

Interventions to improve medication adherence in adult kidney transplant recipients: a systematic review

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ABSTRACT

Background. In kidney transplantation, adherence to immunosuppressive therapy is paramount for long-term graft survival. This systematic review aimed to assess the effectiveness of interventions to improve medication adherence in adult kidney transplantation.

Methods. Eight electronic databases were searched from inception to November 2013. Only primary intervention studies, which reported measurement of adherence to immunosuppressive medications after kidney transplantation, were included. The quality of all studies was assessed using the Consolidated Standards of Reporting Trials and Transparent Reporting of Evaluations with Non-randomized Designs checklists. A synthesis was undertaken to tease out the domains targeted by interventions: (i) educational/cognitive, (ii) counselling/behavioural, (iii) psychological/affective and (iv) financial support. For each study, key information, such as population, location, methods of measurements, comparison group, type of intervention and outcomes, were extracted and tabulated.

Results. Twelve intervention studies were identified. Quality of studies ranged from 16.0 to 80.5%. Effective interventions were implemented for 3, 6 and 12 months. Medication adherence rates were greatly enhanced when multidimensional interventions were implemented whereas one-off feedback from a nurse and financial assistance programmes offered little improvement. Dose administration aids when used in conjunction with self-monitoring also improved adherence. The number of patients who had a drug holiday (at least 1-day interval without a dose) was higher in a once-daily regimen than a twice-daily regimen.

Conclusions. The findings of this review suggest an intervention targeting behavioural risk factors or a combination of behavioural, educational and emotional changes is effective in enhancing medication adherence. Effectiveness of an

intervention may be further enhanced if patients are encouraged to participate in the development process.

Keywords: adults, intervention, kidney transplantation, medication adherence, systematic review

INTRODUCTION

With the incidence of end-stage kidney disease projected to increase dramatically, the demand for kidney transplants will also rise [1]. Kidney transplantation is the preferred treatment for end-stage kidney disease, because it increases the patients' quality-adjusted-life years 5-fold [2] and is more economical when compared with dialysis [3].

Although superior to dialysis treatment, kidney transplantation involves the inherent risk of graft rejection and graft failure that incurs costly hospitalizations, laboratory tests and anti-rejection treatments, which are associated with poor patient outcomes [4]. To minimize the risk of rejection, recipients are placed on life-long regimens of immunosuppressive medication and are monitored for signs of rejection. Not taking immunosuppressive medications as prescribed (defined as taking medications <95.1% of days) is associated with a 60% increased risk of kidney transplant failure [5]. It is therefore evident that immunosuppressive medications are necessary in kidney transplantation, but are only effective if taken as prescribed.

Adherence can be defined as the extent to which people follow the instructions they are given for prescribed treatments [6]. In the usual care setting, healthcare professionals do not explicitly ask patients if they are non-adherent and patients rarely volunteer this information to their doctor [7]. As a result, many cases of non-adherence go undetected. In patients who have not experienced an acute rejection episode, the non-

adherent behaviour may be reinforced [8] by their appraisal that occasional missed doses do not influence the results of routine laboratory tests. This non-adherent behaviour emerges during the initial 6 months after transplantation, with research showing that missed doses of immunosuppressive medication during this period increased acute rejection episodes [9].

Non-adherence to medication may be either an intentional decision (missing or altering doses without consulting healthcare professionals) or unintentional interruption to a patient's routine (forgetting to take medications) [10]. A multitude of factors contribute to the decision whether to take, miss or alter the medication regimen. As categorized by the World Health Organization, five main risk factors can influence adherent behaviour including socioeconomic factors (e.g. financial difficulty, lack of transportation), healthcare organizational barriers (e.g. staff rotation, limited amounts of time allocated to each patient), disease-related factors (e.g. the presence of chronic disease), therapy-related factors (e.g. the presence of debilitating side effects, complex dosing regimens) and patient-related factors (e.g. communication barriers, busy work schedules, health beliefs, attitudes) [11]. Because all patients have different barriers to medication adherence, it is important to implement an intervention that is tailored to their risk factors in order to improve their adherence rate. Ultimately, better medication adherence results in improved general well-being for the transplant patient and reduced healthcare costs.

In 2009, De Bleser *et al.* [12] systematically examined 12 intervention studies that have been conducted to improve medication adherence rates in solid organ transplant patients. Five reports focused on adult kidney transplant recipients [12] and only two of these studies improved medication adherence using multidimensional interventions. Since then, many refinements and developments have occurred to help keep patients engaged in their medication treatment. Innovative health technologies and policies, which were not widely available or thoroughly researched in the early 2000s, have since proven to be effective in enhancing the patient's medication adherence in chronic illness management [13, 14], even in resource-limited settings such as the Nyanza Province [15].

