REVIEW

Psychiatric Issues in Solid Organ Transplantation

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The identification and treatment of psychiatric comorbidity in patients undergoing solid organ transplantation present a unique opportunity for psychiatric involvement in the care of medically complex patients. The burden of psychiatric illness in patients awaiting transplant and following transplant is significant and associated with potential morbidity and mortality. Possibilities for psychiatric liaison with our colleagues in transplant medicine and surgery start with the comprehensive psychiatric evaluation that is often performed with potential organ recipients and donors. The vital role of the psychiatrist continues following transplantation, as adjustment is often a stressful experience with associated psychiatric comorbidity. The treatment of psychiatric illness in patients following transplantation requires an understanding of the immunosuppressant medications that patients may be taking, coupled with an awareness of the associated risks of adverse effects and drug-drug interactions. (HARV REV PSYCHIATRY 2009;17:398–406.)

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Solid organ transplantation has become the most effective treatment for end-stage organ failure. Patients who receive organ transplants would simply not survive for long without them. Unfortunately, the number of organs available is limited, so careful selection of candidates and close monitoring of their progress are important parts of the transplant process. Patients who require transplantation face serious illness, stressful medical evaluations, and a severe curtailing of their usual lives. Psychiatrists and other mental health specialists contribute to organ transplantation by assisting with the selection process and managing psychiatric disorders that predate the transplant, as well as those that may develop thereafter. Given their medical illnesses, these patients require careful monitoring and judicial treatment with psychotropics in order to minimize serious side effects and adverse outcomes. In the long run, though, psychiatrists can greatly improve patients' quality of life and the team's overall success with transplantation. The following article reviews the psychiatrist's role both before and after transplant, and highlights important issues in assessment, pharmacokinetics, and treatment.

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PRE-TRANSPLANT

The psychosocial evaluation is an important part of the process by which patients are selected for transplant. Solid organ transplants represent a limited resource, and significant effort is put into determining who would most likely be a successful recipient. Medical factors play a major role in determining who will be listed for transplant. If patients are too ill or have comorbid conditions such as cancer, they are less likely to be listed because their chances for long-term survival are lower when compared to other candidates. The psychosocial portion of the evaluation serves to ensure that patients are prepared to be successful stewards of their new organs.

Patients awaiting solid organ transplant face a number of stressors that increase their risk of developing signs and symptoms of psychiatric illness. First and foremost, patients struggle with the changes that they face as their health declines prior to transplant. Many patients wait months or years to receive a transplant, during which time they likely experience a gradual decline in function. Kidney transplant candidates are typically undergoing dialysis, a process that affects their ability to work and their quality of life.[1] Unlike kidney transplants, liver transplants are distributed by how ill the patient is rather than by the amount of time they have waited. This approach leads some patients with liver disease to spend years on the list waiting to get sicker, all the while feeling as though they are unable to live a normal life. Although many patients adapt to the limitations that their illnesses create, the sick role remains a major challenge and source of stress for the majority of transplant patients. In addition to facing declining health, patients also must face the possibility that they will not pass the transplant evaluation. This uncertainty can cause tremendous anxiety for patients and their families, and can be addressed at the time of the evaluation.

Evaluation

All transplant programs require a psychosocial evaluation prior to listing a patient.[2] The evaluation, which can range from a one-time assessment by a member of the social work staff to a multisession, multidisciplinary process, usually involves both the patient and his or her family. This broad participation enables clinicians to corroborate information through multiple sources and to assess the patient's presentation of the family situation. The evaluation is designed to identify potential barriers to successful transplant. Some of these are correctable with either individual treatment or with a social or family intervention. Other barriers, once identified, serve as markers of risk for unsuccessful outcome and will influence the committee's decision to list the patient as a candidate. Because the decision to transplant one patient means that another patient will not get a life-extending organ at that time, listing a patient is a decision that affects society as well as the patient. A degree of equipoise is needed when balancing the needs of the patient in front of you with the needs of society and other patients. Professionals from all disciplines who evaluate patients—from psychiatry, psychology, social work, and nursing—must be active and vocal members of the transplant committee to ensure that both the patient and society have their interests heard and understood. Although the power to list a patient or decline to list a patient varies from center to center, it is arguably best to grant veto power over listing to all members of the team; as a consequence, when a decision to list is made, all members can feel that they are ready to move forward with the patient.

