Post-transplant Psychosocial and Mental Health Care of the Renal Recipient

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Introduction

The psychosocial and mental health care needs of kidney transplant recipients assume increasing importance as the size of this population and duration of life expected post-transplant continue to grow. In the United States, over 19,000 individuals received kidney transplants in 2016; this represents a 40% increase over the number of kidney transplants in 2000 [1]. Kidney transplantation accounts for 80% of all organ transplants [1], and kidney transplant recipients enjoy higher survival rates than any other type of solid organ recipient. Patient survival rates are 97%, 93%, and 86% at 1, 3, and 5 years post-transplant, respectively, and graft survival is 95%, 88%, and 78% at these time points [1]. Graft survival exceeds 60% even at 10 years post-transplant [2], and 20 or more years of graft function is not uncommon [3]. Moreover, in the event of graft failure, kidney recipients have more treatment options than other types of organ recipients. In particular, patients may receive dialysis and/or be listed for retransplantation. The retransplantation rate in kidney recipients (13% of all kidney transplants in 2016) is higher than the retransplantation rates for recipients of liver, heart, or lung transplantation (3–5% of transplants) [1]. Given high survival rates plus the possibility of retransplantation, the population of individuals living with a kidney transplant has more than doubled since 2000: as of June 2015, there were more than 200,000 recipients alive with a functioning graft in the United States [2].

Significant resources must be deployed to provide ongoing clinical care and monitoring of this sizable population. Such care necessarily focuses on graft functioning, common medical comorbidities, and complications of immunosuppression. However, the psychosocial and mental health needs of these recipients require consideration as well: it is well-known, for example, that psychosocial and behavioral factors encompassing adherence to the medical regimen, mental health, and substance use can affect clinical outcomes, including risks for both morbidity and mortality [4–10]. Thus, providing care to address emerging psychosocial issues can be essential for prolonging patients' duration and quality of life after kidney transplantation.

In this chapter, we describe the prevalence, risk factors, and interventions tested to prevent or treat three key psychosocial issues in kidney transplant recipients: adherence to the multifactorial medical regimen, mental health problems, and substance use. We consider the implications of this information for the care of kidney recipients and suggest work that is needed in the future in order to expand the set of evidence-based treatment strategies available to healthcare professionals who provide this care. Our review of the evidence and our clinical recommendations pertain to adult kidney recipients. The psychosocial issues of key importance in pediatric transplantation are very different than in adults, and a variety of reviews summarize evidence and care recommendations for pediatric kidney recipients [11–16].

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How Common Are Psychosocial Problems After Renal Transplantation?

Information on prevalence is important for estimating how likely any given kidney recipient is to have psychosocial difficulties. From a clinical standpoint, understanding which types of problems are most common is the first step toward identifying and prioritizing new educational and preventive efforts for this patient population. In addition, such information is relevant for deciding how to modify existing clinical care strategies.

Nonadherence to the Medical Regimen

The post-transplant medical regimen is multifaceted and must be followed by patients for the remainder of their lives with their transplanted kidney. Immunosuppressant medication-taking is a central element, but patients are also expected to adhere to other requirements: they must attend routine clinic appointments for health monitoring by the transplant program, complete required laboratory and other tests, engage in routine self-monitoring of vital signs (e.g., blood pressure, temperature), and engage in healthy lifestyle behaviors (e.g., routine exercise, following prescribed diets, avoiding prolonged sun exposure). Several systematic reviews have reported on the prevalence of medical regimen nonadherence after kidney transplantation [17–20]. Most focus on immunosuppressant medication adherence. In the only analysis to date to report on prevalence rates of nonadherence for each of the multiple areas of the post-transplant medical regimen, we found 147 studies of organ recipients, including 72 studies of kidney recipients [20]. The rates of nonadherence among kidney recipients are shown in Fig. 10.1. Immunosuppressant nonadherence was the most common problem across the various areas assessed: approximately 36 per 100 kidney recipients per year (i.e., 36% during any given year) were nonadherent to these medications. Rates of nonadherence to requirements for blood work and testing, as well as nonadherence to lifestyle requirements including exercise and diet, also appear to be relatively common. However, kidney recipients had low rates of nonadherence to monitoring vital signs (e.g., blood pressure) and attending required clinic appointments. In additional analyses, we found that the immunosuppressant nonadherence rate was in fact significantly higher than the rates found in studies of other types of organ recipients, which ranged from 7% to 14% [20]. However, kidney recipients were indistinguishable from other types of recipients in terms of nonadherence rates for other areas of the regimen [20].

An important question concerns how the prevalence of nonadherence in any given area of the post-transplant medical regimen changes over time. Neither our meta-analysis nor other systematic reviews and meta-analyses have provided a detailed consideration of this issue in kidney or other organ transplantation. However, individual studies examining temporal patterns of change show that, even in such critical areas of the post-transplant regimen as taking immunosuppressants, nonadherence begins within months of the transplant surgery and grows more common over time [21–26]. These findings are consistent with evidence from the general chronic disease treatment literature which also shows increasing rates of nonadherence with time after treatment initiation [27, 28].

Mental Health Problems

There have been several recent reviews discussing the prevalence of psychiatric difficulties in kidney recipients [29–32]. Depressive and anxiety disorders, and elevated levels of depression and anxiety symptoms, are the most common mental health problems identified in organ transplant recipients [33, 34]. In kidney recipients, most studies have focused on depression. Point prevalence rates of clinically significant depressive symptom levels range widely from 4% to 49%, with most rates falling between 20% and 40%. A recent meta-analysis found that the pooled estimate (an

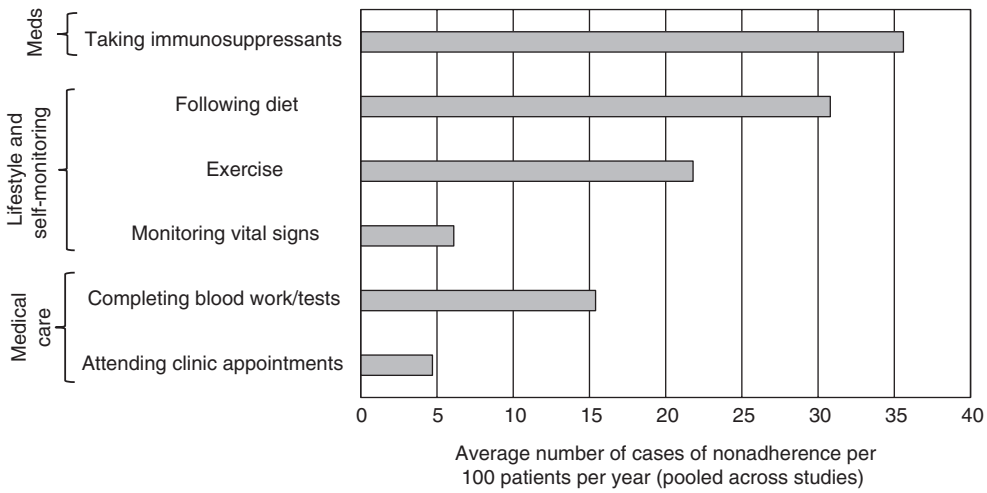

Fig. 10.1 Average rates of nonadherence to components of the medical regimen after kidney transplantation, meta-analysis results [20]

average across studies, weighted by sample size) was 27% [31]. The great heterogeneity in rates across studies likely reflects factors such as variability in measures used to assess depression, cut points chosen to indicate elevated distress, and whether the study sample was one of convenience rather than a sample constructed more systematically. Although the studies' samples also vary in time since transplant, this factor has not been found to be associated with point prevalence rates of depression or other mental health problems [32].