Accordingly, a systematic review of all intervention studies aimed at improving immunosuppressant therapy adherence in adult patients who have received a live (i.e. elective surgery) or deceased (i.e. cadaveric) transplanted kidney was undertaken. This systematic review sought to consolidate information and address the impact of interventions to promote medication adherence in kidney transplant recipients.

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement) was used as a guideline to ensure clarity of the systematic review [16].

Literature search

Eight electronic databases: MEDLINE, PubMed, CINAHL, Web of Science, Embase, ScienceDirect, Scopus and PsycINFO were searched from inception to November 2013. An initial

trial search using Medline and Embase databases with 'intervention' as one of the key terms revealed no studies. This search was then followed by preliminary searches of the National Library of Medicine and Elsevier, with reference to the literature previously identified by De Bleser *et al.* [12], to determine highly relevant topical terms. The term 'intervention' was found to be neither a popular Medical Subject Headings nor a widely used Emtree thesaurus term to categorize interventional studies in medication adherence. To ensure rigour, 'intervention' was used in combination with 'kidney transplantation', which also revealed no relevant studies. Therefore, 'intervention' was omitted except if it was shown in the word index generator of other electronic databases.

For most searches, the key term 'kidney transplant' was used in conjunction with either 'medication adherence' or 'patient compliance' in combination with 'immunosuppressive agents' to retrieve all relevant primary research studies (Appendix 1). Although the terms 'adherence' and 'compliance' are distinct in meaning in the healthcare lexicon as proposed by World Health Organization [11], 'patient adherence' and 'patient compliance' in this context were interchangeable and both referred to the extent to which consumers follow instructions they are given for prescribed treatments [6].

Selection criteria

This review included primary research studies that described interventions to improve medication adherence in kidney transplantation and were written in English. No restrictions were imposed on study design (controlled or uncontrolled) and study duration. While uncontrolled trials are regarded as the weakest type of experimental design [17], it was perceived that these studies would provide relevant information and were therefore included.

Participants living with functional kidney transplants aged 18 years and above were included, regardless of donor sources (living or deceased donor) and the initial cause of kidney failure. The primary outcome measure included in this review was the measurement of adherence to immunosuppressive medication. Where applicable, findings such as clinical surrogate measurement of adherence, healthcare utilization and management of comorbid conditions were reported as secondary outcomes.

Case reports and all published non-primary research articles (présis, letters to the editor, reviews and book chapters) were not included in this review. Published conference abstracts that lacked details on the method and result sections were also excluded to avoid potential risk of bias due to selective reporting.

Reference lists of retrieved studies and reviews on the topic were checked for relevant articles not identified by the previous search strategies. After removing all duplicates, all authors screened study titles and abstracts and discarded those that did not fit the inclusion criteria. As for references without an abstract or when abstracts contained insufficient detail, the full-text paper was sourced. Full text of studies that appeared to include relevant data was examined for inclusion eligibility. Intervention studies that did not address medication adherence as an outcome were deemed ineligible. Two reviewers (J.K.L. and K.C.) independently assessed the articles for

possible inclusion. Differences in assessment were resolved with discussion until the reviewers came to a consensus.

Data extraction

Characteristics of the selected articles such as year of publication, country, study design, patient group and index medications are presented in Table 1. Duration of implementation and monitoring period, control group description, intervention type, measurement of medication adherence and secondary outcome are presented separately for randomized controlled trials (RCTs) and non-RCTs in Tables 2 and 3, respectively. In Tables 2 and 3, either 'adherence' or 'compliance' was used according to the choice of word made by researchers in the original publication. Attempts were made to contact corresponding authors to obtain details not found in the full text. Corresponding authors were given 2 weeks to respond and any field that was left blank in Table 1 provides evidence of a vain attempt.

Data synthesis

The findings were too heterogeneous to be analysed with formal meta-analyses. A synthesis was therefore undertaken using the broad classification of interventions as proposed by De Bleser *et al.* [12] with an additional financial-support intervention:

- (1) Educational/cognitive interventions conveyed transplant-related information delivered by phone, mail or in person, in written or verbal forms.
- (2) Counselling/behavioural interventions attempted to target, mould and foster permanent optimal medication-taking behaviour.
- (3) Psychologic/affective interventions included social support for the patients or constant support from the research team.
- (4) Financial-support interventions were implemented at an individual or organizational level.

Data were extracted by one reviewer (J.K.L.) and another reviewer (K.C.) checked the validity of the extracted data.

