), des coûts (n = 2) et des taux d'erreurs de médicaments (n = 2).

Conclusion : Les données probantes disponibles laissent croire que les pharmaciens peuvent améliorer les résultats thérapeutiques en ce qui concerne les greffes d'organes solides. Les taux d'observance pharmacothérapeutique, les taux de morbidité, les coûts et les taux d'erreurs de médicaments ont été désignés comme les résultats principaux qui ont été améliorés par les interventions pharmaceutiques. Les programmes de greffe doivent investir davantage dans cette ressource.

Mots clés : pharmacien, greffe d'organe, effet, pharmacie clinique, recherche axée sur les résultats

INTRODUCTION

Solid organ transplant has been one of the most important therapeutic advances in medicine over the past 60 years. Since the first transplants were performed, it has become the recommended therapeutic approach for many end-stage chronic diseases. In Canada, 2835 transplant procedures were done in 2016.[1]

Patients who have received a solid organ transplant require lifelong immunosuppressive treatments. Nonadherence to post-transplant drug therapy and recommendations is a major issue that can lead to misdiagnosis of subsequent health problems, poor health affecting quality of life, graft rejection, or death.[2,3]

Pharmacists have been involved in direct patient care since the early 1970s. The first report outlining specific activities of a dedicated transplant pharmacist was published in 1976.[4] This article introduced the transplant pharmacist as an individual with specific expertise in transplantation pharmacology who actively participated in the medical management of organ transplant recipients and provided direct patient medication counselling. Since that time, the overall pharmacy practice model has evolved from a product-oriented to a patient-oriented model, and there have been advances in the field of transplant pharmacy as well. In the United States, for example, a "pharmacology expert" is now mandatory in transplant centres.[5]

A growing body of literature has shown the beneficial effects of clinical pharmacist care on important outcomes for both hospitalized and ambulatory patients; however, in the context of solid organ transplant, the majority of published studies have focused on renal transplant recipients.

There is high heterogeneity among the interventions described in studies evaluating the impact of clinical pharmacy services. Several authors have characterized the descriptions of interventions in pharmacy practice studies as inconsistent or even poor.[6,7] Authors have therefore recommended that interventions be clearly reported, with a detailed explanation of the intervention, a description of the pharmacist–patient and pharmacist–provider relationships, and details about the setting where the study took place.[8] A more comprehensive understanding of clinical pharmacy interventions for transplant patients would help in achieving better outcomes.

The primary objective of this systematic review was to describe the roles and impacts of pharmacists in a solid organ transplant setting. The secondary objectives were to describe and rate pharmacists' interventions.

METHODS

All specifications of the PRISMA 2009 checklist[9] were followed for reporting this systematic review.

Data Sources

Four systematic searches were carried out in 3 databases (PubMed, Embase, and Evidence-Based Medicine Reviews) for articles published between January 1, 1990, and June 16, 2015. Manual reference checks were performed to search for potentially missing studies. Search strategies are presented in Appendix 1 (available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/186/showToc).

Study Selection and Data Extraction

All studies addressing the impact of clinical pharmacy services on the care of patients with solid organ transplant were considered. Studies providing a statistical analysis on the impact of pharmaceutical activities were included. Studies that presented only descriptive results, studies addressing only the economic impact of transplant services, descriptive reviews, case reports, journal letters, journal notes, commentaries, and editorials were all excluded. Also excluded were secondary sources such as literature reviews, systematic reviews, and meta-analyses. Articles in either English or French were included.

All references were screened by 2 independents reviewers (A.G., J.F.B.). If there were any discrepancies in the decision to include or exclude studies, a third researcher was consulted (S.B.). Study selection was accomplished through 3 phases of screening. During the first phase, titles were reviewed for relevance. During the second phase, abstracts from articles retained in the first phase were reviewed for relevance. In the third and final phase, the full texts of articles retained in the second phase were reviewed.

Data extraction was performed by 2 authors (A.G., S.S.), under the supervision of 1 reviewer (J.F.B.). Data from the included studies were synthesized into summary tables.

Rating of Descriptions of Pharmaceutical Interventions

The DEPICT tool[10] was used to evaluate the description of pharmaceutical interventions. Rating was performed by 2 authors (A.G., S.S.), under the supervision of 1 reviewer (J.F.B.), and a DEPICT score was assigned to each study. The DEPICT score evaluates studies according to 12 sections, with multiple items per section. For each section, a score of 1 is assigned if the reviewers answer "yes" for at least 1 item within the section; otherwise, a score of 0 is assigned for that section. The DEPICT score is determined by summing the number of sections with a score of 1 (maximum score = 12).

Risk of Bias in Individual Studies

Individual study limitations, including risk of bias, were reported as described by the authors of each included article. The risk of bias across studies was assessed informally by the authors of the current systematic review.

RESULTS

Literature Search, Study Selection, and Data Extraction

The search yielded 1603 articles. Of these, 1518 were excluded after review of titles and abstracts. Of the 85 potentially eligible studies, 73 were excluded after review of the full-text articles. Twelve studies involving a total of 1837 patients were included in the analysis (Figure 1).[11-22] Manual searching of the reference lists of these included articles yielded no additional eligible articles.

Synthesis of Results

Eight studies focused on kidney transplant, one on liver transplant, one on lung transplant, one on abdominal transplant, and one on general solid organ transplant. The studies were conducted in the United States (*n* = 8 studies), Canada (*n* = 2), and Germany (*n* = 2). No differences were observed in terms of pharmacist roles or patient outcomes in relation to the geographic location of the studies.

The study characteristics are presented in Table 1 and the outcomes of individual studies in Table 2.

The pivotal pharmacist activities in the setting of solid organ transplant included patient education and counselling (*n* = 9 studies), reviewing and optimizing drug therapy (*n* = 7), and medication reconciliation or medical history (*n* = 5). Improvements were reported in the following areas: medication adherence (*n* = 6 studies), morbidity (*n* = 4), cost (*n* = 2), and medication errors (*n* = 2).