Active psychiatric illness is a modifiable risk factor for poor outcome in transplant. If patients have an anxiety or affective disorder, it is often possible to treat them prior to transplant and to produce a meaningful remission of symptoms. It is worth noting, however, that the available evidence suggests that long-standing anxiety or affective disorders do not predict worse outcomes after transplant.[3] Conditions that are chronic, such as schizophrenia, may be more difficult to put into remission, but careful evaluation of the patient's history and compliance with treatment may lead to judicious selection of some such patients with potentially good outcomes.[4] Intensifying treatment for patients with severe, chronic mental illness can often improve their compliance and assist them with required tasks such as smoking cessation (which might involve an inpatient hospital stay or intensive outpatient services). Personality disorders, when severe, are felt by many programs to be a contraindication to transplant.[5] A one-time evaluation may be inadequate when trying to assess a personality disorder, and crisis situations (such as an acetaminophen overdose leading to acute liver failure and the need for urgent transplant) may also impede a comprehensive evaluation. In such situations, past medical and psychiatric records may be the only way to decide about a patient's ability to work with the transplant team. Ultimately, decisions about listing patients with psychiatric illnesses should be as evidence based as possible so that the biases of team members are minimized and patients are given every opportunity to have access to transplant. The presence of a psychiatric disorder is almost never an absolute contraindication to transplant; it must be considered in the context of numerous other factors when making decisions about listing patients.

A special area of interest in transplantation is substance abuse. Many patients who are in need of liver transplants have a history of alcohol misuse or intravenous drug use, which is a risk factor for contracting hepatitis C.[6] Most programs require a minimum of six months' abstinence prior to listing a patient, but that alone does not ensure continued abstinence after transplant. The longer patients have been abstinent, the less likely they are to relapse, but even periods longer than six months, though less than a year, carry a high risk of relapse.[7] A return to drinking may or may not have an adverse effect on overall mortality and graft survival,[8,9] but there is general agreement that it is best for patients to observe complete abstinence. Risk factors for relapse that have been identified include those who were heavy drinkers (more than 17 servings a day), those who have been drinking for an extended period of time (25 years or longer), and those who have failed rehabilitation more than once.[10] As these factors suggest, a comprehensive drinking history, including family history, past attempts at

rehabilitation, and context of use, is essential when assessing patients with alcohol problems. A history of illicit drug use is also a known risk factor for relapse, and these patients must be considered high risk.[8] In patients with a history of opioid dependence, methadone has been used successfully to prevent relapse to illicit use.[11] Random urine toxicology screens should be used to evaluate abstinence. Besides the problems brought about by continued use, positive screens when the patient is denying ongoing use suggest problems in the patient-team relationship. Finally, heart and lung transplant programs typically require patients to be abstinent from cigarettes for at least six months prior to transplant. Smoking after heart transplant is the most significant determinant of survival, so every effort must be made to assist patients with cessation and continued abstinence.[12] Cotinine, a nicotine metabolite with a longer half-life than nicotine itself, can be measured to detect surreptitious tobacco use in patients who are awaiting transplant.

Two important assessment areas prior to transplant are compliance and social support. Post-transplant, patients must endure complex medication regimens and, initially, frequent contact with the transplant team. If patients are unable to follow their treatment plans after transplant, they place the graft and their lives at risk. A careful evaluation of past medical records and examination of the patient's behavior during the pre-transplant workup can provide important data to help assess if a patient will be able to comply following transplant. Social support can also be assessed by evaluating the patient's living situation, close relationships, financial standing, and access to insurance. Many of these factors can be modified in anticipation of transplant; for example, patients can receive assistance with obtaining health insurance. They also can rally family and friends to their side for assistance after transplant. Often, once patients are past the acute post-transplant phase, intense social support is less important, but in the first weeks and months, it is essential.