Quality ratings

The quality of intervention studies in this review was critically appraised using standardized evaluation tools, the 25-item Consolidated Standards of Reporting Trials (CONSORT) checklist for all RCT studies [29] and the 22-item Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) checklist for other study designs [30]. Both checklists are proposed to evaluate the critical factors that should be present in a quality report, which can provide the most reliable evidence on the efficacy of healthcare interventions [29, 30]. In

Table 1: Characteristics of included intervention studies

Author (year)	Number of sites, country	Study design	Quality (0–100%)	Recruitment		Demographics		Medications	
				Kidney transplant group	Months post-transplant	Mean age (year)	% Male	Index medications	Frequency
Chisholm <i>et al.</i> (2000) [18]	One site, USA	One-group post-test only	62.7	All adults	0	48.1	83.3	Cyclosporine or tacrolimus	–
Chisholm <i>et al.</i> (2001) [19]	One site, USA	Randomized controlled trial	45.7	All adults	0	49.2	75.0	Cyclosporine or tacrolimus	–
Hardstaff <i>et al.</i> (2002) [20]	One site, UK	Randomized controlled Trial	26.0	All patients	>12	–	–	Azathioprine or prednisolone	Once daily
Hardstaff <i>et al.</i> (2003) [21]	One site, UK	Randomized controlled trial	16.0	All patients	>12	–	–	Azathioprine or prednisolone	Once daily
Chisholm <i>et al.</i> (2005) [8]	One site, USA	One-group post-test only	62.7	All adults	0	50.4	72.7	Cyclosporine or tacrolimus	–
De Geest <i>et al.</i> (2006) [22]	Two sites, Switzerland	Pilot randomized controlled trial	67.7	Non-adherent adults only	≥12	45.6	78.6	Any IS medication	Once or twice daily
Russell <i>et al.</i> (2011) [23]	One site, USA	Pilot randomized controlled trial	59.4	Non-adherent adults only	All	51.5	47.0	Any IS medication	Twice daily
Hlubocky <i>et al.</i> (2012) [24]	One site, USA	Retrospective observational study	43.5	All adults	0	50.0	63.3	Mycophenolate and valganciclovir	Twice daily and once daily, respectively
Kuypers <i>et al.</i> (2013) [25]	Six sites, Belgium	Randomized controlled trial	69.1	All adults	6 < x < 72	–	45	Tacrolimus	Once versus twice daily
Chisholm-Burns <i>et al.</i> (2013) [26]	One site, USA	Randomized controlled trial	80.5	All adults	≥12	52.1	56.0	Cyclosporine or tacrolimus	–
Tschida <i>et al.</i> (2013) [27]	One site, USA	Retrospective observational study	73.9	All adults	>12	49.8	~60%	Any IS medication	–
McGillicuddy <i>et al.</i> (2013) [28]	One site, USA	Randomized controlled trial	57.4	Non-adherent hypertensive adults	>3	Control: 57.6, intervention: 42.4	57.9	>3 hypertension and IS medications	Up to four doses daily

C, control; I, intervention; IS, immunosuppressive –, not reported in original study.

Table 2: Interventions and outcomes of retrieved RCTs included in this review

Study ID, duration	Number of participants	Dimensions of intervention	Medication adherence		Confirmatory/secondary	
			Measurement	Results	Measurement	Results
Hardstaff (2002) [20] 3 months	C: Plain top bottle <i>n</i> = 25 I: Electronic monitoring device (bottle) <i>n</i> = 75	Behavioural: Incorporated electronic monitoring device	A combination of pill count and interview (control group) or electronic monitoring device (intervention group) Compliance was calculated as a % of missed doses of medications. Percentage of extra doses was calculated for the intervention group	No difference between groups. Percentage of patients with 100% compliance throughout the study: Plain bottle, 54% Smart top, 39%	–	–
Hardstaff (2003) [21] 12 months	C: Usual care and electronic monitoring device <i>n</i> = 25 I: One-off feedback from a nurse <i>n</i> = 23	Behavioural: One-off electronic feedback from a nurse about adherence level	Electronic monitoring: Compliance was calculated as a % of missed or extra doses of medications	No difference between groups. Over 12 months, % of patients that (i) Improved I: 26% versus C: 20% (ii) Worsened I: 39% versus C: 40%	–	–
De Geest (2006) [22] 9 months: 3-month intervention and 6-month follow-up	C: Enhanced usual care group <i>n</i> = 12 I: Patient-tailored self-efficacy group <i>n</i> = 6	Informational: Information about medications Behavioural: Increased self-efficacy by using cues or reminders. Emotional: Feedback and assessment about adherence; one home visit and three telephone contacts; social support	Electronic monitoring: Data were used to calculate (i) taking adherence (% of cap openings versus prescribed doses), (ii) drug holiday (no medication intake >36 h for a twice-daily IS or >60 h for a once-daily IS) and (iii) timing adherence <98% of cap openings was considered non-adherent	There was a trend that the intervention group was more adherent than the control group. However, the difference did not reach statistical significance	Qualitative assessment of intervention: The intervention group was asked an open-ended question about the benefit of the intervention	Patients felt that electronic monitoring feedback was most helpful
Kuypers (2013) [25] 9 months: 3-month baseline and 6-month intervention	C: Twice-daily group <i>n</i> = 74 I: Once-daily group <i>n</i> = 145	Behavioural: Regimen simplification, from twice-daily to once-daily tacrolimus dosing regimen	Electronic monitoring using the Helping Hand™: Adherence was decomposed into (i) persistence (time from the first to the last taken dose during study) and (ii) implementation of each dosing regimen (timing adherence)	Percentage of patients who remained persistent was significantly higher in I: 82% than C: 72%. As was the case for timing adherence, I: 88% versus C: 79%	–	–
Russell (2011) [23] 6 months	C: Attention-control group <i>n</i> = 5 I: Patient-tailored continuous self-improvement group <i>n</i> = 8	Behavioural: Self-improvement plan that fosters medication taking into daily routines Emotional: Feedback and assessment about adherence; one home visit and five telephone contacts; social support	Electronic monitoring: Patients were considered non-adherent with a mean adherence score of <0.85 Medication adherence score was calculated based on within a 3-h window between the cap openings and the scheduled time for the medications to be taken	Adherence score significantly differed between groups during the intervention (over 6 months), I: 0.88 versus C: 0.77 but difference in adherence score was lost at the end of intervention, I: 0.85 versus C: 0.82	–	–

