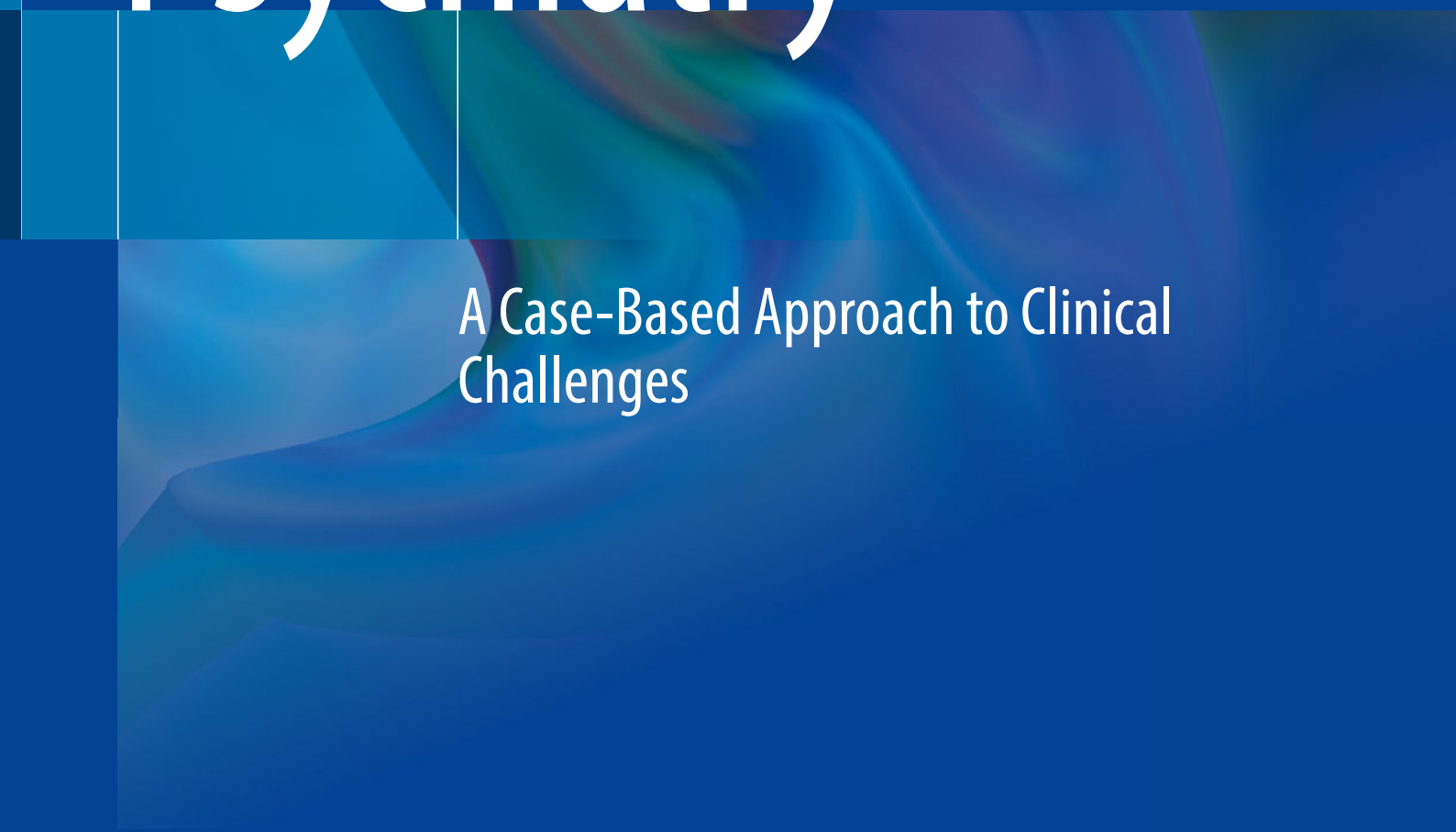
Paula C. Zimbrean · Yelizaveta Sher ·
Catherine Crone · Andrea F. DiMartini
Editors

Transplant Psychiatry

A Case-Based Approach to Clinical Challenges



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Foreword

This book marks the maturation of a subspecialty within consultation-liaison psychiatry and health psychology devoted to the psychiatric and psychological aspects of organ transplantation. From the beginning of organ transplantation, it generated new psychiatric, psychosocial, and ethical issues, but attention to them lagged. In the early years, surgical and immunosuppressive treatments were still nascent. Postoperative courses were often rocky. Psychosocial care was limited or unavailable and public understanding and comfort about transplantation was low. High doses of corticosteroids were the major component of immunosuppression, and many transplant recipients exhibited serious psychopathology. As surgical techniques and medical treatments improved, so did survival. Transplant physicians became more interested in the mental health needs of their patients, particularly after losing patients who had successful transplant outcomes, yet died from suicide, substance abuse, or non-adherence with immunosuppressive drugs. Many changes have occurred since the early years. Organ transplant surgery has become widely available and an increasing number of organ types have been transplanted successfully. Re-transplantation and multiple organ transplants within a single patient are common. Transplantation has been successful in categories of patients previously automatically excluded, for example, alcoholic hepatitis or patients above an age cut-off. New and improved technologies that serve as a bridge to transplant for patients on waiting lists have been developed, as have expanded options for immunosuppression and for treating the complications of immunosuppression. Throughout the history of transplantation, the limiting factor in providing it has been the number of organs available for transplant. Psychiatrists and psychologists focused on psychiatric and behavioral concerns in transplant candidates and recipients, but they also helped develop and expand living donor programs for renal and hepatic transplantation.

The earliest psychiatric and psychological publications about transplantation focused on ethical issues and the intrapsychic challenge of integrating a new organ from another person [1, 2]. The growth of a specialized cadre of psychiatrists and psychologists focused on transplant was catalyzed by the First Biennial Conference on Psychiatric, Psychosocial, and Ethical issues in Organ Transplantation which was convened by the University of Toronto in 1990. The University of Pittsburgh hosted the second meeting in 1992, and the third was at Virginia Commonwealth University in 1994. The emphasis on evaluation of potential candidates moved from a focus on screening out psychosocially inappropriate candidates to identifying modifiable psychopathology that would improve the patient's candidacy status and outcome of transplantation. Psychiatrists refined the application of pharmacotherapy in transplant patients [3]. Expertise in the field grew with the creation of a Transplant Psychiatry Special Interest Group (SIG) within the Academy of Consultation-Liaison Psychiatry over 20 years go, which now has 234 members. This SIG and its list-serve have provided a forum for psychiatrists and psychologists to consult with each other on more difficult cases and challenging policy issues, creating the fertile ground from which this book developed. In 2000, Paula Trzepacz and Andrea DiMartini published *The Transplant Patient: Biological, Psychiatric and Ethical Issues in Organ* Transplantation [4] which summarized the field in 12 chapters by 19 psychiatrists and psychologists. This book has 41 chapters by 68 authors. The vitality and excitement of the field is reflected in the breadth of clinical topics covered and that ten of the authors were

in training when they contributed to this volume. It is a case-based guide devoted to clinical understanding and clinical problem solving.

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Contents

Introduction

It is infinitely better to transplant a heart than to bury it to be devoured by worms.

Christiaan Barnard

When I started working with transplant patients, I was happy to have found my professional niche: transplant psychiatry. I imagined I was walking into a beautiful small garden that I can get to know well (become a clinical expert), "trim" it a little (do research, improve overall clinical care), and invite people over (teach others on this topic). Now, years later, it feels that instead of the garden, I walked onto a spaceship which took off my home planet (psychiatry) and since then is travelling through various constellations: surgery, medicine, infectious diseases, and many others, all while floating into a thick cloud of space dust (major ethical questions). This transplant psychiatry spaceship is sometimes so fast you cannot even tell is moving, other times the ride becomes bumpy, and other times it is spinning or going around in circles. Luckily, there are other psychiatrists and psychologists out there facing similar challenges. No trajectory is the same, but if we share our experiences, it gets easier to figure out our way.

This book is meant to be a guide for starting the journey in transplant psychiatry, a learning and teaching tool for psychiatrists and psychologists either in training or in early career who are starting their work in transplantation. It also aims to offer guidance to non-mental health transplant clinicians about approaching mental health issues in transplantation patients.

Organ transplantation is a unique medical environment which occurs within two borders: a patient in need of an organ and the organ (graft) available. Transplantation occurs when the two unite, therefore we believe it is important for any clinician working in transplantation to have a basic understanding of the trajectories taken by the two: the transplant candidate and the organ available.

The Patient's Journey to Transplantation and Beyond

Patients arrive for the transplant evaluation after coping with physical illness due to organ failure for various amounts of time. In most cases, patients have been ill for months of years, had multiple hospitalizations, medical complications, often surgeries. They had to cope with uncertainties of diagnosis, side effects of medications, the logistical burden of frequent appointments, and cost of health care. They had often suffered multiple personal losses, financial, professional, or relationships. Their role within their social circle changed, usually towards a more dependent role. In extreme cases, they have been disabled and dependent on others for their basic needs. The medical illness and the medical treatment can cause psychiatric symptoms directly (e.g., lethargy from pain medications or posttraumatic stress disorder after an episode of delirium). Some transplant candidates grew up with medical illness, with all the psychological consequences that entails, like body image concerns of lack of self-confidence.

The referral to transplantation itself carries significant meaning for the patient and his or her family: it may be seen as a verdict of incurable illness or a new source of hope [1]. The evaluation of transplant candidates is typically a complex and lengthy process which involves

multiple visits with medical providers, medical tests, and at times invasive interventions. During this time, the level of uncertainty is immense—uncertainty about making to the transplant waitlist, about other medical comorbidities that are unravelling. Medical events can lead to the patient becoming ineligible for transplantation, either temporarily or permanently.

The urgency of the need for transplantation may significantly impact the pre-transplant evaluation. In cases of acute organ failure, the patient interview, the main clinical tool in psychiatry, may not be available as patient may be lethargic, intubated, or too impaired to meaningfully engage in conversation. The need to make a rapid decision may not allow complete collateral information to be obtained. This book discusses some of the most common scenarios of acute organ failure: acute alcoholic hepatitis and acetaminophen following a suicide attempt. In some cases, transplant candidates with acute organ failure move towards transplantation very quickly, even in a matter of hours. This will not allow time for almost any meaningful psychiatric interventions that may reduce some of the psychiatric risk factors. For instance, for a patient with substance use disorder, the only intervention possible (if patient's physical status allows it) may be brief motivational interviewing and education about addiction or beginning detoxification if needed. These urgent evaluations typically occur in the inpatient setting of academic centers and may involve psychiatric trainees or other clinicians on call who are not familiar with transplantation.

Once on the waitlist for transplantation, patient must cope with progressive organ disease and with the uncertainties of having an organ offer occurs, from the patient's standpoint, is quasi unpredictable. In some cases, while waiting for transplantation, patients with organ failure may require help from devices that compensate for the malfunctioning organ, such as dialysis, CVVH[1], ECMO[2], or VAD[3]s. Financial burden and significant shifts in social role may become apparent at any point in the pre- or post-transplantation period.

After transplantation, patient is expected to need medications and medical follow-up for life. Surviving the wait time and the surgery often leads to a period of euphoria immediately after transplantation. However, the challenges of recovery may soon steer to readjustments of patient's expectations. In some cases, the experiences of peri-surgical care and recovery may become themselves traumatic events and lead to persistent anxiety and avoidance. Immunosuppressant medications which are essential to maintain the function of the graft and must be taken for life, increase the risk of infections and malignancies. Indubitably transplantation improves life expectancy and quality of life; however, transplant recipients rarely recover the level of functioning they had before the illness and major life adjustments need to be made. Patient may need to adjust to new physical limitations and make changes in their social or occupational roles. Additionally, the planning of post-transplant care may pose a significant burden with need for close medical follow-up and financial concerns.

For patients with pre-existing psychiatric disorders, this journey is even more difficult. In addition to having to cope with all the difficulties described above, there are concerns about risk of psychiatric decompensation during the transplant process (either due to stress or due to treatments, such as steroid-induced mania) and risk to self via self-injury or substance use. Physical impairments sometimes prevent patients from participating in their mental health follow-up and they may result in recurrence of psychiatric illness.

[1]Continuous veno-venous hemofiltration (CVVH): a short-term type of dialysis used in intensive care units.

[2]Extracorporeal membrane oxygenation (ECMO): a device that provides cardiac and respiratory support.

[3]Ventricular assisting device (VAD): implantable device that helps patients with heart failure to improve the systemic blood flow.

Organ Procurement, Allocation, and Organ Shortage

When after an evaluation, the multidisciplinary committee approves a patient to be placed on the waitlist, patient must wait for an organ to become available. Organs can be harvested from deceased or living donors.

Typically, more than one organ is harvested from a deceased individual. Up to eight solid organs (both kidneys and lungs, the liver, pancreas, intestines, and heart) can be donated from a deceased individual. As of January 2022, over 169 million people in the United States are registered to become donors upon death; however, only 3 out of 1000 people die in such a way that supports organ transplantation [2]. In the United States, registering as a donor is an opt-in process: anyone age 18 and over can opt in when applying for driving licenses at the Division of Motor Vehicles or can register online directly with the Donate Life organization, which maintains the national registration list.

Once brain death is pronounced in an individual who chose to be an organ donor after death, the process for potential organ acquisition begins. Medical representatives from the local organization of organ procurement evaluate the patient; to limit conflict of interest, these medical representatives cannot be the caring physician or physician who pronounced death. Subsequently, the deceased donor's information is entered into the national allocation registry to begin the process of matching, as timing is crucial. Organs are removed surgically and transported to the recipient hospital where transplantation will take place. The deceased family is informed later which organs were transplanted and, while the recipient's information is kept confidential, further contact can be coordinated through the organization [3].

In the United States, since 1984 Organ Procurement and Transplant Network (OPTN) with its administrative branch United Network for Organ Sharing (UNOS, established in 1986), have been overseeing the organ allocation and general guidelines about patient evaluation and clinical care [4]. Organ transplant candidates placed on the official waitlist are matched against the organs that become available according to the organ allocation algorithm established by UNOS. This algorithm is undergoing continuous revision to ensure that organs available are used to the maximum and to increase equality in access to transplantation. Justice and medical utility are the ethical principles governing the organ allocation. When an organ becomes available, UNOS runs the match program, a national computerized system that matches donor organ characteristics against potential recipients on the waitlist. This algorithm takes several factors into account such as recipient body size, blood type, Human Leukocyte Antigen (HLA) compatibility, distance from donor hospital, medical urgency, and time on the waitlist [5]. UNOS developed several tools to prioritize waitlist candidates. These tools incorporate patient and disease-specific factors weighted according to their importance, to produce a numerical score that allows ranking of the transplant candidates. For instance, the Model for End Stage Liver Disease (MELD) score used for liver transplant candidates is based on numerical values of serum bilirubin, sodium, creatinine, and International Normalized Ratio (INR). It is important to know that these calculators are used in conjunction with other clinical criteria to prioritize organ candidates, such as the presence of comorbidities or time since dialysis inception. The treating physicians can "appeal" a patient's place on the organ waiting list for certain clinical exceptions which are organ specific. This complexity of organ allocation translates into an extraordinary level of uncertainty for the patient waiting on a decision about listing and their place on the waiting list. Notably, financial status, ethnicity, religion, gender, or psychiatric comorbidities are not taken into consideration for organ allocation.

Most of the medical care related to transplantation, including mental health care, occurs under the dark cloud of organ shortage. To say that there are not enough organs available to meet the need is an understatement. According to UNOS, in 2022 every day 17 people die waiting for an organ [6]. As of January 29th, 2022, 106,707 patients are waiting for an organ transplant in the United States, while during 2021, 40K transplants were performed (an all-time record) [7]. This shortage of organ available creates the burden of selecting the transplant

candidates most likely to benefit from such a scarce resource. For potential recipients, the criteria to be listed or to remain "active" on the waiting list vary by organ. Transplant candidates must be diagnosed with an organ disease that is suitable for transplantation and must not have any medical contraindications to transplantation, such as active malignancy or infection. The absolute and relative medical contraindications for transplantation vary by organ and are constantly evolving. The transplant psychiatrist or psychologist is often asked to render an opinion about listing/de-listing or inactivating patients on the UNOS list when there is a concern that a psychiatric or behavioral issue may interfere with the ability of the patient to participate in the needed post-transplant care. This is an exceedingly difficult task as psychiatrist or psychologist may be seen as the "gatekeepers" or members of the "death panels" who are preventing patients from obtaining transplantation. Fortunately, the psychiatric consultant can in most cases identify, recommend and/or implement interventions that help patient move through the transplantation successfully.

When a living donor is available, the recipient still must meet the UNOS criteria for being on the transplant waitlist. If the donor is available, the surgery can be scheduled locally by the transplant center. Most recently, the organ exchanges have been made possible: several pairs of unmatched living donors and recipients are combined in order for every recipient to receive an organ. This process can occasionally involve several transplantation centers [3].