The capacity of patients to consent to transplant should also be assessed prior to their being listed as candidates.[13] Families and physicians sometimes apply pressure on patients—some of it not immediately obvious—for them to try and obtain a transplant, but many patients, whether out of their personal beliefs or their exhaustion with being ill, may legitimately choose to forgo transplant and allow their illnesses to take their course. These dilemmas sometimes become apparent, however, only after patients have completed their evaluations and are listed. For example, patients may passively not comply with treatment by refusing to come in for tests or by missing appointments, or they may become explosively angry with transplant personnel for no obvious reason. Both types of behavior may stem from patients' hidden wish to not have a transplant and should be investigated face-to-face with the patient. Another factor that affects consent is cognitive impairment. Whether it is hepatic encephalopathy in liver candidates, low cardiac output in heart candidates, or chronic hypoxia in lung candidates, many patients facing transplant suffer from cognitive impairment and may experience progressive difficulty with understanding the transplant process.

Related to capacity, patient's expectations are worth exploring prior to transplant. For various reasons, patients sometimes have the impression that a transplant will take only a few days and lead to a complete return to their previous, healthy life. In order to give consent, patients must be informed about the range of outcomes after transplant, including death, continued health problems, and the possibility that even a successful transplant will not lead to the patient's pre-illness lifestyle. Only when patients know the full range of outcomes can they provide consent for transplant.

Different programs have different requirements for evaluation prior to transplant. For example, many kidney transplant programs have a social worker evaluate patients prior to transplant and refer only the occasional patient to a psychiatrist or psychologist for further evaluation. By contrast, many heart and lung transplant teams require every patient to be evaluated by a psychiatrist or doctoral-level psychologist. Typically, the evaluation consists of a standard screening battery that examines many of the components discussed above. When problems are identified, patients need to be referred to other members of the team or given a more detailed evaluation. Patients are often evaluated alone initially and then with family; speaking with family without the patient present can also be helpful if the patient consents. Medical records are important and should be reviewed whenever possible.

Living Donor Evaluation

The most successful kidney transplant outcomes come from living donors.[14] Therefore, transplant candidates often recruit relatives to donate a kidney—a process that requires careful psychosocial evaluation. Donors and recipients need two separate evaluators to minimize conflicts of interest. Assessment of donors' motivations for donating is essential to ensure that they are making their own choice.[15] The pressure that a family or a situation can bring to bear on a potential donor can be considerable, especially if the recipient is a child. Much of the pressure experienced by the potential donor comes from within—and remains unspoken. Even when both the donor and recipient are ambivalent about the process of donation, the situation often makes discussion of these feelings seem inappropriate. Inquiring about doubts and concerns may therefore help patients and their families to talk about hidden issues. Facilitating

discussion and allowing both the donor and the recipient to discuss their motivations, expectations, and fears can help to shed light on the dynamics that are working within a family and help patients and donors make more informed, stable decisions. The team should be willing to give patients and families time to make decisions about donation so that emotions do not completely drive the decision-making process. Transplant teams may be eager to perform transplants, and their own evaluations of the donors' risks must be examined.

In some cases, altruistic donors step forward who have no targeted recipient but rather wish to donate for the greater good. These patients should be assessed for any psychiatric disorder that might be contributing to their wishes. The advantage of these donors is that one kidney can start a chain of paired donation in which a candidate that has a willing but unmatched donor receives a transplant, while his or her donor gives to another person.[16] Since financial gain is a potential motivating factor for donation, all reasonable efforts must be made to eliminate that possibility (as it must be in all other cases, too). Likewise, careful assessment of both motivation and expectation is important to ensure that psychiatric illness is not influencing an altruistic donor's decision to donate.

Pharmacokinetic Considerations Pre-transplant

End-stage organ disease leads to serious changes in the metabolism of medications and an increased risk of side effects. Liver disease can alter the function of the cytochrome P450 system and lead to slowed metabolism of medications and to higher, even toxic concentrations of active drug.[17] Decreased synthetic function can also lead to elevated serum levels of medications, particularly for those that are highly protein bound. For patients with hepatic encephalopathy, these changes can lead to recurrent episodes of confusion. Extreme caution in prescribing new medications to such patients is necessary to avoid unnecessary morbidity. End-stage renal disease can also lead to high serum levels of medication, although periodic dialysis may remove some drugs. Toxicity can potentially be minimized by spacing out or lowering treatment doses. Details and strategies for specific drugs are outlined below, with more details available elsewhere.[18]