Pharmaceutical interventions were sufficiently described to understand the role of pharmacists. The average DEPICT score was 8.4 (standard deviation 1.4, minimum 6, maximum 11) (Table 3). The pharmaceutical interventions that were less frequently reported included the timing of the intervention, the support resources provided by pharmacists, and the pharmacist's autonomy to perform some specific tasks.

Risk of Bias

Risk of bias is reported here as described by the authors of each article (Table 1). Many studies lacked a control group and had a small sample size. Three of the included studies were carried out by the same multidisciplinary renal transplant team at the Medical College of Georgia Hospital and Clinics.[15,19,21] A fourth study had the same first author as these 3 studies (Marie A Chisholm-Burns, formerly Marie A Chisholm), but was conducted within a different organization.[17]

DISCUSSION

Our detailed literature search identified few studies describing the inclusion of clinical pharmacists as members of multidisciplinary teams in the organ transplant setting. In these studies, transplant pharmacists were involved in medication reconciliation, drug therapy evaluation and monitoring, patient education, and problem-solving. All of the studies included in our review suggested that transplant pharmacists could improve the management and medication adherence of patients and consequently could have a positive impact on patients' morbidity, medication errors, and costs. However, each of the studies was conducted in a single centre, and it might be difficult to show significant evidence of a pharmacist's impact in small, focused patient populations like these.

The number of studies that met our inclusion criteria (*n* = 12) was low compared with studies examining the roles of pharmacists in other settings (e.g., cancer, hypertension, and asthma).[23] In fact, the involvement of clinical pharmacists in transplant medicine is recent. The American Society of Health-System Pharmacists now offers a pharmacy residency in solid organ transplant,[24] but no European recommendations have been formulated regarding the role of the clinical pharmacist in transplantation. Lack of knowledge and/or experience in designing and administering such services, as well as difficulty in procuring funding and reimbursement for services, can limit

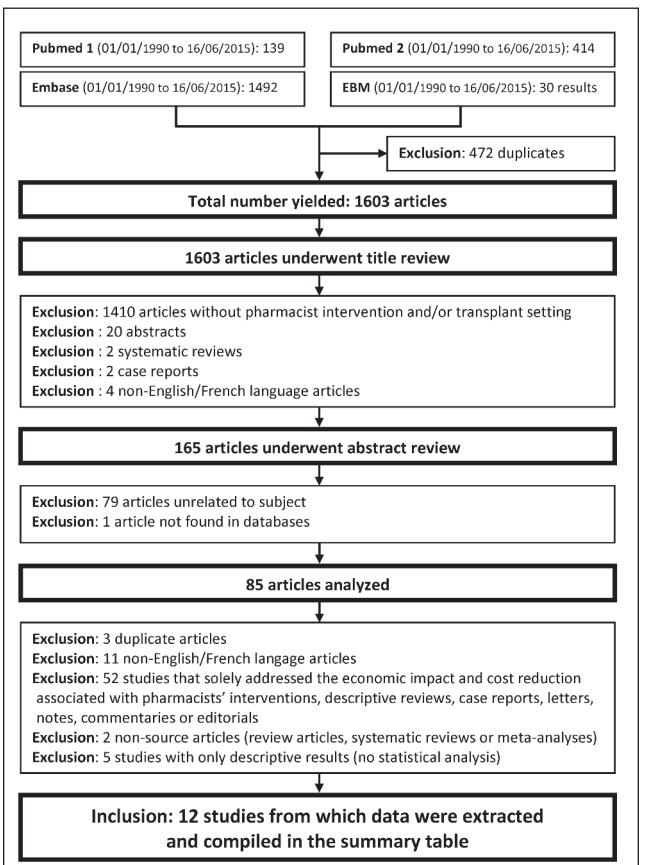

Figure 1. Selection of studies for a systematic review of the roles and impacts of transplant pharmacists.

Table 1 (part 1 of 4). Study Characteristics

Reference	Study Design and Timeframe	Setting	Sample Size and Patient Characteristics	Pharmacists' Interventions	Bias
Randomized controlled trials					
Chisholm et al. 2001[15]	RCT, prospective February 1997 to January 1999	United States: Medical College of Georgia—Hospital and Clinics Renal transplant clinic	Control (C): *n* = 12 Intervention (I): *n* = 12 Mean age ± SD: 49.2 ± 10.2 years Sex, male: 75% (18/24) Kidney transplant recipients	At least monthly direct patient care clinical services in person or by phone: - Obtaining medication histories - Reviewing and optimizing medication therapy - Making recommendations to the nephrologists - Providing oral and/or written medication counselling for patients	- To strengthen compliance assessment, serum drug concentrations were measured, but patients may have increased compliance before the blood samples and may have been inaccurate due to incorrect sampling times in relation to medication administration - Small sample size (*n* = 24)
Chisholm et al. 2002[21]	RCT, prospective Inclusion from November 1996 to March 1998	United States: Medical College of Georgia Renal transplant clinic	Control (C): *n* = 10 Intervention (I): *n* = 13 Mean age ± SD C: 47±12.7 years I: 51±16.8 years Sex, male: C: 70% I: 61.5% African-American kidney recipients	Direct care clinical pharmacy services: - Meeting with patient at least twice monthly during the first 3 months after transplant, at least monthly during months 4–8, and at least once during months 8–12 - Giving information about the medication - Obtaining medication histories - Reviewing medication therapy, with emphasis on controlling blood pressure - Preventing or resolving medication problems - Sending recommendations to the nephrologists	- Contamination bias: members of health care team may have progressively been influenced by the pharmacist's recommendations, affecting the care provided to the control group - Performance bias: study did not prevent patients from seeing additional health care providers - Small sample size (*n* = 23) - No objective measurement of compliance with antihypertensive medication regimen - Exclusively African-American study population may affect external validity
Klein et al. 2009[18]	RCT, prospective Inclusion from September 2003 to January 2005	Germany: University Hospital Mainz Transplant surgery unit	Control (C): n = 24 Intervention (I): *n* = 26 Mean age: C: 50.1 years I: 52.8 years Sex, male: C: 54% I: 54% Liver recipients	Pharmaceutical care services: - 3 or 4 meetings with patients in the week before discharge, for education about immunosuppressive therapy - On discharge, provision of a discharge medication plan, written information about the medication, and a diary for laboratory data and vital signs - 4 to 12 meetings in the first year after transplant to discuss changes in medication, laboratory values, and other problems - Drug therapy review	- Contamination bias: patients in the intervention and control groups visited the outpatient clinic at the same time and were able to exchange written and oral information - Performance bias: control and intervention groups received their immunosuppressant from the same pharmacist, who had to respond to questions and problems from both groups (for ethical reasons) - Minimum threshold of compliance rate to classify a patient as "noncompliant" was set arbitrarily, because it is mostly unknown in literature the point at which noncompliance becomes clinically relevant

