Transplant International

Transplant International ISSN 0934-0874

REVIEW

Interventions to improve medication-adherence after transplantation: a systematic review

Leentje De Bleser,[1] Michelle Matteson,[2] Fabienne Dobbels,[1] Cynthia Russell[2] and Sabina De Geest[1,3]

1 Center for Health Services and Nursing Research, Katholieke Universiteit Leuven, Leuven, Belgium
2 University of Missouri Sinclair School of Nursing, University of Missouri, Columbia, MO, USA
3 Institute of Nursing Science, University of Basel, Basel, Switzerland

Keywords
intervention, noncompliance, organ transplantation, patient compliance, review.

Correspondence
Sabina De Geest, Center for Health Services and Nursing Research, Katholieke Universiteit Leuven, Kapucijnenvoer 35/4, B-3000 Leuven, Belgium. Tel.: +32 16 336981; fax: +32 16 336970; e-mail: sabina.degeest@unibas.ch

Received: 10 November 2008
Revision requested: 12 December 2008
Accepted: 17 March 2009

doi:10.1111/j.1432-2277.2009.00881.x

Summary

Reports of interventions to improve adherence to medical regimens in solid organ transplant recipients are scarce. A systematic review identified 12 intervention studies. These studies focused on renal, heart, and liver transplant recipients. Five reports used randomized controlled trial (RCT) designs. Sample sizes varied between 18 and 110 subjects. The interventions are difficult to evaluate and categorize because of brief descriptions of intervention details. Of the 12 studies identified in this review, only five studies found a statistically significant improvement in at least one medication-adherence outcome with the intervention. In general, most included a combination of patient-focused cognitive/educational, counseling/behavioral, and psychologic/affective dimensions. Eight studies intervened at the healthcare provider, healthcare setting or healthcare system level, but showed a limited improvement in adherence. No single intervention proved to be superior at increasing medication-adherence in organ transplantation, but a combination of interventions in a team approach for the chronic disease management of organ transplant patients may be effective in a long-term perspective. In conclusion, finding the most effective combination of interventions to enhance adherence is vital. Utilizing an RCT design and adhering to the CONSORT guidelines can lead to higher quality studies and possibly more effective intervention studies to enhance medication-adherence.

Introduction

Solid organ transplantation (Tx) is a chronic illness, in which transplant patients are bound to life-long medical follow-up and drug treatment. According to the World Health Organization (WHO), adherence is defined as 'the extent to which a person's behavior corresponds with the *agreed* recommendations from a healthcare provider' [1]. In contrast to the concept 'compliance', the term adherence particularly stresses the importance of establishing a partnership with the patient if a healthcare professional wants to be successful in guaranteeing correct medication intake. Although adherence to drug treatment is crucial to prevent rejection, graft loss and additional morbidity, a substantial proportion of Tx recipients are nonadherent (NA) to their immunosuppressive regimen. NA for different adult Tx populations ranges from 20 to 37% [2–5]. In a recent meta-analysis, Dew *et al.* [5] found medication NA across all organ transplants to be 22.6 cases per 100 patient years (PPY). Evidence shows the detrimental effects of NA to immunosuppressive drugs on economic and short- and long-term clinical outcomes. Systematic reviews demonstrated that an estimated 50% (range 20–73%) of late acute rejections and 15% (range 3–35%) of graft losses are associated with NA [2,3,6]. Minor deviations from prescribed dosing and timing of drug administration are sufficient to increase the risk for poor outcomes [7,8].

It is clear from the above-mentioned evidence that adherence-enhancing interventions as part of state-of-the

art clinical management to improve outcomes should gain momentum in Tx [9,10]. Yet, major review papers [11] have neglected to mention the behavioral aspects in their discussion on how to improve post-Tx clinical outcomes. A systematic review is urgently needed to evaluate the types of interventions that are most effective in improving the adherence with the immunosuppressive regimen.

The purpose of this systematic literature review on the efficacy of adherence-enhancing interventions in adult and pediatric Tx patients is to provide a critical appraisal of the literature by (i) evaluating the methodologic quality of the studies and (ii) describing the content of the interventions. Directions for future research will be provided.

Materials and methods

An Ovid Database search of CINAHL, MEDLINE, PsycINFO and all Evidence-Based Medicine Reviews (Cochrane DSR, ACP Journal Club, DARE, CCTR) was conducted to identify studies (until August 2008) that tested the efficacy of interventions to improve adherence to the immunosuppressive regimen in Tx patients. Combinations of the terms 'transplant*', 'intervention', 'complian*', 'noncomplian*', 'non-complian*', 'adheren*', 'nonadheren*', 'non-adheren*', 'concordance', 'non-concordance', 'education', 'self medication', 'self efficacy', 'behaviour', 'behavior*', 'social support', 'electronic monitoring', 'drugs' and 'medication' were used. A thorough search was done by two independent researchers (LDB, MM). No limits were set on the search. Study inclusion criteria were: testing an intervention aimed at enhancing immunosuppressive medication-adherence in organ Tx, including a measurable medication-adherence outcome. Abstracts [12,13] were also eligible to be included. The literature search resulted in 36 relevant publications in Medline. Repeating the search in the other databases did not reveal additional publications. After carefully reading the abstract and/or full text, most articles did not have a content referring to an adherence-enhancing intervention in Tx or were only describing medication-enhancing interventions without reporting results of an intervention study. Nine publications [9,12–19] were retrieved from the literature. Reviewing the reference list of the identified articles resulted in three additional articles [20–22], resulting in an overall availability of a total of 12 studies for further methodologic and content analysis (Table 1).

Data extraction

The following information was abstracted from the studies: author, year, purpose, sample, setting, design, study period, intervention/control or usual care, intervention dose, measurement method and definition of adherence (Table 1) and study period, intervention/control or usual care, intervention dose, dimension of intervention (educational/cognitive, counseling/behavioral, psychologic/affective), level of intervention (patient, micro, meso, macro), whether the intervention was multi-level, and results (Table 2).

Data extraction definitions

When extracting the information, the authors used following definitions to classify interventions at the patient level:

1 *Educational/cognitive interventions* conveyed information or knowledge, individually or in a group setting, and delivered verbally, in written, and/or audio-visually [7,8].

2 *Counseling/behavioral interventions* targeted, shaped, and/or reinforced behavior, empowered patients to participate in their care, positively changed a patient's skill level or normal routine [3,7,8].

3 *Psychologic/affective interventions* appealed to the feelings and emotions or social relationships and social supports of the patient [8,9]; mixed interventions involved a combination of the above-mentioned intervention types.

The following definitions, based upon the ecologic model of McLeroy *et al.* [23], were used to classify data at the level of intervention:

1 *Patient level interventions* were targeted at the patient only, and include the categories of interventions discussed above (i.e. educational/cognitive; counseling/behavior and psychologic/affective interventions).

2 *Interventions at the micro level or interpersonal level* referred to strategies focused on the patient-provider interactions such as the perceived quality of the patient provider relationship, and communication style [24–26].