Why a casebook, in the era of big data, to illustrate such a complex clinical environment? Case-based study and problem-based learning remain key tools in medical education [8, 9]. Story telling never gets old and is essential in preparing medical trainees [10], holding special value in multidisciplinary settings [11]. Our aim is that this collection of case stories and discussions will guide those who are starting in this field and help those who teach medical trainees. Our book focuses on the evaluation and management of psychiatric or psychological issues in transplant patients, rather than on patient's selection or criteria for transplant listing. Each case story illustrates scenarios the authors encountered in their work. We carefully modified the social characteristics that were not essential to the clinical discussion in order to make the cases unidentifiable.

These case stories are tales of resilience, as patients and their families do face death at some point in their journey towards and beyond transplantation. They are also tales of solidarity and teamwork as transplant can only occur in a multidisciplinary setting. We are grateful to our patients and their families who let us accompany them through their journey and to our transplant colleagues, physicians, nurses, social workers, and all the other disciplines who make this endeavor possible.

We began planning on this book in 2019. Since then, the way we practice medicine has changed dramatically. The world of transplantation had to face tremendous obstacles: high mortality rate from Covid-19 in immunosuppressed patients, uncertainty of impact of Covid-19 infection upon surgery outcomes, reduced rate of elective surgeries such as living organ donation when hospitals are overwhelmed, rapid implementation of telemedicine, to name only a few. In this context, the resilience and teamwork which are foundation of all the case stories presented here are more relevant than ever. Christiaan Barnard's simple justification of the first successful heart transplantation continues to summarize the pragmatic but at the same time sublime reason for this work: to allow the human body to preserve life beyond its own demise.

As for our transplant psychiatry spaceship, the ride remains fascinating, the speed unpredictable, and there are still endless worlds out there to discover.

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Part I

Psychiatric Disease in Transplant Candidates and Recipients

Mood Disorders in Transplantation: Depressive Disorders

1

Thomas Soeprono, R. Michael Huijon, and Spencer Lunbeck

Introduction

Among transplant patients, depressive disorders are the most common psychiatric comorbidity [1]. Although rates of depression vary between different types of organ failure, they can be as high as 60% following organ transplantation [2], significantly higher than in the general population and even above those found in other medically ill populations [3, 4]. Risk factors associated with depression in the transplant setting are similar to risk factors for depression in the general population and include prior psychiatric history, length of hospitalization, level of physical dysfunction, and limited social supports [3]. Risk factors appear to be cumulative; the more risk factors, the higher the risk for onset of depression. The risk for depression also appears to be greatest during the first post-transplant year and may be attributable to the many stressors experienced during early recovery: physical deconditioning, adjusting to transplant directives and immunosuppressive medications, and transition from a state of illness to resuming prior roles and responsibilities [3]. Other risk factors especially relevant in the perioperative period in transplant are as follows: age, low socioeconomic status, length of hospital stay, graft versus host disease, low quality of life, impaired social functioning [5], side effects from immunosuppression medications [6], and length of wait for transplantation [7].

Depression is an independent risk factor for functional disability post-transplant [8]. Importantly across all organ types, depressive disorders and depressive symptomatology either pre- or post-transplant are associated with an increased relative risk of mortality of 65% and in kidney recipients appears to increase the risk of graft loss [9]. No studies have examined a mechanism by which depression may contribute to poor outcomes, although several studies suggest that adequate treatment of depression may improve medical surgical outcomes [10].

Lower or suboptimal adherence with medications and medical recommendations is often feared to be the behavioral link between depression and poorer post-transplant outcomes. Depression may contribute to nonadherence and is associated with difficulties in medical engagement [11]. While depression is an independent risk factor for increased morbidity and mortality after transplant, a relationship between depression and nonadherence to transplant immunosuppression medications has not been established [2]. In addition, it should be remembered that despite commonly attributing nonadherence to a depressive disorder, difficulties adhering to medical recommendations are more commonly rooted in behavioral patterns and environmental barriers within a patient's life. In the case of poor adherence, a thorough evaluation for depression and other potential psychiatric disorders is recommended to assess possible etiologic factors. Treatment of depression when present can remove this confounder and can improve adherence by reducing the neurovegetative symptoms.

Case History

Alejandra is a 48-year-old female with a history of type 2 diabetes and hypertension. She presents to the transplant clinic with end-stage renal disease after being on dialysis for 2 years. She hopes to obtain a kidney transplant so that she can return to work, be a more involved parent, and improve her relationship with her husband. They have two elementary-school aged children. Her loving and supportive family remind her to take her medications daily. Historically she has had difficulty with adherence to medications when she was still working because she had no scheduled breaks and would get "too busy."

But since starting dialysis she has had to quit work and misses having a daily schedule and "purpose." Now she falls

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asleep watching TV at night, sometimes without having taken her evening medications. She denies any substance use history other than having a "wild streak" in her twenties when she was in college. She denies any legal history or exposure to violence or abuse. She suspects that her older brother suffered from depression and that her mother has anxiety, but they were never formally diagnosed and never talked about it because "that's not done in my family."

She reports having first experienced depression in her teens in the setting of obesity and bullying at school but received no formal psychiatric treatment at that time. After the birth of her second son, she experienced in 2–3 month period of feeling down and unmotivated with significant worries that she was an inadequate mother. She received counseling from her priest for a 2-month period which she felt was helpful.

Prior to her transplant evaluation appointments, Alejandra filled out a Patient Health Questionnaire-9 (PHQ-9) which put her in the moderate range for risk of depression. Her most notable symptoms were daily challenges with sleep, energy, appetite, and concentration. This "positive" screen triggered the scheduling of an evaluation by a transplant psychiatrist. The scheduler noted that the patient was resistant to a psychiatric appointment stating that all the symptoms noted in the questionnaire were due not to depression but rather to her kidney disease and dialysis.

Since initiating hemodialysis she has been experiencing anhedonia, reporting that she can no longer participate in activities that she used to love. She recalls previously enjoying bike rides, now limited by her low energy, and traveling, now restricted by the stringent requirements of dialysis. She reports difficulty initiating sleep as a result of worrying about her health and that she might leave her children motherless. Even worse, she wakes up early in the morning "for no reason" and cannot get back to sleep despite staying in bed for many hours. She is not able to sit through an entire movie because she loses track of the plot and becomes disinterested. Although she continues to struggle with her weight, she reports having little to no appetite. She feels tired all the time but especially after dialysis. She denies any desire to be dead but sometimes wonders what the point of living is in her current situation. In her dialysis she notices when other patients suddenly "disappear" and never return. She wonders if or when this might be her story. She feels worthless and believes she has become a burden to her family.

She denies any need for a medication to help with her mood stating, "I don't want to change my personality." Although she is open to counseling given her success in the past with this type of treatment, she notes that she already has too many appointments as-is and adding another one each week would only make her life more difficult. Furthermore, she says that her depression is "situational" and that were it not for her kidney disease and hemodialysis, she would not be depressed. With the suggestion of psychotherapy to provide a time and space to process the stress, she refuses saying "I have all the support I need. Nothing anyone can tell me will make this go away." She adds, "if I could just get a transplant, this would all just disappear."

Clinical Questions

1. What are the best diagnostic methods or tools to assess depression in transplantation patients? Should transplant centers consider screening for depression?
2. In which scenarios should a patient with depression in the transplant setting be required to undergo psychiatric treatment prior to being listed for transplant?
3. What factors would deem a patient with a history of depression as an acceptable candidate for transplant listing?
4. What factors might mitigate risk for a patient with a history of depression?

Discussion

Evaluation of Depression in Transplant Candidates and Recipients

As in the example case, patients in transplant process can be identified for psychiatric evaluation through numerous pathways including medical history found by transplant coordinators, screening tools, and referrals from the multidisciplinary transplant team.

Some transplant programs use screening tools for all candidates as one method of identifying patients who may benefit from an evaluation by a mental health professional. Screening tools do not establish a diagnosis however can be helpful in targeting individuals who are at higher risk of depression. These tools have been helpful in creating a common language and format for psychiatric evaluation and the transplant setting—but they do not substitute for professional psychiatric evaluation and treatment [12]. A patient who screens positive is typically referred to a mental health clinician familiar with transplantation for a more in-depth evaluation with a clear understanding of the comorbidities and presentations of illness in transplant. Only over repeated visits do these measures help providers in guiding diagnosis [13] or evaluating response to treatment.

Screening tools for depression include Patient Health Questionnaire-9 (PHQ-9), Beck Depression Inventory (BDI), Beck Depression Inventory for Primary Care (BDI-PC), the Hospital Anxiety and Depression Scale (HADS), and the Depression in the Medically Ill-18 (DMI-18) all meant to assess patients in more medically intense scenarios. The BDI-PC is differentiated by its complexity and is considered burdensome to many practitioners despite

it consisting of only seven questions. HADS centralizes anhedonia in the conceptual framework of depression which can easily be misunderstood in the transplant population when clear physical limitations as a result of organ failure inhibit participation in pleasurable activities. The PHQ-9, although very specific for depression, relies heavily on neurovegetative symptoms which as previously discussed are common in end-organ failure and may confound the diagnosis. The DMI focuses more on affective symptomatology and is somewhat less prone to influenced by physical symptoms; therefore, it stands out for its sensitivity in medically ill patients [14].

Evaluation of depression in the transplant setting can be difficult as a result of significant impairments in end-organ disease. Severe lethargy, anorexia, insomnia, and impaired concentration are typical signs and symptoms in this setting [8]. These neurovegetative symptoms can both cloud the diagnosis of depression and masquerade as a depressive disorder.

A clinical history and exam by an experienced mental health professional with extensive experience in transplant remains the most effective diagnostic approach [15]. Transplant psychiatrists have seen common patterns in the manifestations of depression in end-stage organ failure that can be difficult to separate from the symptoms associated with organ failure. The following paragraph will differentiate these similarities and differences, focusing sequentially on the symptoms associated with major depressive disorder.

Anhedonia is one of the most frequently misunderstood symptoms among transplant patients. The dictionary definition of anhedonia is focused on an individual's capacity for pleasure. The PHQ-9 asks if patients have had "little interest or pleasure in doing things." The most common response to this question is generally "I can't do anything." This makes ascertaining a person's capacity for pleasure difficulty when there are no outlets for pleasure. The true physical limitations of organ failure force mental health practitioners to glean a patients overall pleasure from the day-to-day activities or ask the patient to imagine participating in an activity, both of which can be suspect from a diagnostic standpoint.

Hopelessness and feelings of depression are quite common as discussed in epidemiology above. The most frequent response in the transplant setting to inquiries of this nature is "who wouldn't be?" This brings up the very real and hard truth that transplant candidates face which is that risks with organ failure and organ availability are dire. Mental health practitioners in transplant must walk a fine line between validation of the dismal statistics, realistic expectation setting, and bolstering resilience and hope in extremely challenging circumstances.

The neurovegetative symptoms of depression (appetite, sleep, energy) are so common in organ failure that it is probably more significant when individuals deny any issues with them. At the same time, many of these symptoms, especially sleep difficulties, often pre-date their need for transplant. As a result, practitioners must have realistic expectations for treatment before and throughout transplant. Even when the neurovegetative symptoms are rooted in end-stage organ disease rather than depression, patients can benefit from pharmacologic, psychological, and behavioral treatment strategies.

Organ failure can often bring with it serious feelings of guilt and regret because of past behaviors such as alcohol use, smoking, and medical nonadherence that contributed to their disease. Similarly, to addressing feelings of hopelessness, the provider must strike a balance between validation, a supportive stance, and providing realistic and truthful feedback. In the post-transplant period, the survivor guilt is often described. Three common cognitive schemas are contributing to the post-transplant survivor guilt: the regret over self-inducing illness by substance misuse or unhealthy lifestyle, the preoccupation that "someone died for me to get a transplant" and the guilt about being the one to eventually receive a graft while many transplant candidates die on the waiting list.

Organ-Specific Presentations of Depression in Transplant Candidates and Recipients

The diagnosis of depressive disorders in transplant candidates is challenging because of the overlay of both neurovegetative and psychological symptoms common to both end-state organ disease and depression. The stressors of the transplant process, social disruption because of illness, and grief associated with morbidity and potential mortality in organ failure contribute to feelings of depressed mood, guilt, and anhedonia, with similar phenomenology to major depressive disorder. Although both depression-specific tools such as the DMI-18 and transplant-specific tools such as the SIPAT can augment a psychiatric evaluation and provide supplemental information in a structured format, ultimately a thorough diagnostic interview by a skilled transplant psychiatrist is the best evaluative practice.

Each organ system has a unique clinical presentation of depression based on the common symptoms and challenges that occur within organ failure of that system. Patients with kidney failure experience a protracted course of demoralization in the setting of years on dialysis or on the kidney transplant list. Although dialysis is a wonderful life-saving treatment, it also is a heavy burden that makes employment and life schedules difficult to maintain leading to nearly 50% of patients on dialysis to develop depression [16, 17]. Patients with end-stage renal disease may endure years of dialysis that cause significant dysfunction in their professional and social life leading to profound isolation. Without work or

school, lack of structure may progress to unhealthy circadian rhythms and depression. In the setting of dialysis and end-stage organ failure, depression is common, but often attributed to the chronic course of the general medical condition [18]. Long-term dialysis patients speak of the grief experienced after the sudden disappearance of a dialysis neighbor.

Individuals suffering from liver failure as a result of substance use often suffer from comorbid-limited coping strategies to confront the significant stresses in the transplant process. These less adaptive means of managing stress, previously hidden by misuse of alcohol, often lead to depressive symptomatology when these patients with liver disease come under the strains of transplant evaluation and declining function. Decreased concentration is a common characteristic of hepatic encephalopathy regardless of the etiology of the liver disease [19]. These cognitive impairments should not be misdiagnosed as depression but may limit an individual's capacity to participate in psychotherapy, develop new coping skills, and practice behavioral activation for treatment.

Both lung and heart transplant patients experience profound exhaustion and inactivity that result in deteriorating moods and isolation from social networks. Although patients will frequently endorse anhedonia when asked directly, it is more often the case that they can no longer participate in their activities from the past. Having the desire to do something without the capacity can cause stress and feelings of dislocation, disconnection, and resentment when these individuals attempt to relate to their peers. Deconditioning, anorexia, and lethargy present a continual battle for patients suffering from lung and heart failure. In patients with heart failure, depression has greater impact on quality of life measures than the patient's ejection fraction [5].

All organ failure patients express an experience of distancing from "regular" people in social settings. They experience quotidian, mundane troubles such as getting stuck in traffic or a mishandled restaurant order as so insignificant in comparison to their worries that they may experience unusual anger and guilt. The anger often stems from feeling slighted by their friends who do not realize what monumental stress they are under, while guilt is rooted in both knowing that they themselves were once focused on "minor" matters and feeling that they cannot be the empathic friend that they strive to be.

In the postoperative period, depression can manifest through guilt related to organ allocation. Recipients may feel that "someone had to die for me to live." Another presentation of this guilt takes on a utilitarian form "I'm not doing my organ justice because I'm not living up to my full potential." Both are clear cognitive distortions and may be rooted in post-transplant depression. A thorough evaluation and discussion of the factors underlying the patient's concern are core features of not just assessment but treatment of this guilt. A frank discussion and realigning of expectations under a patient's current circumstances that may have changed because of complications can allow a patient to more accurately engage in reality testing and feel grounded. Empathy and validation of a patient's concern while providing a clear behavioral pathway to recovery can adequately address the patients concerns and initiate change.

Other Depressive Disorders

There are other depressive disorders other than major depression that afflict transplant patients. Initially, many patients in this setting present with an adjustment disorder, most often in the case of a rapid or dramatic decline in function. As the diagnostic name implies, this can be a matter of adjusting to these significant changes. In these cases, symptoms will often resolve with no intervention other than appropriate support and education. Participation in the transplant evaluation process can also overwhelm patients and precipitate an adjustment disorder [2].

Patients can experience demoralization on the other end of the transplant process as well, often thought of as a depressive "diagnosis of attrition." These demoralized individuals present with clear depressive symptoms, which patients can mask and are much more affectively reactive in specific scenarios around loved ones. Demoralization is amenable to supportive psychotherapy, support, and validation, whereas psychotropic medication tends to be less effective [20, 21].

Some depressive disorders have much more chronic courses such as in dysthymia. A patient may have suffered with chronic depression for a long time but his/her first interaction with a psychiatrist may occur in the transplant evaluation process. This could be the initial identification of a long-term depressive disorder that has influenced the patient's thoughts, feelings, and behaviors for the past decades. In this setting, realistic expectations about treatment and over what time course should be set. At the same time, substantial improvement can be made with simple interventions and thus should not be delayed to the post-transplant period.

Substance-induced mood disorders have been known to persist for up to 1 year after the cessation of substances. More importantly, persistent and heavy substance use that contributes or precipitated organ failure also impairs the individual's capacity to develop alternative and more adaptive coping strategies. These skill deficits put the patient at a disadvantage as they attempt to psychologically manage the stressful process of transplant. This process in turn puts individuals at higher risk of relapse and is discussed in much more depth in other chapters.

Lastly, there are depressive disorders due to general medical conditions. This may often be further complicated by the numerous medications that transplant patients are on that can affect one's mood. As examples, steroids, immunosuppressants, and antiepileptic medications are all well known to

cause or contribute to psychiatric symptoms. On the other hand, there continue to be misunderstandings about common medications such as beta-blockers, which are falsely thought to precipitate depression [22].