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the implementation of clinical pharmacy services in particular settings and locations.[25]

Pharmacists' Activities

The included studies reported a large range of pharmacist activities in solid organ transplant for both hospitalized and ambulatory patients, as described in Table 1.

Alloway and others[5] highlighted the following basic activities of the transplant pharmacist: dedicating time for the care of transplant recipient; attending daily rounds to evaluate pharmacotherapy; coordinating development and implementation of drug therapy protocols; providing medication

Table 1 (part 2 of 4). Study Characteristics

Reference	Study Design and Timeframe	Setting	Sample Size and Patient Characteristics	Pharmacists' Interventions	Bias
Chisholm-Burns et al. 2013[17]	RCT, prospective January 2010 to November 2012	United States: Avella Specialty Pharmacy (specialty pharmacy network), multicentre	Control (C): *n* = 74 Intervention (I): *n* = 76 Mean age ± SD: C: 51.32±13.69 years I: 52.78±13.55 years Sex, male: C: 55.4% I: 56.6% Kidney recipients	Semistructured 20- to 30-min meetings with patients at 0, 3, 6, 9, and 12 months to sign or renew an adherence-promoting behavioural contract and discuss its 6 components: - Goal-setting - Motivation - Social support - Memory techniques - Problem-solving - Consequences of nonadherence	- No "attention" control group receiving interactions with a study pharmacist without the behavioural contract - A single pharmacist performed the intervention, limiting generalizability - No direct collection of utilization and cost data, although the methods used (self-report and Medicare Expenditure Panel Survey) have been validated - No measurement of self-efficacy - White, Hispanic, and female patients were over-represented in the study compared with the general United States population
Quasi-randomized controlled trial					
Joost et al. 2014[11]	Quasi-randomized controlled trial, prospective August 2008 to July 2010	Germany: Erlangen University Hospital Outpatient clinic of Department of Nephrology and Hypertension	Control (C): *n* = 39 Intervention (I): *n* = 35 Mean age ± SD: C: 54±11.9 years I: 51±13.3 years Sex, male: C: 62% I: 77% Kidney recipients	- 3 standardized counselling sessions of 30 min each within first 2 weeks after transplant - 1 to 3 quarterly follow-up counselling sessions over 12 months - Additional pharmaceutical care over phone or by email when necessary	- Selection bias: only 40% of eligible transplant patients agreed to participate in the study (nonadherence could be a cause of refusal) - One-year time horizon: the results cannot be extrapolated beyond 1 year - Contamination bias: patients in the intervention group may have shared their new-found knowledge with patients in control group
Cohort studies					
Harrison et al. 2012[14]	Cohort study, prospective Control: November 2007 to June 2008 Intervention: July 2008 to January 2009	Canada: Toronto General Hospital Outpatient lung transplant clinic	Control (C): *n* = 43 Intervention (I): *n* = 43 Age (years): 18–39: 30% (C) vs 12% (I) 40–59: 47% (C) vs 51% (I) ≥60: 23% (C) vs 37% (I) Sex, male: C: 56% I: 56% Lung recipients	- Primary pharmaceutical care intervention (drug therapy review, therapeutic recommendations) - Patient teaching - Medication reconciliation - Referral of issue for team follow-up - Optimization of medication adherence - Medication information and advice for patients and the team - Assistance with drug coverage issues - Collaboration with community pharmacists	- Performance bias: clinicians may have not performed a comprehensive drug therapy assessment, knowing that patients would be subject to subsequent pharmacist reviews - Inconsistencies of intervention: pharmacists in the study received no formalized training in outpatient practice - Most patients met with pharmacist only once during the timeframe of the study (additional visits over a longer period might lead to greater impact on patient care outcomes)

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reconciliation, medication therapy management, and discharge counselling; providing education to members of the transplant team; facilitating cost and pharmacotherapy optimization to maximize patient outcomes; providing transplant medication education to patients; leading and assisting with clinical and pharmacoeconomic research; and providing 24/7 pharmacotherapeutic support. This list strongly concurs with the interventions summarized in Table 1 of this review, except for research. Indeed, the most frequently reported activities in studies included in our review were patient education and counselling, reviewing and optimizing drug therapy, and medication reconciliation or medical history.