3 *Interventions at the meso level* related to characteristics of the treatment center or hospital [24,27] such as the provision of continuity of care, or the skill mix of teams [28,29].

4 *Interventions at the macro level* referred to interventions focusing on the healthcare system or on the society in which a patient lives [25], such as health insurance coverage and out of pocket expense for medications; and finally, *combination of different level interventions* referred to interventions that incorporated more than one of the previously mentioned levels [24–26].

Two of the authors extracted data to ensure validity of data extraction.

Scoring methodologic quality

The quality of all retrieved articles was checked, using a list of quality appraisal questions [30] (Table 3). Six

Table 1. Characteristics of the reviewed studies.

Author, year	Purpose	Design	Sampling method	Sample & sample size	Medication & dosing frequency	Measurement & timing	Definition of adherence
Chisholm, 2001	Clinical pharmacy services effect on IS medication AH	RCT	Convenience sampling	*N* = 24 renal Tx (I = 12, C = 12) *Time post-Tx*: >1 y *% Male*: 75 *Mean age*: 45 y	Cyclosporine (*n* = 21) & tacrolimus (*n* = 3) *dos. freq.*: NR	*Measurement*: pharmacy refill records for cyclosporine & tacrolimus, measured after 1 y after inclusion	Dividing the number of IS doses filled by pharmacy by the number of IS doses prescribed per time period × 100 <80%: noncompliant;
De Geest, 2006	Test the efficacy of a 3 mos. AH-enhancing i ntervention in NA pts.	Pilot-RCT	Convenience sampling	*N* = 18 renal NA Tx (I = 6, C = 12) *Time post-Tx*: >1 y *% Male*: NR *Mean age*: 45.6 y	NR *dos. freq.*: NR	*Measurement*: EM measured 3, 6, and 9 mos. after inclusion	*Taking AH*: *N* events recorded during the monitoring period/No. of prescribed doses during the monitoring period × 100; *timing AH*: *N* near optimal inter-dose intervals/total *N* observed intervals × 100 (accounting for 25% of the optimal dosing interval); *drug holiday*: no medication intake >36 h for a twice daily dosing regimen NA: <98% taking AH and/or one or more drug holiday
Dejean, 2004	Evaluate the efficacy of educational therapy to improve medication AH & determine factors of NA	RCT	NR	*N* = 110 renal Tx (I = 55, C = 55) *Time post-Tx*: NR *% Male*: NR *Mean age*: 49.1 y	NR *dos. freq.*: NR	*Measurement*: AH questionnaire. Assessment at baseline, end of educational sessions, 3 mos. after sessions	NR
Hardstaff, 2003	Measurement of AH after MEMS report counseling	RCT	Convenience sampling	*N* = 48 renal Tx (I = 23, C = 25) *Time post-Tx*: NR *% Male*: NR *Mean age*: NR	NR *dos. freq.*: NR	*Measurement*: EM measured 3 & 12 mos. after inclusion	% of missed or extra medications during 1 mo
Klein, 2006	Test a pharma. care program effectiveness on medication AH	RCT	Convenience sampling	*N* = 41 liver Tx (I = 20, C = 21) *Time post-Tx*: <1 y *% Male*: NR *Mean age*: NR	NR *dos. freq.*: NR	*Measurement*: EM, IS blood levels, measured regularly	NR

Table 1. continued

Author, year	Purpose	Design	Sampling method	Sample & sample size	Medication & dosing frequency	Measurement & timing	Definition of adherence
Annunziato, 2008	Test the a pilot intervention aiming to facilitate transition in healthcare while patients receive pediatric services	Pilot pre-experimental study	Consecutive sampling	*N* = 22 liver pediatric Tx *Time post-Tx*: >6 mos.*% Male*:55 *Mean age*:15.8 y	Tacrolimus *dos. freq.*: NR	*Measurement:* tacrolimus blood levels, ALT-levels, family feedback (survey) measured 3 mos. after I	Standard deviation of tacrolimus blood level < 3; ALT > 110 IU/l
Beck, 1980	Determine magnitude of pediatric medication NA & the effect of a 6 m. education program on medication AH	Pre-experimental study	Convenience sampling	I = 21 renal pediatric Tx & parents *Time post-Tx*: <1 y *% Male*: 8 *Mean age*: 15 y	Prednisone & azathiopine *dos. freq.*: NR	*Measurement*: pill count measured 6 mos. after inclusion	NA with IS medication: >11% discrepancy in pill count with at least one of the IS medication or >6% discrepancy with IS & other medication: an effect upon allograft function was not required; NA with all other medications: >6% discrepancy in pill counts in more than 1/2 of all other medications.
Chisholm, 2000	Adherence with free IS drugs	Pre-experimental study	Convenience sampling	I = 18 renal Tx *Time post-Tx*: <1 y *% Male*: 83 *Mean age*: 48 y	Cyclosporine & tacrolimus *dos. freq.*: 1–2/day	*Measurement*: pharmacy refill records for cyclosporine & tacrolimus: collected monthly after Tx by pharmacy prescription system for 1 y	Calculated monthly by dividing the number of IS doses filled by pharmacy by the number of IS doses prescribed per time period, multiplied by 100. <80%: nonadherent
Dew, 2004	Tested a web-based psychosocial intervention on QOL and medication adherence	Quasi experimental study	Convenience sampling	*N* = 60 heart Tx (I = 20 pt & family, C = 40 pt & family) *Time post-Tx*: <1 y *% Male*: 75 (both groups) *Mean age*: I: 45.8% <55 y; C: 57.5% <55 y	NR *dos. freq.*: NR	*Measurement*: survey (patient or caregiver) of medical AH in past 6 mos. (at initial interview) or during the period between assessments (at the follow-up interview). Asked whether and how consistently took all prescribed meds 4 mos. after inclusion	Consistence of taking medications: ordinal response format (e.g. respondents were asked whether patients had forgotten to take medications every day, several times a week, etc.); % of missed medications, at least once a m.

Table 1. continued

Author, year	Purpose	Design	Sampling method	Sample & sample size	Medication & dosing frequency	Measurement & timing	Definition of adherence
Fennell, 1994	Family based program to improve medication AH	Quasi experimental study	Convenience sampling	*N* = 29 renal pediatric Tx (I = 14, C = 15) *Time post-Tx.*: NR *% Male*: 59 *Mean age*: 12 y	Azathioprine, prednisone *dos. freq.*: NR	*Measurement:* pill count & blood level concentration measured 4–6 & 8–12 w after inclusion	*N* medication presented at the clinic visit/*N* the pt. should have determined by the dosage and prescription refills; AH to cyclosporine: disparity score of 1, 2 or 3, assigned depending on how far the measured cyclosporine level was outside a predetermined range.
Shemesh, 2008	Clinical program to improve medication AH in pediatric liver Tx pts	Pre-experimental study	Convenience sampling	*N* = 23 liver NA pediatric Tx *Time post-Tx.*: >6 mos *% Male*: 34.8 *Mean age*: 9.7 y	Tacrolimus *dos. freq.:* NR	*Measurement*: tacrolimus blood levels, ALT-levels, biopsy-proven rejection. Measurement every 2/week until stable tacrolimus blood levels; 1/week during 1 mo., monthly for 3 mos.	Standard deviation of tacrolimus blood level <3 and ALT >110 IU/l
Traiger, 1997	Test the Self Medication Administration Program to increase self-efficacy, and medication AH (SMAP)	Pilot Quasi experimental study	Convenience sampling	*N* = 41 heart, lung, heart-lung Tx (I = 10, C = 31) *Time post-Tx.*: <1 w *% Male*: 20 *Mean age*: NR	NR *dos. freq.*: NR	*Measurement*: discharge self-report medication AH survey assessed discharge preparation, medication self-efficacy & self-care management. Measurement at 3–6 w in I and up to 2 y in C	NR