In our case, the patient cites her kidney illness as the primary contributor to the decline in her mental health. On initial evaluation, it is difficult to discern the origin of her symptoms. Upon further questioning, it becomes clear that she is experiencing notable psychological symptoms well beyond the neurovegetative symptoms. In the case that psychological symptoms persist and contribute to impaired function, further evaluation and treatment must be pursued. Because she has a rather robust social support network and no outstanding red flags in terms of substance use, she could easily go undetected—and as a result untreated—if a screening tool was used in isolation. As previously stated, the screening tools although not diagnostic are often utilized by transplant programs in an effort to make the ambiguous concrete. This example is meant to demonstrate an inappropriate use of similar measures which can lead to oversimplification of the interplay of psychosocial factors in transplant and specifically its impact on depression. Ultimately, no assessment measure outperforms a thorough and complete psychiatric interview and physical exam in the evaluation of depression.

Depression in the transplant setting is unique as it can parallel the patient's progression throughout the transplant process [23]. In pre-transplant evaluation, patients are expected to complete a lengthy list of medical assessments and testing that can be uncomfortable and demanding. Once approved and on the transplant list, the waiting period can precipitate diminished participation in life activities for fear of missing "the call" [6, 24]. Patients experience insomnia from worry and medications such as steroids. Postoperatively, patients expect that the struggles that they confronted before transplant will quickly resolve after receiving their graft. They can become demoralized when they find that many of these same challenges persist despite improved physical health and normal organ function. Increased levels of stress have clear correlations with rates of depressive disorders [25]. Transplant centers have an imperative to provide mental health support given the known, expected stress that every transplant candidate will endure throughout the process. Appropriate evaluation and treatment of depressive disorders can lead to improvements in transplant outcomes.

Suicidality in Transplant

Evaluation of suicidality is especially challenging in the setting of organ failure. The lives that patients with organ failure lead are difficult and are experienced as not worth living at many times throughout the course. Suicide is a significant risk in the general population—let alone those with organ failure who are under disproportionate stress with limited options. As a result, transplant professionals have reasonable fears of suicide in their patient population. Aside from the obvious concern for each patient under their care, transplant centers also have an obligation to ensure appropriate stewardship of limited organ allocation [26]. Suicide is not only the loss of the individual's life but also a loss of a potential "other patient's" opportunity for a better and longer life. Suicide in a transplant patient can have long-lasting and ripple effects throughout the transplant community. This is not to say that individuals with suicidal ideation should not be transplanted. Rather, individual who suffer from this affliction need to be aware of protective resources, be willing to reach out for help when needed, and demonstrate an open and honest line of communication with their practitioners. Many patients have difficulty navigating between honesty with providers in expressing normal hesitancy and fear about the realities of their health condition. At the same time, patients must attempt to maintain the hope and drive necessary to get through transplant to enable them to return to a life that is worth living.

In the example case provided, the patient has wishes of being dead, commonly called passive suicidal ideation. She seems to be relating with her peers from dialysis who die, and she never hears from again. These escape fantasies are common in chronic illness where life satisfaction is low, and patients perceive themselves to a burden to those around them. This is not especially concerning from a safety standpoint but can cause transplant teams hesitation given the risk to the scare resource they manage. Appropriate evaluation and safety planning are warranted while providing reassurance and clear assessment to the selection committee.

Evaluation of suicidality can be further complicated by historical/remote suicide attempts. The appropriate length of time or criteria necessary to reassure a transplant team that suicide is not likely in the future is still not clearly established [12, 27]. Rather these instances are evaluated on a case-by-case basis taking into consideration numerous factors including but not limited to social support, coping strategies, recency, ongoing mental health treatment, and severity of attempt. A prior suicide attempt alone should not be considered an absolute contraindication to transplant in and of itself. As with all suicide assessments, the thoughts and actions must be placed into a context with risk factors while seeking to understand motivation and protective forces [27, 28]. See the chapter on suicide for more information.

Treatment of Depression in Transplant

Our example case depicts an individual who is suffering from major depressive disorder, moderate, single episode in the setting of the long-term sequela of kidney failure. Dialysis has precipitated isolation and perceived

purposelessness in life. Despite this, our patient ultimately has low risk of long-term psychiatric illness and expected rapid recovery with appropriate psychiatric treatment if she receives treatment for her current depression.

Our sample highlights a common and challenging situation in addressing depression in the transplant setting. Many patients understandably see their organ failure as the primary driver of their mental health decline; they then draw the plausible but erroneous conclusion that their mental health will suddenly improve post-transplant. This is sadly not usually the case. More importantly, patients cannot know how long their wait for an organ may take. Optimism, although helpful, can also contribute to distorted cognitions and impair a patient's ability to participate in realistic treatment planning. What starts as a mild depression can turn into a severe depression over the course of stressful years waiting on the transplant list and going to dialysis while friends and family live life like nothing has changed. Clinicians can improve patient participation in realistic treatment planning—including early treatment of depressive symptoms—by working with patients to set the appropriate cognitive framework: transplant is a lengthy process, not an event.

Both practitioners and patients accurately see depression as a potential contraindication to transplant candidacy if left untreated. As a result, patients may guard against full disclosure of their psychological state. Without objective measures of depression, mental health providers can be limited by the report of the patient if evaluated alone. Patients may be motivated to "fake it" throughout the evaluation for fear of repercussions on their candidacy. Of course, collateral information can help provide a more holistic picture, but family and friends may also be complicit for similar reasons. Implicit bias against psychiatric illness among medical providers and patients can limit access to mental health care within the medical system. For these reasons, any reassurance surrounding a patient's candidacy that can be given should be given. Furthermore, discussions surrounding the potential risks associated with untreated mental illness and an earnest expression of concern for the patient's overall health in every realm even outside of the transplant setting can build rapport and engagement that minimizes the restraints noted above.

Treatment of depression in the transplant setting should align with the standard practice for depression treatment in the general population. There are a few additional considerations for mental health providers in the transplant setting surrounding psychopharmacology. It should be anticipated that antidepressant medications will be needed by a patient with organ failure or on immunosuppressant medications. Understanding and carefully checking drug—drug interactions is imperative for the safety and health of transplant patients. Understanding the metabolic pathways of the most utilized immunosuppressants is invaluable to providing safe depression treatment.

Sertraline, citalopram, and escitalopram are the mainstays of antidepressant treatments in the transplant setting as a result of their minimal risk of drug—drug interactions and favorable side effect profile [29]. Citalopram should be avoided in patients with higher cardiovascular risk due to QT prolongation. In liver failure, dosing of all antidepressants should be adjusted accordingly. Bupropion is often considered an augmenting agent in transplant because of its stimulating effects, and as a safer alternative to psychostimulants, which are used sparingly. Venlafaxine and mirtazapine are excellent alternatives when the aforementioned agents prove to be in effective [29]. Fluoxetine, fluvoxamine, paroxetine, and duloxetine are the antidepressants most avoided in the transplant setting because of drug—drug interactions, tolerability, and risk of hepatotoxicity. For a more detailed discussion of psychopharmacology in transplant patients, please review the chapter by Gamboa et al. [30].

Antidepressant treatment is indicated at the very least for treatment of moderate to severe depression [29]. However, often in the transplant setting, patients can benefit from antidepressants even in very mild cases where the expected medication profile or side effects are leveraged to treat the consequences of organ failure or other comorbidities. An example would be the use of mirtazapine to address both depression and weight loss from poor appetite in the setting of ascites and liver failure. Another example might be the use of bupropion to treat depression and help with smoking cessation in preparation for lung transplant.

Psychotherapy is recommended for mild to severe depression in the case that a patient can continue to participate in treatment safely [31]. It is especially thought to be a very safe and less intensive method of treatment for mild depression, although there are clear limitations. Denial of severity of illness, lack of emotional vocabulary, and high symptom burden are all known to be associated with worse depression scores [32]; psychotherapy can provide a forum to address each of these issues. The temporal strain associated with frequent psychotherapy treatment can provide significant burden to patients whose lives are already dictated by medical appointments. To address the risk factor of diminished physical activity, behavioral activation and physical exercise are recommended but limited by physical dysfunction in the setting of organ failure [32]. As a result, the treatment of depression throughout the transplant process is often challenging and requires a multipronged and iterative approach. Unfortunately, access is poor to repeated psychiatric care, beyond consultation and evaluation for transplant candidacy alone [33]. Regardless, psychotherapy remains a mainstay of depression treatment and with a solid therapeutic alliance yields excellent results.

When patients are able and willing, psychotherapy can provide significant benefit in the case of demoralization and adjustment disorders. The supportive process, time, and

psychoeducation are active ingredients in the setting of a trusted therapeutic relationship. This can also provide a much-needed respite for caregivers who are often as exhausted as the patients throughout this long process. This is in contrast to antidepressants, which are not considered effective with a low level of evidence for use in these more mild and brief pathologies [34].

Especially in the physically ill, behavioral and social treatments of depression can be especially effective. Many organ failure patients are homebound without strenuous effort and assistance from caregivers. Regular exercise—or even just getting out of the house—can provide significant psychological benefits [35]. Because of the impairments in metabolism with liver disease and filtration with kidney disease, diet can have enormous impacts on a patient's function and mood. Active engagement with a transplant nutritionist in combination with behavioral changes can provide benefits not only to the patient's mood but also to the long-term health and success of the patient even post-transplant. Lastly, socialization is imperative for these patients who spend most of their time isolated due to their illness. Engaging family and friends in a regular visit schedule can lift a patient's spirits, give a patient's day some structure, and provide an outlet for reflection and stress.

As in the case provided, engagement in mental health treatment is often the biggest hurdle. Each patient has his/her own beliefs and bias surrounding mental illness, which impact the acceptable options for treatment. Cognitive deficits and physical disability may decrease patient's ability to participate in routine psychiatric interventions such as psychotherapy. Patients should be encouraged to utilize any existing social supports, both to optimize transplant outcomes and for effective treatment of depression. Often patients with end-stage organ disease experience challenges to physical strength, cognitive space, and daily routine which hamper their ability to follow through on depression treatment plans. Incorporating family and friends into behavioral activation practices can be one tool to overcome these barriers. At the same time, in the transplant setting, patients are very motivated to follow through with medical recommendations; this can be leveraged to the benefit of depression treatment. Just like in other mental health treatment settings, psychoeducation can go a long way in both treating the patient and increasing the motivation for treatment. A combination of biological, psychological, behavioral, and social interventions makes for the most effective treatment approach.

Beyond the improvements to life satisfaction and quality of life associated with depression treatment, substantial concrete health factors can be improved by treating depression preoperatively [15]. Improved rates of adherence, shortened lengths of hospital stays, improved post-operative recovery, and most importantly mortality are all thought to be inversely correlated with severity of depression [9, 36–38]. Beyond survival, depression is an independent risk factor for functional disability after transplant, which clearly has implications for quality of life [8].

To minimize risk to transplant outcomes associated with depression providers should focus on identifying existing coping mechanisms, promoting adaptive and effective strategies, and assist patients with cultivating additional techniques.

Although the context in which depression occurs is extremely important, it is equally important to delineate the functional deficits that occur as result of these symptoms, regardless of specific etiology and precipitants. Often patients use context to explain their hesitation to seek psychiatric treatment.

Depression regardless of etiology warrants aggressive treatment in the transplant setting, especially when it is leading to functional decline and nonadherent behaviors that put their candidacy or graft at risk. Rolling with the patient's preferences for any given treatment approach in depression is helpful, in this setting as in any other. Given the high-stakes nature of the transplant setting, however, it is reasonable to collaboratively create explicit plans to review treatment progress with patients and agreed-upon timelines to consider alternative treatments. Doing so creates a pathway to more aggressive and effective depression treatment if needed.

Patients who exhibit comorbidities that are known to contribute to and perpetuate depressive disorders should be required to undergo more aggressive depression treatment and may be denied transplant candidacy until these factors are better addressed. Treatment refractory depression, concomitant poor self-care with limited social support, or patterns of nonadherence are examples of such issues. Repeated or severe past suicide attempts, personality disorders, or recent major losses (such as the death of a child) may warrant a period of mental health stability to assure the selection committee that the best outcomes in transplant are possible. Unfortunately, there are no distinct time periods at which anyone can fully predict ongoing resolution. But some specified period may allow the patient and transplant team additional time to form a functional working relationship. The relationship between substance use and depressive disorders, a frequent comorbidity, may need to be directly addressed and is covered more thoroughly in other chapters. The dearth of specific recommendations is the result of limited data on these issues in the transplant setting and how they directly impact transplant. As a result, there are no hard-and-fast rules or time scales to guide selection committees. Instead, the consultation of a transplant psychiatrist who has the experience and knowledge of mental health issues in the transplant setting has no substitute.

Under the time pressure and persistent symptoms of end-stage organ disease, it is common for patients to achieve only

partial resolution of their depressive disorders or to continue to experience persistent comorbidities. This also could occur in individuals with chronic and severe depressive disorders. In these difficult cases, a candidate with some combination of self-awareness, insight, understanding a clear pattern in their depressive episodes, willingness to seek help, a strong support system, trust in the medical system, and a relationship with a mental health professional can be an acceptable candidate for transplant.

Take Home Points

1. Stress related to the transplant process can precipitate depressive symptoms that warrant evaluation and treatment.
2. Screening for depression in transplant patients should be considered but final diagnosis should be based on a thorough psychiatric evaluation.
3. Treatment of depressive disorders using psychopharmacologic, psychotherapeutic, and behavioral strategies is recommended at any point throughout the transplant process.
4. Treatment of depressive disorders improves quality of life in transplant candidates and recipients.

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Mood Disorders in Transplantation: Bipolar Disorder Spectrum

2

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Introduction

Bipolar disorder (BD) or bipolar disorders are a group of lifelong illnesses characterized by recurrent episodes of mania or hypomania as well as depression. Bipolar disorders are the third cause of disability in young people (aged 15–24) after depressive disorders and anxiety disorders [1]. Approximately, 30% of patients with bipolar disorder show severe impairment in work role function [2]. Lifetime (and 12-month) prevalence estimates are 1.0% (0.6%) for bipolar I, 1.1% (0.8%) for bipolar II, and 2.4% (1.4%) for subthreshold bipolar disorder [3, 4] Bipolar I disorder affects men and women equally, whereas bipolar II disorder is most common in women [5]. The lifetime risk for suicide among patients with BDs is 20–30 times that of the general population [6]. Evaluating and treating patients with BD pre- and post-organ transplantation poses significant challenges.

Bipolar disorders are associated with significant medical comorbidities and worse medical outcomes. Sylvia LG et al. reported at least one other medical comorbidity among 96.3% of patients with BDs, and higher cardiometabolic comorbidity [7]. Some studies have indicated that despite a higher disease burden, patients with BDs are less likely to be considered for transplant [8]. Patients with BDs can require transplantation due to medical comorbidities (e.g., coronary artery disease, NASH), behaviors (e.g., acetaminophen-induced liver failure after suicide attempt, alcoholic cirrhosis), or a consequence of their BD treatment (e.g., lithium-induced renal impairment) [9]. There is no consensus about if or under what circumstances BD should be a contraindication to listing for transplantation. Some centers have developed their own internal policies about psychiatric illness being an absolute or relative indication for proceeding with transplantation, although few would consider a stable major psychiatric illness to be an absolute contraindication [8]. Transplant clinicians have expressed concerns about bipolar disorder interfering with patients' ability to adhere to medical therapy, ability to cooperate with treatment teams and adhere to complex medical therapy, and adequacy of social support to achieve these goals [10].

There is no defined symptom-free interval for patients before considering patients for transplant listing [11]. Recent studies have suggested that selected patients with BDs can have post-transplantation outcomes comparable with other transplant recipients [12, 13]; however, there is little guidance on what factors contribute to a successful post-transplant course.

In this chapter, we will discuss a case, with review of the evidence regarding different factors that influence transplantation outcomes in a patient with BD.

Case History

Ms. X is a 71-year-old married woman, with a history of BD type 2 who was first referred to the transplant clinic for evaluation of renal transplant due to lithium-induced kidney disease.

Upon interview, patient revealed that she had been diagnosed with BD at the age of 28, when she was psychiatrically hospitalized, and began treatment with lithium. She had been in outpatient treatment since then, mostly on lithium which she had taken for close to 30 years. She knew her psychiatrist was checking her lithium levels regularly, but she did not remember the exact values. She did not recall any episode of acute lithium toxicity. While she was not able to recall any clear manic episodes, she was able to detail several episodes of hypomania and major depression of moderate to severe intensity. She described that her most recent such episode had been 10 years prior to the evaluation for transplantation. Her medications had been lithium CR 450 mg nightly, lamotrigine 150 mg daily, and dulox-

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etine 60 mg daily with good results and no changes for several years. She had never taken valproate or antipsychotics. She took antidepressants as adjuvant therapy to lithium, including tricyclic antidepressants, which were ineffective. Bupropion caused intolerable adverse effects. She mentioned that when she attempted to get off lithium, she became very depressed. She had no history of psychosis, suicidality, substance misuse, and no other psychiatric comorbidities.

