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Understanding Medication Nonadherence after Kidney Transplant

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ABSTRACT

Alloimmunity remains a barrier to long-term graft survival that necessitates lifelong immunosuppressive therapy after renal transplant. Medication nonadherence has been increasingly recognized as a major impediment to achieving effective immunosuppression. Electronic medication monitoring further reveals that nonadherence manifests early after transplant, although the effect is delayed. The etiology of nonadherence is multifactorial, with the strongest risk factors including past nonadherence and being an adolescent or young adult. Other risk factors with smaller but consistently important effects include minority race/ethnicity, poor social supports, and poor perceived health. In children, risk factors related to parental and child psychologic and behavioral functioning and parental distress and burden are also important. Qualitative systematic reviews highlight the need to tailor interventions to each transplant recipient's unique needs, motivations, and barriers rather than offer a one size fits all approach. To date, relatively few interventions have been studied, and most studies conducted were underpowered to allow definitive conclusions. If the kidney transplant community's goal of "one transplant for life" is to become a reality, then solutions for medication nonadherence must be found and implemented.

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Presently, the first-year results of kidney transplantation are significantly better and early acute rejection rates are dramatically lower than only a few decades ago.[1,2] These improvements primarily result from treatment protocols combining potent oral immunosuppressant medications.[3] However, graft survival rates beyond the first year have not proportionately improved.[2] Alloimmunity manifesting as late rejection, clinical and subclinical, primarily associated with donor-specific antibodies (DSAs) is now recognized as the dominant cause of late graft loss.[4]

The principal independent correlates of late rejection and *de novo* DSAs are class 2 HLA mismatching, younger age, and medication nonadherence (MNA).[4,5] Indeed, a model has emerged that HLA mismatching, particularly class 2 mismatching, sets the stage for T cell–mediated rejection (TCMR) and/or *de novo* DSA formation.[6] After a *de novo* DSA forms, in >50% of patients, it results in antibody-mediated rejection (ABMR) that smolders over time and eventually results in chronic ABMR reflected in the biopsy as transplant glomerulopathy.[5] The interstitial fibrosis and tubular atrophy that are detected in late post-transplant biopsies for cause are correlated with early TCMR and MNA.[5] The model suggests that alloimmune-mediated late graft loss ensues as a result of ongoing ABMR and/or TCMR, and both of these processes are accelerated in the presence of patient MNA or physician-guided immunosuppressive minimization.[6] From this model, two major strategies emerge to improve long-term graft outcomes—class 2 HLA matching and early detection/reversal of patient MNA.

Unfortunately, MNA is a complex issue, and even physicians, experts who know the importance of a prescribed medication regimen, have personal difficulties with adherence. For example, in the Physicians' Health Study, approximately one third of volunteering physicians showed significant MNA (by self-report) in a trial of once daily aspirin or placebo.[7] As transplant recipients resume active (healthier) roles in their personal "real world," disrupted daily schedules, postponed work, delayed travels, and laboratory and clinic visits as well as a host of new time constraints irregularly distort their daily routines. The goal of this review is to provide a summary of our current understanding of the factors associated with MNA, the strategies used to date to overcome MNA, and the effectiveness of these approaches.

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DEFINITION AND MEASUREMENT OF MNA

In the arena of clinical transplantation, patient adherence is a multilayered and dynamic clinical concept. It encompasses a spectrum of behaviors ranging from lifestyle changes to regular attendance at clinic and laboratory visits. However, medication adherence, with a focus on post-transplant immunosuppressive medications, refers very specifically to the patient following agreed on recommendations and instructions from health care professionals concerning the taking of these drugs. In this context, medication adherence may be seen as two linked activities, namely adherence and persistence. Adherence indicates that the medication is taken at the prescribed dosage and times, whereas persistence measures the duration and consistency of this specific adherent behavior.

Unfortunately, health care providers are very poor judges of patient adherence and even seem perhaps biased to believe their patients are more adherent than average.[8] Because post-transplant adherence with immunosuppression is pivotal to the success of the transplant, two questions are logically asked: "when does MNA begin?" and "how much adherence is enough?" Although it is true that MNA may gradually appear later in a patient's clinical course, electronic medication monitors have now clearly shown dramatic early immunosuppressive MNA in renal transplantation.[9] Indeed, this pattern is not unique to transplantation; early nonadherence to a variety of medications is regularly observed in a number of other chronic conditions.[10,11] Importantly, this general observation may permit earlier interventions to improve adherence and delay or avoid later adverse outcomes.