Only rarely have diagnosable depressive disorders been considered in kidney recipients. Vasquez et al. [35] reported a point prevalence rate of 12% for depressive disorders in a Central American sample, and Dobbels et al. [36], relying on Medicare claims data in a national sample in the United States, found that the cumulative annual incidence of depression was 5%, 7%, and 9% across the first 3 years after kidney transplantation.

Kidney recipients' risk for depression appears to be lower than that of end-stage renal disease patients, including candidates listed for transplant [31]. However, recipients' risk remains elevated above that of the general population [32]. Despite lack of evidence that the point prevalence rates of depression vary with time post-transplant, a better understanding of patients' typical trajectory of depression over time is needed. For example, duration of episodes and patients' risk for episode recurrence are unknown.

Anxiety-related conditions have received little attention in kidney recipients, despite the well-known high comorbidity between anxiety and depression. From 10% to 25% of kidney recipients have been found to have elevated anxiety symptom levels [37, 38]. Vasquez et al. [35] reported a 15% point prevalence rate of anxiety disorders in their cohort. Anxiety levels in kidney recipients appear higher than those found in healthy general community samples [39].

There is limited evidence on the prevalence of rare but severe psychiatric disorders, such as psychosis and bipolar disorder, after any type of organ transplantation. In a national renal transplant database in Ireland, less than 1% of kidney recipients had histories of schizophrenia or bipolar disorder. However, this report did not consider recurrence of symptoms after transplant [40]. In the largest study to date, Abbott et al. [41] examined administrative data from the United States Renal Data System and found that the incidence of hospitalized psychosis after kidney transplantation was 7.5 per 1000 person years (PY) of observation. This rate did not differ from that of the population of patients on dialysis (7.2/1000 PY). However, 94% of the transplant recipients were aged 65 or less. When the dialysis population was restricted to those aged 65 or less, the risk of hospitalized psychosis was lower in kidney recipients than the rate of 9.6/1000 PY in dialysis patients [41]. This report did not compare these rates to rates in the general population.

Substance Use

Transplant programs require abstinence from illicit drug use after kidney transplantation. Recipients should also refrain from tobacco use. Although recipients are not generally required to abstain from all alcohol consumption, alcohol use must be limited. Research has largely focused on tobacco smoking in kidney recipients, with less consideration of alcohol or other substance use [4, 7, 10, 20]. In our meta-analysis of adherence-related behaviors after organ transplantation [20], we found a rate of tobacco smoking of 3 per 100 kidney recipients seen in any given year (3% annually), while the rates of annual use of illicit drugs and annual use of alcohol above limits set by patients' transplant programs were each 1%. Consistent with these findings of particularly low rates of alcohol and illicit drug use, research since our analysis has concluded there is little evidence that alcohol abuse or dependence are prevalent problems in the kidney recipient population [42]. (This is unlikely to be due to selection of patients for transplantation; it more likely reflects relatively low rates of alcohol use in the population of patients needing kidney transplants, especially compared to other populations such as patients needing liver transplants [10].)

Whether substance use reflects a relapse to prior use or incident cases is an important issue. With respect to tobacco, a study examining Medicare claims data in the United States identified kidney recipients who had no history of tobacco smoking before transplantation but had claims on which post-transplant tobacco use was recorded [43]. The authors report that the incidence rate of smoking (i.e., new-onset smoking) was 4.6% (and this was apparently across a maximum of 5 years post-transplant). The time to smoking use onset (adjusted for censored observations due, for example, to patient death) was 1.3 years post-transplant.

We have not identified any studies of incident alcohol or illicit drug use in kidney recipients. However, there is a literature on rates of relapse to alcohol and illicit drug use in organ recipients with histories of substance abuse or dependence before transplantation, as summarized in a meta-analysis [44]. (Studies examining this subgroup of patients were excluded from our previous meta-analysis described above, which focused on general samples, and not samples selected on the basis of pre-transplant histories.) While there were no studies of relapse to alcohol use in kidney recipients with histories of abuse/dependence (all studies focused on liver recipients), we found that relapse to illicit drug use was 6% annually in kidney recipients, a rate equal to that in heart recipients but lower than the 2% annual rate found in liver recipients.

There has been little to no examination of the specific types of illicit drugs used by kidney recipients. One recent report examined recreational marijuana use in kidney recipients (in a state in the United States where use is not legal) and estimated 3% of patients were active users (by on either

self-report or urine toxicology screen data) [45]. However, patients differed dramatically in time since transplant, and, given no adjustments for survival time, the 3% rate may underestimate the risk of marijuana use post-transplant.

The timing of substance use onset after kidney transplantation has received no consideration. However, as for other behavioral problems post-transplant such as medication nonadherence, it seems likely that substance use would begin in the early months post-transplant. This pattern has been documented in other types of transplant recipients (e.g., liver recipients [44]).

What Factors Increase Risk for Psychosocial Problems After Renal Transplantation?

Identification of key risk factors can be important for targeting patients who may need additional monitoring and early intervention, should they begin to show any signs of psychosocial problems.

Nonadherence to the Medical Regimen

In chronic disease populations in general, five categories of risk factors appear important for medical regimen adherence [46]. These are listed below, along with specific examples of factors found relevant for nonadherence risk in kidney transplant recipients [5, 9]:

- Sociodemographic characteristics (e.g., younger age, minority race/ethnicity, low socioeconomic status).
- Patient-related psychosocial factors (e.g., past nonadherence, low health literacy, low knowledge about one's illness and treatment options, psychological distress, low self-efficacy, poor social supports, forgetfulness/cognitive impairment, daily routine changes).
- Treatment-related factors (e.g., more frequent medication doses, greater total number of medications, side effects of medications or other treatments).
- Condition-related factors (e.g., longer time since transplant, transplant from a living donor, better perceived health, physical limitations).
- Healthcare system and provider-level factors (e.g., insurance status, access to care, provider-patient communication, transition from a pediatric to an adult transplant program).

In kidney transplantation, as in other areas of transplantation, the strongest and most consistent risk factor for post-transplant nonadherence, particularly with respect to immunosuppressant medications, is a history of nonadherence before transplantation [8, 19, 20, 23, 47]. Similar to findings in other chronic disease groups [48], more complex regimens (involving multiple doses of one or more medications daily and a greater total number of medications) also increase risk for medication nonadherence in kidney recipients [17]. It is noteworthy, however, that the impact of each of the factors listed above may be modest [9, 20], and thus interventions would likely need to simultaneously address and ameliorate more than a single factor in order to be effective. Additionally, in some cases, the evidence for a given factor's importance is inconsistent. For example, minority race/ethnicity emerges as a risk factor for medication nonadherence after kidney transplantation in some studies [26, 49–52] but not others [53–56]. The inconsistency in findings may arise because race/ethnicity likely is a proxy for characteristics such as insurance status and access to care that are the true contributors to nonadherence risk.