Table 1 (part 3 of 4). Study Characteristics

Reference	Study Design and Timeframe	Setting	Sample Size and Patient Characteristics	Pharmacists' Interventions	Bias
Maldonado et al. 2013[12]	Cohort study, retrospective Control cohort: 2007 Intervention cohort: 2011	United States: Providence Sacred Heart Medical Center & Children's Hospital Inpatient and outpatient transplantation clinic	Control (C): *n* = 60 Intervention (I): *n* = 54 Mean age at transplant: C: 51.4 years I: 55.0 years Sex, male: C: 65% I: 63% Kidney recipients	- Daily rounds with the interdisciplinary team - Pharmacotherapy recommendations to physicians, surgeons, and midlevel practitioners - Active drug monitoring - Medication reconciliation and discharge planning - Patient education	- Performance bias: changes in usage of anti-thymocyte globulin induction therapy, a new program director, and addition of a transplant nurse practitioner may have influenced the results - No assessment of patient health literacy or medication compliance, which are viewed as the primary contribution of transplant pharmacists
Musgrave et al. 2013[13]	Cohort study, prospective Retrospective cohort: 2006 to 2008 Prospective cohort: 2011	United States: Medical University of South Carolina Department of Transplant Surgery	Retrospective cohort (C): *n* = 128 Prospective cohort (I): *n* = 64 Median age: C: 51.5 years I: 54 years Sex, male: C: 65.6% I: 68.8% Abdominal transplant patients	- At discharge, 5–30 min (median 15 min) spent per patient to verify medication reconciliation - At the first follow-up appointment (next business day following discharge), 0–90 min (median 20 min) spent per patient to review medications - Prevention and/or correction of the identified drug-related problems	- Chart review to identify errors was done with retrospective records, which do not always provide explanations for changes that might seem like errors but could have been intentional - Analysis bias: chart review was conducted by a single reviewer - Analysis bias: classification of errors by severity was performed by a single reviewer (but this was controlled by use of a validated rating tool) - In the retrospective period, no correlation of the errors to detrimental clinical outcomes
Tschida et al. 2013[20]	Cohort study, retrospective Inclusion from August 2007 to December 2007	United States: United Healthcare Pharmacy (specialty pharmacy network), multicentre	Retail pharmacy group (C): *n* = 519 Specialty pharmacy group (I): *n* = 519 Mean age (years): C: 49.78 years I: 49.78 years Sex, male: C: 62% I: 61% Renal transplant patients	Transplant medication specialty pharmacy program: - Monthly face-to-face consultations for the first 3 months after transplant, then about every 3 months - Additional clinical counselling sessions by phone - Provision of clinical expertise and patient education in transplant medications and comorbid conditions - Monthly refill reminders, adherence screening (intervention with physician if necessary) - 24/7 pharmacist support available to patient	- Selection bias: patients may have self-selected into either the specialty or retail pharmacy benefit programs (sicker patients may have differentially chosen one type of pharmacy over the other) - Adherence estimations using retrospective data do not always give an accurate representation of whether the medication was taken exactly as prescribed - No measurement of how consistently and how many patients participated in the pharmacy consultations on an ongoing basis of monthly and every 3 months meetings

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Patient education and teaching sessions aimed to educate patients about all aspects of their medications and the risks of nonadherence, and to answer questions. Handing out information sheets and providing support by phone or e-mail were activities performed by pharmacists in many of the studies.

Nonadherence to the immunosuppressive regimen after transplant is a major issue than can lead to serious outcomes, such as transplant rejection or even death. Clinical pharmacists can improve patient adherence to medications.[15] In a unique approach, Chisholm-Burns and others[17] used a behavioural

Table 1 (part 4 of 4). Study Characteristics

Reference	Study Design and Timeframe	Setting	Sample Size and Patient Characteristics	Pharmacists' Interventions	Bias
Pre–post studies					
Partovi et al. 1995[22]	Pre–post study, prospective March to June 1993	Canada: Vancouver Hospital and Health Sciences Centre Solid organ transplant clinic	Group: *n* = 28 Mean age: 47.2 years Sex, male: 43% Solid organ recipients	Medication counselling program: - Oral counselling by a pharmacist and provision of medication teaching sheets (step 1) - Patient participation in self-medication program (step 2) Four identical tests given to patients throughout the program to evaluate knowledge retention: - Pre-test (just before step 1) - Post-test 1 (2–3 days after step 1) - Post-test 2 (3–5 days after step 2) - Post-test 3 (5–7 days after post-test 2)	- Only short-term knowledge retention was assessed - Inconsistency of the quality of teaching provided by each of the 4 pharmacists involved in the counselling and testing - Confounding factors: patients who had health-related jobs scored higher; central nervous system depressive drugs lowered test performance - No control group
Chisholm et al. 2007[19]	Pre–post study, retrospective Inclusion from November 1999 to September 2005	United States: Medical College of Georgia Renal transplant clinic	Group: *n* = 36 Mean age ± SD: 52.78±13.37 years Sex, male: 61.1% Kidney recipients	Medication therapy management services (provided at least once a month): - Review of medication profile to ensure therapeutic outcomes and minimize adverse drug events - Identify, resolve, and prevent medication-related problems - Interview patients - Answer drug information questions - Make therapeutic recommendations	- No control group - Small sample size (*n* = 36)
Pinelli et al. 2014[16]	Pre–post study, prospective 2014	United States: Henry Ford Hospital Transplant institute	Group: *n* = 22 Mean age ± SD: 59.3 ± 9.5 years Sex, male: 79% Kidney recipients	Establishment of a pharmacist-managed diabetes and cardiovascular risk reduction clinic (PMDC): - 60-min appointment within 7 days of discharge by inpatient transplant team - 30-min follow-up appointments at least monthly over 3 months - Disease state management for diabetes, hypertension, and dyslipidemia - Standardized diabetes self-management education curriculum - Referral to transplant nutrition support services as needed - Medication reconciliation at each visit - Standardized discharge process from PMDC at 3 months to endocrinologist or primary care provider	- Small sample size (*n* = 22) - No control group

RCT = randomized controlled trial, SD = standard deviation.