AH, adherence; NA, nonadherence; I, intervention group; C, control group; CR, compliance rate; IS, immunosuppressive medication; QOL, Quality of Life, pt., patient; NR, not reported; Tx, transplantation; y, years; w, weeks; mos., months; ↑, increase; ↓, decrease; *N*, number, dos. freq., dosing frequency.

Table 2. Overview of described interventions in literature.

Author, year	Total study period	Intervention/control or usual care	Dimension			Level	Results
			Informational	Behavior	Affective		
Chisholm, 2001	12 mos.	I: clinical pharmacy services: Monthly review of pt. medications to optimize med. therapy to achieve desired outcomes Clinical pharmacist counseled pt. concerning medication (verbally/written) Contact number of pharmacist given If pt. has no clinic visit in a 1-m period, pharmacist-pt. interaction occurred by phone C: routine clinic services	Medication intake instructions (verbally/written)	Clinical pharmacist counseled pt. concerning medication	Contact number pharmacist given	Patient Meso	*Primary outcome* Statistically sign. difference in AH between groups: I had a higher AH rate after 1 year ($P < 0.001$), longer duration of AH ($P < 0.05$), and achievement of target blood levels ($P < 0.05$) than C. *After 1 year* I: mean AR of 96.1 ± 4.7% C: mean AR of 81.6 ± 11.5% ($P < 0.001$). m 6–8 and 10–12 post-Tx sign diff AR between I & C, ↑ rates in I ($P < 0.05$) I: mean monthly AR: I = 89 to 100%; C = 64 to 100% *AH duration after 1 year* 75% AH in I and 33% AH in C mean time to first NA m.: I = 11 mos. (CI: 10–12) C = 9 mos. (CI: 10–12) *Serum IS concentration at 1 year* I: 64% target serum IS blood level C: 48% target serum IS blood level ($P < 0.05$)
De Geest, 2006	9 mos.	I: tailored intervention: 1 home visit (with educational, behavioral, social support interventions based on individual assessment of reasons for NA) +3 telephone contacts (monthly); EM printouts used for feedback C: usual care only	Education	Self-efficacy	Individual EM-feedback &. assessment of NA; 3 telephone contacts with home visit & social support	Patient	*Primary outcome* Statistically sign. ↓ in NA at 3 mos. ($P < 0.06$), but during the follow up period, no statistically sign. difference between groups. *NA within I & C* NA sign. ↓ in I & C (I $\chi^2 = 3.97$, $P = 0.04$; C $\chi^2 = 3.40$, $P = 0.06$). at 9-mos. NA ↓ a probability lower than calc. at start in I *NA between I & C* No sign NA ↓ in I & C at 3 or 9 mos. $\chi^2 = 1.05$, $P = 0.31$ $\chi^2 = 0.3$, $P = 0.58$

Table 2. continued

Author, year	Total study period	Intervention/control or usual care	Dimension			Level	Results
			Informational	Behavior	Affective		
Dejean, 2004	NR	I: 8 sessions of 3 h each education program & counseling, each consisting of 8 sessions lasting 3 h, given by multidisciplinary team C: Routine care	Education program	Counseling by multidisciplinary team	None	Patient Meso	*Primary outcome* Statistically sign. change in medication AH between groups at the end of the intervention period ($P < 0.02$) and at the end of follow up ($P < 0.006$) *Baseline*: no difference in mean AH score (317) in I & C; AR: 47.3%. NA associated with: high education level (OR 2.4 [1.2–5.8]), living alone (2.7 [1.2–6.1]), negative QOL (1.2 [1–1.5]), uncomfortable housing (1[1–1.2]), time since Tx (1.03 [1.05–1.1]), number of IS (0.8 [0.7–1]), use of hypolipemiant (2.6[1.1–6.1]) Side-effects of drugs: not associated with NA except acnea (2.7[1.1–6.9]). *End of intervention program*: AH significantly improved (69.1% I vs. 45.5% C, $P = 0.02$) *3 mos. after education:* AH was still improved (74.5% I vs. 47.3% C, $P = 0.006$)
Hardstaff, 2003	12 mos.	I: Received EM feedback at 1st outpatient clinical appointment, no further feedback; time until feed back ranged between 2–6 mos. C: Monitoring without feedback	None	EM-feedback	None	Patient	*Primary outcome* I: 26% subsequently improved, 39% worsened, 8% no difference; C: 20% subsequently improved, 40% worsened, 40% no difference after 1st outpatient visit *3 mos.*: 48% missed at least 1 dose, 25% took extra doses, 6% missed consecutive doses, 38% was 100% compliant *12 mos.*: 83% missed at least 1 dose, 54% took extra doses, 23% missed consecutive doses, 3% were 100% AH

Table 2. continued

Author, year	Total study period	Intervention/control or usual care	Dimension			Level	Results
			Informational	Behavior	Affective		
Klein, 2006	12 mos.	I: during hospitalization, regular appointments (not defined); counseling by clinical pharmacist regarding IS medication & discharge medication at regular appointments with pharmacist in ambulatory setting. C: no interactions with clinical pharmacist	Counseling by a clinical pharmacist	Counseling by a clinical pharmacist	None	Patient Meso	*Primary outcome* Statistically sign. ↑ in DA between groups ($P < 0.015$). I: mean DA = 90% (CI: ±6%); range 77–100% C: mean DA = 81% (CI: ±12%); range 57–99% ($P = 0.015$) I : 2 (10%) pt: DA < 80%; >C: 9 (43%) pt: DA < 80% ($P = 0.032$) I: ↑ achievement of target IS blood levels (92% vs. 78%) (no other data given) rejection: 2/11 pt (18%) with DA < 80% in comparison to 4/30 pt (13%) ↑ AH ($P = 0.651$)
Annunziato, 2008	Max. 6 mos.	I: education: module 1: information regarding liver disease & treatment regimen, pt. identified medication regimen and made personalized information sheet; module 2: family education concerning transition of health care (in total: 4–6 sessions)	Education	None	Involvement of family	Patient Micro	*Primary outcome*: statistically sign. ↓ in mean ALT levels with I ($P = 0.01$). For referred patients, SD of tacrolimus ↓ from 3.33 to 2.23, $t = 2.52$, ($P = 0.04$); Mean ALT ↓ from 120.33 to 63.99, $t = 3.01$, ($P = 0.01$); Maximal ALT values ↓ overall from 284.10 to 101.20, $t = 2.61$, ($P = 0.03$).
Beck,1980	6 mos.	I: *At start of program:* written & oral information with aid of medication calendars, schedules, pamphlets, involvement of parents *At each clinic visit:* physician and pharmacist discussed medication changes with child and/or parent for 6 mos. (duration not reported)	Written & oral information with aid calendars, schedules, pamphlets	Clinical pharmacist discussed medication changes with child and/or parent-	None	Patient Micro	*Primary outcome*: No statistically sign. change in AH, but statistically sign. ↑ in knowledge ($P < 0.01$). *Pill count: primary measure* At start: 9/21 (43%) NA; 6 m: only 4/21 (19%) NA *Secondary outcome* *Interview*: if the pt maintained a notebook: more AH at start; no difference after 6 mos. ($P < 0.005$); NA child more frequently came alone to consultation ($P < 0.007$) *Knowledge & AH:* at beginning of study: 60% (range 7–89%); at 6 mos. 83% (range 62–100%) ($P < 0.01$)