As for medication adherence adequacy, the focus has most frequently been on whether doses were taken rather than issues of timing and taking doses erratically. Indeed, research is required to clarify the effect of nonadherence to timing of immunosuppressive medication dosing. With respect to dose-taking adherence, an oft-used value, drawn from the BP literature, is ">80%,"[12,13] but in transplantation, this metric is of little clinical relevance. Consider that any single percentage overlooks both the duration and pattern of the adherent behavior. For example, a patient prescribed an immunosuppressant drug twice daily should take 60 doses in 1 month. Thus, 80% adherence could be achieved by either randomly missing a single dose about three times a week or taking a drug holiday for the last 6 consecutive days of the month. Biologically, the consequences of these two patterns will likely be dramatically different. Moreover, while recognizing that each kidney donor-recipient pair differs immunologically, in missing definitive prospective data, for most patients with transplants, the 80% cut point is far too low: adherence rates of <95%–100% are associated with increased risk of acute rejection and graft loss.[14]

Because medication adherence is so important, how can it best be measured? Apart from parenteral medications administered in a clinic or directly observed therapy, any clinical measurements of medication adherence will have inherent limitations. Methods to assess medication adherence, including pill counts, questionnaires, patients' diaries, and random measurements of blood drug concentrations, can overestimate adherence.[15] Tracking an individual's prescription refills or awaiting adverse events are, by nature, retrospective and indirect measures, and they limit the effectiveness of any proactive approach to improve adherence.[16] Still, the absence of any measurable drug in a patient's blood, failing to refill a prescription for an extended time, or openly admitting nonadherence to a health professional likely confirm MNA. Although convincing, such isolated clinical events are relatively uncommon.

An inexpensive measure of adherence is to simply ask the patient. Although self-report can overestimate adherence, positive responses to either of two questions have been shown to reliably identify likely MNA.[17] (*1*) How often did you miss a dose of your immunosuppressive medication in the past 4 weeks? (*2*) Did you miss more than one consecutive dose of your immunosuppressive medication in the past 4 weeks? Clearly, such queries will miss patients unwilling to self-identify and those who cannot remember forgetting a dose. Nevertheless, any positive answers indicate some degree of MNA and provide the basis for immediate conversations about all medication-taking practices.

A slightly more expensive approach uses the coefficient of variation (CV) of a patient's tacrolimus levels to suggest MNA. Often, nonadherent patients will be more careful with their medication dosing, even increasing their dose, at times of laboratory testing and clinic visits.[18] Because the calculated CV should best reflect the patient's steady state, nonroutine drug levels obtained for clinical reasons (intercurrent illness, dose changes, *etc.*) should be excluded from any CV calculation. With that caveat, in renal transplantation, elevated tacrolimus CVs have been associated with increased adverse events and accelerated biopsy-proven graft fibrosis.[19–21]

Since the introduction of electronic monitoring (EM) of medications in 1988, it has become increasingly widely accepted as providing the best estimate of adherence. This approach is occasionally flawed, because the event of opening the vial does not ensure that the patient then actually takes the medication. Nevertheless, the Food and Drug Administration recently endorsed "smart bottles" as an approach to improving drug development trials by confirming protocol fidelity.[22] In situations where the drug regimen is complex and the drug's therapeutic index is narrow (HIV infection and kidney transplantation), EM has been useful to quantify adherence and compile individual drug-dosing histories. In prospective studies of adult renal transplant recipients, such dosing histories have been directly associated with clinical outcomes, even showing a dose-response relationship between measured MNA and adverse events.[23] In patients with kidney transplants followed for up to 4 years, EM has documented that MNA begins early in the

post-transplant period and that the pattern regularly persists thereafter.[14] Such studies also show a gradual erosion of medication adherence over time.

RISK FACTORS FOR MNA

Two literatures provide evidence on risk factors for immunosuppressant MNA after kidney transplantation: quantitative reports of empirical associations between putative risk factors and adherence outcomes and qualitative studies that ask patients directly what factors affect their adherence.

Quantitative Studies

The World Health Organization conceptualization of five categories of risk factors likely to be important for adherence to chronic disease treatment regimens[24] provides a framework for considering risk factors examined in kidney recipients to date (Figure 1). Among adult recipients, there is at least some support for the role of variables in all five categories (examples are in Figure 1).[16,25–29] Among the most consistently found and most potent risk factors is past MNA.[16,25,30,31] A meta-analysis found that three factors—nonwhite ethnicity, poor social supports, and poor perceived health—increased patients' risk for immunosuppressant MNA, but the effect of these factors, although consistent, is relatively small.[32] Other factors emerging as important in recent studies include cognitive elements, such as forgetting; treatment-related features, such as regimen complexity; condition-related factors, such as receipt of a living donor transplant and perceiving one's health to be better; and health care system factors, such as insurance coverage and copayments.[25,26,30,33,34]