Continued

Table 2: Continued

Study ID, duration	Number of participants	Dimensions of intervention	Medication adherence		Confirmatory/secondary	
			Measurement	Results	Measurement	Results
Chisholm (2001) [21] 12 months	C: Usual care, <i>n</i> = 12 I: <i>n</i> = 12	Informational: Verbal or written instructions about medication intake Behavioural: Monthly face-to-face medication counselling with clinical pharmacist Emotional: Patients were given contact number of clinical pharmacist; positive reinforcement	Pharmacy refill records. Monthly compliance was estimated by comparing refill records to the prescribed regimen documented in medical records <80% of the compliance rate was considered non-compliant	Mean compliance rate significantly differed between groups, I: 96% versus C: 82% % of patients that were compliant differed significantly between groups, I: 75% versus C: 33%	Serum concentration of IS was on-target if it fell within the range, cyclosporine: 250–400 ng/mL tacrolimus: 8–15 ng/mL	Percentage of patients with on-target IS serum level differed between groups I: 64% versus C: 48%
Chisholm-Burns (2013) [26] 15 months: 12-month intervention and 3-month follow-up period	C: Standard specialty pharmacy care group <i>n</i> = 74 I: Standard care and patient-tailored behavioural contract <i>n</i> = 76	Informational: Discussion about consequences of non-adherence Behavioural: Identified life routines, tools or strategies to enhance adherence Emotional: Involved significant others and enhanced patients' motivation	Pharmacy refill records: Adherence rate was 1.0 if day between refills was less than or matched with total number of days' supply. Monthly adherence was estimated by comparing refill records to the prescribed regimen documented in medical records	<i>t</i> -test revealed that mean medication adherence score of I was significantly higher than C: At 6 months, I: 0.89 versus C: 0.80 At 9 months, I: 0.91 versus C: 0.81 and during the follow-up period (adherence rate not reported)	Monthly healthcare screening questionnaire: Using monthly recall, participants were asked about healthcare utilizations	Intervention was beneficial as lower % of patients from the intervention group (23.9%) was hospitalized as compared with the control group (57.3%)
McGillicuddy (2013) [28] 4 months: 30-day baseline and 3-month intervention	C: Standard care group and MedMinder™ tray <i>n</i> = 10 I: Standard care and mHealth group <i>n</i> = 9	Behavioural: MedMinder™ tray, which was used to organize medications had the reminder functions enabled; self-monitored blood pressure	Electronic monitoring: Patients were considered non-adherent with a mean adherence score of <0.85, as calculated using a modified version of Russell's [24] adherence scoring system (for different dosing frequency)	Adherence rate of I was significantly higher than C during the intervention: At 1 month, I: 0.87 versus C: 0.53 At 2 months, I: 0.92 versus C: 0.59 At 3 months, I: 0.94 versus C: 0.57	Resting blood pressure taken either clinically (control group) or at home (mHealth group)	Only systolic blood pressure of I was significantly lower than C At 1 month, I: 129.7 versus C: 147.2 At 3 months, I: 121.8 versus C: 138.8

C, control group; I, intervention group; IS, immunosuppressive medication; –, not reported in original study.

order to compare the quality of retrieved studies that were assessed with different evaluation tools, a percentage of the score was calculated.

RESULTS

The initial search yielded 1742 citations, of which 1739 were found through electronic databases and three citations through references [28, 31, 32]. A total of 772 citations were duplicates. After close examination, 12 studies met the inclusion criteria (Figure 1) whereas three highly relevant citations were excluded because full texts were either not published [31] or published in a language other than English [32, 33]. Of the 12 studies included in this review, two studies did not explicitly state the age group of individuals who were recruited [20, 21]. Both studies were included because the corresponding author was not successfully contacted and terms indicative of a non-adult patient

group (e.g. children, paediatric, adolescent, parents, <18 years old) were not used in the articles [20, 21].