POST-TRANSPLANT CARE

The stress experienced by the potential organ recipient does not entirely abate following transplantation. Organ transplantation requires significant adaptation by the patient and the patient's caregivers. How patients manage this adjustment is very individualized, as every patient who undergoes transplantation is unique. In addition to the obvious effects of age and developmental stage, patients have their own histories, personality styles, and coping mechanisms that shape this adaptation. Unfortunately, patients are often very ill medically and may suffer from significant physiological and psychological stressors during the transplant process. In addition, some patients may be confronted by the burden of medical and surgical complications following transplant. Recovery from surgery, as well as life following organ transplantation, requires a strict and often stressful adherence to medications, medical surveillance, and diet. The patient is also faced with omnipresent risk of organ rejection and the potential of medication side effects that can range in severity from nuisance to life threatening. Many of the aforementioned stressors are not limited to the individual receiving the organ; the recipient's family and friends may also experience significant challenges following the transplant. The consulting psychiatrist's role in the care of these patients often continues following successful transplantation as new issues arise and challenges are confronted.

Adherence to Treatment Following Transplantation

The potentially disastrous consequences of nonadherence to post-transplant medications, particularly the antirejection agents, and to medical regimens make compliance with prescribed therapy imperative. Overall, nonadherence rates range from almost 25% to over 50%, depending on the type of transplanted organ and the scope of compliance studied.[19,20] Importantly, poor compliance has been shown to impair both the patient's quality of life and life expectancy, as nonadherence to medications appears responsible for up to 25% of deaths following initial postsurgical recovery.[21] One of the goals of the comprehensive psychosocial evaluation, discussed above, is to reduce this preventable morbidity and mortality by identifying and addressing the risks for postoperative noncompliance.

Problems with adherence following transplant may result from many factors. Noncompliance with care prior to transplantation represents a major risk factor for future compliance issues. A discussion about the patient's beliefs and concerns about the transplant is essential as one seeks to uncover potential motivations for noncompliance. Psychiatric problems before transplantation have been associated with suboptimal compliance after transplantation.[22] Post-transplant depression has been associated with an increased risk of medical nonadherence,[23] as have elevated levels of anxiety and hostility.[3] Personality disorders, such as borderline personality disorder with its inherent instability of feelings, actions, and relationships, may complicate the treatment of patients postoperatively, leading to poor

treatment adherence. Dew and colleagues[3] found a significant "dose-response" relationship between predictors for nonadherence and actual impaired compliance. In other words, as risk factors for nonadherence accumulate in a specific patient, the actual level of noncompliance for that patient increases. Noncompliance with care often leads to psychiatric referral as frustrated transplant clinicians attempt to address this significant and potentially dangerous problem.

Immunosuppressant Medications

The immunosuppressant medications utilized following solid organ transplantation attempt to prevent the recipient's rejection of the grafted organ. The psychiatric consultant must be aware of the numerous neuropsychiatric adverse effects of these drugs and of their pharmacokinetic and pharmacodynamic properties. Important drug interactions may occur when immunosuppressants are used together or administered with other medications used to treat comorbid illnesses.[24] These medications often have a narrow therapeutic index and present the risk of ineffectiveness or toxicity. A brief review of the commonly encountered immunosuppressants follows. For a more comprehensive discussion of these complex medications, the reader is referred to an excellent review article by Fireman and colleagues.[25]

Glucocorticoids, particularly prednisone, remain a common immunosuppressant in transplant patients. This class of medication has multiple, well-documented medical and neuropsychiatric adverse effects. Chronic use of glucocorticoids may induce adrenal suppression, osteoporosis, and glucose intolerance. Psychiatric complications may include depression, mania, psychosis, and delirium. The risk of psychiatric side effects appears related to dose, with higher doses presenting greater risk.[26] Managing the psychiatric complications of glucocorticoid treatment requires reducing the steroid to the lowest effective dose, coupled with symptomatic treatment with an antidepressant, mood stabilizer, or antipsychotic as appropriate. Additionally, since prednisone is metabolized by the P450 3A4 isoenzyme system, the prescribing clinician must be aware of potential pharmacokinetic interactions.