Table 2 (part 1 of 3). Outcomes of Individual Studies

Reference	Type of Outcome	Main Study Outcomes	Main Results
Randomized controlled trials			
Chisholm et al. 2001[15]	Compliance	1. Compliance rate (mean ± SD)	1. At 1 year post-transplant: control 81.6% ± 11.5% vs intervention 96.1% ± 4.7%; $p < 0.001$
		2. Duration of compliance (as proportion of compliant patients at 12 months after transplant)	2. Control $n = 4/12$ vs intervention $n = 9/12$; $p < 0.05$
		3. Rate of patients achieving target serum cyclosporine and tacrolimus concentrations	3. Control 48% vs intervention 64%; $p < 0.05$
Chisholm et al. 2002[21]	Morbidity	Mean systolic and diastolic blood pressure change:	
		1. From baseline for 1st quarter	1. Control –8/–4 mm Hg vs intervention –7/–1 mm Hg; $p > 0.05$
		2. From baseline for 2nd quarter	2. Control +17/+5 mm Hg vs intervention –12/–7 mm Hg; $p < 0.01$
		3. From baseline for 3rd quarter	3. Control +13/–1 mm Hg vs intervention –14/–12 mm Hg; $p < 0.01$
		4. From baseline for 4th quarter	4. Control +18/+8 mm Hg vs intervention = –5/–6 mm Hg; $p < 0.01$
Klein et al. 2009[18]	Compliance	1. Dosing compliance, as % of days (mean ± SD) with correct number of MEMS bottle openings (compliance threshold is 80%)	1. Control 80.8% ± 12.4% vs intervention 90.2% ± 6.2%; $p = 0.015$. *Noncompliant patients*: control 43% vs intervention 10%; $p = 0.032$
		2. Timing compliance: % of days (mean ± SD) on which bottle was opened within 3 h of target time	2. Control 81.1% ± 13.8% vs intervention 87.9% ± 8.0%; $p = 0.088$
		3. Compliance according to pill counts (tablets or capsules remaining in MEMS bottles during each patient visit) (mean ± SD)	3. Control 97.2% ± 13.6% vs intervention 101.1% ± 2.6%; $p = 0.030$
		4. Rate of immunosuppressant serum concentrations achieving "target"	4. Control 51% vs intervention 78%; $p < 0.001$
		5. Compliance according to Morisky score	5. 62% of control group vs 87% of intervention group answered "no" to all questions (good compliance); $p = 0.083$
		6. No. of rejection episodes	6. Control 5 vs intervention 3; $p = 0.456$
Chis holm-Burns et al. 2013[17]	Compliance	**Adherence**	**Adherence**
		1. At baseline	1. No significant difference
		2. At 3 months	2. No significant difference
		3. At 6 months	3. Intervention group had significantly greater adherence than control group; $p = 0.0099$
		4. At 9 months	4. Intervention group had significantly greater adherence than control group; $p = 0.0065$
		5. At 12 months	5. Intervention group had significantly greater adherence than control group; $p = 0.0076$
		6. Over 1-year study period	6. Intervention group had significantly greater adherence than control group; $p = 0.0071$
		7. At 3 months post-intervention	7. Intervention group had significantly greater adherence than control group; $p = 0.044$
	Cost	**Health care utilization**	**Health care utilization**
		8. Proportion of patients with at least 1 day in hospital among patients who reported any hospitalization during 1-year study	8. Control 57.3% vs intervention 23.9%; $p < 0.001$
		9. Probability of not being hospitalized	9. Intervention increased the probability of not being hospitalized by ~78% (RR 1.785, 95% CI 1.314–2.425)

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contract and trimestral meetings to maximize patient adherence.

Reviewing and optimizing drug therapy helps in identifying, resolving and preventing drug-related problems. Musgrave and others[13] reported a "significant" decrease of medication errors per patient at discharge because of pharmacist interventions. Chisholm and others[15,19,21] also reported that pharmacist recommendations helped nephrologists to optimize prescriptions for transplant recipients.

Few of the included studies reported medication reconciliation. Nevertheless, this has been shown to be an essential component in optimizing the quality of prescriptions, prevent-

Table 2 (part 2 of 3). Outcomes of Individual Studies

Reference	Type of Outcome	Main Study Outcomes	Main Results
Quasi-randomized controlled trial			
Joost et al. 2014[11]	Compliance	1. Daily adherence (as % of days with correct dosing of MMF/MPA) during 1-year monitoring period	1. Control 57% (20/35) vs intervention 84% (27/32); $p = 0.015$
		2. Taking adherence (as % of doses taken [bottle opening] compared with overall doses prescribed)	2. Control 57% (20/35) vs intervention 84% (27/32); $p = 0.015$
		3. Timing adherence (as % of doses taken within a 6-h interval [±3 h] of standard intake time)	3. Control 86% (30/35) vs intervention 97% (31/32); $p = 0.110$
		4. Adherence rate (as measured by pill count)	4. Control 63% (22/35) vs intervention 84% (27/32); $p = 0.047$
		5. No. of drug holidays (defined as no MMF/MPA intake for > 48 h)	5. Control 43% (15/35) vs intervention 81% (26/32); $p = 0.001$
		6. Adherence, as measured with Morisky questionnaire	6. Control 63% (22/35) vs intervention 63% (20/32); $p = 0.695$
		7. Self-reported adherence	7. Control 77% (27/35) vs intervention 72% (23/32); $p = 0.193$
Cohort studies			
Harrison et al. 2012[14]	Medication errors	1. No. of DTPs identified per visit (control group, clinic visits; intervention group, clinic visits and pharmacist visits) (mean ± SD)	1. DTPs identified per: - Intervention pharmacist visit: 1.05 ± 1.34 - Intervention clinic visit 0.51 ± 0.64; $p = 0.018$ relative to intervention pharmacist visit - Control clinic visit 0.74 ± 0.81; $p = 0.19$ relative to intervention pharmacist visit
Maldonado et al. 2013[12]	Morbidity	1. Mean hospital length of stay	1. Control (2007) 7.8 days vs intervention (2011) 3.4 days; $p < 0.001$
		2. All cause 30-, 90-, and >90-day readmission rates	2. No significant differences; $p > 0.09$ for all comparisons
Musgrave et al. 2013[13]	Medication errors	1. No. of medication errors per patient at discharge avoided through pharmacist intervention (mean ± SD)	1. Retrospective 0 vs prospective 1.9 ± 1.7; $p < 0.0001$
		2. No. of medication errors per patient at discharge persisting until first follow-up appointment (mean ± SD)	2. Retrospective 3.4 ± 1.9 vs prospective 1.1 ± 1.4; $p < 0.0001$
		3. % of discharges with no medication errors	3. Retrospective 3.9% vs prospective 25%; $p < 0.0001$
Tschida et al. 2013[20]	Cost	1. Mean total cost per patient in the first follow-up year	1. 13% lower in the specialty pharmacy group ($24 315 vs $27 891); $p = 0.03$
	Compliance	2. Mean no. of oral transplant prescriptions dispensed per patient	2. Retail pharmacy group 17.90 vs specialty pharmacy group 18.67; $p < 0.05$
		3. Weighted medication possession ratio	3. Retail pharmacy group 0.83 vs specialty pharmacy group 0.87; $p < 0.0001$
		4. No. of patients with medication gap (at least 60 days without immunosuppressive drugs but followed by re-initiation within study period)	4. Retail pharmacy group 53 vs specialty pharmacy group 29; $p = 0.006$
		5. No. of patients with discontinuation (at least 60 days without immunosuppressive drugs, never followed by re-initiation within the study period)	5. Retail pharmacy group 104 vs specialty pharmacy group 39; $p < 0.0001$
		6. Mean no. of dialysis-related inpatient hospital stays per patient	6. Retail pharmacy group 0.04 vs specialty pharmacy group 0.02; $p < 0.03$
Pre–post studies			
Partovi et al. 1995[22]	Other	% change in knowledge score (mean ± SD)	
		1. Pre-test to post-test 1	1. 24.8% ± 10.6%; $p < 0.05$
		2. Pre-test to post-test 2	2. 36.7% ± 11.8%; $p < 0.05$
		3. Pre-test to post-test 3	3. 40.9% ± 12.7%; $p < 0.05$
		4. Post-test 1 to post-test 2	4. 11.9% ± 9.7%; $p < 0.05$
		5. Post-test 2 to post-test 3	5. 4.21% ± 8.9%; $p < 0.05$