Risk factors for nonadherence in pediatric kidney recipients have also received consideration, and among the strongest such factors is recipient age.[30,35–37] Adolescents/young adults (*i.e.*, age <25 years old) are at considerably greater risk for nonadherence to the medical regimen and medication taking in particular than either younger or older recipients. In pediatric recipients of kidneys and other types of organ transplants, there is also relatively consistent evidence that sociodemographic characteristics of the family (*e.g.*, parental marriage not intact), family psychosocial characteristics (lower family cohesion/support and greater parental distress and burden), child psychosocial status (poorer behavioral functioning and greater psychologic distress), and health care system–related factors (receipt of public rather than private insurance) increase risk for medical regimen

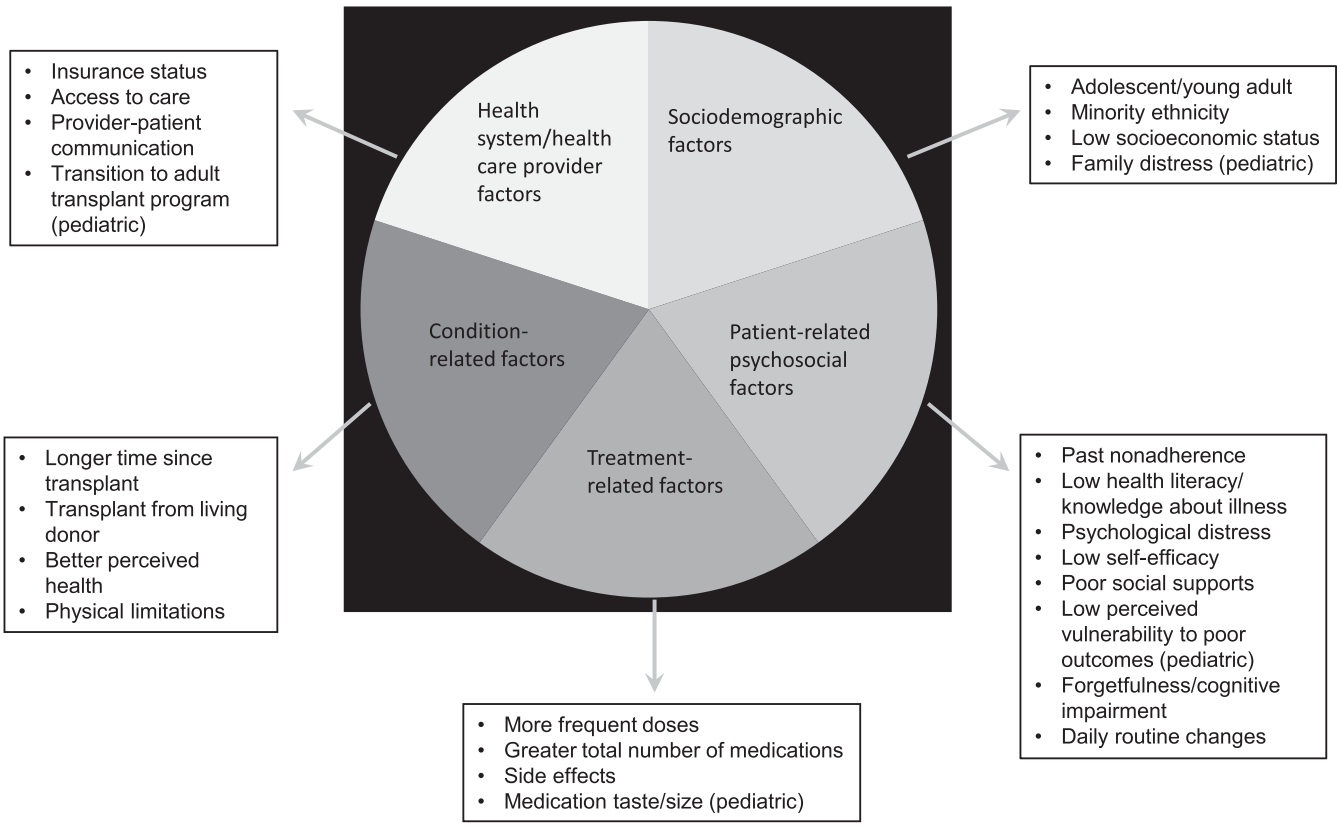

Figure 1. Major categories of risk factors for nonadherence in chronic disease based on reviews of the empirical literature (the work by Sabaté and World Health Organization[24]). For each of the five categories of risk factors identified, examples are provided to illustrate findings specific to studies of kidney transplant recipients.

nonadherence.[35,36] However, this literature is smaller than that available for adults, and studies have not always distinguished between risk factors specifically for immunosuppressant nonadherence as opposed to other areas of the regimen.