The calcineurin-inhibiting immunosuppressants, cyclosporine and tacrolimus, are associated with a significant risk of neurotoxicity. Cyclosporine has commonly been associated with restlessness, tremor, and headaches. In addition, a minority of patients may suffer from more severe neuropsychiatric toxicity, such as delirium, psychosis, and seizures. Tacrolimus has also been associated with multiple neuropsychiatric side effects, such as sleep disturbances, tremor, headache, and irritability. Much like cyclosporine, tacrolimus has also been associated with more severe neurotoxicity, such as delirium, seizures, agitation, and cortical blindness. Calcineurin-inhibitor neurotoxicity may also lead to the development of posterior reversible encephalopathy syndrome, a significant neurotoxicity in which the patient develops headache, visual disturbances, delirium, and potential seizures.[27] When working with transplant patients who have psychiatric comorbidities, the risk of intentional overdose must be considered. Overdoses of cyclosporine have been associated with significant neurotoxicity.[28] In contrast, tacrolimus overdose has been well tolerated with minimal adverse sequelae.[29]

Cyclosporine and tacrolimus both utilize P450 3A4 hepatic metabolism, and many drug-drug interactions have been reported in the literature. Since both of these medications are metabolized by 3A4, inhibitors of this isoenzyme have been shown to increase cyclosporine[30,31] and tacrolimus levels,[32,33] potentially leading to toxicity. In addition, medications that induce 3A4 have been reported to decrease blood levels of those immunosuppressants, potentially leading to graft rejection.[34] The many possible clinical drug interactions, coupled with a narrow therapeutic index, make monitoring levels of these medications essential whenever medications are added or subtracted to the patient's established medication regimen.

The immunosuppressants sirolimus and mycophenolate are not calcineurin inhibitors. Sirolimus appears to have a much more benign neuropsychiatric side-effect profile than cyclosporine and tacrolimus. Mycophenolate mofetil may cause some restlessness or anxiety, but these side effects appear to be less prevalent than with the calcineurin inhibitors. Sirolimus is metabolized by the hepatic isoenzyme P450 3A4. As a result, caution must be employed whenever substances that either inhibit or induce this enzyme system are administered or withdrawn. However, likely because sirolimus is a fairly well-tolerated medication, reports of drug interactions with it are minimal. Since mycophenolate mofetil's primary route of elimination is renal, there should be little concern of pharmacokinetic drug interactions via the P450 isoenzyme system.[35]

Psychiatric Comorbidity Following Transplantation

In spite of the psychosocial difficulties associated with transplantation, most patients find organ transplantation a positive experience overall. For example, in the case of renal transplantation, if the transplant is successful, the patient's quality of life usually improves.[36] However, one must recognize that it is common for transplant patients to exhibit psychiatric distress after transplantation. Individuals with a history of pre-transplant psychiatric disorders and poor social support may be at an increased risk for psychiatric disorders post-transplant.[37] Given the substantial risks and demands associated with organ transplantation, this

psychiatric consequence is not surprising. The psychiatric conditions experienced by patients following transplantation include cognitive, affective, anxiety, and substance use disorders—which may be caused by psychological stressors, medications, or physiological disturbance. Given the multiple potential etiologies for post-transplant psychiatric symptoms, it is important that the psychiatrist initiate an appropriate medical evaluation. Physicians need to obtain a comprehensive history of all prescribed medications, over-the-counter medications, and herbal supplements, as these may contribute to a multitude of psychiatric symptoms. The evaluation should be followed by appropriately selected treatment modalities and subsequent close follow-up.

Depression appears to be one of the most common psychiatric disorders in patients following organ transplantation. The occurrence of post-transplant depressive disorders has been reported to be in the range of 5% to 25% across both organ systems and the time post-transplant.[38,39] Depressed patients may experience a reduced quality of life, more somatic complaints, and poor coping. These behaviors may lead to a sense of futility and to subsequent impaired compliance, along with a return to unhealthy behaviors such as smoking. In fact, depression following solid organ transplantation has been associated with increased morbidity and mortality.[38] Additionally, in an observational study of U.S. patients with end-stage renal disease transplanted between 1988 and 1997 who died with graft function, the suicide rate was higher in the transplanted population (15.7 deaths per 100,000 person-years, compared with 9.0 deaths per 100,000 person-years [$p < 0.001$] in the general population).[40] It is therefore imperative that clinicians identify depression promptly and initiate effective treatment to reduce the potential for these negative outcomes. Although multiple symptoms of chronic medical conditions may mimic some of the diagnostic criteria for depressive disorders, an attentive history and careful evaluation are often sufficient to clarify this diagnosis in patients following organ transplantation.