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Table 2 (part 3 of 3). Outcomes of Individual Studies

Reference	Type of Outcome	Main Study Outcomes	Main Results
Chisholm et al. 2007[19]	Morbidity	1. Clinical indicators for diabetes mellitus (fasting blood glucose and HbA1c) (mean ± SD)	1. Fasting blood glucose: 129.22 ± 18.25 mg/dL (pre) vs 112.22 ± 17.43 mg/dL (post); $p = 0.001$ HbA1c: 8.07% ± 0.81% (pre) vs 7.42% ± 0.61% (post); $p = 0.002$
		2. Clinical indicators for hyperlipidemia (LDL and total cholesterol) (mean ± SD)	2. LDL: 305.48 ± 66.20 mg/dL (pre) vs 191.78 ± 27.39 mg/dL (post); $p < 0.001$ Total cholesterol: 345.83 ± 108.33 mg/dL (pre) vs 239.91 ± 47.24 mg/dL (post);$p < 0.001$
		3. Clinical indicators for hypertension (systolic and diastolic blood pressure) (mean ± SD)	3. Systolic: 140.52 ± 7.81 mm Hg (pre) vs 134.30 ± 7.54 mm Hg (post); $p < 0.001$ Diastolic: 79.19 ± 3.97 mm Hg (pre) vs 77.04 ± 4.24 mm Hg (post); $p < 0.001$
		4. Serum tacrolimus concentration (mean ± SD)	4. 8.67 ± 3.5 ng/mL (pre) vs 10.17 ± 1.17 ng/mL (post); $p = 0.343$ No significant difference in no. of patients achieving target concentrations
		5. Serum cyclosporine concentration (mean ± SD)	5. 178.77 ± 61.4 ng/mL (pre) vs 214.7 ± 44.14 ng/mL (post), $p = 0.007$ Significant improvement in no. of patients achieving target concentrations; $p = 0.008$
		6. No. of graft rejections (mean ± SD)	6. 0.50 ± 0.51 (pre) vs 0.22 ± 0.42 (post); $p = 0.008$
		7. Health-related quality-of-life scores	7. Significantly increased scores for General Health, Social Functioning, Role Emotional, Mental Health, Physical Component Summary, and Mental Component Summary scales; $p < 0.01$
Pinelli et al. 2014[16]	Morbidity	**HbA1c (mean ± SD)** **Intention-to-treat analysis**	**HbA1c (mean ± SD)** **Intention-to-treat**
		1. At 3 months in patients with baseline HbA1c < 7.0%	1. Baseline 6.0% ± 0.5% vs 3 months 6.6% ± 0.9%; $p = 0.20$
		2. At 6 months in patients with baseline HbA1c < 7.0%	2. Baseline 6.0% ± 0.5% vs 6 months 6.2% ± 0.6%; $p = 0.48$
		3. At 3 months in patients with baseline HbA1c ≥ 7.0%	3. Baseline 8.1% ± 1.0% vs 3 months 7.3% ± 1.2%; $p = 0.07$
		4. At 6 months in patients with baseline HbA1c ≥ 7.0%	4. Baseline 8.1% ± 1.0% vs 6 months 7.5% ± 0.8%; $p = 0.16$
		Per protocol analysis	**Per protocol analysis**
		1. At 3 months in patients with baseline HbA1c < 7.0%	1. Baseline 6.0% ± 0.5% vs 3 months 6.3% ± 0.8%; $p = 0.55$
		2. At 6 months in patients with baseline HbA1c < 7.0%	2. Baseline 6.0% ± 0.5% vs 6 months 6.1% ± 0.6%; $p = 0.48$
		3. At 3 months in patients with baseline HbA1c ≥ 7.0%	3. Baseline 8.3% ± 1.0% vs 3 months 6.8% ± 1.2%; $p = 0.0041$
		4. At 6 months in patients with baseline HbA1c ≥ 7.0%	4. Baseline 8.3% ± 1.0% vs 6 months 7.5% ± 1.0%; $p = 0.15$

CI = confidence interval, DTP = drug therapy problem, HbA1c = glycated hemoglobin, LDL = low-density lipoprotein, MEMS = medication event monitoring system, MMF = mycophenolate mofetil, MPA = mycophenolic acid, RR = rate ratio, SD = standard deviation.

ing drug-related problems, and significantly reducing readmission rates in the emergency department.[26] In the study by Maldonado and others,[12] pharmacists proposed a discharge plan to the patients, in addition to performing medication reconciliation. Harrison and others[14] described collaboration with community pharmacists; such collaborations reflect the importance of continuity of care between the transplant team and community practitioners to ensure an optimal prognosis. The development of telepharmacy tools may help with post-transplant home care.

Outcomes

Improvements in medication adherence, morbidity, costs, and medication errors were reported in the selected studies, but these outcomes were not linked to specific pharmacist activities.