Study characteristics

As summarized in Table 1, the final sample consisted of eight RCTs [19–23, 25, 26, 28] and four non-RCTs, of which, two were retrospective cohort studies [24, 27] and two studies included no paired-comparison data [8, 18]. In one study conducted in Switzerland, two hospital sites were used [22] and in one study conducted in Belgium, six clinical sites were used [25] whereas the remainder were carried out in single sites in the UK (*n* = 2) [20, 21] and the USA (*n* = 8) [8, 18, 19, 23, 24, 26–28]. Only two studies pre-determined the sample size needed to obtain sufficient power to support findings on interventional efficacy [25, 26]. The number of patients allotted to the control or intervention group ranged from 5 to 519 and were aged on average from 42.4 to 52.1 years. Overall, more male participants were recruited except for studies conducted

Table 3: Interventions and outcomes of retrieved non-Randomized Controlled Trials (non-RCTs) included in this review

Study ID, duration	Number of participants	Dimensions of intervention	Medication adherence		Confirmatory / Secondary	
			Measurement	Results	Measurement	Results
Chisholm (2000) [18] 12 months	C: No control group I: n = 18	Financial: IS were provided at no cost	Pharmacy refill records: Monthly compliance was estimated by comparing refill records to the prescribed regimen documented in medical records <80% of compliance rate was considered non-compliant	Cost factor alone was not a determinant of compliance. % of patients that remained compliant at each month decreased over time: At 5 months, 95% At 7 months, 75% At 12 months, 48%	Serum concentration of IS was on-target if it was at least 250 ng/mL for cyclosporine and 8 ng/mL for tacrolimus	Good surrogate measure. Percentage of patients with on-target IS serum level was higher in the compliant group (86%) than the non-compliant group (52%)
Chisholm (2005) [8] 12 months	C: No control group I: n = 33	Financial: IS were provided at no cost	Pharmacy refill records: Monthly adherence was estimated by comparing refill records to the prescribed regimen documented in medical records <80% of adherence rate was considered non-adherent	Types of IS influenced compliance rate. % of patients that remained adherent differed: Tacrolimus, 63% Cyclosporine, 33%	Serum concentration of IS was on-target if it was at least 250 ng/mL for cyclosporine and 8 ng/mL for tacrolimus	Good surrogate measure. Percentage of patients with sub-target IS serum concentrations was higher in the non-adherent (75%) group than the adherent group (24%)
Hlubocky (2012) [24] 6 months	C: Control group, n = 217 (no refill records) I: Specialty pharmacy program n = 188	Behavioural: Refill reminder; identify and resolve barriers to medication adherence Emotional: Patients were proactively contacted by pharmacist Financial: Financial advices was given to patients to manage medication coverage issues	Continuous measures of medication adherence (CMA) of ≥ 1 was an indication that patients had sufficient quantities of medication to allow for perfect adherence (No comparison data were available and data for the intervention group were incomplete)	No comparison data were available for the intervention group. Of 158 patients, 53% had a CMA of ≥ 1 for mycophenolate Of 125 patients, 68% had a CMA of ≥ 1 for valganciclovir	Healthcare utilization: Hospital admission rates within 90 days of transplantation and length of hospital stay after transplantation	Hospital readmission rates were similar in both groups of patients, C: 85 (of the 217 patients) versus I: 78 (of the 188 patients) As was the case for length of hospital stay: C: 4.5 ± 1.9 days I: 4.6 ± 4.6 days
Tschida (2013) [27] 12 months (Patients enrolled in transplant specialty pharmacy program)	C: Retail pharmacies group n = 519 I: Transplant specialty pharmacy program n = 519	Informational: Educational materials about transplantation, comorbid conditions and medication adherence Behavioural: Refill reminder calls; face-to-face consultation with dispensing pharmacist Emotional: Adherence assessment via telephone; patients could contact a specialty pharmacy nurse or a pharmacist	Prescription refill records: Records were used to evaluate (i) medication possession ratio (MPR), (ii) medication gaps (MG: defined as a ≥ 60 -day period without IS) and (iii) discontinuation of therapy	MPR of I (0.87) was significantly higher than C (0.83) Lower number of patients in I (n = 29) had MG than C (n = 56); and rate of discontinuation was lower in I (n = 39) than C (n = 104)	Healthcare costs, clinical resource utilization and transplant complications	Mean total cost per patient was lower in I (\$24,315) than C (\$27,891) However, healthcare utilization and transplant complications were not significantly different between groups

C, control group; I, intervention group; IS, immunosuppressive medication.

by Russell *et al.* [23] and Kuypers *et al.* [25]; however, two studies did not report the male-to-female ratio [20, 21]. Regardless of the dosage frequency, all studies included a measurement of adherence to immunosuppressive medications.