Even after a successful surgery, transplant patients face a continuing risk of organ rejection, followed by a return to illness and organ failure. The multitude of stresses associated with organ transplantation, coupled with medication side effects, results in rates of anxiety ranging from 17% to 28%.[38,41] Many different types of anxiety disorders have been observed in the transplant population: panic disorder, generalized anxiety disorder, and adjustment disorder with anxious mood, in addition to anxiety secondary to medications or a general medical condition. A growing body of literature is also beginning to recognize the complication of posttraumatic stress disorder in patients and caregivers.[42] In addition, as mentioned previously, the clinician needs to be aware that cyclosporine and tacrolimus have a fairly high rate of medication-induced anxiety and akathisia. As with depression, early identification and treatment of these disorders is necessary in an attempt to maximize adaptation and functioning following transplantation.

Delirium, in all its varied forms, is a common occurrence immediately post-transplant. The presence of a delirious state must remind the clinician to be aware of potential medical/surgical decompensation or medication toxicity as a potential cause of altered mental status. Etiologies for delirium may be as diverse as infections, narcotics, immunosuppressants, rejection, and residual end-organ dysfunction. The management of delirious patients following organ transplantation is similar to the treatment of delirium pursued in the nontransplant population. Identification and reversal, when possible, of the reason(s) for the delirious state are critical to achieving resolution of the delirium. Antipsychotic medications (high-potency and atypical classes) are considered the first-line pharmacological treatment of delirium, except for benzodiazepines in alcohol withdrawal delirium. Another cause of subacute cognitive decline is progressive multifocal leukoencephalopathy, which has been rarely reported in immunosuppressed transplant patients.[43]

Patients with personality disorders, if deemed appropriate for transplant, may pose many problems for those trying to care for these challenging patients following the surgery. The personality disorders that routinely cause the greatest distress in caregivers are the antisocial and borderline personality disorders. The behaviors of most concern in these patients are nonadherence, substance misuse, and problems relating to the individuals who provide care post-transplant. These patients will often require a specialized behavioral treatment plan, hopefully initiated prior to organ transplant, in an effort to mitigate these potential problems.

Treatment of Comorbid Psychiatric Conditions Following Transplantation

Prompt treatment of identified neuropsychiatric complications and psychiatric comorbidity in transplant patients is essential to improve outcomes. Failure to treat these conditions may raise the risk of morbidity and mortality in these complex patients. The treatment of comorbid psychiatric disorders in patients following organ transplantation does not vary greatly from the treatment of these conditions in patients with chronic medical illness. Management of these conditions remains based on an individualized combination of psychopharmacology and psychotherapy, both informed by the patient's current medical status.

The pharmacotherapy of psychiatric disturbances in post-transplant patients requires careful consideration of the pharmacokinetic and pharmacodynamic properties of the medications prescribed. As in patients with chronic

Table 1. P450 Enzymes Involved in Drug Metabolism

	Substrate of	Inhibits	Induces
Antidepressants			
Fluoxetine	2D6, 3A4, 2C9, 2C19	2D6, 3A4, 2C9, 2C19	None
Paroxetine	2D6	2D6, 3A4, 2B6,	None
Sertraline	2D6, 3A4, 2C9, 2C19	2D6 (at higher doses)	None
Citalopram	2D6, 3A4, 2C19	None	None
Escitalopram	2D6, 3A4, 2C19	None	None
Fluvoxamine	1A2, 2D6	1A2, 3A4, 2C9, 2C19	None
Venlafaxine	2D6	2D6	None
Duloxetine	2D6, 1A2	2D6	None
Mirtazapine	2D6, 3A4, 1A2	None	None
Bupropion	2B6	2D6	None
Nefazodone	3A4	3A4	None
St. John's Wort	Unknown	None	3A4
Anxiolytics			
Buspirone	3A4	None	None
Alprazolam	3A4	None	None
Lorazepam	None	None	None
Clonazepam	3A4	None	None
Diazepam	3A4, 2C19	None	None
Immunosuppressants			
Prednisone	3A4	None	None
Cyclosporine	3A4	3A4	None
Tacrolimus	3A4	3A4	None
Sirolimus	3A4	None	None
Mycophenolate mofetil	None	None	None