There is also an informative qualitative literature describing kidney recipients' own views about factors that affect their self-management of health issues, including adherence to the post-transplant medical regimen. In a systematic review of this literature, Jamieson et al. [57] concluded that patients' comments about their self-management challenges reflected five themes: (a) empowerment (strategies used to gain personal control over the medical regimen); (b) fear of adverse health outcomes (e.g., graft loss); (c) managing medical regimen demands (e.g., attempts to adhere despite changes in daily routines); (d) feelings that life has become overmedicalized (e.g., feelings of burnout at having to manage the medical regimen); and (e) accountability to others (e.g., gratitude to the donor and the transplant program, motivation to care for the kidney).

Recipients' comments indicated recognition of the need to overcome many of the factors found in empirical studies to increase risk for nonadherence (e.g., by gaining a better understanding of the regimen and their responsibilities, by establishing daily routines, and by setting up reminders for various activities). Patients also introduced additional ideas about areas potentially relevant for nonadherence risk reduction, including the need to improve problem-solving skills and the opportunity to learn from peers about ways to remain adherent.

In a separate systematic review focused specifically on kidney recipients' medication-taking activities, Tong et al. [58] extracted themes that characterized recipients' beliefs, experiences, and perspectives on medication-taking. Thus, poor adherence was often described as the result of patient forgetfulness, intolerable side effects, inability to pay for medications, difficulty accessing a pharmacy to obtain the medications, and the occurrence of disrupting life events. In contrast, high degrees of vigilance and adherence to the medication regimen were described by patients who strongly

endorsed a desire to protect their new chance at life, who felt powerful obligations to both donors and the transplant team, and who described the importance of taking personal responsibility for their health. Patients able to maintain a high level of medication adherence also felt that they were able to tolerate side effects and had developed strategies to keep from forgetting doses. Finally, patients who showed variable degrees of success at taking their medications felt that this arose because they were attempting to change drugs or dosing requirements in order to manage side effects. They also felt that they missed doses due to forgetfulness or took doses late due to changes in routines. Taken together, the findings from the qualitative literature indicate the importance of asking patients directly about the factors they consider to be the most important barriers and facilitators for achieving high levels of medication adherence.

Mental Health Problems

In all types of organ transplant recipients, the strongest risk factor for depression, anxiety, other psychiatric disorders, or elevated symptom levels is a pre-transplant history of distress in these areas [30, 33, 34]. The bulk of research in kidney recipients has focused on risk for depression, and several key risk factors have emerged. Principal among these are clinical factors: a longer duration of dialysis before transplantation [36, 59], poor graft function after transplantation [59–61], the occurrence of rejection episodes [62], and the presence of physical comorbidities, including obesity [36, 59–61, 63].

A range of psychosocial factors have also been examined. Demographic characteristics such as female sex and lower levels of education are well-known risk factors for depression in kidney recipients [29], just as they are in other transplant populations and in general community samples. In addition, in kidney recipients, among the psychosocial factors found to most consistently increase depression risk are post-transplant unemployment and personal financial difficulties [35, 59, 61, 64] and poor social support [35, 60–62, 64]. Both poor availability of support persons and poorer perceived quality of support appear important. Thus, unmarried individuals and individuals living alone are at higher risk than married individuals [38, 60–62, 64], and perceptions of low social supports, including tangible support and emotional support, also increase depression risk [35, 61].

There is less evidence on whether other aspects of recipients' psychosocial environments are associated with depression risk. Thus, factors related to coping styles and strategies may increase risk or in some cases may protect against depression. However, the findings are inconsistent to date. For example, Christensen et al. [65] found that a coping style characterized by information-seeking in order to manage health problems reduced kidney recipients' risk for enduring or increasing depression symptom levels after transplant. In contrast, Knowles et al. [37] found no large or statistically significant association between either "maladaptive" coping strategies (e.g., attempting to avoid thinking about problems) or "adaptive" strategies (e.g., active problem-solving efforts), and other studies have also failed to find that coping strategies are related to depression [38]. However, so few studies have evaluated coping styles and strategies that it is difficult to conclude whether they play an important role for depression or not.

Very little work has examined risk factors for anxiety or severe mental disorders such as psychosis. One report found that greater severity of self-reported transplant-related stressors (in areas such as perceived medication side effects, occurrence of problems such as graft rejection, and perceived physical limitations) was related to higher anxiety levels [66]. Interestingly, these authors did not find social supports to be correlated with anxiety levels. Knowles et al. [37] reported that illness perceptions (encompassing greater perceived impact of illness on daily life and feelings of little control over the illness) were associated with heightened anxiety symptoms. Similar to findings for depression, whether or not coping strategies affect risk for anxiety symptoms is unclear. Two recent studies suggest that maladaptive coping strategies, such as avoidance and denial, are associated with increased anxiety [37, 39]. With regard to psychosis, in the study described earlier on the occurrence of hospitalizations for psychosis after kidney transplantation [41], both delayed graft function after transplant and the occurrence of graft rejection episodes were risk factors for psychiatric hospitalizations. No demographic risk factors for hospitalization for psychosis were identified.

Unlike the literature on medical adherence, which includes rich quantitative as well as qualitative reports, studies identifying risk factors for poor mental health are empirical and have not routinely sought to include patient views on factors that affect their psychological status. One qualitative report notes that patients may feel that their expectations for life after the transplant are not met, which can lead to disappointment and disillusionment [67]. However, it is not clear that patients were specifically queried about any linked feelings of depression or anxiety. The qualitative literature on self-management of the medical regimen, however, notes that patients themselves feel that poor graft function and the risks of serious side effects (e.g., cancers from the immunosuppressants) lead to considerable anxiety [57]. The feelings of "burnout" at being a patient, feelings that their lives have become "overmedicalized", and patient descriptors of such experiences appear to include depressive elements [57]; it seems likely that patients with heightened feelings of burnout either are at risk for depression or are depressed [68].

Substance Use

Not surprisingly, a history of substance use is the most important risk factor for post-transplant substance use in organ recipients, including kidney recipients [7, 20, 44]. Organ transplant recipients who use one substance are likely to use others (e.g., smoking is correlated with alcohol and illicit drug use; alcohol and illicit drug use are correlated [7, 42, 43, 45]).

There has been relatively limited consideration of other risk factors. The bulk of work pertains to post-transplant tobacco smoking. Duerinckx et al. [7] provide a comprehensive examination of risk factors and correlates of smoking post-transplant, but they do not distinguish between types of organ received. Kidney transplant studies were, however, more numerous than studies of other types of recipients. They found that male sex, younger age, and higher body mass index (BMI) increased risk for smoking, while prevalent comorbidities including hypertension, diabetes, and cardiovascular disease were not reliable risk factors. They noted that many potential factors (e.g., psychiatric symptoms, coping styles) had been examined in very few studies, thus precluding firm conclusions about their possible roles. In particular, they found that duration of abstinence from smoking before transplantation has been examined in only a few studies, with conflicting results. Duerinckx et al. [7] focused largely on studies of recipients with histories of tobacco use before transplant. In a large US study of tobacco use incidence after kidney transplantation, Hurst et al. [43] found that new smokers were more likely than nonsmokers to be male, younger, and African American. They were also likely to have more medical comorbidities and to have histories of alcohol and/or drug dependence.