Quality ratings

A quality assessment was performed individually for each study using the CONSORT or TREND statements. Papers assessed using the TREND checklist [8, 18, 24, 27] achieved an

average score of 60.7%, and the quality ranged from 43.5 to 73.9%. Two out of four non-RCT studies appraised using the TREND checklist only examined the adherence rate of one group of patients [8, 18]. For these studies, the intervention was relatively simple and easy to execute because all patients were provided with free immunosuppressive agents [8, 18]. Therefore, group assignment, delivery method and statistical methods to compare group differences were non-applicable and were excluded [8, 18]. The quality of RCTs ranged from

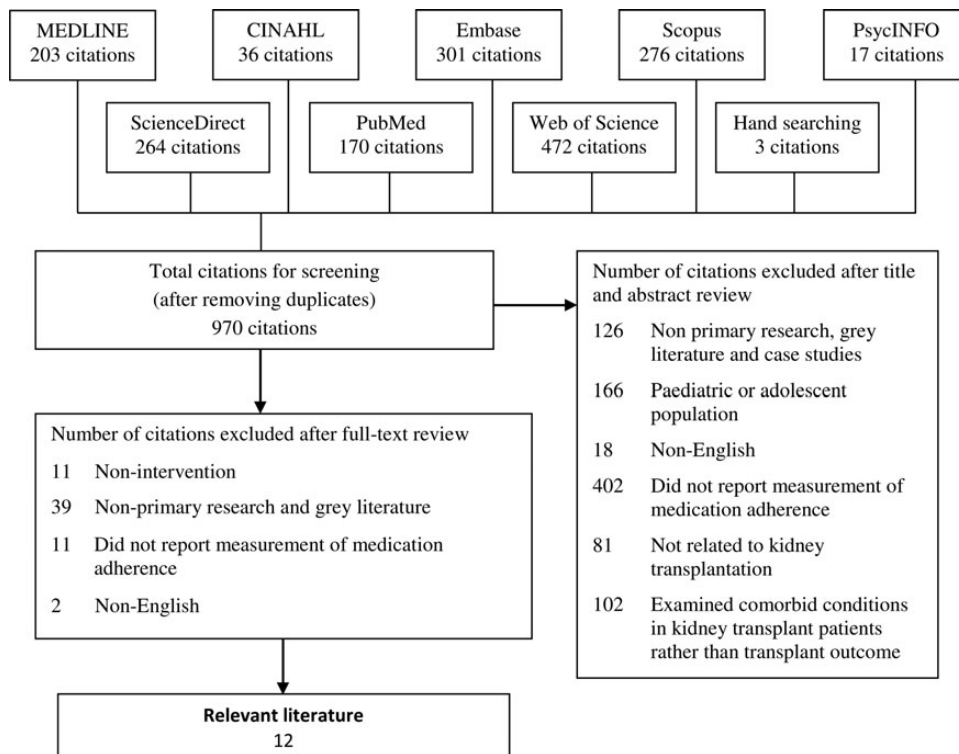


FIGURE 1: Flow chart providing an overview of the study selection process—literature search from inception to 30th November 2013 on intervention to improve medication adherence in adult kidney transplantation.

16.0 to 80.5% with an average score of 52.7%. Most of the included RCT studies lacked transparency when detailing the steps taken to randomize participants. Study participants, coordinators and investigators of most studies were not blinded to group assignment.

Measurement of medication adherence

Methods for measuring and monitoring medication adherence in patients varied across the studies, ranging from labour-intensive pill counts [20] to the incorporation of electronic monitoring devices into daily routine [20–23, 25, 28] and review of prescription records [8, 18, 19, 24, 26, 27]. Using missed doses to represent non-adherence, an arbitrary threshold value of 80% [8, 18, 19] was applied to adherence measured with prescription refill records whereas adherence rates of 85% [23, 28] and 98% [22] were applied when measuring with electronic devices. Patients with an adherence rate less than these cut-off points were categorized as non-adherent in respective studies [8, 18, 19, 22, 23, 28]. On the other hand, the operational definition of non-adherence was different in the RCT led by Hardstaff *et al.* [20, 21], where both incidences of missed and extra doses of medications were considered to be non-adherence. To confirm adherence, some studies included routine laboratory tests of immunosuppressive serum concentrations [8, 18, 19]. Further details regarding adherence rate calculations are summarized in Tables 2 and 3.

Interventions

Twelve interventions were identified in this review, with RCTs being presented in Table 2 and non-RCTs in Table 3.

All interventions were implemented for at least 3 months [8, 18–20, 22–28], except for the trials that involved one-off interview or feedback from a registered nurse [21]. Of the 12 studies identified in this review, four multidimensional interventions [19, 23, 26, 27] and one behavioural intervention [29] found a significant improvement in medication adherence.