Table 2. continued

Author, year	Total study period	Intervention/control or usual care	Dimension			Level	Results
			Informational	Behavior	Affective		
Chisholm, 2000	1 year	I: received monthly IS drugs free of charge for 12 mos.	None	None	None	Macro	*Primary outcome* No statistically sign. difference in AH between those receiving and not receiving free IS AH ↓ over time: 5 mos. post-Tx: 95% AH; 7 mos. post-TX: 75% AH; 12 mos. post-Tx: 48% AH mean time to first NA m. = 9.8 m (CI: 8.60–11.0) *Secondary outcome* Statistically sign. difference in sub-target serum IS levels between those who received free IS and those who did not ($P < 0.001$); 6 (33%) NA pt below target drug levels AH pts. = 14% sub-target serum drug levels; NA pts. = 48% sub-target serum drug levels ($\chi^2 = 12.9$, $P < 0.001$)
Dew, 2004	4 mos.	I: Variable (depending on patient preferences) web-based intervention with stress & medical regimen management workshops, monitored discussion groups, electronic communication with Tx team + usual clinical care C: usual care only	Medical regimen management workshops	Stress management workshops	Monitored discussion groups electronic communication with Tx. team	Patient Meso	*Primary outcome* No statistically sign. difference in H between pts. receiving the web-based intervention and those who did not. % *missed medication (*≤1/m) I: web-based program users: 16.7% I: web-based program nonusers: 35.7% C: 44.4% ($\chi^2 = 1.76$; $P = 0.461$) *Secondary outcome* QOL improved for pts.& caregivers
Fennell, 1994	2–3 mos.	I: reviewed once educational booklet about transplantation; watched brief peer modeling videotape; used medication calendar to record AH; received weekly rewards from parents for AH behavior C: usual care	Educational booklet	Medication calendar to record AH	Peer modeling videotape; weekly rewards from parents for AH behavior	Patient	*Primary outcome*: No statistically sign. difference in AH between pts. who received program and who did not, but sign. interaction between time and group for prednisone ($P < 0.05$ and $P < 0.02$) *At beginning of study*: trend for I ↑ AH ($P = 0.06$) I: 67% AH with azathioprine; 56% AH with prednisone C: 33% AH with azathioprine; 35% AH with prednisone

Table 2. continued

Author, year	Total study period	Intervention/control or usual care	Dimension			Level	Results
			Informational	Behavior	Affective		
Shemesh, 2008	4 years	I: increased monitoring (intensified clinic visit schedule & increase frequency of medication blood level monitoring) with education Visit schedule: 2/week until stable tacrolimus blood levels, then 1/week during 1 mo., than monthly for 3 mos.	Education	Continuous monitoring of AH	Individ. tailored support	Patient Meso	*Primary outcome*: Statistically significant ↓ in the number of pts. with high ALT levels ($P < 0.01$). tacrolimus SD < 3: ↓ 50% ($P = 0.16$) Median ALT: ↓ 16% ($P = 0.5$) ALT > 100: ↓ 50% ($P < 0.01$) Biopsy-proven rejection episodes: ↓ 100% ($P = 0.08$)
Traiger, 1997	Mean: 13.5 days	SMAP: Self-Medication Administration Program; Phase 1: initiation; Phase 2: learning about medication; Phase 3: pt. took medication independently; Phase 4: day of discharge; Several times/day (depending on medication rounds on ward)	Phase 1: program initiation; Phase 2: learning about medication	Phase 3:pt. took med. independently; Phase 4: discharge planning	None	Patient Meso	*Primary outcome*: I: less adherent (data NR); I: higher self efficacy

AH, adherence; NA, nonadherence; CI, confidence interval; DA, dosing adherence; I, intervention group; C, control group; AR, adherence rate; IS, immunosuppressive medication; QOL, Quality of Life, pt., patient; NR, not reported; Tx, Transplantation; w, week; mos., month; ↑, increase; ↓, decrease; *N*, number.

Table 3. Summary score of appraisal questions (Forbes, 2002).

Author, year	Annunziato, 2008	Beck, 1980	Chisholm, 2000	Chisholm, 2001	Dejean, 2004	De Geest, 2006	Dew, 2004	Fennell, 1994	Hardstaff, 2003	Klein, 2006	Shemesh, 2008	Traiger, 1997
1. Was the study prospective or retrospective? (1 = retrospective study; 3 = prospective study)	3	3	3	3	3	3	3	3	3	3	3	3
2. Were the outcome measures appropriate and clearly linked to the intervention?	3	2	4	4	2	4	2	4	3	3	3	1
3. What method was used for the study? (Grade methods 1–4, 1 = expert opinion, 4 = RCT)	2	1	2	4	4	4	2	3	4	4	2	3
4. Were the methods adequately described and appropriate, following EPOC guidelines?	2	2	2	3	1	3	2	2	3	1	2	1
5. How strong was the impact of the intervention on the identified outcomes?	3	1	2	3	3	2	1	1	2	2	2	1
6. How accurate/precise was the measure of impact (*P*-values and CI)?	3	2	2	4	3	3	3	2	1	2	3	0
Summary Score W = Weak (score 0–9) M = Moderate (score 10–16) S = Strong (score 17–23)	M	M	M	S	M	S	M	M	M	M	M	W

EPOC, Cochrane Effective Practice and Organisation of Care Group, http://www.epoc.cochrane.org/Files/Website%20files/Documents/Reviewer%20Resources/datacollectionchecklist.pdf

questions on evaluating the clarity of the research questions, sampling methods, description of the nonresponse, reported definitions, measurements, statistical analysis and presentation of results were asked to evaluate the quality of the investigated research. Each of the appraisal questions were scored on a scale from 0 (=very poor) to 4 (=excellent), except question one, which had a score between 1 (=retrospective study) and 3 (=prospective study). The scores can be summarized into 'Weak' (i.e. score 0–9), 'Moderate' (i.e. score 10–16) or 'Strong' (i.e. score 17–23). Besides, the CONSORT criteria were used to specifically evaluate methodologic quality of the randomized controlled trial (RCT) studies (Table 4). These 22 criteria allow uniform assessment of RCT quality by providing a checklist of key factors that should be present in the highest quality RCTs. These factors include: title and abstract (one item), introduction (one item), methods (10 items), results (seven items), and discussion (three items). One point was assigned to each item if it was present with a possible range of scores from 0 to 22. All authors came to consensus on the final article scores.