Few studies have considered risk factors for alcohol or drug use specifically in kidney recipients. Male sex appears to increase risk for post-transplant heavier alcohol use, while age is not a risk factor [42, 69]. Zelle et al. [42] found that kidney recipients who used alcohol had a shorter time on dialysis before transplant. However, post-transplant kidney function or ability to return to work was not associated with alcohol use risk. Similarly, Fierz et al. [69] found that clinical variables such as comorbidities and occurrence of graft rejection were not related to alcohol use, but they found that patients who returned to work were at higher risk for alcohol use. They speculated that kidney recipients who are employed may be those who perceive their health to be better. Fierz et al. [69] examined but found no evidence that level of education, depressive symptoms, coping styles or strategies, or clinical variables such as comorbidities and the occurrence of graft rejection were independent risk factors for alcohol use.

Finally, Greenan et al. [45] reported that kidney recipients who used marijuana recreationally were more likely to be unmarried, have less education, currently use alcohol and tobacco, and have histories of treated substance addiction. Interestingly, in contrast to the risk factors we have discussed for other substance use in kidney recipients, male sex was not associated with marijuana use.

What Interventions Have Been Tested to Address Psychosocial Problems After Renal Transplantation?

In order to provide evidence-based care to transplant recipients, clinicians must understand the range of treatment options that have been tested for efficacy specifically in kidney transplant recipients. Gaps in that evidence may be partially filled by considering intervention efficacy studies in other transplant or chronic disease populations, although whether or not the findings would generalize to kidney recipients is often unclear.

Nonadherence to the Medical Regimen

Among the psychosocial problems that we have addressed in this chapter, the greatest focus of intervention trials has been on immunosuppressant medication adherence after transplantation. Table 10.1 shows the interventions tested and key results in studies published since 2000 [70–86]. The majority of studies used multicomponent interventions focused on providing education about medication-taking, assessing barriers to adherence, providing feedback on adherence levels achieved (often using data from electronic medication monitoring devices in pill bottles given to patients), and encouraging problem-solving and goal setting. These interventions usually required multiple sessions with an interventionist over a period of months. Interventionists were often nurses but sometimes included pharmacists, psychologists, or multidisciplinary teams. Exceptions to these "coaching" interventions included an intervention that simply involved switching from twice-daily dosing of the key immunosuppressant to once-daily dosing [75] and an intervention that used electronic medication monitoring along with text messaging and feedback to clinicians on medication-taking patterns [84]. Studies varied in terms of whether medication adherence was assessed by electronic monitoring, patient self-report, blood levels of the immunosuppressant medication, or combinations of these assessments.

Across these 16 trials, 11 found that the intervention improved medication-taking. Interestingly, although most of the trials involved labor-intensive complex interventions, even some of those with simpler strategies (e.g., the modification in doses per day) found benefits in improved adherence. Important remaining issues concern the durability of intervention effects,

Table 10.1 Controlled trials testing interventions to improve immunosuppressant medication adherence in adult kidney recipients[a]

First author, year	Sample size and follow-up duration	Intervention	Impact on adherence
Chisholm, 2001 [70]	*N* = 24, end of intervention (first year post-transplant)	– Medication review, education – 12 monthly face-to-face or phone sessions with clinical pharmacist	Intervention group had significantly higher adherence (pharmacy refills) than usual care control group
Hardstaff, 2003 [71]	*N* = 48, up to 6 months post-intervention	– Feedback (appeared to focus on EM data) – 1 clinic visit with nurse practitioner	No differences noted between intervention and usual care control groups in adherence (based on EM)
De Geest, 2006 [72]	*N* = 18, 6 months post-intervention	– EM data feedback, education, goal setting, problem-solving, use of social supports – 1 home visit, 3 monthly phone calls with research nurse	Nonsignificant trend for intervention group to show greater initial adherence increase (based on EM) than enhanced usual care control group, but advantage not maintained
Russell, 2011 [73]	*N* = 15, end of intervention	– EM data feedback, planning and review of behavior change efforts – 1 home visit, 6 monthly phone calls with research clinical nurse specialist	Intervention group had significantly higher adherence (based on EM) during follow-up than health education control group, but no between-group differences by the end of trial
Chisholm-Burns, 2013 [74]	*N* = 150, 3 months post-intervention	– Behavioral contracting, education, adherence barrier identification, goal setting, problem-solving – 5 20–30 min face-to-face or phone sessions over 12 mos with clinical pharmacist	Intervention group had significantly higher adherence (pharmacy refills) than usual care group at each time point after baseline
Kuypers, 2013 [75]	*N* = 219, 6 months post-randomization	– Switch from twice- to once-daily tacrolimus	Intervention group had significantly higher adherence (based on EM) compared to usual dosing group
McGillicuddy 2013 [76]	*N* = 19; end of intervention	– EM medication box with alerts, BP monitoring, text message reminders, transplant team alerted to medication or BP monitoring nonadherence, physician given feedback on patient data – 3 mos of use of strategies	Intervention group had significantly higher medication adherence (based on EM) than usual care controls at each time point after baseline
Joost, 2014 [77]	*N* = 67, end of intervention (12 months after hospital discharge post-transplant)	– Medication-taking education, adherence barrier identification, goal setting, use of social support – 3 30-min sessions pre-discharge, outpatient sessions ≥ quarterly for 12 mos	Intervention group had significantly higher adherence (based on EM and pill count) than usual care group
Annunziato, 2015 [78]	*N* = 22, 1 year after transfer from pediatric to adult program	– Education on transfer process, patient self-management problem-solving – ≥ 2 meetings with patient/family by pediatric team social worker, social worker completion of transition checklist and discussion with adult team	No significant group differences between intervention and usual transfer control group; all patients showed adherence decline (blood levels) with trend toward less decline in intervention group
Garcia, 2015 [79]	*N* = 111, 3 months post-transplant	– Medication-taking education, goal setting, problem-solving – 10 weekly 30-min clinic sessions with nurse	Intervention group had significantly better adherence (self-report) than usual care control group
McQuillan, 2015 [80]	*N* = 32, 1 year after transfer to adult program	– 1 visit by patient/parent to new transfer clinic, patient and parent small groups to discuss transition and self-management, patient completion of online education, adult and pediatric team meeting	Intervention group had significantly less nonadherence (self-report) during follow-up and greater decline in nonadherence from pre- to post-intervention than usual transfer control group. No significant group differences on blood level data
Bessa, 2016 [81]	*N* = 126, end of intervention	– Medication-taking education – 9 sessions (duration not noted) in first 90 days post-transplant	No significant differences in adherence (blood levels, self-report) between intervention and usual care groups No significant differences between groups in rates of infections, acute graft rejection, graft function, death, graft loss, or hospital readmissions