Interventions and outcomes of retrieved RCTs

As summarized in Table 2, interventions of the retrieved RCTs ($n = 8$) were implemented either with a focus on behavioural change [20, 21, 25] or a combination of behavioural and educational strategies with [19, 22, 26, 28] and without educational materials [23]. To improve medication adherence, individualized interventions were more effective than universal approaches.

Three out of four unidimensional interventions with a focus on behavioural changes did not record a significant improvement in the patients' medication adherence. These interventions included an electronic monitoring device [20], one-off feedback about adherent behaviour [21] and regimen simplification of tacrolimus [25]. Percentage of patients with perfect adherence was 15% lower in electronically monitored patients ($n = 75$) than those whose medications were in plain top containers ($n = 25$) [20]. Medication adherence was worse after 12 months in 39% of the participants who received a one-off feedback from a nurse ($n = 23$) compared with 40% of the patients who did not receive any feedback ($n = 25$) [21]. On the other hand, regimen simplification implemented by Kuypers *et al.* [25] benefitted patients immediately after the conversion from the twice-daily (adherence score: 82.2%) to the once-daily (adherence score: 88.2%) dosing regimen [25]. However, a higher

proportion of patients had a drug holiday (1-day interval without a dose) in the once-daily (62%) than the twice-daily (40%) dosing regimen [25].

The remaining and only effective unidimensional intervention included a 28-compartment medication tray, a personalized reminder system and a blood pressure self-monitoring device [28]. McGillicuddy *et al.* [28] proved that this behavioural intervention, driven by self-improvement theory effectively kept patients' ($n = 9$) adherence rate consistently above 85% for 3 months during implementation of the intervention [28]. In comparison, adherence rates of the control group ($n = 10$) equipped with only the medication tray were consistently lower than 60% [28].

Three individualized multidimensional interventions, which included a behavioural contract [26], a self-improvement plan [23] and medication counselling session [19], effectively improved patients' adherence during implementation. Adherence scores of intervention groups ranged from 88% [23] to 96.1% [19] as compared to the range of 77% [23] to 81.6% [19] for the control groups. A pilot study conducted by De Geest *et al.* [22] which was patient-tailored and multidimensional, lacked statistical significance although trends suggested that the intervention was beneficial.

These multidimensional interventions targeted multiple risk factors of non-adherence, including patients' behaviour, health literacy level and emotion. To modify patients' behaviour, instruction about the time to take medications were given specifically (e.g. 8.00 a.m. and 8.00 p.m. instead of twice-daily) and medicine-taking time was scheduled to coincide with regular routine [19, 23, 26]. Patients were educated about the benefits of adherence [19] and consequences of non-adherence [26]. When possible, significant others were encouraged to be engaged with patients therapies [23, 26], and patients were encouraged to contact their pharmacist or nurse when in doubt [19]. All adherence-enhancing multidimensional interventions were implemented for at least 6 months [19, 23, 26].

Interventions and outcomes of retrieved non-RCTs

A total of four non-RCTs were retrieved and summarized in Table 3. Two non-controlled trials, with no paired-comparison group, revealed that financial assistance alone did not improve medication adherence [8, 18]. Although these studies lacked paired-comparison data, both studies led by Chisholm *et al.* [8, 18] provided insight into the development of suboptimal adherence among those who received medications at no cost [8, 18]. After 5 months, more than 90% of the patients remained adherent, whereas at 12 months this had reduced to <50% [8, 18].

The remaining non-RCTs were retrospective observational studies, which examined the beneficiary effects of transplant specialty pharmacy programs on helping patients to take their medications [24, 27]. The structure of the specialty pharmacy programme differed slightly between the two studies. Hlubocky *et al.* [24] reported a behavioural-affective-financial intervention whereas Tschida *et al.* [27] described the programme as targeting informational, behavioural and affective changes. A comparison between these two programmes was not possible because the study by Hlubocky *et al.* [24] was relatively weak, not having medication adherence comparison data in addition

to an incomplete data set. This study, however, was included because it met the broad inclusion criteria of this review.

Tschida *et al.* [27] detailed that patients received refill reminder calls, educational materials about transplant-related issues in the mail, and adherence was assessed by a pharmacist over the telephone [27]. Patients also had the contact details of a specialty pharmacy nurse and pharmacist [27]. Compared with patients served by retail pharmacies, patients in the specialty pharmacy program were more persistent and adherent (as summarized in Table 3) [27], where the intervention group saved more than \$3000 a year per patient on healthcare costs [27].