Qualitative Studies

A growing qualitative literature has focused on self-management issues in general and MNA more specifically after organ transplantation. Three recent systematic reviews summarized this evidence for adult kidney recipients[38,39] and adolescent organ (including kidney) recipients.[40] The strength of this literature is its emphasis on eliciting the experiences of transplant recipients in their own words (*i.e.*, the perspective that the patients—rather than the researchers—are the real experts on what limits and promotes adherence).[41] This approach has the potential to suggest possible risk factors for nonadherence that researchers may have overlooked or assessed inadequately.

Adult kidney recipients' views about self-management issues and challenges in this literature seem to reflect five broad areas or themes[38]: (*1*) empowerment (difficulties and strategies for gaining a sense of control over the post-transplant medical regimen), (*2*) fear of consequences (*e.g.*, fear of graft loss and medications' adverse effects), (*3*) managing regimen demands (coping with forgetfulness, side effects, and lifestyle disruptions), (*4*) concerns about overmedicalizing life (feelings of fatigue at being a patient and feeling burned out at performing self-management tasks), and (*5*) social accountability and motivation (indebtedness to the donor and gratitude to the medical team). In adolescent organ recipients (kidney and/or other organs), similar concerns with respect to the medical regimen and medication adherence emerged, with an emphasis on moving from dependence on caregivers to assuming responsibility for self-management.[39]

Tong *et al.*[40] focused more narrowly on medication taking after kidney transplantation in adults ages 18 years old and older. On the basis of their synthesis of the evidence, they judged that the themes that patients emphasized could be integrated to offer general perspectives on the factors contributing to patients' degree of medication adherence. As shown in Figure 2, patients fall along a spectrum ranging from complete MNA (for a variety of reasons described by patients, some of which are shown in Figure 2) to partial adherence (in which patients may seek to change their dosing, miss doses, or take them at the wrong times) to complete adherence (motivated by factors, such as protecting the new organ, or because patients have developed their own systems and ways of relying on others' help). In all three systematic reviews, the authors suggest that interventions to improve self-management or more specifically, adherence to the post-transplant medical regimen would have greater potential for success if they explicitly considered the themes reflected in patients' comments. This would lead logically to the need to tailor interventions to each transplant recipient's unique needs, motivations, and barriers rather than offer a one size fits all approach.

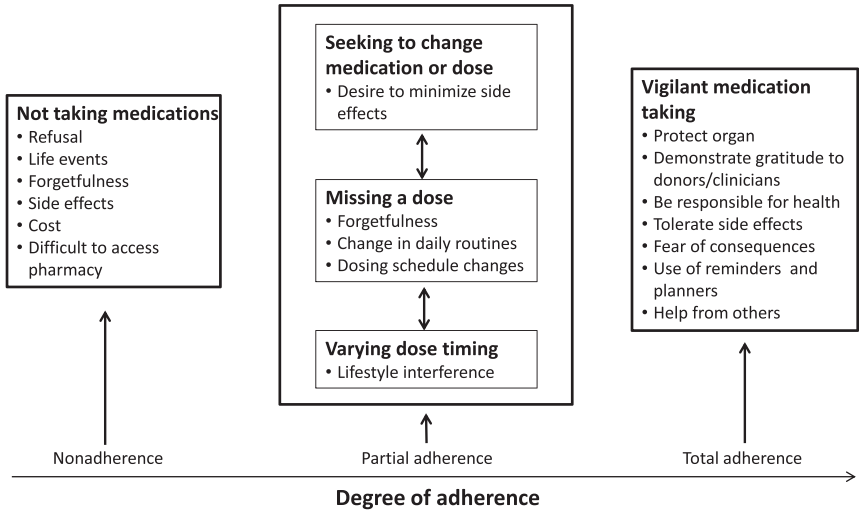

Figure 2. Themes reflecting challenges and decisions about medication taking after kidney transplantation. Results from qualitative studies in adults are modified from Tong *et al.*[40], with permission.

MNA INTERVENTION STUDIES

Descriptive Information

Since 2000, 13 studies have evaluated interventions targeting immunosuppressant medication adherence after kidney transplantation (Table 1).[42–56] The focus of these predominantly single-site investigations has been on adults; only one study targeted pediatric or young adult recipients.[50] Sample sizes varied widely from 15 to 219 (median, 67) Most studies used randomized, controlled trial designs and examined multicomponent interventions delivered by health care professionals across multiple face to face and/or telephone sessions.[42,44,46,47,49–52,55,56] These multicomponent interventions typically included education and counseling on medication taking, discussion of adherence barriers and motivation to adhere, goal setting to maximize adherence, and problem solving to eliminate barriers. Feedback on patients' past adherence, typically on the basis of ongoing EM, was sometimes included. Some interventions attempted to enlist patients' social supports by, for example, including the family in intervention sessions or counseling patients about how to involve others in their care. Among the single-component studies, one examined EM feedback only,[46] and two focused on medication dosing strategies (effect of