(continued)

Table 10.1 (continued)

First author, year	Sample size and follow-up duration	Intervention	Impact on adherence
Breu-Dejean, 2016 [82]	*N* = 110, 3 months post-intervention	– Medication-taking education – 8 weekly 2-hr small group sessions with multidisciplinary team	Intervention group had significantly better adherence (self-report) than usual care group at end of intervention and end of follow-up
Cukor, 2017 [83]	*N* = 33, ~4 weeks post-intervention	– Cognitive behavioral therapy, motivational interviewing focused on barriers to and motivations for adherence – 2 2-hr small group sessions with psychologists over 1–2 week period	Intervention group had significantly higher adherence (self-report pill counts) at follow-up and more improvement in adherence pre- to post-intervention than usual care control No significant difference in blood level data from baseline but significant improvement in intervention group after intervention compared to control group
Reese, 2017 [84]	*N* = 117, last 90 days of intervention (EM data), 6 mos post-intervention (blood levels), end of intervention (self-report)	– EM monitor with alerts, used alone or with provider notification. Text and email reminders could be sent. Providers in one intervention arm called patients if adherence declined and informed clinical team – 6-mo use of monitor and other components	Reminders+provider notification group and reminder alone group had significantly better adherence (based on EM) than usual care control group; the former group was also marginally better than reminder alone group No group differences in blood levels or self-report
Schmid, 2017 [85]	*N* = 46, end of intervention (first year post-transplant)	– Telemonitoring, education, support and coaching provided on demand – Daily monitoring by nurse case manager (with physician support), case management	Intervention group had significantly better adherence (composite of clinician ratings, self-report, blood levels) at all assessments than usual care control group

Abbreviations: *BP* Blood Pressure, *EM* Electronic Monitoring

[a]All studies in the table were randomized controlled trials except for Joost et al. [77], Annunziato et al. [78], and McQuillan et al. (who compared the intervention cohort to historical or sequential controls) [80]. All samples varied in time since transplant except as noted. An additional report by Henriksson et al. [86] examined medication nonadherence in kidney recipients, but was excluded from this table because the authors did not distinguish adult recipients from pediatric recipients (many of whom were not responsible for their own adherence and would have required caregiver administration of medications)

whether the interventions benefit some patients more than others, and whether—as would be hoped—the interventions lead not only to improved medication-taking but to improved clinical outcomes. The follow-up periods in most of the trials were relatively brief: some studies followed patients only until the intervention ended; others continued to follow patients for a few months after the intervention. The studies did not identify subgroups of patients who appeared to show particular benefit from the interventions. However, the qualitative literature that we reviewed earlier suggests that medication adherence after kidney transplantation may be improved through explicit consideration of patients' perspectives and by tailoring a given intervention to address patients' perceived adherence barriers and facilitators [87].

Despite evidence that most of the interventions tested led to some improvement in immunosuppressant medication adherence, the studies' results concerning intervention impact on clinical outcomes have been disappointing. Several examined clinical outcomes, including rehospitalizations [74, 81, 85], emergency and outpatient visits [74, 85], infections [81], graft function [77–81], rejection episodes and graft loss [77, 78, 80, 81], and death [79, 81, 82]. Although rehospitalization risk was lowered by adherence interventions in two studies [74, 85], no other study in Table 10.1 observed any effects on clinical outcomes.

Another important consideration in future adherence-promoting trials in kidney transplantation would be to go beyond medication adherence to consider impact on other types of outcomes. Hsiao et al. [88] evaluated a support group-based intervention designed to increase feelings of self-care empowerment and found that participants improved in their overall self-reported ability to adhere to the medical regimen, relative to control participants receiving usual care. Some evidence in other areas of organ transplantation suggests that electronic health (e-health) interventions, including smartphone apps in particular, can lead to improved medical regimen adherence [5, 89].

A few studies have tested interventions in kidney recipients designed to improve lifestyle behaviors (e.g., weight control, exercise, diet [90, 91]). These interventions were modestly effective at changing patients' behaviors and improving related health parameters, at least in the short-term. Maintenance of these effects was not examined. In addition, large proportions of the patients in these studies dropped out. This suggests low intervention or research trial design acceptability.

Mental Health Problems

Mental health outcomes have been considered in only a very limited number of intervention trials in kidney recipients. Two investigative teams have examined nonmedication psychotherapeutic interventions. First, Baines et al. [92, 93] examined recipients randomized to receive 12 weeks of individual psychotherapy or 12 weeks of group sessions. A "control" group receiving usual care was also included (but this group was constructed separately and patients were not randomized into it). The psychotherapy sessions focused on adaptation to the transplant. Patients' depression symptom levels in both active psychotherapy conditions declined significantly from pre- to post-intervention, with sustained effects 12 months later. Individual psychotherapy appeared more effective than group therapy. Control group depression levels, in contrast, worsened over time.

Second, Gross and colleagues [94–96] conducted two studies examining an 8-week group-based Mindfulness-Based Stress Reduction (MBSR) intervention for reducing symptoms of depression, anxiety, and sleep disturbance in kidney, lung, or pancreas transplant recipients. In an initial study, Gross et al. [94] enrolled kidney, lung, or pancreas transplant recipients, and although they did not examine effects in kidney recipients alone, they found that across all types of recipients, both depression and sleep improved from baseline (pre-intervention) to immediately after the intervention ended. At 3-month follow-up [94] and at 6-month follow-up [96], sleep effects were maintained and anxiety was significantly lower than baseline. Depression symptom reductions were not maintained at either follow-up time point. A subsequent, larger study randomized kidney, kidney/pancreas, liver, heart, and lung recipients to receive the MBSR intervention or receive health education sessions [95]. The MBSR intervention showed significant and sustained anxiety and sleep disturbance reductions, relative to the control group, with effects sustained through 12 months post-intervention. Although depression levels also improved, they did not show as dramatic a change and were not distinguishable from control group depression levels.

Beyond kidney transplantation, other nonpharmacologic psychotherapeutic intervention trials in organ candidates and recipients suggest that telephone-based counseling using cognitive behavioral therapy principles and internet-based interventions involving problem-solving therapy can lead to reductions in depression and anxiety [95]. It seems likely that such interventions would be effective in kidney recipients. Additional strategies have been described for kidney recipients, but they have not been evaluated for efficacy. These include peer mentoring, internet-based education and support, and intensive support and education before discharge after the initial transplant surgery (see Dew and DiMartini [33] and DiMartini et al. [97], for reviews).

Psychopharmacologic strategies have not received study in controlled trials in kidney recipients. Randomized trials comparing the impact on depression of sertraline vs. placebo in chronic (nondialysis) kidney disease patients [98] and sertraline vs. cognitive behavioral therapy in dialysis patients [99] are completed or ongoing. In the former trial, sertraline was found to be no more effective than placebo at reducing depressive symptoms. It would be important to consider whether these findings would generalize to kidney transplant recipients.