Collateral history from her community psychiatrist (who had been treating her for the past year) and husband revealed that 3 years prior, when her creatinine value started to rise, her prior psychiatrist stopped her lithium and prescribed lamotrigine and duloxetine. He also referred her to a nephrologist, who subsequently referred her to a transplant center for early listing, anticipating her kidney disease would progress and she would eventually need renal replacement therapy. During the initial transplant visit, she was told that after transplantation she would have to avoid lithium to preserve the graft. However, within a month after stopping lithium, she became severely depressed, anhedonic, barely able to get out of bed or care for herself. She gained weight (her BMI reached 38 kg/m^2), started skipping her medications as well as her psychiatric and medical appointments. This continued for the next 6 months. Her transplant evaluation was closed due to lack of follow-up and being overweight. After several months of significant depression, at the urging of her family, patient agreed to return to psychiatric care and started seeing a new psychiatrist. She was adamant about wanting to resume lithium despite her ongoing kidney disease. She felt lithium was the medication that worked the best for her. Her psychiatrist appreciated that she had capacity to make that decision as she fully understood the risks and benefits of resuming lithium.

Her kidney function continued to decline steadily over the years to the point that she required renal replacement therapy. She experienced moderate anxiety around the time she started hemodialysis and was prescribed hydroxyzine with good effect.

Her medical history included, in addition to chronic kidney disease (CKD) stage 5, essential hypertension, Graves' disease, nephrogenic diabetes insipidus, and obstructive sleep apnea. Patient also had undergone several surgeries (bilateral total hip arthroplasty, hysterectomy, bladder suspension surgery, carpal tunnel release, and bunionectomy) without significant adverse events or psychiatric decompensation. Patient's family psychiatric history was significant for a sister with BD type 1.

At the time of the second evaluation for transplantation, the patient, who has a college degree, had been retired real estate agent for 4 years. She was married and described a strong support network that included her husband and two adult daughters and their families. Being able to spend more time with her grandchildren was her main motivation to pursue kidney transplantation.

The transplant psychiatry team met with the patient twice prior to listing for transplantation for an extended evaluation and treatment planning. Her mental status examination was unremarkable. She had mild bilateral hand tremor. Her Montreal Cognitive Assessment 7.1 score was 28/30. Diagnosis was Bipolar I disorder, most recent episode depressed, in full remission.

A trough lithium level was 0.8 mg/dL. Patient and her husband were very interested in learning about the psychiatric aspects of organ transplantation and discuss possible treatment options. In collaboration with her treating psychiatrist, the following changes were suggested in her medication regimen: (a) change in the lithium dosage to three times a week after dialysis and (b) cross-tapering of duloxetine to another antidepressant (as duloxetine is not indicated when Glomerular Filtration Rate (GFR) is less than 30%). However, she remained adamant that she wanted to continue taking lithium daily, while on dialysis and after transplantation, due to fear of recurrence of depression, while being very aware of the medical risks. She agreed to discuss with her treating psychiatrist changing the duloxetine to another agent. She agreed to accept adjuvant agents if needed in case she developed immunosuppressant-induced psychiatric symptoms. She and her husband felt capable of identifying the onset of a psychiatric decompensation and agreed to seek help early in such an event. Patient was added to the kidney transplant waitlist and continued to meet with the transplant psychiatrists every 6 months during the first 2 years she was on the kidney waiting list. She remained stable, was continued on lithium and lamotrigine, while duloxetine was discontinued without recurrence of symptoms. Thereafter to monitor her mental health while she was waitlisted for transplant the transplant psychiatry team scheduled follow-up reevaluations when she returned for her annual waitlist protocol medical reevaluation. In addition, plans were made for the patient to be followed by the inpatient psychiatry consultation team after her transplant surgery.

Clinical Questions

1. For patients with BD, what are the associated risk factors that can influence the treatment outcomes or treatment choices before and after organ transplantation?
2. What is the potential impact of transplantation upon the course or stability of the psychiatric disorder?
3. What are important pharmacologic considerations in treating BD transplant recipients?

Discussion

Risk Factors Associated with Transplant Candidates with BD

Patients with BD have an increased risk of medical and psychiatric comorbidities which can influence post-trans-

plant outcomes and there is also concern about the potential for increased risk of poor adherence to medical care. Additionally, some specific agents used in treatment of BD have a risk of direct organ toxicity that must be taken into consideration.

Medical Comorbidities in Patients with BDs

Patients with severe mental illnesses (SMI) (e.g., schizophrenia, BD, recurrent BD) have disproportionate medical burden compared to patients without SMI. Persons with BD may be less likely than the general population to receive primary, preventive medical care [14]. On average, patients with SMI live for 25 years less compared to the general population [15]. These data were first reported in the 1990s and unfortunately, the gap seems to be worsening [16, 17]. Various population-based studies have identified medical comorbidities to be a rule rather than exception in patients with BD [16]. Bipolar patients have higher rates of cardiovascular risk factors (e.g., smoking [18], diabetes mellitus [19], and obesity [20]) and tend to develop these diseases 4–7 years earlier than their non-bipolar counterparts [21]. Not only is the rate of medical comorbidities in patients with BD is high, but the prognosis is worse compared to the general population. A cohort study of over 17,000 patients with BDs followed for 14 years showed almost twice the rate of mortality when compared to a cohort controlled for age, gender, calendar year, area-level deprivation, ethnicity, and records of follow-up. The death risk was over three times in patients between the age 16 and 50. Cardiovascular risks were elevated in patients with BD (HR = 1.37), and smoking, hypercholesterolemia, hypertension, BMI, and diabetes mellitus did not fully explain the increased rates [22]. It is, therefore, important to ensure that patients being considered for transplant are in regular follow-up with their appointments and are adherent to the recommendations of treatment teams.

Psychiatric Comorbidities Including Substance Use Disorders

Patients with BD have high levels of psychiatric comorbidities that may impact the health outcomes in a negative fashion. Smoking rates are reported to be high (almost 80%), and nearly double that of general population [18]. Patients are more likely to smoke in their teens [23], and smoke more heavily [18]. Substances use disorders are higher compared to general population, and they are associated with worse outcomes in graft survival [24–26]. Suicide risk is reported to be 22 times that of general population [27]. Coexistent anxiety disorder, substance use, rapid cycling type, childhood abuse, age of onset, or the presence of over 20 episodes were correlated with a poorer prognosis of medical illness in patients with BDs [28]. A thorough psychiatric history including substance use is essential in transplant evaluation of patients with BD.

Risk of Difficulty with Adherence with Medical Treatment Associated or Not with Psychiatric Decompensation

Patients with severe mental illnesses including BD are feared to have low adherence to medications. Most large studies reveal BD patients, in general, not transplant specifically, have nonadherence levels of 20–50% [29–32]. It is important to note that these studies explored mostly the adherence with psychotropic medications and that a significant proportion of nonadherence was related to the denial of the psychiatric diagnosis [29]. It is not clear if adherence with psychiatric medications parallels adherence with treatment for medical condition or with health-related behaviors. Depressive symptoms in BD (which are present more frequently than manic/hypomanic symptoms) are considered to account for negative health behaviors including smoking, poor diet, overeating, and sedentary lifestyle [33]. Identification and resolution of negative health behaviors and psychiatric decompensation are likely to aid in success of transplantation.

The Pharmacological Treatment of Psychiatric Disorders May Impact the Graft Directly Through Direct Toxicity or Indirectly through Side Effects or Drug-to-Drug Interactions

Among the direct organ toxicity from psychiatric agents, a common scenario that comes to the transplant psychiatrist's attention is lithium-induced end-stage renal disease. Other direct toxic effects of psychiatric medications are less likely to lead to an indication for transplantation, so they will not be discussed here. Transplant psychiatrists are often asked to recommend optimal psychopharmacology treatment for chronic psychiatric disease in transplant candidates and recipients. It is therefore important to understand the risks of psychopharmacological treatment in this population.

In general, when a medication leads to organ failure and need for transplantation, the first tendency from the part of patients and medical providers is to permanently discontinue the responsible agent. There are cases, however, when a detailed risk—benefit analysis may be warranted, as alternative treatments may not be efficacious. The following domains of knowledge are relevant in this risk analysis: (a) the efficacy of the treatment in question; (b) the risk of discontinuation of the medication; (c) metabolic, psychodynamic, or psychokinetic consideration for end-stage organ disease of post-transplantation; and (d) the risk of organ toxicity (on the native organ if still functional and on the graft).

Our patient's story illustrates how these questions are approached when making the decision to continue or not lithium for a patient with CKD who is a transplant candidate. Lithium is an effective agent for the management of acute mania, bipolar depression, and maintenance mood stabilization [34–36], may have anti-suicide properties [37, 38], and is effective against impulsive violence [39, 40]. Efficacy of

lithium in various stages of BD has been well established across many studies [41, 42]. In a metanalysis of 31 studies including 85,229 patients, lithium was found to reduce the rate of suicide attempts and completions by almost 5-times (reduction in incidence from 2.63% per year to 0.436% per year) [43], although newer studies find less convincing evidence [44].

Furthermore, discontinuation of lithium therapy in patients with BD was followed by an increase of suicidal acts by 7–20 times [45, 46] and a ninefold increase in fatalities [46]. In our population of transplant candidates with lithium-induced kidney disease, we found a small segment of this group who does not respond to any other mood stabilizers and can achieve remission of psychiatric symptoms on lithium only.

Chemically, lithium is a bivalent ion that is completely absorbed after oral administration (bioavailability 80–100%). It peaks within 1–1.5 h after immediate release preparations, and within 2–6 h after a delayed release preparation. It circulates freely (not plasma protein bound) and does not undergo metabolism. Its plasma half-life is 18–36 h, and achieves steady state in 5 days [47]. Up to 98% of lithium gets filtered in the glomeruli as an unchanged drug. In the proximal convoluted tubules, almost 80% gets reabsorbed allowing 20% of lithium to get cleared. A small portion is reabsorbed distally in the collecting ducts.

Lithium has been used in patients on dialysis when benefits were considered significant. Lithium is completely dialyzed. Typical doses are 300–600 mg single dose on the days of hemodialysis only, administered after completion of hemodialysis session. Levels should not be checked until 2–3 h after dialysis to allow for equilibration [48].

On the other hand, lithium treatment carries the well-known risk of renal disease. Chronic consumption of lithium has been linked with four types of renal injuries, namely nephrogenic diabetes insipidus (NDI), nephrotic syndrome, renal tubular acidosis, and chronic interstitial nephritis (CIN).

Nephrogenic diabetes insipidus (NDI) may occur in up to 40% of patients on lithium (the most common renal change in people taking lithium long term). Its underlying mechanism is lithium accumulation in the collecting ducts, leading to resistance to Antidiuretic hormone (ADH), which manifests with polyuria and polydipsia. The defect tends to be irreversible [49, 50].

Chronic interstitial nephritis (CIN) is a more severe adverse effect seen with chronic lithium consumption. Renal biopsies reveal varying degrees of interstitial fibrosis along with tubular cysts [51]. Clinically, it manifests as asymptomatic reduction in glomerular filtration rate (GFR), to mild proteinuria, to progressive worsening of renal function [9, 52]. Smith et al. reported nearly a twofold increase in likelihood of stage III Chronic Kidney Disease (HR 1·93, 95% CI 1·76–2·12; $p < 0.0001$) with lithium use, with adverse effects occurring early in treatment [53]. However, progression to renal failure is rare, with most meta-analyses and population-based studies placing the absolute risk of renal failure and renal replacement therapies to be 0.5–2% [9, 54, 55].

In population-based studies, higher prevalence of chronic kidney disease (CKD), end-stage renal disease (ESRD), and renal replacement therapy (RRT) has been shown among patients who were treated with lithium compared to general population [54, 56, 57]. The most consistent risk factor for CKD in these studies is duration of lithium treatment [58]. High rates of ESRD on lithium could also be due to use of higher doses and infrequent monitoring of renal function, as was common practice before 1980s [59]. More recent cohort studies have found that with current guidelines about maintaining therapeutic lithium levels, the incidence of progression to ESRD (GFR less than 5) from lithium is low [55, 59, 60]. Severe loss of renal function and end-stage renal disease (ESRD) are uncommon with lithium treatment, with a prevalence of approximately 1.5%, but sevenfold higher than the general population [61]. Werneke et al. quantified the risk—benefit analysis for continuing lithium in CKD and found that stopping lithium would only be advantageous only if the likelihood of progression to ESRD exceeded 41.3% or if anticonvulsants always outperformed lithium regarding relapse prevention [62].

The guidelines for continued treatment with lithium are not as clear after development of CKD. Most authorities consider a risk—benefit approach in continuation of lithium [62]. Furthermore, other maintenance medications also have comparable adverse effects [60]. However, there have not been many controlled studies to study the progression of renal disease on lithium due to ethical reasons. In one elaborate study done by Tondo et al. in 2017 reported a median decline in GFR by 30% more than by ageing alone amount per year, with age of patient and duration of treatment being major risk factors [63].

In our experience and in the literature review, we did not find any information to suggest that a transplanted graft may be more sensitive to medication-induced organ failure than a native organ.

The Impact of Transplantation upon the Course or Stability of the Psychiatric Disorder

Psychological Stress Associated with Transplantation

The end-stage organ dysfunction is associated with fear of death, pain, loss of autonomy, loss of socialization, loss of employment, and social contacts. Furthermore, waiting for a transplant can be extremely distressing due to uncertainty, leading to increased scores of anxiety and depression in

waitlisted patients [64]. Post transplantation, other uncertainties emerge such as change of prognosis or treatment course (e.g., graft failure), development of severe adverse effects (e.g., Graft versus Host Disease GVHD), rehospitalization, or changes in treatment setting such as discharge from transplant center to a community provider [65]. It could be expected the psychological stress of transplantation may precipitate BD recurrence.

There is only limited data regarding the course of BD immediately after transplant. A major study involving 3000 renal transplants among which 15 patients with BD and 7 with schizophrenia showed no difference in relation to patient survival, graft survival, and graft function. In addition, length of hospital admission for transplantation and frequency of acute rejection episodes were comparable among the three groups [66].

Pang et al. studied the perioperative outcomes, especially readmissions related to psychiatric reasons in 19 liver transplant recipients with BDs compared to 19 matched controls, and found that overall readmissions were low, and there was no difference of post-op readmission rate between patient with or without diagnosis of BD prior to transplant [67]. In a case series of eight patients with BD receiving liver transplant, five of them needed psychiatric admission after transplant. The main associations were history of hepatic encephalopathy, the use of medications with primary hepatic metabolism, and pre-transplant psychiatric dose reduction of >50% paired with slow post-transplant up-titration. Four out of five psychiatric admissions were reported for mania and aggression. Most cases did not report the timing of development of mania, except one (post-operative day 12). One case with suspected catatonia was managed with intravenous haloperidol and increasing doses of quetiapine, but without description of catatonic symptoms or explanation for use of antipsychotics in catatonic patients [68]. A recent retrospective study of 3680 US veterans who underwent kidney transplantation found that a prior history of mania was not associated with negative post-transplantation outcomes (such as mortality, graft loss, and rejection) compared to patients without a history of psychiatric disease [69].

Psychiatric Side Effects of Immunosuppressant Medications can Overlap with Symptoms of BD

Patients with a history of BD are at risk of developing steroid-induced mood disturbances [70]. Calcineurin inhibitors have been linked to treatment refractory psychosis in transplant recipients [71]. For a more detailed discussion of steroid and immunosuppressant-induced psychiatric side effects, please see Chaps. 34 and 35. Steroids sometimes cause secondary mania or worsening of symptoms in patients with existing BD [72, 70]. Mostly, symptoms subside with time, but sometimes require change of immunosuppressive agents [73, 74], or symptomatic management with antipsychotic medications or mood stabilizers [71]. For treatment planning purposes, we find that having a detailed psychopharmacology history for our transplant candidates, which includes medications, doses used, duration of trials, response, and side effects can help significantly post-transplant management of steroid-induced psychiatric side effects in transplant recipients with a history of BD. Close postoperative follow-up by mental health providers coordinated with the transplant team can provide monitoring and early identification of mental health symptoms and facilitate treatment adjustment as needed to avoid psychiatric decompensation.

What Are the Important Pharmacologic Considerations in Treating BD Transplant Recipients?

The use of regular psychotropic medications in transplant recipients must take into consideration metabolic changes, pharmacokinetic and pharmacodynamic interactions with immunosuppressant agents, and adverse effect profile. Usually, the same psychotropics that were effective before transplant are continued after transplant. This becomes challenging when the agents carry a significant risk of toxicity for the same organ that was just transplanted (e.g., use of valproate after liver transplant, use of lithium after renal transplant).

For our patient, we had to decide if she should continue lithium after transplantation. In general surgery, lithium is discontinued 48–72 h before surgery and restarted when patient is fully hydrated [75, 76] to prevent lithium toxicity associated with perioperative volume changes. Evidence for use of lithium after renal transplantation is limited: two case reports describe successful treatment with Lithium after kidney transplantation [77, 78], while one other author reports a patient who developed lithium toxicity on day 10 after kidney transplantation, leading to lithium discontinuation [79]. Dube G, et al. conducted a single-center retrospective study of 15 adults with BDs who received a renal transplant. In all patients, BD was well controlled on a stable medical regimen, with no symptoms at the time of initial evaluation or transplant. All 15 patients received transplant, out of whom 14 patients had ESRD from lithium use. All patients underwent standard treatment with thymoglobulin, mycophenolate, tacrolimus, and steroids. During the 4 years follow-up, the patient survival was 80%, 2 patients had post-transplant psychiatric hospitalizations and one patient returned to taking lithium to control symptoms of BD [80]. Literature search revealed three other cases in whom lithium was started after renal transplant, with successes in two cases and acute lithium toxicity leading to discontinuation in the third, highlighting a need for case-by-case approach [77–79].