Table 1. Studies evaluating interventions to improve immunosuppressant medication adherence in kidney transplant recipients

Authors, Year, Country (Ref.)	Study Design and Sample	Intervention	Control[a]	Method of Adherence Assessment and Definition of Adherence	Duration of Outcomes Assessment	Findings for Adherence and Any Clinical Outcomes[b]
Chisholm *et al.*, 2001, United States[42]	RCT *n*=24 (12 intervention, 12 control), one site Enrolled shortly post-transplant Age 18–60 yr; M=49.2±10.2	Method: 12 monthly face to face or phone sessions with clinical pharmacist Content: medication review; counseling/education on need for and how to take medications	Usual care	Pharmacy refills (cyclosporin or tacrolimus) Adherence: percentage of prescribed doses that were refilled	12 mo (first year post-transplant)	Mean adherence significantly higher in intervention than comparison group (large ES)
Hardstaff *et al.*, 2003, United Kingdom[43]	RCT *n*=48 (23 intervention, 25 control), one site >1 yr Post-transplant Ages not specified	Method: one clinic visit with nurse practitioner 2–6 mo after study inception Content: feedback (appeared to focus on EM data)	Usual care	EM (prednisolone or azathioprine) Adherence: whether there were missed or extra doses	4–12 mo Total (2–6 mo before, 2–6 mo after clinic visit)	No differences between groups in whether adherence level changed during period before or after clinic visit (no statistical tests reported)
De Geest *et al.*, 2006, 2007, Switzerland[44,45]	RCT *n*=18 (6 intervention, 12 control), two sites ≥1 yr Post-transplant; nonadherent to immunosuppressants during 3-mo EM screening Age ≥18 yr	Method: one home visit (alone or with family present) at enrollment and three monthly phone calls by research nurse Content: feedback on EM data; goal setting; problem solving; education and motivational discussion; use of patient's social supports	Enhanced usual care: care providers told if patients were nonadherent or depressed	EM (cyclosporin, MMF, tacrolimus, sirolimus) Adherence: percentage of doses taken or occurrence of drug holiday (no dose >36 h)	9 mo Total (through 6 mo postintervention)	On average, sample's adherence rate significantly increased during first 3 mo and decreased during next 6 mo Nonsignificant trend for intervention group to show greater increase in adherence during first 3 mo (ES cannot be determined) No significant group differences in 6 mo postintervention (ES cannot be determined)
Russell *et al.*, 2011, United States[46]	RCT *n*=15 (8 intervention, 7 control), one site Nonadherent to immunosuppressants during 3-mo EM screening (time since transplant not specified) Age ≥21 yr	Method: one home visit and six monthly phone calls by research clinical nurse specialist Content: feedback on EM data; planning for behaviors to change; review of attempts to change behavior	Attention control: one visit, six calls; health education	EM (an immunosuppressant taken twice daily; no medication named) Adherence: summary measure on the basis of dose taking and timing	6 mo (until end of intervention)	On average across the study period, intervention group had higher adherence than control group (large ES) At final assessment point, intervention and control groups' mean adherence levels were identical
Chisholm-Burns *et al.*, 2013, United States[47]	RCT *n*=150 (76 intervention, 74 control), one regional pharmacy ≥1 yr Post-transplant, M=3.0±3.3 Age ≥18 yr; M=50.4±8.8	Method: five 20- to 30-min face to face or phone meetings (baseline and 3, 6, 9, and 12 mo) with a clinical pharmacist Content: behavioral contracting (patient agreement to work on improved adherence); education on nonadherence consequences; identification of adherence barriers; strategies to increase motivation to adhere; goal setting; problem solving	Usual pharmacy care	Pharmacy refills (tacrolimus) Adherence: percentage of days in past 3 mo for which patient had enough pills to take required doses	27 mo Total (1 yr before baseline and at 3, 6, 9, 12, and 15 mo after baseline)	Intervention group had significantly higher adherence at each time point after baseline (small to moderate ESs) Intervention group was significantly less likely to be hospitalized during 12 mo after baseline (moderate ES) No significant group differences in hospital days, emergency or outpatient visits, home health care visits (ES cannot be determined)