Substance Use

Ten years ago, Tome et al. [100] noted that very little was known about addictions and their treatment in recipients of organs other than the liver and that this should be a research priority. However, there continues to be a dearth of intervention research. In kidney recipients, a recently published study protocol described a trial focused on smoking cessation using a nonpharmacologic intervention involving brief counseling plus feedback on patients' carbon monoxide oximetry [101]. No results have yet been reported and we could not identify any other completed studies focused on the efficacy of interventions for substance use in kidney recipients. Recent literature on liver recipients suggests that facilitating availability of alcohol addictions treatment specialists (by, e.g., embedding them within the transplant team) may reduce relapse rates post-transplant [102]. Whether this intervention would be feasible in kidney transplant programs—given that fewer kidney recipients have histories of alcohol abuse/dependence than do liver recipients—is not clear. A more feasible approach in kidney transplantation might employ a written "alcohol contract" (or contract for any other type of substance use), in which transplant candidates commit to abstinence after transplantation. However, Masson et al. [103] tested this approach in liver transplantation and found no effect on relapse rates among liver recipients with histories of alcoholic liver disease.

Clinical Strategies to Provide Psychosocial Care to Kidney Recipients After Transplantation: Recommendations

The evidence on prevalence, risk factors, and empirically evaluated interventions leads to two major types of recommendations regarding care for kidney recipients. First, such patients should be routinely screened for psychosocial problems in the areas of medical regimen adherence, mental health, and substance use. Recipients with strong risk factors for such problems may require more frequent or extensive screening. Second, when patients with psychosocial

Table 10.2 Strategies kidney transplant programs could use in order to improve psychosocial outcomes after kidney transplantation

Establish a foundation of trust to encourage patients to speak openly about psychosocial problems, including nonadherence to the medical regimen, mental health problems, and substance use.
Develop collaborative partnerships with patients' other healthcare providers.
Embed a focus on psychosocial outcomes into the transplant team's culture, including routine screening for and tracking of patient status on these outcomes.
Stratify patients by their needs and risk factors so that interventions can be appropriately deployed by the team or so that timely referrals can be made for care by specialists.
Employ multiple interventions; one size does not fit all.

Adapted from Oberlin et al. [104]

problems are identified, the choice of interventions to be offered should be guided by the evidence base on efficacious interventions in kidney recipients. In the absence of such evidence, the interventions should have been established as efficacious in other organ transplant and/or chronic and end-stage disease populations.

Although we focus below on these two major areas of recommendations, we note that additional factors will also likely need to be in place so that transplant programs can successfully screen for and intervene to treat psychosocial problems. Thus, a recent review focused on medication adherence intervention activities by kidney transplant programs concluded that transplant teams must change their "cultures" regarding their approach to addressing nonadherence in their patients [104]. We believe that a similar culture change may be needed to effectively address other psychosocial outcomes, including mental health and substance use problems. Therefore, we have adapted the elements that Oberlin and colleagues suggest are most important in order to encompass psychosocial outcomes in general, and our adaptation is shown in Table 10.2. As detailed in the table, screening and intervention are critical activities for improving psychosocial outcomes, but elements such as building collaborative relationships with kidney recipients' other healthcare providers and building a foundation of trust in order to encourage open conversation with patients may ultimately be equally important.

Screening for Psychosocial Problems

The importance of screening activities to identify psychosocial problems is well-recognized in clinical care guidelines for kidney recipients [105, 106]. Screening should be incorporated into every follow-up clinical visit after transplantation. We noted earlier that problems related to nonadherence, for example, can emerge very soon after transplantation. Fortunately, from a screening standpoint, kidney recipients return to their transplant centers relatively often during the first year after transplant. During routine follow-up clinic visits post-transplant, they typically see a nurse coordinator and a transplant team physician (often a nephrologist), and it is likely that these professionals would have the greatest opportunity to perform routine psychosocial screening. Most teams providing post-transplant care do not include assessments by mental healthcare providers or other specialists in psychosocial issues, and the professionals who conduct the pre-transplant psychosocial evaluations of patients do not routinely follow patients post-transplant. Therefore, the nurse coordinator and team physician who are most likely to see patients during follow-up must be provided with psychosocial screening tools that are easy to use and provide clear indications of which patients are experiencing problems and may need referral to specialists within or beyond the team for intervention.

Beyond the first year post-transplant, patients are likely to return less frequently to the transplant program for care. In some cases, patients may only return if they develop problems related to the graft or to medical comorbidities linked to immunosuppression or other transplant-related medications. Thus, face-to-face screening may become less feasible. For patients with risk factors for psychosocial problems, programs could consider remote screening options including telephone screening. Recommending to recipients' local healthcare providers (e.g., primary care physicians or local nephrologists) that they should engage in screening may also be an option.

Nonadherence to the Medical Regimen As summarized in Table 10.3, several types of tools could be used to screen for adherence problems, including simple patient-report measures, biologic assays, and routine review of information in patients' electronic health records for trends and patterns on key parameters [107–147]. Historically, self-report screens for nonadherence, especially with regard to medication-taking, have been viewed as inferior to methods such as electronic medication monitoring. However, despite its use in research, electronic monitoring is generally not feasible in clinical practice [148]. Careful use of self-report measures can yield valid information on medication nonadherence [149]. A common clinical practice in transplant programs is to use open-ended questioning about medication-taking rather than any specific self-report questionnaire or checklist [150]. If such a strategy is adopted, clinicians should draw on lines of questioning recommended by experts [48], which focus on understanding the patient's perspective and building rapport. However, open-ended questions may not be asked in the same way across patients or across clinicians and thus may lead to varying degrees of success in identifying nonadherent patients. A stronger, more systematic alternative is to employ one of the several very brief, validated self-report measures of medication-taking recommended for clinical use with transplant patients [149, 151]. Prime examples are listed in Table 10.3. These measures focus on immunosuppressant nonadherence but may be adapted for other types of medication-taking. In fact, both the ITAS and the

Table 10.3 Approaches to screening for psychosocial problems after kidney transplantation