There were clear benefits in terms of patient adherence to immunosuppressive treatments.[11,15,17-20] Chisholm and others[19] reported a significant reduction in transplant rejections from 1 year pre-enrollment to 1 year post-enrollment ($p = 0.008$). Klein and others[18] found fewer rejection episodes in the intervention group, although the difference was not significant (small sample size). Three studies showed an increase in achievement of target serum concentrations of oral immunosuppressants.[15,18,19]

Significant positive outcomes were found in terms of comorbidities such as diabetes mellitus, hyperlipidemia, and hypertension, but the results were inconsistent for morbidity outcomes.[16,19,21]

In the study by Tschida and others,[20] implementation of a transplant pharmacy program resulted in a significantly lower

Table 3 (part 1 of 2). Rating of Pharmaceutical Interventions with DEPICT Tool[10]

	Study (by Reference Number)											
Element of Tool	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
A. Contact with the patient												
1A. Face-to-face contact	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2A. Remote contact	Y	N	N	N	Y	N	Y	N	N	Y	Y	N
B. Timing of the intervention												
3B. At patient admission to a hospital, nursing home, or emergency department	N	Y	N	N	N	N	N	N	N	N	N	N
4B. During hospital or nursing home stay	Y	Y	N	N	N	N	N	Y	N	N	N	N
5B. At patient discharge or interfacility transfer	N	Y	Y	N	N	N	N	Y	N	N	N	N
6B. When a new or changed prescription is provided	N	N	N	N	N	N	N	N	N	N	N	N
7B. At the time of drug dispensing	N	N	N	N	N	N	N	N	N	N	N	N
C. Setting of the intervention												
8C. Participant's home	N	N	N	N	N	N	N	N	N	Y	N	N
9C. Community pharmacy	N	N	N	N	N	N	Y	N	N	Y	N	N
10C. Ambulatory or primary care setting co-located with medical services	Y	Y	N	N	N	Y	N	N	N	N	N	N
11C. Independent ambulatory or primary care setting	N	N	N	N	N	N	N	N	N	N	N	N
12C. Hospital	Y	Y	Y	Y	Y	N	N	Y	N	N	Y	Y
13C. Long-term care facility	N	N	N	N	N	N	N	N	N	N	N	N
D. Target population												
14D. Condition-specific intervention	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
15D. Population-specific intervention	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
E. Clinical data sources												
16E. All current medications in use by the patient	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N
17E. Pharmacy or dispensing records	N	N	Y	N	Y	N	Y	N	N	N	Y	N
18E. Laboratory tests or drug monitoring data	N	Y	N	N	Y	N	N	N	N	N	Y	N
19E. Disease self-monitoring data	N	N	N	N	N	N	N	N	N	N	N	N
20E. Patient's physical or functional assessment	N	N	N	Y	N	N	N	N	N	N	N	N
21E. Medical records	N	Y	N	N	Y	N	N	N	N	N	Y	N
22E. Patient interview (anamnesis)	N	N	N	N	N	N	N	N	N	N	N	N
F. What is assessed												
23F. Medication-use process (errors)	N	N	Y	Y	N	N	N	N	N	N	N	N
24F. Legal or administrative aspects of drug prescriptions	N	N	N	N	N	N	N	N	N	N	N	N
25F. Patient's knowledge, health literacy, or communication skills	N	N	N	N	N	N	N	N	N	N	N	Y
26F. Patient's adherence to treatment	Y	N	N	N	Y	N	Y	Y	Y	Y	N	N
27F. Health outcomes	N	Y	N	N	N	Y	N	N	Y	N	Y	N
28F. Patient's quality of life	N	N	N	N	N	N	N	N	Y	N	N	N
29F. Patient's satisfaction	N	N	N	Y	N	N	N	N	N	N	N	N
30F. Costs of treatment	N	N	N	N	N	N	N	N	Y	Y	N	N
G. Pharmacist's autonomy to perform an action												
31G. Change dosage regimen	N	N	N	N	N	N	N	N	N	N	N	N
32G. Suspend medication	N	N	N	N	N	N	N	N	N	N	N	N
33G. Start a new medication	N	N	N	N	N	N	N	N	N	N	N	N
34G. Order laboratory tests or perform drug monitoring	N	Y	N	N	N	N	N	N	N	N	N	N
H. Pharmacist communication												
35H. Directly with the patient	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
36H. With the physician or health care team	N	Y	N	Y	Y	Y	N	N	Y	N	Y	N
37H. Written recommendations to the physician or health care team	N	N	N	Y	N	N	N	N	N	N	N	N
38H. Face-to-face or telephone recommendations to the physician of health care team	N	N	N	Y	N	N	N	N	N	N	N	N

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Table 3 (part 2 of 2). Rating of Pharmaceutical Interventions with DEPICT Tool[10]

	Study (by Reference Number)											
Element of Tool	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
I. Support resources provided by the pharmacist												
39I. A patient's medication list to the physician	N	Y	N	N	N	N	N	N	N	N	N	N
40I. A medication list or summary to the patient	N	Y	N	Y	N	N	N	Y	N	N	N	N
41I. Written, video, or audio educational material to the patient	Y	N	N	N	Y	N	N	N	N	N	Y	Y
42I. Medication adherence or administration aid	Y	Y	N	Y	N	N	N	N	N	N	N	N
43I. Disease self-management diary	N	N	N	N	N	N	N	Y	N	N	N	N
J. Education and counselling												
44J. Disease-specific or medication counselling to the patient	Y	Y	N	Y	Y	Y	N	Y	N	Y	Y	Y
45J. Lifestyle or self-management education to the patient	N	N	N	N	N	N	Y	Y	N	N	N	N
46J. Education program to a group of patients	N	N	N	N	N	N	N	N	N	N	N	N
L. Follow-up												
47L. Focus on medication-use process	N	N	Y	N	N	N	N	N	N	N	N	N
48L. Focus on health or therapeutic outcomes	Y	Y	N	N	N	Y	N	Y	Y	N	N	N
49L. Follow-up is performed through face-to-face encounters	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	N
50L. Follow-up is performed through remote contacts	Y	N	N	N	Y	Y	Y	N	N	Y	Y	N
51L. Duration of the follow-up (write the number of months)	Y	N	N	N	Y	Y	Y	Y	N	Y	Y	N
M. Other actions												
52M. Screening for disease risk factors	N	N	N	N	N	Y	N	N	N	N	N	N
53M. Development of a drug formulary, guideline, or clinical protocol	N	N	N	N	N	N	N	N	N	N	N	N
54M. Provider or prescriber education	N	N	N	N	N	N	N	N	N	N	N	N
DEPICT score*	9	11	7	8	9	9	8	10	6	8	9	7