Table 1. Continued

Authors, Year, Country (Ref.)	Study Design and Sample	Intervention	Control[a]	Method of Adherence Assessment and Definition of Adherence	Duration of Outcomes Assessment	Findings for Adherence and Any Clinical Outcomes[b]
Kuypers *et al.*, 2013, Belgium[48]	RCT *n*=219 (145 intervention, 74 control), six sites 6 mo to 6 yr Post-transplant, M=3.0 y Adults receiving twice daily tacrolimus dosing	Method: switch to a once a day tacrolimus regimen	Twice daily tacrolimus regimen	EM (tacrolimus) Adherence: not withdrawing from the medication protocol (persistence); percentage of doses taken; percentage of doses taken within 2 h of when dose was due	9 mo Total (3 mo before, 6 mo after randomization)	Intervention group had significantly lower risk of missing daily doses and not taking doses in timely way (ES cannot be determined) No significant differences in persistence with medication protocol (ES cannot be determined) Intervention group was more likely to have 24 h intervals without any dose (no statistical test reported; ES cannot be determined)
Joost *et al.*, 2014, Germany[49]	Quasi-experimental (sequential control group design) *n*=67 (32 intervention, 35 control), one site 1 wk Post-transplant Age ≥18 yr, M=53.0±12.6	Method: three 30-min sessions before hospital discharge; outpatient sessions quarterly or more frequently until 12 mo postdischarge with clinical pharmacist Content: education/counseling on need for and how to take medications; identification of adherence barriers; tips to promote adherence; goal setting; use of social supports	Usual care	EM, pill count, self-report (MMF) Adherence: percentage of days with correct dosing; drug holiday (no dose >48 h); percentage of total doses taken, percentage of doses taken in timely way; self-report of missing any dose	Approximately 13 mo (12 mo postdischarge after transplant)	Intervention group had significantly higher average percentage of days with correct dosing, higher average total doses taken, fewer drug holidays, better adherence by pill count (ESs cannot be determined) No significant differences on dose timing, self-reported adherence, clinical outcomes (eGFR, graft rejection; small ESs), or HRQOL or psychiatric symptoms (ESs cannot be determined)
Annunziato *et al.*, 2015, United States[50]	Quasi-experimental (historical controls; retrospective chart review) *n*=22 (12 intervention, 10 control), one site Had ≥1 yr of follow-up after transfer from pediatric to adult transplant program Age, M=21.4	Method: at least two meetings with patient/family by pediatric team social worker Content: education on transfer process and adult program; address patient self-management issues; problem solving; completion of transition checklist with patient/family; discussion with adult team	Usual transfer preparation	Blood levels in medical record (tacrolimus) Adherence: SD of tacrolimus blood levels	12 mo after transfer to adult program	Adherence worsened across year in all patients; no significant group differences (moderate ES; less adherence decline in intervention group) No significant differences in risk of acute graft rejection (moderate ES in favor of reduced risk in intervention group) No significant differences in change in GFR or BP (ESs cannot be determined)

Table 1. Continued

Authors, Year, Country (Ref.)	Study Design and Sample	Intervention	Control[a]	Method of Adherence Assessment and Definition of Adherence	Duration of Outcomes Assessment	Findings for Adherence and Any Clinical Outcomes[b]
Garcia *et al.*, 2015, Brazil[51]	RCT *n*=111 (55 intervention, 56 control), one site Enrolled at first clinic visit post-transplant Age >21 yr, M=47.6	Method: ten weekly 30-min sessions at clinic with nurse Content: education/counseling on need for and how to take immunosuppressants; monitoring of adherence goal setting; strategies to increase motivation to adhere; tips to promote adherence	Usual care	Self-report (immunosuppressants) Adherence: summary score of self-report items	3 mo Post-transplant (adherence); 12 mo post-transplant (other measures)	Intervention group had significantly better adherence (moderate ES) No differences in risk of acute rejection, graft loss, death, renal function (mean creatinine, creatinine clearance), or tacrolimus blood levels within 12 mo post-transplant (ES very small)
Breu-Dejean *et al.*, 2016, France (2004 published abstract)[52,56]	RCT *n*=110 (55 intervention, 55 control), one site 5 yr Post-transplant, M=1.9±1.7 Age >18 yr, M=48.8±12.3	Method: Eight weekly 2-h small group sessions with multidisciplinary team (*e.g.*, physician, psychologist, nurses) Content: education/counseling on need for and how to take immunosuppressants	Usual care	Self-report (immunosuppressants) Adherence: summary measure from self-report	5 mo Total (at end of intervention and 3 mo later)	Intervention group had significantly better adherence at end of intervention (small ES) and end of follow-up (moderate ES) and marginally better adherence preintervention (small ES) No group difference in 10-yr graft survival (small ES favoring better survival in control group)
Henriksson *et al.*, 2016, Sweden[54]	RCT *n*=80 (40 intervention, 40 control), one site 1–2 wk Post-transplant Age 2–69 yr, M=44.5	Method: 1-yr use of electronic medication dispenser for immunosuppressants Content: dispenser emitted visual and audible alerts for patient; it sent message to study software if medications were dispensed or not	Usual care	Blood levels in medical record (tacrolimus) Adherence: trough levels of tacrolimus	1 yr (Until end of intervention)	No significant difference in intervention and control group in tacrolimus blood levels (ES cannot be determined) No significant differences in risk of rejection, missed clinic visits, emergency readmissions, creatinine levels (ESs cannot be determined but favor better outcomes in intervention group)
Cukor *et al.*, 2017, United States[55]	RCT *n*=33 (15 intervention, 18 control), one site M=3.1 yr post-transplant ± 13.4; <98% adherent to tacrolimus during 4-wk screening period Age >25 yr, M=52.1±11.9	Method: two 2-h small group sessions with two psychologists over 1- to 2-wk period Content: cognitive behavioral therapy and motivational interviewing to address barriers to and motivations for adherence, tailored to transplant- and ethnicity-specific issues	Usual care	Self-reported pill counts from unannounced phone calls to patients; blood levels in medical record (tacrolimus) Adherence: percentage of pills prescribed that were taken; trough levels of tacrolimus	Approximately 4 wk after intervention (6 wk postrandomization for controls	Intervention group had significantly better adherence at follow-up and significantly greater improvement in adherence from pre- to postintervention (large ESs) No significant difference in tacrolimus trough level change from baseline (moderate ES) but significantly less variability in trough levels in intervention group after intervention compared with control group (ES cannot be determined)