Results

A total of 12 articles were included in the review (see Table 1). Seven reports [9,13–15,17,20,21] focused on renal Tx patients, three [12,18,19] on liver Tx and two [16,22] on heart/heart-lung Tx patients. Four studies focused on pediatric patients [18–21]. The sample size ranged from 18 [9,14] to 110 [13] subjects though small sample sizes were the norm. One study addressed sample size, clearly identifying the study as a pilot intervening in

Table 4. Scoring of RCT studies using the CONSORT guidelines.

Paper section & topic		Descriptor	Chisholm 2001	De Geest 2006	Klein 2001	Dejean 2004	Hardstaff 2003
1	**Title & abstract**	How participants were allocated to interventions (e.g. random allocation, randomized or randomly assigned)	1	1	1	1	1
Introduction							
2	Background	Scientific background and explanation of rationale	1	1	1	0	1
Methods							
3	Participants	Eligibility criteria for participants and the settings and locations where the data were collected	1	1	0	0.5	0
4	Interventions	Precise details of the interventions intended for each group and how and when they where actually administered	0	1	0	0	0
5	Objectives	Specific objectives and hypotheses	0.5	1	0	0	0
6	Outcomes	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g. Multiple observations, training of assessors)	0.5	1	0	0	0
7	Sample Size	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	0	1	0	0	0
Randomization							
8	Sequence generation	Method used to generate the random allocation sequence, including details of any restriction (e.g. blocking, stratification)	0	1	0	0	0
9	Allocation concealment	Method used to implement the random allocation sequence (e.g. Numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned	0	0	0	0	0
10	Implementation	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups	0	0	0	0	0
11	Blinding (masking)	Whether or not participants, those administrating the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated	0	0	0	0	0
12	Statistical methods	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses.	1	1	1	1	0
Results							
13	Participant flow	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	0	1	0	0	1
14	Recruitment	Dates defining the periods of recruitment and follow-up.	0.5	1	0.5	0.5	0
15	Baseline data	Baseline demographic and clinical characteristics of each group.	1	1	0	0.5	0
16	Numbers analyzed	Number of participants (denominator) in each group included in each analysis and whether the analysis was by intention to treat. State the results in absolute numbers when feasible (e.g. 10/20, not 50%)	0.5	1	0.5	0.5	0

Table 4. continued

Paper section & topic		Descriptor	Chisholm 2001	De Geest 2006	Klein 2001	Dejean 2004	Hardstaff 2003
17	Outcomes and estimation	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g. 95% confidence interval)	0.5	1	0.5	0.5	0
18	Ancillary analyses	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory.	1	1	0	1	0
19	Adverse events	All important adverse events of side-effects in each intervention group	0	0	0	0	0
Discussion							
20	Interpretation	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes	0	1	0	1	0
21	Generalizability	Generalizability (external validity) of the trial findings	1	1	0	0	0
22	Overall evidence	General interpretation of the results in the context of current evidence	1	1	1	0	0
	Total score		10.5	18	5.5	6.5	3

NA patients only [9]. There were four studies from Europe [9,12,13,17], the remaining from the United States.

Five (42%) studies used an RCT design [9,12,13,15,17], Three authors used an quasi-experimental design [22,28,29], and four [14,18–20] had a pre-experimental design and did not use a control group.

Most authors used pill count [14,15,20,21] and blood concentration of immunosuppressive medications [12,14,15,21] while only three publications [9,12,17] used electronic monitoring (EM) to assess NA. When multiple measurement methods were used, the prevalence resulting from these methods was not always reported. Moreover, various operational definitions of NA were used. In two studies [14,15], for instance, the patient was labeled as nonadherent when less than 80% of the prescribed medication was taken. In the study of Hardstaff *et al.* [17] both the missed or extra doses were considered as nonadherent. In the study of De Geest *et al.* [9] patients were NA if patient had less than 98% taking adherence and/or one or more drug holidays during a 3-month time period.

Using the list of quality appraisal questions [30] (Table 3), one study [22] was classified as 'Weak', nine studies were classified as 'Moderate' [12–14,16–21] and two studies [2,15] had been categorized as 'Strong'. Results of the CONSORT scoring for the five RCT studies are presented in Table 4. CONSORT scores ranged from 3 [17] to 18 [9], with a median score of 6.5. De Geest's *et al.* study received the highest quality study score of 18. The most important shortcomings were found in the methods section, specifically on allocation concealment, implementation, and blinding, with none of the studies including these aspects. The results section was described sufficiently in most studies.

Content of the intervention

Interventions were implemented for varied lengths of time, e.g. from 5 days to 12 months [12,15,17], and in varied locations, e.g. in-hospital [22], clinic [13,15,17], home [9], or in-hospital and clinic [12]. One intervention was delivered over the internet [16]. Interventionists included clinical pharmacists [12,15,20], clinical nurse specialists [9,22], a nurse practitioner [17], or an entire Tx team [13]. Only De Geest *et al.* [9] and Traiger and Bui [22] identified a theoretical framework, with both using Bandura's Social Cognitive Theory. Proposed interventions referred to education [13,15,18,20,21], internet-based interventions [16], financial support programs for drugs [14], EM feedback [9,12,17], a self-medication administration program as part of discharge planning [22] and a clinical program to improve medication-adherence [22]. All reports except two [14,17] used a mixed approach focusing on at least two of the three dimensions (educational/cognitive, counseling/behavioral and psychologic/affective).

Studies with a focus on educational/cognitive interventions

Three studies focused on education/cognitive intervention strategies [13,18,20]. Samples varied between the studies. Beck *et al.* [20] and Annunziato *et al.* [18] assessed 21 and 23 pediatric patients respectively, while Dejean *et al.* [13] recruited 110 adult patients. Beck's 6-month intervention consisted of education and counseling by a pharmacist and physician, who provided written reinforcement using calendars, schedules and pamphlets. Annunziato *et al.* [18] organized one-to-two sessions giving information concerning the disease and three-to-four sessions concerning the transition to adult healthcare. Dejean *et al.* [13] utilized an intensive educational program provided by a multi-disciplinary team, consisting of eight sessions lasting 3 h each. Medication-adherence outcomes were measured differently, Beck *et al.* [20] measured medication-adherence using pill counts at the end of the 6-month intervention. Annunziato *et al.* [18] used immunosuppressive blood levels, alanine aminotransferase (ALT) levels, and self-report. Dejean *et al.* [13] measured medication-adherence with a self-report questionnaire administered before, during and 3 months postintervention. Beck *et al.* found that knowledge of medications significantly improved ($P < 0.001$), but no statistically significant impact on medication-adherence was found. In the study of Annunziato *et al.* [18] there was a statistically significant decrease in the tacrolimus blood level standard deviation ($P = 0.04$) and the mean ALT level ($P = 0.01$). Study by Dejean *et al.* [13] resulted in a statistically significant improvement in medication-adherence ($P < 0.02$) and this improvement further increased at the 3-month postintervention evaluation ($P < 0.006$).