Psychosocial domain	Examples of screening approaches and tools for routine clinical use	Relevant references
Nonadherence to the medical regimen	*Medication-taking*	
	Patient self-report surveys	
	Immunosuppressant Therapy Adherence Scale (ITAS)	Chisholm et al., 2005; Wilks et al., 2010 [107, 108]
	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	Shäfer-Keller et al., 2008 [109]
	Calculation of medication blood level variability	
	Medication Level Variability Index (MLVI)	Shemesh & Fine, 2010; Supelana et al., 2014 [110, 111]
	Coefficient of Variation (CV)	Maclean et al., 2011; Scheel et al., 2017 [112, 113]
	Clinic appointment attendance, completion of required blood work, and lifestyle issues	
	Review of patient medical record for repeated failure to complete clinic appointments and blood work	
	Review of medical record for elevated or rising BMI levels	
	Patient self-report of physical activity	
	International Physical Activity Questionnaire, Short Form "Past 7 days" (IPAQ-S7S)	Craig et al., 2003 [114]
	General Practice Physical Activity Questionnaire (GPPAQ)	Dept. of Health, UK, 2009 [115]
	Patient self-report of diet	
	Rapid Eating and Activity Assessment for Participants-Short Version (REAP-S)	Segal-Isaacson et al., 2004 [116]
Mental health problems	*Depression* (patient self-report surveys)	
	Patient Health Questionnaire-2 (PHQ-2)	Kroenke et al., 2003 [117]
	Patient Health Questionnaire-9 (PHQ-9)	Kroenke et al., 2001 [118]
	MOS-Depression Screener	Burnam et al., 1988 [119]
	Beck Depression Inventory-II (BDI-II)	Beck et al., 1996 [120]
	Beck Depression Inventory FastScreen for Medical Patients (BDI-FS)	Beck et al., 2000 [121]
	Center for Epidemiologic Studies-Depression Scale (CES-D)	Radloff et al., 1977 [122]
	CES-D Short Form (CES-D-SF)	Kohout et al., 1993 [123]
	Anxiety (patient self-report surveys)	
	Generalized Anxiety Disorder-2 (GAD-2)	Kroenke et al., 2007 [124]
	Generalized Anxiety Disorder-7 (GAD-7)	Spitzer et al., 2006 [125]
	Multiple areas of distress (patient self-report surveys)	
	Hospital Anxiety and Depression Scale (HADS)	Snaith, 2003 [126]
	Patient Health Questionnaire (PHQ)	Spitzer et al., 1994 [127]
	Hopkins Symptom Checklist and derivatives (e.g., Brief Symptom Inventory; Symptom Checklist-90-Revised)	Derogatis, 1974; 1993; 1994 [128–130]
	General Health Questionnaire (GHQ)	Goldberg & Williams, 1988 [131]
Substance use	*Tobacco use* (patient self-report surveys)	
	Fagerström Test for Nicotine Dependence (FTND)	Heatherton et al., 1991 [132]
	Fagerström Test for Nicotine Dependence-Smokeless Tobacco (FTND-ST)	Ebbert et al., 2006 [133]
	Alcohol use (patient self-report surveys)	
	CAGE Questionnaire	Mayfield et al., 1974 [134]
	Michigan Alcoholism Screening Test (MAST)	Selzer, 1971 [135]
	Short MAST (SMAST)	Selzer et al., 1975 [136]
	Brief MAST	Pokorny et al., 1972 [137]
	Alcohol Use Disorders Identification Test (AUDIT)	Saunders et al., 1993 [138]
	AUDIT-Alcohol consumption questions (AUDIT-C)	Bush et al., 1998 [139]
	Patient Health Questionnaire Alcohol items (PHQ-Alcohol items)	Spitzer et al., 1994 [127]
	Drug use and multiple areas of substance use (patient self-report surveys)	
	Single-Item Screen	Smith et al., 2010 [140]
	Drug Abuse Screening Test and its derivatives (DAST; DAST-20; DAST-10)	Skinner, 1982; Yudko et al., 2007 [141, 142]
	Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)	WHO ASSIST Working Group, 2002 [143]
	CAGE Questionnaire Adapted to Include Drugs (CAGE-AID)	Brown & Rounds, 1995 [144]
	RAFFT Questionnaire (RAFFT)	Bastiaens et al., 2002 [145]
	Biologic measures of tobacco, alcohol, or other drug use	
	Blood, urine, hair, and saliva samples can be tested for tobacco, alcohol and other drug use	Richter & Johnson, 2001; Grigsby et al., 2017 [146, 147]

BAASIS originated from assessments of other types of medications.

Concerning use of biologic assays and other indicators of medication nonadherence, transplant programs have often relied on biopsy evidence of graft rejection or low blood levels of a given medication to infer nonadherence. However, the use of such data for this purpose should be avoided. Both biopsy results and blood levels may be influenced by factors other than nonadherence. For example, blood levels of immunosuppressants commonly fluctuate over time and can be affected by blood draw timing, other medications' impact on immunosuppressant metabolism, and dosing changes. To appropriately examine blood levels with respect to patient adherence, clinicians should employ one of the recently developed measures that determines whether blood level variability over time exceeds that expected due to biological factors or measurement error. Two examples of such measures are shown in Table 10.3. The calculations for these measures would not be difficult to perform routinely using the repeated laboratory testing results available in patients' medical records.

Both the self-report and blood level assessment strategies that we suggest focus on medication adherence. In some other areas of the regimen, nonadherence may relatively easily determined by periodic review of the patient's medical record. For example, repeated failure to attend clinic appointments or complete blood work and tests indicates nonadherence to these requirements. Similarly, elevated and/or rising BMI would suggest difficulties with lifestyle issues (e.g., diet and perhaps exercise). A variety of screening tools exist for physical activity and level of exercise, although these measures have not been evaluated in kidney recipients. Two such measures are shown in Table 10.3. The IPAQ-S7S appears particularly suitable for routine clinical use given its strong research base [152]. A second measure, the GPPAQ, has been recommended for use in primary care practice in the UK [153], and thus may be appropriate as well, although the evidence base for this measure's psychometric properties is incomplete [154]. A brief measure to evaluate diet and nutrition, the REAP-S, may also be useful as a screen for identifying eating habits that are problematic.

Mental Health Problems Similar to the common practice of asking a few open-ended questions to assess adherence issues in kidney recipients, transplant teams may not systematically screen for psychological distress aside from asking general, open-ended question about how patients are feeling or how their mood has been. There are, however, many self-report measures available that can be used to screen patients for the presence of the most common problems, depression and anxiety. Prime examples are listed in Table 10.3. For depression, an ultra-brief screener, such as the PHQ-2, takes less than 1 minute to complete. Other measures such as the PHQ-9, the MOS-Depression Screener, the BDI-Primary Care, and the CES-D short form are also quite brief. Longer versions of these and other measures are also available, widely used, and have well-documented psychometric properties. The measures can be used as continuous scales to determine degree of distress. However, even more important from a screening standpoint, each has a cut point that can be used to identify patients with clinically significant distress warranting more extensive evaluation and, potentially, treatment.

Screeners such as the GAD-2 and GAD-7 are available to evaluate anxiety symptoms, and measures such as the HADS, the Patient Health Questionnaire, the Hopkins Symptom Checklist and its derivatives, and the General Health Questionnaire assess multiple areas of distress. Each of these measures has strong psychometric properties and, as for the depression scales, established thresholds to indicate clinically significant distress.

Substance Use Transplant teams do not routinely monitor kidney recipients for tobacco, alcohol, or other drug use unless patients were identified before transplant as having a substance use disorder. For patients with no history of diagnosable disorder (the majority of kidney recipients), resumption of substance use—particularly use at levels that exceed post-transplant care recommendations—may be discovered only if patients or families volunteer such information or if patients develop medical complications that lead to team suspicions and subsequent evaluation to determine whether patients are using proscribed substances. For patients at risk for substance use, transplant programs could consider employing self-report screens for areas of substance use that are of concern (see Table 10.3). There are many such screeners available, including those that are specific to one type of substance use and those that assess use of any of multiple substances.