Table 1. Continued

Authors, Year, Country (Ref.)	Study Design and Sample	Intervention	Control[a]	Method of Adherence Assessment and Definition of Adherence	Duration of Outcomes Assessment	Findings for Adherence and Any Clinical Outcomes[b]
Reese *et al.*, 2017, United States[56]	RCT *n*=117 (40 in first intervention, 39 in second intervention, 38 control), one site Within 2 wk post-transplant Age ≥18 yr, M=50±11	Method: 6 mo use of electronic medication monitor either alone or in combination with provider notification Content: monitor emitted visual and audible alerts; text message and email reminders could be sent; providers in one intervention arm called patients if adherence declined and forwarded information to clinical team	Usual care plus use of monitor with no alerts	EM, blood levels in medical record (tacrolimus), self-report (immunosuppressants) Adherence: percentage of days with correct dosing; CV of blood levels; self-reported nonadherence	EM: last 90 d of intervention Blood levels: 6 mo Self-report: end of study	Reminders and provider notification group and reminder alone group had significantly better dosing adherence than control; the former group was marginally better than reminder alone group as well (ESs not reported) No group differences in blood levels or self-report (small ESs)

RCT, randomized, controlled trial; ES, effect size; M, mean; MMF, mycophenolate mofetil; HRQOL, health-related quality of life.
[a]In each study using usual care or enhanced usual care as a control, the intervention group received that care as well.
[b]Because a variety of statistical tests were performed, leading to different ES metrics, we categorized ESs—when they were reported or we could calculate them—on the basis of Cohen's general guidelines of what constitutes small, moderate, and large effects in behavioral sciences research (*e.g.*, correlation coefficients between receiving the intervention and the study outcome of 0.1, 0.2, and 0.5 or Cohen's *d* indicating the difference between intervention and control group means of 0.2, 0.5, and 0.8 were considered to represent small, moderate, and large effects, respectively).[57]

switching from twice daily to once daily dosing; effect of a pill dispenser that alerted patients when doses were due).[51,57]

Studies varied widely in how they assessed adherence outcomes. Some relied exclusively on EM,[43,44,46,48] whereas others used pharmacy refills,[42,47] blood levels,[50,54] or self-reported adherence.[51,52] Only three reports assessed adherence using a multimethod strategy.[49,55,56]

Intervention Efficacy

Because some studies allow effect sizes to be determined, whereas others report only whether statistically significant effects were achieved (with insufficient information to calculate effect size), we summarize the findings by commenting on both overall trends across the reports (*i.e.*, did they find statistically reliable effects?) and the magnitude of intervention effect (*i.e.*, how large were the intervention effect sizes?). In general, findings are mixed. Eight reports found significantly better adherence in intervention recipients relative to control groups (which typically received only usual care) by the end of the intervention period.[42,47–49,51,52,55,56] Effect sizes were mostly small to moderate (*i.e.*, *r* values of 0.10–0.30, where *r* is the size of the association of intervention [versus control] group membership with better adherence outcomes). Seven of these eight studies tested multicomponent interventions. One additional multicomponent intervention study found better adherence in intervention participants during the intervention period, but the effect dissipated by the last intervention session.[46] Four reports failed to identify significant intervention effects[43,44,50,54]; one of these studies obtained a moderately sized effect favoring the multicomponent intervention, but the sample was too small (n=22) to detect the effect.[50] The remaining three reports with nonsignificant findings (one testing a multicomponent intervention and two testing single-component interventions) did not provide effect size information. Method of assessing adherence (*e.g.*, EM, pharmacy refills, or self-report) did not seem linked to whether an intervention was effective.