Studies with a focus on behavioral interventions

One study focused on behavioral/counseling interventions [17]. Hardstaff *et al.* used an RCT design with 48 renal Tx patients to examine the effect on medication-adherence of an intervention involving a nurse practitioner reviewing EM of medication record with the patient during the first clinic visit. The time until feedback was inconsistent, ranging from 2 to 6 months. Only descriptive statistics were presented with 26% in the intervention group improving, 39% worsening, and 8% showing no difference. Twenty percent of the control group improved, 40% worsened, and 40% showed no difference.

Studies with a focus on psychologic/affective interventions

No studies used a psychologic/affective intervention alone.

Studies with mixed interventions

Five studies [9,15,16,19,21] had adopted a combination of educational/cognitive, counseling/behavioral, and affective/psychologic interventions. De Geest *et al.* studied the effect of increasing self-efficacy to enhance medication-adherence [9]. Her intervention included a home visit and three follow-up phone interviews in NA renal Tx patients. Intervention by Fennell *et al.* [21] involved the entire family. The intervention included an educational booklet, videotape on adherence, medication calendar, and weekly rewards from parents for adherent behavior. Shemesh *et al.* [19] implemented regimented, individually tailored clinical schedules for NA pediatric liver Tx patients. Dew *et al.* studied a web-based support program for heart Tx patients and their families, which [16] offered discussion groups and information and electronic communication with Tx staff. The entire healthcare team participated, and the duration of the intervention was 4 months.

One study using mixed interventions reported a statistically significant improvement in medication-adherence [12,15,19]. Shemesh *et al.* found that immunosuppressive levels decreased significantly ($P = 0.16$) and high ALTs decreased by 50% postintervention ($P = 0.01$). The remaining studies documented other important results. Fennell *et al.* concluded that by month 3, transplant recipients in the experimental group ($P = 0.05$) were more knowledgeable about Tx than those in the controls. Adherence in the experimental group improved on average 67% with azathioprine and 56% for prednisone, while the control group noted only 33% and 35% improvement respectively [21]. The authors also discussed whether the intervention affected the parents' behavior as well as the child's behavior, thereby increasing adherence.

De Geest *et al.* found in both groups that the NA rate showed the greatest decrease after 3 months ($P = 0.06$), with the intervention group having the greatest decrease in NA ($P = 0.31$); however, both groups reached comparable levels at the end of the 6-month follow-up [9]. This study is the first to test an intervention in NA patients and in doing so found that just by being in the study, adherence improved. Dew *et al.* concluded that although adherence did not change ($P > 0.05$), there were small subgroup differences within the intervention group, depending on the internet 'dose' received [16]. However, psychologic factors (depression and anxiety symptoms, caregivers anxiety and hostility symptoms) did significantly improve ($P = 0.05$) and the quality of life indicators improved as well [16].

Multilevel interventions

Eight studies intervened on other levels of the healthcare system in addition to the patient-level approaches discussed above [12–16,19,20,22].

Micro level

In the study of Beck *et al.* [20], parents were actively involved in improving the medication-adherence of their children. In this study, it was concluded that children that were not accompanied by their parents, were less adherent ($P < 0.007$).

Meso level

Traiger and Bui [22], Dejean *et al.* [13], Dew *et al.* [16] and Shemesh *et al.* [19] implemented meso-level interventions. Dejean *et al.* organized multidisciplinary information sessions; Shemesh *et al.* implemented a 'clinical program' in the hospital; Traiger *et al.* introduced a Self Medication Administration Program (SMAP) administered during hospitalization and at discharge from the hospital post-Tx [22], but the program also targeted self-efficacy, which is a patient-level intervention. Their intervention educated the patient about medications and dietary restrictions and involved practice filling medication planners and taking the medications independently and accurately before discharge [22]. Traiger *et al.* concluded that the SMAP did not result in increased adherence. According to self-report surveys, 22% indicated that they sometimes forgot to take their medication versus 15% in the control group. The SMAP group did have higher self-efficacy, but poorer adherence (neither one statistically significant) [22]. Intervention by Dejean *et al.* [13] resulted in a significant increase of adherence in the intervention group: 69.1% vs. 45.5% in the control group ($P = 0.02$). In addition, 3 months after the education sessions, adherence remained improved (74.5% IG vs. 47.3% CG, $P = 0.006$). In the study of Shemesh *et al.* [19], postintervention, median ALT decreased to 16% ($P = 0.5$) and biopsy-proven rejection episodes decreased ($P = 0.08$).

Klein *et al.*'s [12] study may have involved a meso-level intervention, though assessment is difficult because of lack of intervention detail in the report. The monthly intervention included a pharmaceutical care program initiated prior to hospital discharge. The authors concluded that adherence in the intervention group was statistically significant ($P = 0.015$) and that significantly more intervention patients had target immunosuppressant blood levels (92% vs. 78%) than the control group [31].

Macro level

Chisholm *et al.* [14], using a cohort design with adult renal Tx patients, studied the effect of 1 year of free immunusuppressants and concluded that Tx patients were generally adherent until the 10th month. Afterwards, they became NA even with free medications. Ninety-five percent of patients were adherent 6 months post-Tx while only 48% were adherent at 12 months. The authors concluded that cost does not appear to influence adherence and they recommend an intensive effort to increase adherence before the ninth month post-Tx.

Discussion

The high prevalence of NA to the immunosuppressive regimen and its associated poor clinical and economic outcomes necessitate the development of effective adherence-enhancing interventions as a powerful pathway to improve post-Tx outcomes. This systematic review, however, revealed that limited *intervention research* exists in the Tx literature, and that the majority of 12 existing studies showed major shortcomings, related to the methodology and the content of the interventions used.

Methodologic weaknesses of included studies

First, the quality of articles using a list of quality appraisal questions [30] (Table 2) varied from 'Weak' [22] to 'Moderate' [12–14,16–21] and only two studies [2,15] had been categorized as 'Strong'. Besides, only five out of the 12 studies used an RCT [9,12,13,15,17] and most of these studies did not provide sufficient study report detail to adequately replicate the study or judge study quality. Two of the RCTs scored were published abstracts [12,13], and scoring was based on the published information only. No manuscripts have been published from these abstracts to date to clarify any missing CONSORT information. The average CONSORT score was 8.7, with the study of De Geest *et al.* [9] having the highest quality score. If this score had been excluded, the average score of the remaining studies would have only been 6.4. This lack of study detail has been a concern in the intervention literature in general [32].