The benefits of mood stabilization, suicide prevention, and stabilization of BD need to be weighed against nephrotoxicity. Alternatives to lithium may not be effective or they may cause cardiometabolic adverse effects that impact graft survival. For our patient, lithium had proven to be effective, she had at least two other pharmacological trials and its discontinuation led to severe symptoms, so our assessment was that the benefits of continuing lithium outweighed the risks.

- A detailed discussion of all pharmacological agents used in the treatment of BD is beyond the scope of this chapter. Atypical antipsychotics, often prescribed as main treatment for BDs, have been widely used in organ transplant recipients, often for management of delirium. Long-term treatment with antipsychotics must take into consideration the risks of side effects that can overlap with side effects of immunosuppressants such as metabolic side effects, QTc prolongation, seizures, and neutropenia. Carbamazepine, another mood stabilizer, has multiple interactions with immunosuppressants. For further in-depth knowledge on use of psychotropic medications after transplantation, we recommend Fireman, M et al. Chap. 16 Organ Transplantation in Clinical Manual of Psychopharmacology in Medically Ill, Edits Levenson J and Ferrando S [81]. and Chap. 42 Gamboa MT et al., Psychopharmacology in Transplant patients, in Psychosocial Care of End-stage organ disease and Transplant Patients, Edits Sher, Y. and Maldonado, J [82].

In addition to pharmacology, psychotherapy can play a significant role in maintaining stability or preventing decompensation in patients with BD. Although there are no reports of psychotherapies for BD who are organ transplantation patients, in general, BD population adjunctive psychotherapy especially when done with family participation significantly reduces the relapse of the illness [83]. Due to multiple health care needs, however, transplant patients often find participation in office-based psychotherapy challenging. New delivery mechanisms such as smartphones [84] or telepsychiatry which expanded during the 2020–21 COVID-19 pandemic, may help overcome some of these barriers to care, but more research about the efficacy of these interventions is needed.

Our center has developed a workflow sheet for assessment of transplant candidates with BD, focused on addressing residual symptoms of BD which may interfere with medical care, psychiatric comorbidities when applicable and planning interventions for possible relapses of BD (Fig. 2.1: Suggested workflow for transplant candidates with BD). Deciding upon long-term treatment for BD in the postoperative phase, when patient must adapt to the new needs of medical care, new physical status and the intense postoperative follow-up are extremely difficult. We are advocating that the plan for post-transplant care should start at the initial pre-transplant evaluation. Due to long wait times in many cases, reevaluation when patient is getting close to surgery may be necessary. Proactive consultation post-transplantation (not waiting until symptoms develop) may help with early identification and treatment of psychiatric symptoms postoperatively.

In summary, the evaluation and treatment of patients with BD in need of organ transplantation pose significant challenges due to risk of psychiatric decompensation, risk due to medical and psychiatric comorbidities, risks related to the psychopharmacological treatment and risk of psychiatric decompensation triggered by the perioperative stresses. Careful planning should involve collaboration with the patient's support group, community psychiatry providers, and close postoperative mental health follow-up.

Take Home Points

1. With expert mental health treatment, mental health stabilization and symptom remission, and stable social supports, patients with BD can be successful organ transplant recipients. Mental health care should be established prior to transplant with plans for longitudinal care pre- to post-transplant.
2. Transplant candidates with BD require careful pre-transplant evaluation to identify all the risk factors that can interfere with post-transplant care.
3. Post-transplant psychopharmacological management must take into consideration not only the risk of repeated organ toxicity, pharmacokinetic and pharmacodynamic interactions with immunosuppressant medications, but also efficacy in maintaining psychiatric stability. Psychotherapy also has significant impact in reducing the number of relapses in patients with BD.
4. Due to the complexities of managing patients with BD in the transplantation setting, we are advocating that treatment planning should start at the initial pre-transplant evaluation.

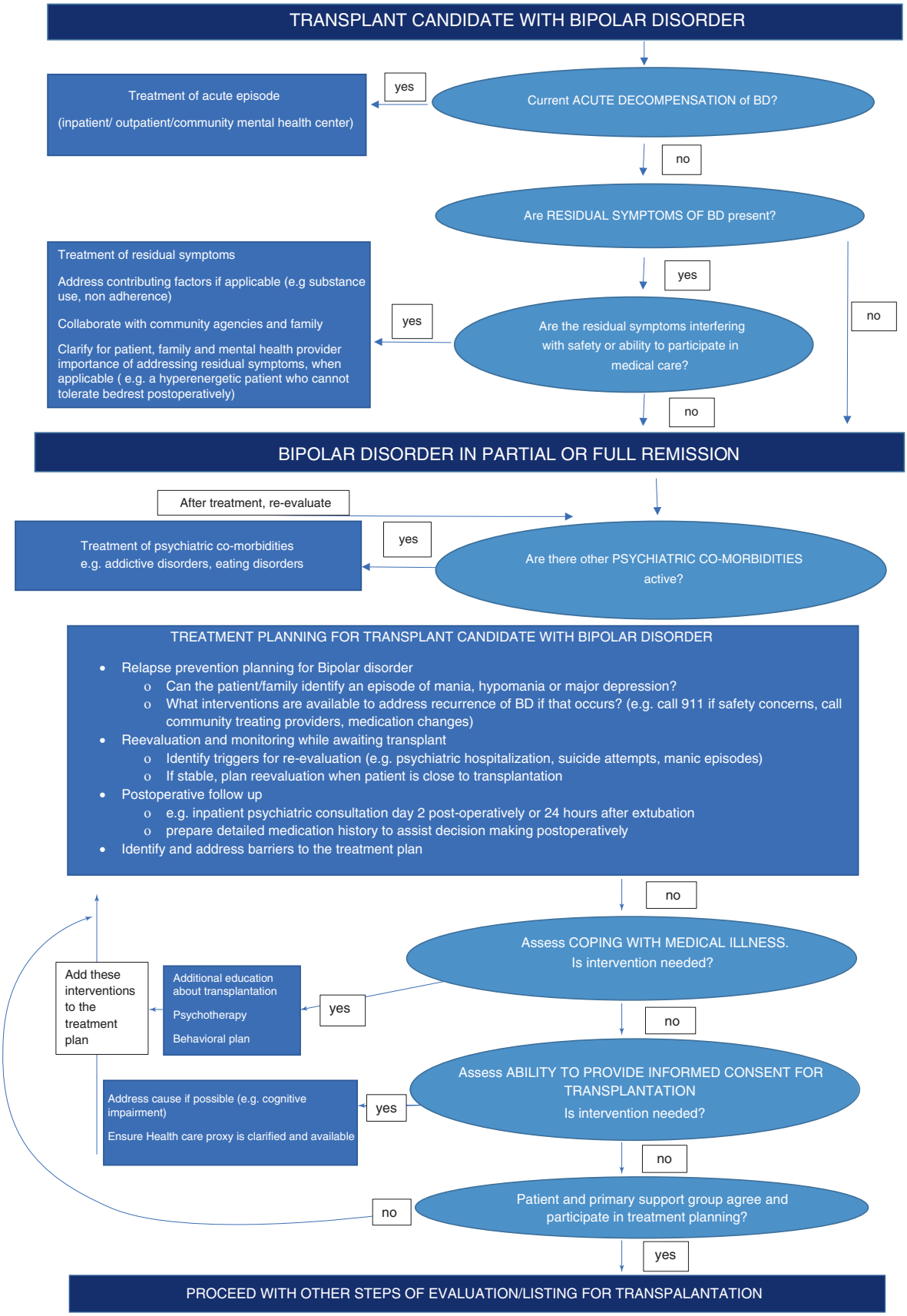

Fig. 2.1 Example of workflow for transplant candidates with bipolar disorder

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The Suicidal Patient in Organ Transplantation

3

Jacqueline Posada and Catherine Crone

Background

Suicide and organ transplantation may initially seem incompatible. Organ transplantation is a life-prolonging, sometimes heroic, and lifesaving procedure, whereas suicide is a volitional desire and action to end one's life. From the multitude of clinical scenarios that may be encountered in the transplant setting, we chose two that are in our experience, are the most common and challenging: a patient who presents after a suicide attempt and needs a liver transplant to survive or a patient who develops suicidal ideation after transplant. This chapter will present two clinical cases exploring both scenarios. It will also present information on risk factors for suicide in general and how to apply them in a risk assessment for the transplant population. Before the cases are presented, the following points highlight major themes to keep in mind when first encountering a potential transplant candidate or individuals who have received a transplant and are experiencing psychiatric symptoms.

For patients who undergo a psychosocial evaluation before organ transplant, this evaluation is an ideal time to identify risk factors for future suicidal ideation or attempts. These evaluations include questions about mental health diagnoses and substance use which are important factors in suicide risk [1]. A clinician who completes these evaluations typically asks about how a transplant candidate handles stress, uncertainty, and life challenges. Eliciting this type of information is clinically relevant as life stressors count as a dynamic risk factor for suicide. Additional questions focused on the quality of social support may illuminate the individual's risk of suicidal ideation and behaviors from the perspective of the interpersonal theory of suicide. Specific questions would include inquiry into the person's sense of belonging to their family or social network, their sense of burdensomeness to their social supports before and after transplant, and a detailed understanding of family and social support dynamics [2].

Even without a history of psychiatric illness, candidates for and recipients of any solid organ often have positive risk factors for suicide which are inherently associated with a chronic medical illness and social consequences of their disability. Such factors that increase the suicide risk include: (1) Medical comorbidities, including pain, and physical illness with subsequent hospitalizations [3, 4]; (2) psychosocial stressors like unemployment or disability; (3) recent life stressors such as surgery and risk of rejection, and (4) strained social supports at risk of caregiver burnout [5].

Even if a transplant candidate is considered "low risk" for suicide at the time of evaluation and transplant, the prospect of major life stressors and difficult emotions in response to the organ transplant process like frustration, disappointment, and hopelessness can elevate the risk of suicidal ideation and suicide attempt.

Research studies suggest those who complete suicide more commonly have their last clinical contact with a primary care provider or other non-mental health medical specialists [6]. Collaboration between transplant centers and psychiatrists could address suicide risk by educating all providers involved about suicide, screening for risk factors, and together planning how to handle mental health crises when they arise.

Brief Overview of Risk Factors of Suicide

In 2008, suicide, identified as death by intentional harm to self, became the tenth leading cause of death across all ages in the United States exceeding septicemia [7]. The rates of suicide in the US have risen by 1.5% every year since 2000

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leading to a 30% increase in suicide deaths in some states. The general rate of suicides in 2017 was 14 per 100,000. In men aged 45–64, the rates of suicide increased from 21 suicides per 100,000 in 1999 to 30 per 100,000 in 2017 [8]. This age range in men overlaps with 35–65, the age range which receives the most organ transplants [9].

Risk factors for suicide are stratified as chronic (predisposing) and acute (or precipitating). A previous suicide attempt, no matter the time frame, remains the strongest predictor for future suicide attempts. Almost 60% of first-time suicide attempts end in death, particularly if lethal means are accessible and used such as a fire-arm or hanging [10, 11]. In the US, 50% of suicide deaths were attributed to firearms, and suffocation was the second most common form of completed suicide; women were equally likely to die by suicide from poisoning (31.4%) or firearm (31.2%) [12]. Other important predisposing risk factors include the presence of psychiatric illness, physical illness, substance use disorder, and family history of completed suicide, and environmental factors such as adverse childhood events, unemployment, and stressful events, social isolation, and poor social support [13, 14]. Attempting suicide is such a personal event that special attention should be paid to the dynamic risk factors that change from visit to visit. These would include presence and intensity of suicidal ideation, recent stressful events such as change in income, loss of a relationship, worsened substance use, and psychiatric symptoms like insomnia, worsened mood, increased anxiety, despair, a sense of hopelessness, feeling trapped or like a burden to social supports command auditory hallucinations, delusions of reunion with a lost loved one [5, 14].

Suicide and Transplant Recipients

Death by suicide in transplant patients is a rare event. Limited literature exists on the topic as both organ transplant and suicide completion are low-frequency events in the general population. More is known about the prevalence of mental health disorders in transplant patients [15]. A few studies give concrete statistics on completed suicide in transplant patients; however, those must be interpreted with caution as certain behavior (e.g., cessation of dialysis) is no longer universally considered suicide. In a Danish national healthcare registry study of 380 lung, kidney, and liver transplant recipients, the suicide rate was 5.6 per 1000 person-years (adjusted hazard ratio of 1.8 (95% CI: 0.9, 3.6)) compared to non-transplant controls who had a suicide rate of 2.8 per 1000 person-years [16]. A study of 209 first-time kidney transplant recipients in Denver, Colorado examined 54 autopsy reports from 1974–1979. Washer et al. identified that 15% ($n = 8/54$) of patients with a mean age at transplant of 27.8 years died "as a result of overt or veiled suicide, including refusal to undergo dialysis after unsuccessful transplantation." [17] Although not solid organ transplantation, in 2012 the European Group for Blood and Marrow Transplantation released data from a cohort and case control study demonstrating the risk of suicide after hematopoietic stem cell transplantation (20.7/100,000) was two times that of the general population (9.2/100,000) [18]. Cancer recurrence and graft versus host disease were more common in the patients who completed suicide. When a transplant fails, disappointment and despair may follow precipitating a desire to die as a means of escape. The previously described studies suggest the risk of suicide is elevated in transplant recipients compared to the general population.

Patients with end-stage renal disease (ESRD) on dialysis are another group in whom death by suicide has been researched. Although not all ESRD dialysis patients are eligible for transplant or even seek transplant, their similar disease processes may be indicative of similar risk factors as ESRD transplant candidates on dialysis. Two large retrospective cohort studies of ESRD patients receiving dialysis in the US and Taiwan showed the risk of suicide was significantly greater in dialysis patients compared to the general population, and the risk was highest in the first 3 months to 1 year after starting dialysis [19, 20]. The early months of dialysis represent a period of major transition in a person's life.

Suicide Risk Factors Specific to Transplant Patients

Stressors specific to transplant patients require consideration as these medical and functional stressors represent a change in suicide risk and may trigger changes in psychiatric symptoms and psychological wellbeing. A body of research suggests a relationship between physical illness and risk of suicide behavior and mortality. The number of medical comorbidities a patient has and the extent to which multimorbidity diminishes physical functioning and quality of life is associated with an increased risk of death by suicide [21, 22]. While receiving a transplant should be a positive transition, for some recipients organ rejection or a change in functional status are also potential risk factors for the development of suicidal ideation and behaviors. Several new stressors arise post-transplant that can lead to suicidal ideation and risk if not addressed like physical pain immediately after transplant and feeling overwhelmed with new self-care responsibilities. Nonadherence to medications and lifestyle recommendations has been linked to mood disorders in transplant recipients [23]. Setbacks such as frequent hospitalizations, limited functional progress, and disappointment with changes in their functional status, or news of acute or chronic rejection are all transplant-specific stressors that

should prompt inquiry about suicidal ideation, thoughts of death, or not wanting to proceed with care. Most transplant recipients have experienced their share of adversity in life from their medical and physical challenges and resulting psychosocial hardships. Yet transplant clinicians must not fall into the trap of believing depression or suicidal ideation are expected or "normal" considering all the transplant patient has suffered; statements of hopelessness and fear related to an uncertain future after transplant must be addressed [24]. After the transplant, patients may be hesitant to admit suicidal ideation and appear unappreciative of their new organ. If a clinician suspects a mental health diagnosis, thoughts of death or suicidal ideation, proper evaluation and intervention are necessary and may change long-term outcomes for the better by preventing graft loss and even death [24].

Given the limited data on suicide-related behaviors and transplant patients, a case series about suicidal ideation in five lung transplant recipients provides insight by identifying post-transplant psychosocial variables contributing to suicidal ideation [25]. Specific transplant stressors like acute rejection and slow recovery, familial discord post-transplant, limited and taxed social support, prescription mismanagement of controlled substances, presence of psychiatric illness before and after transplant, and negatively charged emotions like disappointment, frustration, and hopelessness were present in at least two out of the five cases. Hospitalization for any physical illness increases a patient's risk of suicide, even when adjusting for the presence of psychiatric illness. A nested case-control study from the Danish national register using the entire Danish population showed that the risk of completed suicide progressively increased with the frequency and recency of hospitalizations for physical illness in any organ or system. Specifically, the risk of death from suicide increased by 8% if the person had been hospitalized within the last 30 days [4]. Psychiatric illness was more common in those who completed suicide, compared to those without, further supporting the cumulative, jeopardizing effect that the combination of physical and mental illness has on the body and mind.