Source: Fireman et al. (2004),[25] Carlat DJ (2006).[45]

medical conditions, medications should be prescribed in the "start low and go slow" method, with a clear awareness of the signs and symptoms of toxicity. Transplant patients often suffer from medical conditions such as hypertension, diabetes, and obesity—which may further complicate the choice of pharmacotherapy. Most of these patients are on complex, multidrug medication regimens and are at significant risk for drug-drug interactions when new medications are started or old medications discontinued. An up-to-date medication list is an absolute requirement for the treating psychiatrist when prescribing for a patient following organ transplantation. The clinician's ability to anticipate and avoid potential drug interactions when prescribing medications will significantly lower the chances that the patient will experience adverse outcomes relating to pharmacotherapy. What follows is a brief review of the pharmacotherapy of depression and anxiety in the transplant population; for a more comprehensive review of the literature, the reader is referred to a thorough review by Crone and Gabriel.[44]

In cases of depression the selective serotonin reuptake inhibitors (SSRIs), particularly sertraline, escitalopram, and citalopram, are considered first-line pharmacotherapy due to a combination of good efficacy and a relative paucity of pharmacokinetic drug-drug interactions. Lower doses of this class should be utilized in patients with hepatic impairment or significant uremia. SSRIs differ in their pharmacokinetic profiles, which must be taken into account by the prescribing clinician (see Table 1). In addition, since SSRIs have been linked to a slight increase in the risk of gastrointestinal bleeding, patients with other risk factors for spontaneous bleeding require close monitoring.[46] Mirtazapine is metabolized by multiple hepatic enzymes and does not significantly inhibit any hepatic enzyme, with the consequence that drug interactions are rare. The pharmacodynamic profile of mirtazapine may also prove beneficial for patients suffering from insomnia, anorexia, and nausea. Bupropion is vulnerable to drug-drug interactions through pharmacokinetic mechanisms. In addition, the potential for electrolyte abnormalities and polypharmacy that many transplant patients experience may lower the seizure threshold, making bupropion administration suboptimal. Venlafaxine, when compared to other antidepressants, represents a decreased risk of drug-interactions secondary to limited protein binding, but it may also cause increased blood pressure at higher doses.[47] Little is known about duloxetine use in transplant patients. The psychostimulants have been used for decades in the treatment of the neurovegatative symptoms of depression in the medically ill. The stimulants have

demonstrated a more rapid onset of action than typical antidepressants and do not appear to be associated with a significant risk of abuse when used in the medically ill.[48] The tricyclic antidepressants and monoamine oxidase inhibitors should be rarely considered for the treatment of depression or anxiety in transplant patients due to pharmacokinetic and pharmacodynamic issues involved in their use.

The benzodiazepines are very effective in the acute management of anxiety. Ideally, their use should be time limited to avoid the complications of tolerance, dependence, and cognitive impairment. The choice of which benzodiazepine to utilize depends on the particular medication's pharmacokinetic properties (hepatic metabolism, active metabolites, and elimination half-life). Lorazepam, oxazepam, and temazepam undergo only glucuronidation and do not require oxidative metabolism, often making them the benzodiazepines of choice.

Various forms of nonpharmacological interventions have been shown to be beneficial in the treatment of psychiatric conditions in patients following organ transplantation. These psychotherapeutic interventions have included educational-behavioral interventions to improve compliance,[49] group psychotherapy,[50] individual psychotherapy,[51] and mindfulness meditation.[52] Given that a majority of transplant patients rely heavily on family and friends in the months and years following organ transplantation, the patient's support system must also be a focus of clinical attention. Participation in psychological support programs by patients and their families has been shown to improve adherence, enhance social support, and increase the patient's sense of control. Finally, electroconvulsive therapy has been reported to produce beneficial results in transplant patients.[53,54]

CONCLUSION

Although transplant patients routinely suffer considerable psychosocial stress throughout the course of transplantation, the benefits of transplant lead most patients to accept the risks. The careful selection of candidates—based on a number of evidence-based psychosocial criteria—can improve outcomes. Transplant psychiatrists and psychologists can prepare patients for surgery by offering support and treatment. Following transplant, patients develop psychiatric disorders at greater rates than the general population, making it essential for clinicians to carefully monitor them for psychiatric symptoms during the post-transplant period. Fortunately, there appears to be effective means to treat these potentially dangerous, comorbid conditions. When treating these conditions pharmacologically, it is extremely important to keep in mind the risk of drug-drug interactions and associated adverse sequelae.

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