Second, diverse operational definitions of NA were used. The WHO definition of adherence underscores a partnership between the patient and the provider, but does not provide a description on how much adherence is enough to prevent poor clinical outcomes. The absence of a taxonomy resulted in much confusion, resulting in most authors using arbitrary cut-offs or percentages to classify patients into an adherence or nonadherence group [33]. In our review, for instance, two studies [14,15] labeled patients as nonadherence when less than 80% of the prescribed medication was taken. In the study of Hardstaff *et al.* [17] both missed or extra doses were considered as NA. Satisfactory adherence is only achieved

when the gaps between the recipients dosing history and the prescribed dosing regimen have no effect on therapeutic outcome. In other words, future studies investigating NA in Tx would benefit from a clear operational definition, identifying the cut-off point below which poor clinical outcomes such as late acute rejections or graft loss occur. To our knowledge, only two studies specifically looked at clinically meaningful cut-offs, both showing that minor deviations from the prescribed immunosuppressive regimen (i.e. taking <98% of the drugs) are already sufficient to be associated with late acute rejections [7] or graft loss [8], indicating that, in contrast to other chronic diseases such as hyperlipidemia or hypertension, partial adherence (<100%) may not have a long-term salutary benefit. More studies are urgently needed, but are not easy to conduct, as the relationship between medication-taking behavior and clinical outcomes may be influenced by multiple mechanisms other than just adherence.

A fourth weakness in most studies was that there was no clear definition of the usual care patients received before the intervention or when being part of the control group. A shortcoming of some intervention studies [14,18–20] also was that there was no control group for comparison.

Fifth, there was no baseline assessment of adherence before the start of the intervention in four studies [12,14,15,22]. Therefore, it was difficult to make an evaluation of the effects of the intervention(s). In most studies the intervention was only done once or for a short period, making it difficult to evaluate the effect size of the intervention on clinical outcomes over a longer period of time.

A final methodologic shortcoming relates to statistical power. All studies have a rather small sample size. The sample size ranged between 18 [9,14] and 110 subjects [13]. Only one study [9] calculated the number of patients needed in both treatment arms to obtain sufficient power to substantiate findings on efficacy of interventions. However, their data lacked statistical power to support their assumptions, as only data from a pilot study were available [9].

Concerns with respect to the content of the intervention

In general, one in four Tx patients do not adhere to prescribed drug therapy. Finding the right combination of interventions to enhance adherence is vital to our Tx patients in order to preserve organ function. Out of the 12 studies identified in this review, only five studies [12,13,15,18,19] had statistically significant results. No single intervention proved to be superior at increasing medication-adherence in Tx. The reasons why the effects of the published interventions in Tx are limited are multifold.

First, adherence-intervention studies should build upon theoretical models explaining behavioral change, and should be multidimensional and multilevel. None of the studies except two [9,22] mentioned which theoretical framework was used to develop the adherence-enhancing intervention. Theoretical models may guide research efforts to build adherence-enhancing interventions, leading to better adherence and overall outcomes. For example, the Integrated Model of Behavior Change states that intentions and environmental or personal constraints are the primary determinants of behavior. According to this model, intentions are in turn determined by beliefs about social norms, self-efficacy (i.e. beliefs of behavioral control), and attitudes (i.e. covert feelings of favorability or unfavourability, e.g. outcome expectancy beliefs, weighing of pros and cons of adherence). This model, as well as other models, have in common that they provide guidance on which factors interventions should focus in order to be successful.

Second, based on meta-analyses [34,35] and systematic reviews [36,37] summarizing the evidence on adherence-enhancing interventions in other chronic illness populations, interventions should be multidimensional targeting as many risk factors as possible by combining educational/cognitive counseling/behavioral and psychologic/affective interventions. Yet, most of the interventions described have a focus on only one aspect, e.g., improving knowledge by providing education, or cost of the medication, ignoring that nonadherence is usually a multi-factorial and complex problem.

Third, in most studies, it was unclear as to what was meant by 'intervention' in terms of dosage, duration, content of intervention, and who performed the intervention. Most of the patients may not have received an adequate dose of the intervention as the interventions were administered only once or repeated infrequently during a short period of time (e.g. 6 months). Ideally, an intervention 'boost' should be provided on a regular basis to maintain medication-adherence.

Another weakness is that most interventions are not patient-tailored. In most studies, the intervention is identical for every patient and ignores the fact that an individual patient has his or her own risk profile. Using the WHO taxonomy [1], identified risk factors for NA are *patient-related* (e.g. low self-efficacy, patient's beliefs of efficacy of medications, former nonadherence, poor knowledge, higher perceived barriers to adhere to regimens), *socio-economic* (e.g. younger age, lack of effective social networks, family dysfunction), *treatment-related* (e.g. longer time since Tx, higher cost of medications, symptom distress associated with side-effects of

immunosuppressive regimen), *condition-related* (e.g. more self-care disability, more complications, psychiatric diagnosis such as depression, and substance abuse) [2], and *healthcare system- and healthcare team-related factors* [2,3,38]. The latter category should receive more attention as a potential resource for adherence-enhancing interventions. In line with the definition of adherence, underscoring the importance of establishing a partnership with the patient, the role of the healthcare professional and healthcare setting cannot be ignored. Indeed, publications on interventions performed in other chronic illness populations revealed that even the most effective interventions at the patient level (combination of more convenient care, information, reminders, self-monitoring, reinforcement, counseling, family therapy, psychologic therapy, crisis intervention, manual telephone follow-up and supportive care) did not lead to large improvements in adherence and treatment outcomes [39], suggesting that future interventions should focus more on the role of the professional and the healthcare system in which the patient is imbedded. Indeed, given that a partnership in view of adherence involves both the patient AND the professional, future studies should attempt to look at determinants at the micro, meso and macro level and develop interventions accordingly.

Based on the results from our systematic review, it appears that a combination of interventions, combining strategies at the patient, healthcare provider, setting and system level may be effective in the long term. A team approach for the chronic disease management of Tx patients is therefore recommended.

Conclusion

No single intervention proved to be superior at increasing medication-adherence but it does appear that a combination of interventions may be effective in the long term. Utilizing an RCT design and adhering to the CONSORT guidelines can lead to higher quality studies and possibly more effective interventional studies to enhance medication-adherence. Results also point towards extending the duration or the 'dosage' of intervention to reach enduring adherence and positively affect outcomes [40]. Future research on adherence-enhancing interventions should take notice of methodologic as well as content aspects to improve the outcome of adherence-enhancing interventions for organ Tx patients.