Individuals without a mental health diagnosis who die by suicide were likely see a medical outpatient provider at least once before their death. Ahmedani et al. published a study evaluating the records of nearly 6000 completed suicides from eight affiliated health maintenance organizations (HMO) in the US from 2000–2010, and their sample size made up 1.6% of suicides from that period [6]. They found that half of those who completed suicide visited a primary care provider or medical specialist 4 weeks before their death, and 22% of those who died used medical services in the week before their death. In the year before death, 62–64% of patients did not receive a mental health diagnosis during their primary care or medical specialty visits. While the presence of physical illness and subsequent interactions with the health care system might be associated with the risk of suicide attempts, they also represent an opportunity for intervention. Most organ transplant recipients are more likely to see their transplant specialist provider or their primary care provider on a regular basis than a psychiatrist. With more awareness and knowledge about the risk of suicide, all providers can be vigilant for the warning signs of suicide.

Suicide Attempts That Lead to Organ Transplantation

A challenging scenario is when a patient presents with acute liver failure directly resulting from a suicide attempt, most commonly an ingestion of medications that include acetaminophen. Acute liver failure is rare with approximately 2000 cases diagnosed in the US annually and some cases require emergency liver transplant to prevent death; the causes include drug toxicity, viral and autoimmune hepatitis, and indeterminate cause [26]. Emergency liver transplants comprise 5–12% of all liver transplants and their survival rates are poor relative to liver transplants for chronic liver failure [8, 27]. Drug-induced liver injury is the most common cause of acute liver failure [28, 29], and in the United States, acetaminophen overdoses account for nearly 50% of acute liver failure cases and carry at 30% mortality rate without transplantation [30]. A retrospective study of seven European countries reflected similar findings, as overdose represented 19% of the cases (114/600) requiring transplant for acute liver failure, and paracetamol (acetaminophen) was involved in 97% of the overdose cases whether intentional or not [31]. Among a Swiss urban population with acute liver failure secondary to acetaminophen overdose, 79% had overdosed intentionally [32]. Even patients who overdose unintentionally, using acetaminophen for pain, had significant psychiatric comorbidities, most commonly significant impulsivity [33] In 1998, the United Kingdom attempted to restrict the availability of paracetamol in hopes of decreasing morbidity and mortality from overdose, but the effects of this legislation have been underwhelming without a sustained significant decline in deaths from poisoning [34, 35].

Transplant mental health clinicians may be asked to make recommendations about whether the transplant team should pursue liver transplantation. It is beyond the scope of this chapter to suggest criteria for when transplantation should or should not be pursued. Mental health clinicians are central in helping the transplant team weigh the future risks of suicide in a patient after a presenting overdose. Our first case will illustrate the challenges of these evaluations as the patient is often encephalopathic or intubated, therefore unable to provide detailed history and time to complete the evaluation is limited. Obtaining essential collateral information, especially

from psychiatric providers, can be difficult due to time constraints, and the family may be tempted to minimize or withhold information knowing that a liver transplant is at stake.

Mental health providers are expected to weigh the evidence-based risk factors and examine the psychological and behavioral clues to give guidance on future risk of suicide. Suicide risk assessment tools and scales can aid clinical decision making, especially in high-risk groups like immediately after suicide attempt or inpatient psychiatric hospitalization, by providing consistency to the risk assessment [29, 36, 37]. Yet predicting death by suicide has proven incredibly challenging as most scales used in hospitals are meant to predict suicidal ideation and/or attempts not deaths by suicide [38]. The Columbia-Suicide Severity Rating Scale (C-SSRS) has become widely used in clinical and research settings and is a useful tool for understanding the severity and granular details of a person's suicidal ideation [39]. While a high total score on the C-SSRS and the suicidal ideation intensity item are associated with increased risk of suicidal behaviors such as a non-fatal attempt or death [40], the sensitivity and specificity of the tool are low limiting its value in predicting suicide mortality [40, 41]. Because suicide risk scales are still not reliable enough to predict risk of suicide, some researchers have turned to machine learning to analyze the data within electronic health records, including extensive demographic information and embedded clinical data such as the number and types of health care visits and medications, to predict risk of suicide [42, 43]. At the time when this chapter is being edited, no suicide risk assessment tools have been validated in transplant candidates or recipients.

In some cases of acute liver failure secondary to ingestion, it is difficult to distinguish an unintentional overdose without suicidal intent from an intentional overdose; in one study, the reason for overdose was unclear in 8% of the cases [31] and in another study 28% of cases had uncertain intentionality [44]. A prospective multicenter in the US showed the overdose groups, intentional versus unintentional, had similar risk factors for overdose including chronic pain, depression, and substance abuse, including alcohol, which also overlap with risk factors for future suicide attempts and poor adherence to transplant regimens [44]. After an overdose, medical providers will be faced with the difficult question of whether to provide a liver transplant for a patient who attempted suicide with acetaminophen. Understanding their risk factors for mental health disorders and future suicide attempts is essential in deciding whether to recommend transplant, and there is wide variation in practices because the decision about whom to allocate a transplant after suicide attempt is not easy to make [45]. A recent study of 910 patients evaluated for liver failure secondary to acute acetaminophen overdose showed that psychiatric illness did not have an impact on listing for transplantation or posttransplant survival [46].

Case Histories

Case 1: Moira—Acetaminophen Overdose and Acute Liver Failure Requiring a Liver Transplant for Survival

Moira is a 25-year-old female, originally from Central America, who is married with two children ages 2 and 4. She moved to the US about 5 years ago and has been married to her husband for the same length of time. Most of her family remains in Central America and she has a few friends through her husband's family. Her husband works as a cab driver, and she is home with the children. Moira was admitted to the hospital with acute liver failure due to an intentional acetaminophen overdose. Her husband is shocked by the news and does not know of any past suicide attempts or mental health diagnoses. He reported Moira had been moody in the past couple weeks, depressed one moment and at the next she was happier and expressing affection toward him. Five days prior to her overdose, she had become angry with her husband after an argument over their finances and stopped talking with him. He later overheard a phone call with her mother in which patient commented "Don't worry about me, I don't want to live anymore," but he did not think she was actually considering suicide. Her husband assumed she would never do anything to harm herself and leave her two young children without a mother.

The night of her overdose, she left the house after dinner to go to the grocery store to purchase items for the children. Her husband went to bed without her. When he awoke the next morning, she seemed to be asleep in her young daughter's bedroom, so he did not awaken her at first. Later in the morning, he tried to awaken her, and she was minimally responsive. He discovered a suicide note indicating she wanted to die, and it was no one's fault along with a nearly empty bottle of acetaminophen 500 mg tablets. Her hospital records mention a history depression elicited during an ED visit for neck pain 1 year prior (husband is unaware of this ER visit). She has been going to a local county clinic for help with headaches and sinus problems, and she usually takes ibuprofen for pain. She has been seen at the clinic twice in the last month for worsening physical symptoms. At the time of assessment for the transplant, her husband begged for any treatment that would let Moira live and save their children from growing up without a mother.

Case 2: Frank—Descending into Depression and Suicidal Ideation After a Lung Transplant

Frank is a 45-year-old single male with a medical history of idiopathic pulmonary fibrosis and an unclear psychiatric history. He moved from out of state approximately 6 months prior to receiving a bilateral lung transplant. He had been diagnosed with bipolar disorder years prior when he received

mandated mental health treatment in a different state after a drug trafficking charge. For the 2 years before his transplant, he would drink between 12 and 18 beers a night to alleviate the stress of unemployment and separation from his wife. He stopped drinking completely when he learned a lung transplant was a possibility and remained sober for the year before his transplant.

He grew up with a tumultuous childhood that included emotional and physical abuse by his mother. He dropped out of high school and worked as a skilled laborer. When he developed pulmonary fibrosis and could no longer work, his wife left him taking with her their 3 adolescent children. Feeling alone and hopeless, he reached out to his brother who lived near to his eventual transplant center. Even though they had been estranged for 10 years, his brother offered to move him and help him get a lung transplant. Frank moved in with his brother, sister-in-law, and their three young children. Before his transplant, he underwent a basic psychosocial evaluation using the Stanford Integrated Psychosocial Assessment for Transplant tool [47], and was identified as a marginal candidate for lung transplant. He underwent transplantation and 2 months later he was hospitalized for symptoms of an upper respiratory infection and suspicion for acute graft rejection.

In the hospital, Consultation Liaison Psychiatry (CLP) was asked to see Frank for depression and medication management for his history of "bipolar disorder." At the time of evaluation, he had not taken any psychotropic medications for over 1 year. He denied any past suicide attempts or psychiatric hospitalizations. During the psychiatric evaluation, he endorsed sadness over his separation from his wife and missing his children. He ruminated on how his wife left him at his most vulnerable moment making him feel worthless. He recounted a long history of explosive anger starting from childhood and being sent to a reform school at age 14. From a young age, he was on and off psychotropic medications including antidepressants and mood stabilizers. The psychiatrist did not elicit any history of mania or hypomania. Instead, Frank's history included life-long irritability with periods of depression and concurrent alcohol use that would resolve with time.

He reported a strong relationship with his brother and enjoyed helping take care of his young nieces and nephews. He worried about becoming a burden on his brother and family especially as he struggled to manage his irritability and "anger issues." He was happy that he recouped significant physical functioning after his lung transplant but was frustrated that he was still not well enough to work and contribute to his family. In the hospital, the CL psychiatrist diagnosed Frank with major depressive disorder recurrent episode, alcohol use disorder moderate in remission, and attributed his irritability and poor emotional regulation to a trauma or stressor-related disorder stemming from his history of childhood abuse. The psychiatrist started fluoxetine for depression and quetiapine for mood stabilization and irritability. Psychotherapy was also suggested, and the transplant social work team helped the patient identify community clinics in his area to obtain psychotherapy and further medication management.

Frank was eventually diagnosed with acute rejection and decompensated psychiatrically with worsening depression and irritability. Although he continued his psychotropic medications, he never received psychotherapy because of lack of accessible community mental health services in his town in and limited transportation to the therapist. His relationship with this brother became strained. He began to voice suicidal ideation saying he felt worthless and like a burden to his social supports. Despite his family's support, he struggled to take his immunosuppressant medications. He returned to drinking which he described as his only coping skill because he could not work, exercise, or have a social life of his own. During a clinic visit, he presented to his transplant physicians complaining of depression and suicidal ideation. His desire to die, depression, and alcohol use interfered with his ability to care for himself. At a follow-up evaluation in the transplant center, he was seen on an emergency basis by CLP who recommended inpatient psychiatric hospitalization. Frank had a 14-day psychiatric hospitalization, and his fluoxetine was titrated up to 60 mg and quetiapine up to 200 mg. He said that talking to the individual psychotherapist and attending group sessions was helpful in learning to deal with his distress. His brother was closely involved in his treatment and a plan was made to help Frank continue outpatient treatment with a psychotherapist and psychiatrist once he returned home. From the hospital, he was transitioned to a 30-day inpatient substance abuse program as he had never received intensive treatment for his alcohol use, and Frank pledged to continue addiction treatment by attending a 12-step mutual support group near his home.

Discussion

Moira in case 1 depicts a complex decision about evaluating the risk of suicide in a patient who presents after a suicide attempt via acetaminophen overdose and liver failure. Factors influencing lethality such as conception and implementation of the attempt, risk of medical damage, and rescue conditions are important to analyze as part of the suicide risk assessment once a patient presents to the hospital after an overdose or any suicide attempt [48]. The risk-to-rescue ratio of a suicide attempt compares lethality, probability of irreversible medical damage, to the likelihood of rescue [49]. A short amount of time to presentation can be thought of as a proxy for desire to survive after overdose if the patient called for help and asked to be rescued, though other factors could also delay their rescue. Co-ingestion of other medications,

substances, or alcohol should also be considered by taking into account how much of each poison was used, if alcohol or substance use contributed to an impulsive suicide attempt, or if the amount of acetaminophen ingested was calculated to cause death—bearing in mind not all people are aware of the toxicity of acetaminophen and think they are only making a suicide gesture. Trying to ascertain the extent of planning is important as unintentional acetaminophen overdose occurs in patients prescribed narcotic/acetaminophen compounds who may not understand of the toxicity of acetaminophen [44]. If a person delays their presentation to the hospital, for example by isolating themselves to prevent rescue, or co-ingests other substances to increase lethality, this could suggest that a suicide attempt was more serious with a greater desire to die. For individuals with or without a history of psychiatric hospitalization, an intentional overdose with acetaminophen carries a persistently elevated risk of suicide attempt in the future ranging from 1-week post overdose to 3 years afterward [50].

Her husband provided a limited history of her past psychiatric history and her psychological state before the attempt. On the one hand, Moira does not have any diagnosed psychiatric disorders, previous psychiatric hospitalizations, or suicide attempts. The history is vague, but we know that she has physical pain symptoms, and in the past month she had an increased her frequency of outpatient visits with medical providers for physical complaints. She has also had several traditional "protective factors" including female gender, her marriage, and the presence of two young children for whom she is the primary caregiver. Several of her behaviors are worrisome and indicative of a suicide attempt with a strong desire for death. She had her fight early in the week with her husband and made a comment about wanting to die. We can wonder if she had been planning her attempt all week, and that she went to the grocery store to buy sufficient acetaminophen to make a lethal suicide attempt. She slept in a room separate from her husband thus delaying her time to rescue and treatment. The history also alludes to other risk factors like financial stressors in the family, prodromal mood, and personality changes. In this case, the transplant team decided to move forward with a liver transplant. The psychiatrist was concerned about the high risk of suicide of Moira and emphasized the details that her suicide attempt was planned and her children were not as protective as her husband suggested. In contrast, others on the transplant team, including the surgeons, heavily weighed her relative lack of predisposing risk factors for suicide before her overdose and thought that the factors that precipitated her attempt (factors like financial stress, social isolation, and mood changes) are modifiable. This divergence of views between members of the transplant team is not uncommon. In a survey of 49 transplant mental health clinicians asking about their practice and experience with recommending liver transplants after intentional acetaminophen overdose, 18% reported that when consensus could not be reached within the team, the final decision about transplant candidacy was made by the surgeon [45].

Frank in case 2 has many "typical" risk factors for development of mental health complications and suicidal ideation in a transplant patient: at the time of his transplant, he was unemployed, had a history of mood disorder, alcohol use disorder and a tenuous social support system. With a vague psychiatric history that was unlikely bipolar disorder, but he had taken psychotropic medications for long periods of time, and he had a relapsing alcohol use disorder. Frank's bother stepped up to move him to be near a hospital where he could obtain a lung transplant. However, their fraternal relationship was fragile and immediately thrust into a high-stakes situation of Frank's bilateral lung transplant and a turbulent recovery. The most notable risk factors for suicide before transplant include the history of an unspecified psychiatric disorder that included periods of depression, substance use disorder, and alcohol as a primary coping mechanism. Using the interpersonal theory of suicide, the risk assessment should also consider Frank's tenuous social support provided by his sibling. The social support was at risk of being burdened by the requirements of transplant [2]. The diagnosis of acute rejection and slower than expected physical recovery with continued functional deficits preventing him from working or socializing contributed to emergence of depressed mood which Frank attempted to address with alcohol. As Frank himself predicted, he alienated his brother with his anger and alcohol use and this strained social support made it even more difficult for Frank to recovery physically and psychologically. Psychotropic medications were prescribed by the inpatient CL psychiatrist at the hospital affiliated with his transplant center. However, the lack of adequate mental health follow-up in the surrounding area where Frank lived meant he could not access the psychotherapy and medications he needed to navigate the emotional hardships that come with a solid organ transplant. The eventual inpatient admission for suicidal ideation was a turning point for Frank and his support system and highlighted the need for comprehensive outpatient mental health services focusing on addiction, past traumas, and how to cope with current psychosocial stressors.

Both our cases highlight the need for close psychiatric follow-up after a solid organ transplant in a person who receives a liver transplant after an overdose or someone who has known risk factors for psychiatric decompensation or suicide before their transplant. In Moira's case, after receiving a liver transplant and the physical rehabilitation that follows, psychiatric treatment and follow-up cannot be forgotten. For most patients who present with serious medical problems directly caused by a suicide attempt, admission to an inpatient psychiatric unit allows a comprehensive for the presence of a psychiatric disorders and safe titration of

psychotropic medications. The inpatient admission would be an excellent opportunity for psychoeducation, family education, and introduction to individual and group psychotherapy. Moira's suicide attempt now exists as a risk factor for future suicidal ideation and attempts, and the events leading up to her suicide attempt must be discussed with her family and healthcare providers so everyone is aware of her risk.

Moira and Frank both faced financial barriers in accessing the recommended mental health care, as their health insurance limited the options for mental health treatment outside the hospital. Ultimately, Moira did not qualify for any intensive outpatient psychiatric services besides seeing a psychiatrist and therapist at a local community mental health clinic. Frank struggled to find outpatient services in his area without a significant waiting list. In most situations, the outpatient mental health care occurs in a fragmented system, and it is up to the patient and the transplant team to establish tight follow-up and open channels of communication.

What Can Be Done to Modify Risk of Suicide in Transplant Candidates and/or Recipients?

Receiving an organ transplant is a monumental event for a patient. After the transplantation surgery, the transplant teams manage an array of interventions focused on maintaining a good function of the graft, including monitoring and/or administration of immunosuppressant medications and addressing medical comorbidities. For patients with significant psychiatric conditions, the transplant psychiatrist can play a crucial role in ensuring the patient receives the care needed to achieve a good outcome.