Maintenance of Intervention Effects

Five studies examined adherence at least several months after the intervention had ended. Two multicomponent studies found that intervention effects endured through 3 months of follow-up.[47,52] However, the three others (two multicomponent studies and one single-component intervention study) failed to find any effects at 2–12 months postintervention.[43,44,50]

Effect on Clinical or Psychosocial Outcomes

Six studies examined whether the interventions influenced outcomes beyond medication adherence,[47,49–52,54] including service utilization (*e.g.*, rehospitalization and emergency department visits), clinical measures (*e.g.*, acute graft rejection and mortality), and psychosocial measures (*e.g.*, health-related quality of life). Only one report found any intervention effect: intervention recipients were less likely to be rehospitalized during the 12-month intervention period.[47]

SUMMARY

Relatively few interventions have been tested. Despite evidence that adolescents and young adults are at greater risk for nonadherence than any other age group,[16,35–37] studies that included patients as young as age 18 years old did not consider whether age affected intervention efficacy. Efficacy has been evaluated primarily during the period in which the intervention is offered; whether any effects are maintained after the intervention ends is unclear. Many studies were likely underpowered. Consistent with the literature on intervention effects on medication adherence in other solid organ transplant[58–62] and chronic disease populations,[63–66] effect sizes were generally small to moderate, indicating that no adherence interventions to date are as effective as would be hoped for in terms of producing successful patient behavior change.

Among the 13 studies, multicomponent interventions seem more likely to be efficacious than single-component interventions; this is similar to the larger literature on medication adherence interventions in transplantation and chronic disease.[62–66] However, whether such labor-intensive and often complex interventions would be feasible for general use or beyond the resources and capabilities of transplant teams remains unknown. Moreover, the multicomponent interventions offered to date consist most often of packages of strategies, each created by a single investigative team and not necessarily involving any components previously validated or known to be able to be reliably offered to patients. It is not clear whether the specific educational content, problem-solving efforts, or approaches to motivation and goal setting used in any one investigation are identical to those offered in other investigations. Such differences may contribute to the inconsistent findings on efficacy. Interestingly, when patients are asked what they find most helpful, they cite feedback on their own past adherence (*e.g.*, dosing history from EM),[44] and a recent meta-analysis shows feedback to be the most potent component of multicomponent interventions in chronic disease populations.[64] This is consistent with the notion of tailored interventions suggested by the results of the qualitative studies discussed earlier.[38–40] However, feedback has not consistently been included in the intervention studies with kidney recipients to date (Table 1); those including it tended to be small and underpowered.

In contrast to the potential difficulties of mounting multicomponent interventions, a simple approach, like modification of immunosuppressant dosing from twice to once daily, would seem very reasonable to implement.[48] However, Kuypers *et al.*[48] noted important caveats to their findings, including the problem that patients prescribed once daily dosing were more likely to have periods of 1 day or more with no doses taken compared with patients on a twice daily regimen. This report did not examine long-term clinical outcomes, and in general, the intervention studies do not provide strong evidence that any adherence intervention led to any clinical or psychosocial benefits. Lack of compelling evidence from MNA intervention studies may be largely due to power limitations; not only were studies' sample sizes generally small, but also, follow-up periods were short, likely resulting in too few clinical events for meaningful analysis. Furthermore, as noted in the adherence intervention literature beyond transplant, there is no permanent cure for MNA.[65] Thus, adherence interventions likely need to be maintained for as long as the medical treatment in question is needed, requiring that interventions be permanently integrated into care. However, all interventions in transplant recipients have been time limited, and this may explain why they have had minimal clinical effect.

COMMENT

To conclude, MNA, which adds between $100 and $300 billion to America's annual health care costs,[67,68] is increasingly recognized in kidney transplant recipients. In transplantation, the costs of MNA leading to premature allograft loss go far beyond a simple monetary calculus. Much has been learned about the factors leading to MNA, although our understanding remains far from complete. Research focused on addressing these gaps is one priority area on which to expand. Various intervention strategies have been evaluated, but none to date have been as effective as one would have hoped. Emerging is the complex nature of MNA and the requirement for comprehensive multifaceted interventions. Therefore, clinical trials evaluating multifaceted interventions are a second priority area for research investment. In designing these clinical trials, it will be critical to evaluate not only surrogate end points (*i.e.*, decreasing MNA) but also, the intervention's effect on clinical outcomes as well (*i.e.*, *de novo* DSA, late acute rejection, and graft and patient survival). This last point is key if the expectation is for insurers to pay for the costs of interventions. A third priority area is to identify biologically modifiable factors that may limit the effect of MNA in a given patient. For example, transplanting patients with

an HLA-mismatched donor below a defined threshold mitigates the effect of MNA.[6,69] In summary, MNA is a common problem limiting graft and patient survival, and as such, it should be a top priority area for the academic community, research funders, and insurers.

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