References

1. Sabate E. *World Health Organization Report: Adherence to Long-Term Therapies. Evidence for Action*. Switzerland: World Health Organization, 2003.
2. De Geest S, Dobbels F, Fluri C, Paris W, Troosters T. Adherence to the therapeutic regimen in heart, lung, and heart-lung transplant recipients. *J Cardiovasc Nurs* 2005; **20**: S88.
3. Denhaerynck K, Dobbels F, Cleemput I, *et al.* Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: a literature review. *Transpl Int* 2005; **18**: 1121.
4. Denhaerynck K, Desmyttere A, Dobbels F, *et al.* Nonadherence with immunosuppressive drugs: U.S. compared with European kidney transplant recipients. *Prog Transplant* 2006; **16**: 206.
5. Dew MA, DiMartini AF, De Vito DA, *et al.* Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation. *Transplantation* 2007; **83**: 858.
6. Dobbels F, Damme-Lombaert R, Vanhaecke J, De Geest S. Growing pains: non-adherence with the immunosuppressive regimen in adolescent transplant recipients. *Pediatr Transplant* 2005; **9**: 381.
7. De Geest S, Abraham I, Moons P, *et al.* Late acute rejection and subclinical noncompliance with cyclosporine therapy in heart transplant recipients. *J Heart Lung Transplant* 1998; **17**: 854.
8. Takemoto SK, Pinsky BW, Schnitzler MA, *et al.* A retrospective analysis of immunosuppression compliance, dose reduction and discontinuation in kidney transplant recipients. *Am J Transplant* 2007; **7**: 2704.
9. De Geest S, Schafer-Keller P, Denhaerynck K, *et al.* Supporting medication adherence in renal transplantation (SMART): a pilot RCT to improve adherence to immunosuppressive regimens. *Clin Transplant* 2006; **20**: 359.
10. Gordon EJ, Prohaska T, Siminoff LA, Minich PJ, Sehgal AR. Can focusing on self-care reduce disparities in kidney transplantation outcomes? *Am J Kidney Dis* 2005; **45**: 935.
11. Pascual M, Theruvath T, Kawai T, Tolkoff-Rubin N, Cosimi AB. Strategies to improve long-term outcomes after renal transplantation. *N Engl J Med* 2002; **346**: 580.
12. Klein A, Krämer I, Otto G. Impact of a pharmaceutical care program on liver transplanted patient's compliance with immunosuppressive medication - a prospective, randomized, controlled trial using electronic monitoring. *Am J Transplant* 2006; **6**: 212.
13. Dejean NB, Rontaing L, Lapeyre-Mestre M, Roge B, Durand D. Educational program to reduce noncompliance after renal transplantation. *41st Congress Abstract (European Renal Association and the European Dialysis and Transplantation Association)*. Lisbon (Portugal), 2004.
14. Chisholm MA, Vollenweider LJ, Mulloy LL, *et al.* Renal transplant patient compliance with free immunosuppressive medications. *Transplantation* 2000; **70**: 1240.
15. Chisholm MA, Mulloy LL, Jagadeesan M, DiPiro JT. Impact of clinical pharmacy services on renal transplant patients' compliance with immunosuppressive medications. *Clin Transplant* 2001; **15**: 330.

16. Dew MA, Goycoolea JM, Harris RC, *et al.* An internet-based intervention to improve psychosocial outcomes in heart transplant recipients and family caregivers: development and evaluation. *J Heart Lung Transplant* 2004; **23**: 745.
17. Hardstaff R, Green K, Talbot D. Measurement of compliance posttransplantation – the results of a 12-month study using electronic monitoring. *Transplant Proc* 2003; **35**: 796.
18. Annunziato RA, Emre S, Shneider BL, *et al.* Transitioning health care responsibility from caregivers to patient: a pilot study aiming to facilitate medication adherence during this process. *Pediatr Transplant* 2008; **12**: 309.
19. Shemesh E, Annunziato RA, Shneider BL, *et al.* Improving adherence to medications in pediatric liver transplant recipients. *Pediatr Transplant* 2008; **12**: 316.
20. Beck DE, Fennell RS, Yost RL, Robinson JD, Geary D, Richards GA. Evaluation of an educational program on compliance with medication regimens in pediatric patients with renal transplants. *J Pediatr* 1980; **96**: 1094.
21. Fennell RS, Foulkes LM, Boggs SR. Family-based program to promote medication compliance in renal transplant children. *Transplant Proc* 1994; **26**: 102.
22. Traiger GL, Bui LL. A self-medication administration program for transplant recipients. *Crit Care Nurse* 1997; **17**: 71.
23. McLeroy KR, Bibeau D, Steckler A, Glanz K. An ecological perspective on health promotion programs. *Health Educ Q* 1988; **15**: 351.
24. Miller NH, Hill M, Kottke T, Ockene IS. The multilevel compliance challenge: recommendations for a call to action. A statement for healthcare professionals. *Circulation* 1997; **95**: 1085.
25. Kothari AR, Birch S. Multilevel health promotion research: conceptual and analytical considerations. *Can J Nurs Res* 2004; **36**: 56.
26. Lyons KS, Sayer AG. Using multilevel modeling in caregiving research. *Aging Ment Health* 2005; **9**: 189.
27. Sellstrom E, Bremberg S. Is there a ''school effect'' on pupil outcomes? A review of multilevel studies. *J Epidemiol Community Health* 2006; **60**: 149.
28. Chesney M. Non-adherence: the Achilles heel of multiple drug therapies. *Bridg Wash DC* 1998; **2**: 4.
29. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness: the chronic care model, Part 2. *JAMA* 2002; **288**: 1909.
30. Forbes A, Griffiths P. Methodological strategies for the identification and synthesis of 'evidence' to support decision-making in relation to complex healthcare systems and practices. *Nurs Inq* 2002; **9**: 141.
31. Bartlett SJ, Lukk P, Butz A, Lampros-Klein F, Rand CS. Enhancing medication adherence among inner-city children with asthma: results from pilot studies. *J Asthma* 2002; **39**: 47.
32. Conn VS, Cooper PS, Ruppar TM, Russell CL. Searching for the intervention in intervention research reports. *J Nurs Scholarsh* 2008; **40**: 52.
33. Fine RN, Becker Y, De Geest S, *et al.* Nonadherence consensus conference summary report. *Am J Transplant* 2009; **9**: 35.
34. Peterson AM, Takiya L, Finley R. Meta-analysis of trials of interventions to improve medication adherence. *Am J Health Syst Pharm* 2003; **60**: 657.
35. Roter DL, Hall JA, Merisca R, Nordstrom B, Cretin D, Svarstad B. Effectiveness of interventions to improve patient compliance: a meta-analysis. *Med Care* 1998; **36**: 1138.
36. McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. *JAMA* 2002; **288**: 2868.
37. Haynes RB, Yao X, Degani A, Kripalani S, Garg A, McDonald HP. Interventions to enhance medication adherence. *Cochrane Database Syst Rev* 2005; **4**: CD000011.
38. Desmyttere A, Dobbels F, Cleemput I, De Geest S. Noncompliance with immunosuppressive regimen in organ transplantation: is it worth worrying about? *Acta Gastroenterol Belg* 2005; **68**: 347.
39. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2008; **2**: CD000011.
40. Haynes RB. Introduction. In: Haynes RB, Taylor DW, Sackett DL, eds. *Compliance in Health Care*. Baltimore: The John Hopkins University Press, 1979: 1.