Key strategies to managing patients at risk of suicide include the following: [14, 45].

1. Address modifiable risk factors such as diagnosing and treating underlying psychiatric disorders and substance use disorders.
2. Develop mental health treatment plants with input from all relevant parties: the patient, their support system, and the transplant team. If subsequent mental health treatment is being arranged outside of the transplant center, communication should be established with these providers before discharge or soon after. The outside providers must be informed of the special needs of a transplant patient with focus on how to identify and address nonadherence and clinical deterioration [45].
3. For patients with many risk factors for suicide or who develop suicidal ideation, a crisis/safety plan must be created. Many studies support the use of safety plan interventions to reduce the risk of suicidal behaviors after discharge from an ED or clinic and improved engagement during times of distress [51–53]. The evidence-based safety plans are multifaceted and include the following parts [52]: (A) Warning signs of an impending crisis and suicide include returning to maladaptive coping like substance abuse or even medication nonadherence or alienating social supports. (B) Short lists of coping strategies, people, and places which provide distraction from the crisis. (C) Names and contact information of people to call for help. (D) Locations and contact information of the professionals and agencies to contact or present to during a crisis including a designated mental health provider, family member, the location of the nearest emergency department or psychiatric crisis center, and contact information for a suicide hotline. For transplant patients, this list might include a designated member of the transplant team. (E) Counseling to make the environment safe including identifying means of suicide such as fire-arms and poisons like acetaminophen.
4. Collaborating with and educating transplant team members about the psychiatric needs of patients with mental health disorders and those at risk of suicide. Education can occur with individual patient cases such as emphasizing that specific patients will need more frequent follow-up from their transplant team and identifying the more overtly medical signs of suicide risk like medication or lifestyle nonadherence, missed clinic appointments, and abnormal lab values [14, 45]. Mental health providers on the team and other team members who will use psychiatric risk factors to decide on organ distribution should take part in continuing education or trainings about mental health in transplant recipients and suicide risk assessment and treatments.
5. Detailed risk assessment prior to listing and when clinical assessment suggests a change in the risk level. See Table 3.1 for a summary of risk factors for the suicidal transplant patient and suggestions for risk assessment and possible interventions. Table was modified from the SAFE-T protocol developed through SAMHSA which is a useful resource to help clinicians assess risk and document in the medical record [54, 55].
6. For patients without a history of mental health diagnosis, psychiatrists can help other transplant clinicians identify a person who is at risk of suicide by ensuring that risk factors are identified, and immediate evaluation is available for those found at risk. Polypharmacy may elevate risk of suicide mediated through increased side effect burden, medication interactions, and the use of prescribed medications for overdose [56]; specifically, a patient prescribed mental health medications and analgesics in the last 6 months has increased odds of attempted suicide [57]. For patients without a history of mental illness, an increasing number of visits to an outpatient medical provider could help determine individuals at risk of suicide attempt [58]. Clinic visits also represents an opportunity for inter-

Table 3.1 Summary of risk factors, risk assessment, and interventions for the suicidal transplant patient

Risk level	Suicidality	Risk factors	Transplant-specific risks	Possible interventions
High	Recent history of a potentially lethal suicide attempt Persistent ideation with strong intent suicide rehearsal	Multiple acute risk factors like suicidal ideation, substance abuse, uncontrolled anxiety, insomnia, and acute stressors or losses such as end of a relationship or unemployment Many static risk factors like uncontrolled mood disorder, history of suicidal ideation or attempts Evidence of poor self-control such as relapse to substances or misuse of medications Minimal protective factors	Acute organ rejection or graft loss Change in prognosis Loss of social support system or important relationship Social isolation and sense of burdensomeness to their social supports More than one acute stressor, social and/or related to transplant	Evaluation for inpatient hospitalization either voluntary or involuntary Evaluation can be done by on-site psychiatric professional or through an emergency room Do not leave patient alone in the office during assessment After hospitalization, close follow-up and means restriction
Moderate	Suicidal ideation with plan, no intent or behavior	Baseline chronic risk factors like past suicide attempts or substance use Mood and/or anxiety symptoms present New acute risk factors Some identifiable protective factors	Recent inpatient hospitalization Recent infectionincreased number of medical outpatient visits Persistent periods of nonadherence Chronic organ rejection Acute stressor such as decline in physical functioning Strained social supports	Psychiatric admission may be necessary depending on risk factors Involve social support system like family Increase frequency and/or duration of outpatient visits Provide frequent follow-up with phone calls or home visits Control mood symptoms with medications or psychotherapy Repeated evaluation of need for hospitalization Develop a safety plan with emergency and crisis numbers Means restriction
Low	Thoughts of death, no plan, intent or behavior	Few chronic risk factors modifiable risk factors such as mild mood or anxiety symptoms Evidence of self-control and use of coping skills	Multiple medical comorbidities Periods of medication and/or lifestyle nonadherence	Outpatient referral to mental health provider Symptom reduction such as treatment of psychiatric disorders with medications or therapy Give emergency/crisis numbers Means restriction

Adapted from https://www.sprc.org/resources-programs/suicide-assessment-five-step-evaluation-and-triage-safe-t-pocket-card [63].

vention, even with commonly used screening questions about depression and thoughts suicide. Outpatient clinics of any specialty can quickly administer a validated depression screener such as the Patient Health Questionnaire (PHQ-9) which can guide if and the type of intervention that would best serve a patient with risk factors for suicide [59]. Data from two large studies suggest that individuals of any age who answer affirmatively to item number 9 of the PHQ-9 ("Thoughts that you would be better off dead, or thoughts of hurting yourself in some way?") have a significantly elevated risk of attempting or dying from suicide [60, 61]. If any of the dynamic risk factors for suicide are noted in a transplant patient, a screening tool like the PHQ-9 is straightforward mode of screening for not only a mood disorder but also risk of suicide. That said, if a transplant clinician suspects suicidal ideation, they can also ask directly about thoughts of wanting to die and thoughts of suicide such as desire to end one's life or intent to do so. Asking about suicide does not increase a person's risk of suicide by suggesting the possibility of suicide [62]. However, as with any screening decision, clinics must have a plan for how to address uncovered suicidal ideation or passive death wish.

Take Home Points

1. There is limited research about the risk of suicidal ideation and suicide completion in transplant patients.
2. Patients for whom the indication for transplantation was directly due to a suicide attempt require intense mental health follow-up, typically in the inpatient setting to provide comprehensive assessment, careful titration of psychotropic medications, and individual and family psychotherapeutic interventions.
3. In addition to the traditional risk factors for suicide, solid organ transplant recipients present with additional risk factors such as their existing medical comorbidities with risk of physical disability and

hospitalizations, potentially strained social support networks, and a relatively high likelihood of a stressful events related to their medical transplant.
4. New risk factors for suicide can occur after the transplant, so teams must be vigilant for these stressors which can exacerbate underlying mental illnesses and lead to suicidal ideation.
5. Suicide is an important topic to discuss as a transplant team and the wish for death after transplant can impair a patient's ability to care for themselves and the transplanted organ.

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Psychotic Disorders and Organ Transplantation

4

Cullen Truett and Jonathan Punzi

Introduction

The lifetime prevalence of schizophrenia is often estimated to be around 1 in 100, but there is considerable variation between studies depending on methodology. A 2008 systematic review suggested the prevalence may be closer to 0.7% [1]. When other psychotic disorders such as schizoaffective disorder, psychotic mood disorders, delusional disorder, and substance-induced psychotic disorder are included, this prevalence is estimated at around 3% [2]. Such disorders significantly raise the lifetime risk of substance use, homelessness, and overall mortality due to medical illness. Despite having an increased risk of chronic medical illnesses leading to end organ failure such as diabetes mellitus, hypertension, alcohol use disorder, and other cardiovascular diseases, patients with psychotic disorders are relatively underrepresented among the transplant population [3].

Psychosis, both active and controlled, can create a barrier to organ transplantation. Organ transplant professional organizations and institutions have developed guidelines and consensus statements for transplant eligibility, although most transplant programs consider potential recipients on a case-by-case basis. A 1989 international survey of psychosocial evaluators at US cardiac transplant centers found that 92.3% of respondents viewed *active* schizophrenia as an absolute contraindication to transplantation, but only 33.3% viewed *controlled* schizophrenia as an absolute contraindication. In a second 1993 survey, these numbers were found to be lower for liver (67.4% for active schizophrenia, 15.2% for controlled schizophrenia) and renal (72.9% for active schizophrenia, 6.5% for controlled schizophrenia) transplant centers [4]. However, these views seem to have evolved over time. In a 2017 review of guidelines from multiple transplant organizations including the American Society of Transplantation (2001), International Society for Heart and Lung Transplantation (2014 for lung, 2016 for the heart), and the American Association for the Study of Liver Diseases (2013), no specific psychiatric disorders were considered absolute contraindications for transplantation [5]. In fact, the guidelines from the American Association for the Study of Liver Diseases state "…there is no psychiatric disorder that is an absolute contraindication to transplantation and even the most psychiatrically complex patient, for example, with a psychotic disorder or mental retardation, with proper evaluation and preparation, as well as adequate social support, can have successful long-term outcomes." Psychiatric illness was listed as a relative contraindication in the American Society of Transplantation guidelines, which state "Renal transplant candidates with a history of mental illness should undergo evaluation, counseling and, if necessary, treatment by appropriate mental health professionals prior to transplantation." Otherwise, medical nonadherence and poor social support were consistently considered to be contraindications [5]. It is important to emphasize that although the serious mental illness does carry potential risks in regard to transplant outcomes, with appropriate pre-transplant assessment, adequate mental health treatment and management, sufficient social support, and post-transplant monitoring, many of these risks can be mitigated.

One concern when evaluating a patient with a psychotic disorder for transplant might be that the patient would have difficulty complying with post-transplant care. With all-cause graft loss reaching up to 40% of renal transplants, nonadherence is a significant concern even among the general transplant population [3]. Adherence for the psychotic patient may be compromised by additional factors such as thought disorders, poor social supports, interpersonal difficulties with medical care, housing instability, and increased risk of medication interactions or toxicity [6]. Despite these concerns, there are limited data regarding the negative impact

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of psychosis on post-transplant outcomes. The largest study on psychosis in renal transplant recipients conducted by *Abbot* et al. examined 39,628 renal transplant cases. Their results showed patients requiring a post-transplant hospitalization for psychosis (type of psychotic disorder not specified) had significantly increased graft loss due to nonadherence [7]. However, this study excluded patients with a history of psychosis prior to transplant who were not hospitalized, leaving questions regarding generalizability. A later survey of transplant centers from the United States, Canada, and Australia over a 2-year period identified 35 cases of transplantation in patients with psychotic disorders across 12 institutions. Of these patients, 14.7% had nonadherence resulting in a rejection episode, while 11.8% had nonadherence resulting in decreased graft function or graft loss [8, 9]. Furthermore, homelessness, living alone, and substance use seemed to significantly increase the risk of nonadherence among these patients. In an analysis of 822 solid organ transplants in the Veterans Administration health system, Evans et al. found that 17% of transplant recipients suffered from serious mental illness (including schizophrenia and other psychotic disorders, bipolar disorder, major depressive disorder, and severe PTSD), and 31% carried other psychiatric diagnoses. They found no difference in follow-up visit attendance, frequency of immunosuppressant medication fills, or 3-year mortality between the serious mental illness, other psychiatric diagnosis, or no psychiatric diagnosis groups [9]. In a review of 3000 renal transplants in the Irish National Renal Transplant Programme database, fewer than 1% of kidney recipients carried diagnoses of bipolar disorder or schizophrenia, and there was no significant difference in length of transplant hospitalization, frequency of acute rejection, graft function, graft survival, or patient survival in this group compared to the other renal transplant recipients [10]. Perhaps unexpectedly, patients with predominantly negative symptoms were associated with better adherence than patients presenting with hallucinations or delusions. Having at least 1 year of stability regarding psychotic symptoms predicted significantly improved immunosuppressant adherence [8]. Another more recent descriptive study by Zimbrean and Emre identified 34 potential transplant patients with a history of psychosis, 19 of whom were determined psychiatrically and medically appropriate for transplant. Of the 10 patients who received organ transplantation, none experienced nonadherence to psychiatric medications and no episode of rejection was attributable to psychosis or immunosuppressant nonadherence. Four of the patients in this study were noted to experience psychosis post-transplant, all of which were considered substance related [6]. Thus, as described by Price et al. in a 2014 review, the evidence for the impact of psychosis both pre-transplant and post-transplant varies widely [11]. In the same review, it was noted that poor post-transplant outcomes seem to correlate more with poor social support in general than with psychosis specifically. As outlined by the first reported cases of transplant patients with schizophrenia, adequate psychiatric follow-up and multidisciplinary support may provide for successful transplant and minimize the risk of post-transplant psychosis [12].

Given the vulnerability of patients with psychotic illness to experience barriers to transplant due to their mental health history, the transplant psychiatrist has an invaluable role in pre-transplant evaluation to assess the patient's candidacy, identify and mitigate risk factors for poor transplant and psychiatric outcomes, and ensure patient engagement in adequate mental health treatment that will continue following transplant. The following case is designed to highlight common challenges in evaluating and managing the psychotic transplant patient.

Case History

VG is a 47-year-old African American male with a history of alcohol-induced cirrhosis, schizophrenia, and severe alcohol use disorder in full remission. VG initially presented a decade earlier with multiple admissions due to alcohol-related hepatitis and sequelae of alcohol-induced liver disease including esophageal varices and portal vein hypertension. VG struggled with maintaining abstinence despite multiple detox and alcohol rehabilitation admissions over a 5-year period. VG was followed by hepatology who noted worsening hepatic function, thrombocytopenia, and steadily progressive hyperammonemia. Given the increasing frequency of hospitalizations for upper gastrointestinal bleeds related to worsening gastric and esophageal varices, VG with the support of his family was able to engage in alcohol use disorder rehabilitation program along with medication-assisted therapy to achieve abstinence 2 years prior to transplantation evaluation. His liver function continued to decline despite abstinence from alcohol, so his medical team recommended pursuing listing for liver transplantation.

VG's comorbid diagnosis of schizophrenia significantly impacted his alcohol-related liver disease. At age 27, VG experienced his first psychotic episode during his third year of teaching. Prior to his onset of schizophrenia, he was a successful student in graduate school and a talented pianist. At first, VG attempted to hide these experiences from his mother and family, fearing loss of independence. However, as his symptoms worsened, VG had increasing trouble focusing on work, becoming highly distracted and irritable with his students. After several months, VG's mother intervened and requested an emergency evaluation when VG's attendance to personal hygiene declined, and he began to express paranoia that he was under FBI surveillance due to the subversive nature of his music. At that time, he was acutely hospitalized and diagnosed with schizophrenia.

Concurrently, VG had begun drinking up to a liter of Vodka a day in attempt to mitigate his auditory hallucinations. In addition to initial treatment of psychosis, VG was treated with a benzodiazepine taper for alcohol detoxification during that admission as well as antipsychotic medication. There was no notable family history of psychotic illness, although VG's father and paternal grandfather struggled with alcohol use disorder. Following discharge from his first hospitalization, VG's family enrolled him in a young adult treatment through the local community service board (CSB) targeting early intervention in first-break psychosis. The program included enrollment in the CSB's substance abuse treatment program to provide support for alcohol cessation. VG attempted to engage in Alcoholics Anonymous in addition to these services but attended only a few meetings off and on over time as he felt overwhelmed in group settings.

VG was assigned an outpatient psychiatrist through the CSB and remained abstinent from alcohol for the initial 3 months of his treatment following his first hospitalization. However, VG's auditory hallucinations never completely remitted, and he ultimately relapsed into heavy alcohol use citing his perceptual disturbances. VG would go on to have multiple hospital admissions over the next decade, with course complicated by alcohol withdrawal, nonadherence to treatment, and only partial remission of psychotic symptoms despite multiple medication trials. Treatment with clozapine provided VG with his most prolonged period of stability and remission of hallucinations but it was ultimately discontinued due to concerns for hepatotoxicity and lowered seizure threshold during episodes of alcohol withdrawal.

Two years prior to transplantation evaluation, VG was set up with a psychiatrist and case manager and was ultimately moved into to his mother's house for supervision and full-time care. Given his tenuous hepatic function, he was transitioned to oral paliperidone. He underwent a brief medical admission for alcohol detoxification and was started on acamprosate, having failed previous trial of oral naltrexone. VG began monthly meetings with his psychiatrist and weekly meetings with his case manager. While he continued to maintain abstinence from alcohol, remission of psychotic symptoms and good adherence with medical and mental health treatment, his physical health deteriorated. His hepatic function worsened and was hospitalized several times for hepatic encephalopathy and bleeding esophageal varices.

Although his history of heavy alcohol use and multiple prior psychotic episodes were noted as a concern, he was found to be in remission at the time of the evaluation. The transplant psychiatrist was able to obtain collateral information from his mother and his outpatient providers, which provided further reassurance of his stability and engagement in treatment. It was determined that there were no psychiatric contraindications to transplant, provided his outpatient providers would continue to maintain close follow-up. VG was ultimately able to successfully undergo liver transplant. He was continued on oral paliperidone initially, but this was ultimately transitioned to a long-acting injectable formulation. He continued to live with his mother and maintained regular visits with the transplant team, his psychiatrist and weekly follow-up visits with his case worker. Although he has continued to experience mild hallucinations, he has been able to maintain sobriety from alcohol after transplant.