DISCUSSION

Strict adherence to prescribed medications is essential to ensure best treatment outcomes, especially in organ transplantation in which taking at least 97% of prescribed immunosuppressive medications is required to prevent rejection [34]. However, evidence suggests that adherence is suboptimal [35, 36], with about 52% [18] to 67% [8, 19] of patients being non-adherent. Although none of the studies included in this review were designed and powered to detect graft rejection or graft loss, the hospitalization rate was doubled when patients had an adherent rate of 80% as compared with 90% [26]. It is therefore evident that non-adherence not only increases the risk of hospitalization [26] but also causes poor long-term kidney outcomes [37], which negatively impact on the patient's health and quality of life.

Medication adherence is a continuum, shaped through a complex interplay of influential factors at the individual and interpersonal level. The decision whether to take, alter or miss doses can be influenced by patients' perceived importance of their medications [35], ease of access to the healthcare facility, medication costs, wait times at the pharmacy [38], time since transplant [39] and presence of family or social support [40]. The barriers to medication adherence are complex and varied among individuals and thus, an individualized intervention that targets multiple risk factors is necessary. Since the systematic review published by De Bleser *et al.* [12] in 2009, a growing body of evidence suggests that an intervention targeting multiple behavioural risk factors [28] or a combination of behavioural and emotional changes with [26, 27] or without [23] educational materials is effective in enhancing medication adherence.

However, the methodological shortcomings previously identified by De Bleser *et al.* [12] are still apparent. Most studies failed to include a clear description of patient demographics, healthcare settings, usual care provided and most importantly, content of interventions performed. This situation makes it very difficult for future investigators to adopt, reproduce and refine strategies examined in past research. Without a secondary confirmation measurement, it was impossible to suggest that patients were taking their medications after they refilled their prescription [24, 27] or removed the medications from either the blister pack [25] or bottle [20–23]. Results of this current review also point towards extending the monitoring period whenever possible, to include a baseline

monitoring period and a follow-up period, to better assess the impact of the intervention.

A question that frequently arises in systematic reviews is the potential selection bias produced by the key terms used to generate the list of references. To address this issue, preliminary searches of the National Library of Medicine and Elsevier, with reference to the literature previously identified by De Bleser *et al.* [12], were conducted to determine highly relevant topical terms. The electronic database search strategy adopted in this systematic review was sufficiently broad enough to capture most studies of interest as demonstrated by the low number of studies found through retrieved references ($n = 3$).

Surprisingly, out of the 970 retrieved citations, 17% were related to biomedical characteristics such as drug development, assay and effect; 10% measured patients' beliefs and expectations; whereas only around 1% was dedicated to improving medication adherence. This review revealed that suboptimal adherence to medication regimens is a well-recognized but poorly managed problem. Owing to the limited number of relevant publications, all studies that met the broad inclusion criteria were included in this review despite the weak quality of studies as demonstrated by the low average quality score of 56.5%. Although superior to non-RCT design, the average quality score of RCTs was less because most of the included studies did not describe the methods and results sections in sufficient detail. In general, most RCT studies omitted the steps taken to determine sample size, generation of randomization and concealment of group allocation. Additionally, the two weakest studies included in this review were both RCTs [20, 21]. It is therefore evident that attention to detail in measuring outcomes and reporting research according to validated guidelines, such as CONSORT and TREND, is important for meaningful analysis of the findings and also for future research. Additionally, most corresponding authors were not able to be contacted to follow up on details in their studies. Another limitation is that this review was limited to articles published in English. There may be articles published in other languages which can provide significant insight into the efficacy of intervention.

In conclusion, the six-month continuous self-improvement intervention, which was patient-tailored effectively enhanced medication adherence scores throughout the study [23]. Similarly, Chisholm-Burns *et al.* [26] successfully demonstrated that patients continuously benefitted from the behavioural contracting intervention even at 3 months after its completion [26]. Both interventions delivered by Russell *et al.* [23] and Chisholm-Burns *et al.* [26] assisted patients to identify both barriers to medication adherence and strategies for overcoming these barriers. Additionally, interventions led by a pharmacist coupled with medication counselling and refill reminder demonstrated promising results [27]. A simple behavioural intervention driven by a self-regulatory approach, with the incorporation of a dose administration aid and self-monitoring, was also proven to be effective [28]. Self-monitoring increases the patients' awareness about their non-adherent behaviour and also allows healthcare professionals to monitor the patients' performance. If a patient is detected to be having difficulty in following the medication regimen, early interventions can be implemented to improve medication intake.

One major setback of most of these effective patient-tailored interventions is the involvement of a pharmacist or a nurse, which is time-consuming and costly to implement. Nevertheless, this workforce cost may be off-set by the reduction of healthcare costs as a result of medication non-adherence [13]. Additionally, future adherence-enhancing interventions may focus on a supportive, cost-effective and multidimensional intervention delivered by a non-nursing personnel who are not responsible for the daily care of the patient. Kidney transplant recipients should also be encouraged to be involved actively in the design of an intervention to increase medication adherence.

CONFLICT OF INTEREST STATEMENT

None declared.

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