N = no (item not reported in study), Y = yes (item reported in study).
*For each of the 12 sections, a score of 1 was assigned if the reviewers answered "yes" to at least one element of the section. The number of sections with a score of 1 was summed to generate the overall DEPICT score (maximum 12).

mean total cost per patient ($24 315 versus $27 891, 13% decrease; $p = 0.03$), which the authors attributed mainly to a significantly lower mean transplant-related medical cost ($5960 versus $8486, 30% decrease; $p = 0.04$).

Musgrave and others[13] described the avoidance of discharge medication errors through pharmacist intervention, a decrease in discharge medication errors per patient persisting until the first follow-up appointment, and a greatly improved percentage of discharges with no medication errors. Harrison and others[14] reported a decrease in the mean number of drug therapy problems identified per visit.

Patients' knowledge of medications was appraised in only one study.[22] The benefits for short-term information retention were significant, but the study did not examine long-term retention. Given that patient motivation and care intensity often diminish with time, long-term persistence of pharmacist-induced outcomes needs to be evaluated.

Description of Pharmaceutical Interventions

In studies designed to evaluate the roles and impacts of health care professionals, it is very important to have a clear and complete description of the intervention. Associating an intervention with specific outcomes is especially difficult where multidisciplinary teams are involved. According to the DEPICT tool,[10] the descriptions of the interventions in the included studies were generally of good quality. Nonetheless, more complete descriptions should be provided in future studies, especially regarding the timing of the intervention and pharmacists' autonomy.

As for most pharmacy practice research studies, the studies included in this review had small sample sizes, some had no control group ($n = 3$), and the interventions were insufficiently described to be fully reproducible. Usual sources of bias were reported, including performance bias and contamination bias. In clinical practice within a hospital, it is usually difficult to eliminate these 2 types of bias.

Transplant Pharmacy Training

Transplant recipients are treated with multiple drugs, including medications with a narrow therapeutic index. It was therefore surprising to find only a limited number of articles describing pharmacists' roles and outcomes in this area. This systematic review highlights the need to structure teaching and internships in this discipline and to further document the practice of pharmacists in transplant medicine. Professional specialty networks may certainly contribute to better training,

organization, and documentation. For instance, the American Society for Transplantation has a transplant pharmacy community of practice.[27] In addition, the American College of Clinical Pharmacy has an immunology/transplantation practice and research network.[28] The Board of Pharmacy Specialties received a petition to recognize solid organ transplantation pharmacy as a new specialty; the Board's public comment period on this petition closed on May 15, 2018.[29]

In Canada, the Canadian Society of Transplantation has a pharmacist group whose mission is to "provide leadership and a collaborative forum for the advancement of pharmacist clinical practice in transplantation and pharmacist-led research and education".[30] The Canadian Society of Hospital Pharmacists has a transplant Pharmacy Specialty Network that promotes "practice excellence and the enhancement of patient-centred pharmacy practice through information sharing, educational events, and the facilitation of research for pharmacists who are interested in the area of transplant pharmacy practice (solid organ and hematopoietic stem cell transplant)".[31]

There is currently no published literature about transplant-specific training offered in pharmacy, in Canada or elsewhere. Such training may vary substantially among regions and programs, which may explain the paucity of data as well as the wide variety of roles described in the literature.

Limitations

The systematic literature search was conducted in only 4 databases, and all articles published in a language other than English or French were excluded. As a result, some eligible studies may have gone undetected. Although descriptive results lack statistical proof of significance, they may carry compelling information that could prove useful in establishing a more accurate image of the roles and impacts of the pharmacist. However, for practical reasons (notably the difficulty of screening for quality), they were omitted from this review. Eight studies involved kidney transplant recipients exclusively, and the 4 remaining studies were spread among recipients of abdominal, liver, lung, and unspecified transplants. Most anti-rejection medications are lifelong treatments, yet the temporal horizon was limited to a year or less in virtually all of the studies. It is unknown whether pharmacist interventions have lasting effects, especially in the case of temporary activities. It would be interesting to explore which interventions were the most time-effective.

CONCLUSION

Currently available evidence suggests that pharmacists can improve patient outcomes in solid organ transplant settings. Adherence, morbidity, costs, and medication errors were identified as the main outcomes that were improved by pharmaceutical interventions. Transplant programs need to invest more in this resource.

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ON THE FRONT COVER

Near the North Branch of the Thames River London, Ontario

The cover photograph was taken by pharmacist Linda Hooper along the bike path that parallels the north branch of the Thames River in London, Ontario, near her workplace (University Hospital, London Health Sciences Centre). The camera was a Canon EOS 40D.

Linda commented that the scene brought to mind a poem by Canadian poet William Wilfred Campbell. "When I was a kid, this Canadian poem was our memory work at school."

The *CJHP* would be pleased to consider photographs featuring Canadian scenery taken by CSHP members for use on the front cover of the Journal. If you would like to submit a photograph, please send an electronic copy (minimum resolution 300 dpi) to publications@cshp.ca.

Indian Summer

Along the line of smoky hills
The crimson forest stands,
And all the day the blue-jay calls
Throughout the autumn lands.

Now by the brook the maple leans
With all his glory spread,
And all the sumachs on the hills
Have turned their green to red.

Now by great marshes wrapt in mist,
Or past some river's mouth,
Throughout the long, still autumn day
Wild birds are flying south.

~ William Wilfred Campbell (1858?-1918)