There are also a variety of biological assessments available, as noted in Table 10.3. However, such assessments are more costly than self-report screeners, require the patient to be seen at the follow-up clinic or a laboratory and may not detect sporadic use. In general, their findings will depend on the timing of the sample relative to actual substance use. They should be reserved for situations in which substance use risk is high or when substance use is suspected to be occurring on a regular basis [146]. Careful clinical interviewing about possible substance use, conducted in conjunction with the use of self-report measures, may yield higher rates of substance use identification than a reliance on biological measures [155].

Clinical Intervention for Psychosocial Problems

The interventions tested in research summarized earlier should be considered for potential use with kidney recipients struggling with adherence or mental health problems. We noted earlier that there is a dearth of research evidence on substance use interventions in kidney recipients. It is noteworthy that, although the evidence base on adherence-related and mental health-related interventions appears to be growing within transplantation, there has been very little consideration of whether the interventions tested would be able to be translated into routine clinical use. Most of the successful adherence-focused interventions and psychotherapeutic interventions have involved multiple face-to-face sessions with patients. Perhaps the most important message from these studies is that one-on-one coaching of patients can indeed improve adherence, and that both individual and group-based nonpharmacologic psychotherapeutic strategies can be helpful for reducing patients' depressive and anxiety symptoms. However, these interventions are likely to be labor-intensive for most transplant teams, and teams may not have the expertise to mount some of the effective interventions. If patients have healthcare insurance coverage that allows for referral for counseling-based strategies for adherence problems (including interventions for "lifestyle" health-related issues such as diet, exercise, and obesity management) and/or for mental health services, such studies suggest that positive results could be obtained. Of note, the intervention tested by Reese and colleagues, involving text messaging and email reminders about medication-taking, was also quite effective and may be a more realistic option for transplant programs to adopt. However, it also required electronic medication monitoring which, as we noted above, is not generally feasible for routine use. Nevertheless, the study suggests that use of mobile or e-health intervention strategies may hold particular promise for kidney recipients, and this is supported by intervention research in other types of organ recipients, as we discussed earlier.

We also noted earlier that there have been few tests of pharmacologic strategies for mental health issues in kidney recipients. Clinicians, therefore, must draw on the evidence regarding the safety and efficacy of strategies tested in other populations. Concerns have been voiced that altered drug clearances, drug-drug interactions, and prevalent cardiovascular comorbidity may alter the risk/benefit profile of antidepressant and anxiolytic medications in patients with chronic kidney disease, even after kidney transplantation [31]. These concerns notwithstanding, there is a large practice-focused literature showing that psychopharmacologic options can be used safely and effectively with transplant recipients with stable organ function, including kidney recipients [34, 97, 156, 157]. DiMartini et al. [97] provide a detailed consideration of which psychotropic medications should be used as first-line strategies in organ recipients, who take a cocktail of immunosuppressants and other medications. In particular, many immunosuppressant agents are primarily metabolized by the cytochrome P450 (CYP 450) enzyme system. Thus, psychotropic medications that strongly inhibit CYP 450 3A4 should be avoided (e.g., fluvoxamine and nefazodone). The selective serotonin reuptake inhibitors escitalopram and citalopram are likely the best choices. They may also be the best choices for long-term treatment of anxiety in organ recipients [157]. Although sertraline may be considered, the recent trials that we reviewed earlier, which showed no benefit for the treatment of depression in patients with chronic kidney disease, suggest that sertraline may not be the best initial choice of antidepressant medication for kidney recipients if other options are available. Sertraline's efficacy for anxiety in kidney disease populations has not been examined.

With respect to substance use, little to no research has focused specifically on kidney recipients. However, Corbett et al. [4] summarized evidence on efficacy of tobacco smoking cessation therapies across multiple meta-analyses and systematic reviews in a variety of study populations, showing that all major nicotine replacement therapies were effective. In addition, nicotine replacement therapy in combination with smoking cessation counseling appeared to be particularly effective. The use of the medications bupropion and varenicline was also found to be effective. However, these medications require caution with transplant recipients [97]. Bupropion should not be used in patients with a seizure disorder history or with electrolytes disturbances that could contribute to a seizure. Varenicline is renally excreted and thus should be appropriately adjusted in kidney recipients, especially in the context of impaired graft function.

With respect to alcohol and other substance use, Parker et al. [10] provide an overview of counseling-based strategies of potential use in transplant recipients, including motivational interviewing and mutual self-help approaches (e.g., Alcoholics Anonymous and Narcotics Anonymous) that can be considered. Transplant programs would likely refer patients to such programs rather than attempt to offer them in-house. In transplant populations, care is needed in the use of pharmacotherapies for alcohol and other substance use [34, 97]. Medications to reduce cravings and relapse risk for alcohol (e.g., acamprosate, ondansetron, naltrexone) or opioids (naltrexone) have not been studied in kidney or other organ transplant patients. Acamprosate is renally excreted and, therefore, the dosage may require adjustment in kidney recipients with impaired renal function. Naltrexone has a small risk of hepatotoxicity and would not be recommended in kidney recipients with liver dysfunction. Disulfiram is not recommended in transplant recipients. Please refer to Chap. 42 for more details on psychopharmacology in transplant recipients.

Conclusions and Future Directions

Recent years have seen a great expansion in research examining psychosocial problems in the areas of medical regimen adherence, mental health, and substance use after kidney transplantation. The bulk of work has been descriptive and has focused on prevalence and risk factors for problems. Nevertheless, our understanding of true risk factors, as opposed to correlates of post-transplant psychosocial difficulties, has remained incomplete. The most potent risk factor for post-transplant psychosocial problems is a history of such problems before transplantation. This information, at the very least, is valuable because it allows transplant programs to identify kidney recipients who require more careful follow-up post-transplant regarding psychosocial outcomes. Future work to provide a more definitive risk factor profile, plus continued emphasis on exploring patients' own perceptions of the causes of nonadherence, mental health problems, and substance use problems, may allow (a) better identification of patients who may need close monitoring post-transplant and (b) tailoring of interventions to be more responsive to the specific issues of concern to patients.

The evidence base indicating what interventions are most effective for psychosocial problems is also relatively slim. The bulk of evidence focuses on interventions to reduce or avoid immunosuppressant medication nonadherence, with very limited work testing interventions for other areas of nonadherence or for mental health problems. Virtually no research has examined interventions for substance use in kidney recipients. Drawing on available evidence in kidney recipients, as well as intervention research findings from other transplant, chronic disease and/or community populations, several recommendations for the care of kidney recipients can reasonably be made. Thus, screening for psychosocial problems is critical, and many tools are available to accomplish such screening efficiently during routine follow-up care after kidney transplantation. In the case of nonadherence, transplant programs will likely need to develop and administer their own interventions to assist patients, ideally modeled after interventions already tested. While some research-based interventions may not be feasible for transplant programs to employ (e.g., because the interventions may be too labor-intensive given program resources), transplant programs may be able to employ elements of these interventions to assist their patients with adhering to the medical regimen. In the case of mental health and substance use interventions, it is likely that patients will need to be referred to specialists for care, unless transplant teams include mental health and addictions experts as team members. Future research with a focus on the dissemination and update of efficacious psychosocial interventions by kidney transplant programs is needed in order to provide teams with the best resources for aiding their patients with adherence-related, mental health, and substance use issues after transplantation.

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