Clinical Questions

1. What aspects of the psychosocial pre-transplantation evaluation are most relevant to the candidacy of a patient with a serious mental illness?
2. What adjustments or psychiatric treatment considerations should be made perioperatively to improve the chance for optimal outcomes?
3. What factors can the multidisciplinary team address post-transplantation to improve patient and graft outcomes?

Discussion

Unfortunately, VG's psychotic illness directly contributed to his need for transplant and was perhaps his greatest barrier to acceptance for transplantation. However, transplant teams must avoid a reductionist approach to the care of the psychotic individual which could limit the patient's opportunity to engage in this lifesaving intervention. The role of the mental health assessor is to provide a thorough pre-transplant evaluation, with careful attention to planning for perioperative psychiatric care, and determination of appropriate post-transplant biopsychosocial supports, so that patients such as VG can be selected for and successfully undergo transplantation.

As commonly occurs, VG's positive symptoms of psychosis catalyzed his decompensation into significant alcohol use, which ultimately led to alcohol-induced cirrhosis. Neurobiologically, similar alterations in reward circuitry in patients with alcohol use disorder are also present in patients with primary thought disorders, suggesting a biological predisposition. Substance use and psychotic disorders often co-occur, and several studies have demonstrated hypoconnectivity between the nucleus accumbens and the frontal cortex in these patients [8]. One study suggests 36.4% of patients experience alcohol use disorder symptoms prior to the onset of their psychosis [13]. Recent research has focused on a unifying hypothesis for biological vulnerability to schizophrenia and substance use disorders. Previously, the diathesis-stress model and self-medication models have received significant attention. In a 2017 review, Khokhar et al. suggest that a combination of both models is most accurate. Developmental dysfunction in the hippocampus as

demonstrated in rat models with schizophrenia-like phenotype shows hypersensitivity to dopamine activity in the mesolimbic and demonstrated increased behavioral sensitization to cocaine [14]. Functional neuroimaging further supports these animal findings and suggest that patients with schizophrenia are at risk of dangerous dance between their psychotic symptoms and risk of substance use.

While the self-medication hypothesis alone tends to have less evidence in the current literature, there is an undeniable correlation between the vulnerability to psychosis and alcohol use disorder. In this case, VG entered a cycle of relapse and remission for alcohol use that correlated with poor control of his psychosis. Maintenance of sobriety depended on intensive outpatient community mental health treatment consisting of psychiatric services, addiction treatment, and case management. Furthermore, by allowing VG to move in with her, his mother was able to provide a supportive living environment in which he was able to maintain sobriety and psychiatric stability.

The behavioral and cognitive symptoms of psychosis warrant further evaluation given their possible impact on capacity to consent and participate in organ transplantation and subsequent required self-care. Paranoia, disorganized behavior, and negative symptoms of psychosis have the potential to impact any of the four criteria for decision-making capacity [15]. The presence of any of these symptoms does not necessarily preclude capacity, and a thorough pre-transplantation evaluation can establish in detail a patient's understanding, appreciation, reasoning, and desire to proceed regarding transplant recommendations. For example, VG may not have necessarily related his conspiratorial delusions regarding the FBI to his need for organ transplantation. Adequate exploration with the patient may reveal a true appreciation of his hepatic failure as well as a level of understanding that surpasses assumptions often made by providers regarding his overshadowing diagnosis. However, elucidating the nature of his auditory hallucinations is key both to capacity assessment and addressing another potential cause of nonadherence. For example, command auditory hallucinations regarding medications may place a patient at greater risk of discontinuing immunosuppressants post-transplant. One potential psychotic symptom which can interfere with treatment is a delusion in which patients think they are protected from the effects of organ failure by supernatural intervention [8]. However, the existing literature suggests that psychotic patients may sometimes appreciate the burden of their illness to a tragic degree. A case report of patient with schizotypal personality disorder undergoing transplant described the patient's death by suicide 3 months after transplant. Although he had seemed psychiatrically stable to his providers, he was found with wrists cut in his bathroom and the bill for his transplantation in the waste basket nearby [16]. Thankfully, another 2015 report of transplant patients with psychotic illness outlined an additional nine cases in which long-term positive prognosis and medication adherence were maintained [6]. All of these examples further underscore the necessity of the pre-transplant evaluation in characterizing and addressing concretely how the patient's psychiatric history and life circumstances might impact their care.

Following the pre-transplantation evaluation, the transplant psychiatrist must also consider the reciprocal effect transplantation may have on the patient's psychiatric care. In VG's case, this included both the neuropsychiatric sequelae of immunosuppressant drugs as well as the expected changes in drug metabolism inherent to hepatic transplant. Calcineurin receptors and associated calmodulin-dependent protein phosphatase play significant roles in both the immune and central nervous systems. Immunologically, calcineurin activates T-cell-mediated transcription of cytokines to mount an immune response. Within the central nervous system, calcineurin also appears to activate neurite extension, increase synaptic plasticity, and learning and memory. Additionally, mice models with calcineurin gene knockouts have demonstrated disorganized behavior reminiscent of psychosis [17]. However, calcineurin's position as an immunologic gatekeeper has made its blockade the mainstay target for immunosuppression. Thus, neuropsychiatric symptoms appear to be an inevitable risk with transplant immunosuppression. As the cornerstone of calcineurin-mediated immunosuppression, tacrolimus has demonstrated a relatively higher risk of neuropsychiatric symptoms compared to cyclosporine or mycophenolate. The adverse effects associated with tacrolimus range from mild tremors to treatment-resistant psychosis and mania [18]. A 2020 case report in *Psychosomatics* even reported mania in the presence of supratherapeutic tacrolimus trough levels in a patient with no past psychiatric history. As reflected in previous cases, the patient in this study required discontinuation of tacrolimus as well as treatment with antipsychotics and mood stabilizers [19]. However, supratherapeutic tacrolimus levels are not a prerequisite for decompensation of psychotic illness. A 2013 case report by Ithman et al. is notable in that a previously stable patient with Bipolar I Disorder decompensated into treatment-resistant mania with psychosis following an increase in tacrolimus level within the therapeutic window. This patient would go on to be resistant to increases in olanzapine and divalproex, ultimately improving with cross-taper of tacrolimus to cyclosporine [20].

Another common concern among transplant teams may be the risk of steroid-induced psychosis. Despite some of the first neuropsychiatric side effects of steroids being identified as early as 1950, most studies to date have focused on the medical sequelae. The Boston Collaborative Drug Surveillance Program in 1972 noted a 3% incidence of psychiatric side effects in 718 hospitalized patients receiving

prednisone. This incidence was found to increase with 18.4% of patients demonstrating some psychiatric symptoms at doses greater than 80 mg per day. However, this study did not demonstrate a significant correlation among magnitude, type, or duration of symptoms [21]. A 2012 review in *Psychosomatics* examined the literature published since the Boston group's original publication. Unfortunately, given the exclusion of psychiatric symptoms and history, it is difficult to generalize regarding the use of corticosteroids in the psychiatric patient. However, the review noted that of 55 patients in which psychiatric history was included, only 12% demonstrated neuropsychiatric adverse effects following steroid treatments. There was no correlation between neuropsychiatric adverse effects and family history of psychosis. Additionally, antipsychotics appeared to be effective in treating steroid-induced psychotic symptoms [22].

In considering VG's treatment history, the risk for refractory psychotic illness must be considered. While there was likely a significant contribution of his alcohol use to prior symptom relapses, prudence suggested optimizing his antipsychotic regimen in addition to increased monitoring of tacrolimus levels. Fortunately, hepatic transplant itself may have expanded opportunities to improve VG's psychiatric care. It is also important to recognize one of the commonly used calcineurin inhibitors, tacrolimus, is associated with QT prolongation and drug interactions should be considered. As noted in the case description, the patient was transitioned to paliperidone to avert worsening hepatic function as well as maintain treatment effectiveness given its bypass of CYP2D6 function [23]. Restored hepatic metabolism post-transplant opened the opportunity for alternative treatment considerations should VG experience relapse of psychotic symptoms. Clozapine, given its previous benefit, could be re-trialed with close monitoring, particularly if tacrolimus-induced psychosis required change of antipsychotic regimen. While typically discouraged, a treatment refractory case may warrant antipsychotic polypharmacy, which prior to transplant would be inadvisable. However, a recent JAMA Psychiatry cohort study identified that clozapine with aripiprazole decreased the risk of re-hospitalization compared to clozapine monotherapy over a 20-year follow-up period [24]. Improved hepatic function post-transplantation also increases the variety of long-acting injectable antipsychotics available to the patient. Consideration of long-acting injectable in the post-transplantation period presents a dual advantage of both sustained adherence to antipsychotic regimen as well as decreasing the burden of maintaining the extensive medication regimen required in the post-transplantation period. In VG's case, contingency planning regarding his psychotropic regimen was as crucial as initial optimization.

Finally, but perhaps most importantly, the transplant psychiatrist may find themself at the center of the multidisciplinary team advocating on the patient's behalf. Although more investigation is needed in determining which factors most impact transplant outcomes in patients with psychotic disorders, the role of adequate psychosocial support appears inarguable. Case reports and small studies suggest that poor psychosocial supports appears to be one of the most predictive variables for poor graft outcomes [11]. Living alone, or homelessness have been cited as some of the largest contributors to nonadherence to immunosuppressive therapy. One study noted that nonadherence was observed among 45.5% of homeless patients as opposed to 9.5% of patients living with family or another individual in the same dwelling. In the same study, patients with schizophrenia were noted to be more likely to miss appointments and be medication noncompliant than patients with other psychotic illness such as bipolar disorder [8].

Considering VG, there were both protective and risk-inducing factors regarding his social circumstances. For example, moving in with his mother significantly improved his likelihood of graft success and long-term outcomes. However, his primary thought disorder placed him at a distinctly increased risk for graft failure over other psychotic patients. Despite this, VG's access to intensive community services was an undeniably mitigating factor since it provided him with close monitoring by his primary psychiatric provider as well as social work and case management. Ultimately, post-transplant management of VG's case did not directly involve transplant psychiatry, and thus relied on adequate communication and coordination between the transplant service and his outpatient care team. An important aspect of such a handoff is closed loop communication among all parties involved. This consisted of family meetings with the treatment team that included VG's mother as a care partner, as well as review of treatment regimen provided by both the psychiatric and transplant physicians. As this can be a costly process, social work played an important role in screening and identifying potential financial barriers or housing instability that could have jeopardized VG's participation in his care. These barriers may also eventually necessitate that VG's mother return to work or obtain employment that reduces her capacity to constantly monitor her son's activity. As such, community mental health programming in a supervised environment should be considered a part of his transplant treatment plan to provide VG with social interaction and support as well as an environment conducive to maintaining sobriety and remission from psychosis.

Patients with chronic psychotic illness are at an increased risk for chronic disease, substance use, and overall mortality. Unfortunately, they are also uniquely disadvantaged in their access to transplant services. Yet, the data garnered thus far demonstrate that given the appropriate care, transplant patients with psychotic illness may be afforded transplant outcomes on par with the general transplant population. With appropriate pre-transplant assessment, adequate periopera-

tive care and planning, and engagement of the multidisciplinary team post-transplantation, it is possible to close the equity gap of the seriously mentally ill in transplant medicine.

Take Home Points

1. While *active* psychosis is often viewed as a relative or absolute contraindication to organ transplantation, with good pre-transplant assessment, mental health stability, treatment planning appropriate for the severity of illness, and social support patients with serious mental illness can have post-transplant outcomes similar to patients without mental illness.
2. Poorer graft outcomes for psychotic patients are closely tied to nonadherence, concomitant substance use, and especially poor social supports.
3. While the transplant psychiatrist can advocate for patients with serious mental illness, careful evaluation and preparation of a potential candidate are essential. Care should be optimized through detailed and inclusive pre-transplant evaluation, careful consideration of psychopharmacological management with contingency planning, and engagement of a multidisciplinary care team.
4. Successful outcomes post-transplant depend on stable social support and close engagement with transplant and mental health teams.

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Anxiety, Cystic Fibrosis, and Organ Transplantation

5

Anna Lisa Derrien

Introduction

Anxiety disorders are among the most common psychiatric disorders, and in patients with chronic illnesses, anxiety is even more common [1]. In patients awaiting lung transplantation, it has been estimated that up to 40% of patients have a current anxiety disorder [2]. In our experience in a cystic fibrosis clinic, untreated or under-treated anxiety disorders in patients in need of organ transplantation can contribute to multiple adverse effects including care avoidance, medication nonadherence, substance abuse, psychosocial distress, and negative medical outcomes, affecting both pre-transplant and post-transplant care.

The assessment of eligibility for organ transplantation involves many components including multiple medical appointments and tests, screening for alcohol and drug use, and assessment of psychosocial circumstances. Patients under consideration for transplant have a significant disease burden, often chronic and progressive over years. The listing process involves a detailed assessment, wait, and uncertainty. In patients with anxiety disorders, coping with the scrutiny of assessment, uncertainty of transplant listing, and subsequent wait for an organ can exacerbate anxiety symptoms, such as the excessive apprehensive expectation in generalized anxiety disorder (GAD). Organ transplant programs commonly require patients with active psychiatric illness to engage in treatment during the pre-transplant period. During this time, management of anxiety can be optimized with psychoeducation, medication, psychotherapy, lifestyle modifications, and/or attention to psychosocial factors that may be contributing to functional impairment.

Patients with cystic fibrosis (CF) in particular frequently anticipate future needs for lung transplantation. CF, a chronic lung disease with multi-organ involvement caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel gene, is one of the most common genetic disorders among Caucasians in the United States (US) [3]. Most patients are now diagnosed in infancy with newborn screening (in all states since 2010) and grow up with the understanding that they have a progressive, life-limiting disease. Despite the recent advancements with the introduction of CFTR modulator medications, lung transplantation is an option for many patients with advanced lung disease due to CF to improve duration and quality of life, with criteria for candidacy at times varying among the centers [4]. Eligibility for transplantation is usually considered longitudinally, with the goal of early referral before acute need is present in order to begin education and optimize candidacy. Among other factors, symptoms of anxiety and other psychiatric symptoms can influence the decision to be considered for lung transplantation.

Anxiety and depression are especially common in patients with CF, with an estimated one-third of adult CF patients experiencing substantial anxiety symptoms [5]. From a developmental perspective, patients with CF might deal with a sense of foreshortened future, early familiarity with severe illness, disrupted family dynamics, and varying ability or desire to grapple with the likelihood of early mortality. From a physiological perspective, illness itself, through as-yet poorly defined pathways related to inflammation and stress, is thought to contribute to the development of psychological distress. As with other respiratory diseases, anxiety related to dyspnea and hypoxia can occur in patients with CF as the disease progresses, with anxiety both triggered by and contributing to difficulty breathing. In some patients, unnecessary medical appointments and testing may be requested as the result of frequent reassurance-seeking. In contrast, procedural anxiety can develop with frequent exposure to invasive testing during times of illness and directly lead to avoidance of care.

In addition, anxiety symptoms related to organ transplantation can influence patients with CF at many stages of life. Since the potential future role of organ transplantation is

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generally considered early in the course of illness, anxiety related to transplant can begin with anticipation well before there is a medical need. Anxiety can also occur during periods of early education at CF care centers, in the setting of pre-transplant assessment and listing, and as part of post-transplant life. The pre-transplant period, during evaluation for candidacy, is particularly difficult for many future organ recipients, with high rates of active anxiety disorders [2]. Symptoms such as excessive worry, avoidant behaviors, irritability, catastrophic thinking, and fatigue can be both distressing and detrimental to health. Psychological distress due to depression and anxiety has been associated with many negative outcomes in patients with CF, including reduced lung function, poorer adherence with care, more frequent hospitalizations, and decreased quality of life [6]. The following case is fictional and reflective of select issues commonly encountered in CF patients with generalized anxiety. In this case, the role of anxiety in the decision for a patient with CF to be referred to a transplant center will be explored.

Case History

KG is a 30-year old married woman with a history of cystic fibrosis (CF) and generalized anxiety disorder (GAD) who is under consideration for lung transplant candidacy. She was diagnosed with CF at 2 months of age and has many extrapulmonary manifestations of CF, including CF-related diabetes and malnutrition due to pancreatic insufficiency. Her body mass index is 19, which is significantly below the goal for a female patient with CF. Her lung function has progressively declined in adulthood, as is typical in CF, with a forced expiratory volume (FEV1) of 35% predicted at age 29. KG has reported adherence with recommended care, including prescribed medications, exercise, and airway clearance. She has had three hospital admissions in the last year for respiratory infections. For several years, her medical team has attempted to discuss indications for lung transplantation with her, with the goal of early referral to optimize eligibility before acute need for listing for transplant. She has been reluctant to consider this referral.

KG was diagnosed with GAD in adolescence and was briefly treated with sertraline at age 16 before self-discontinuing due to preference to take fewer medications. She has never been in psychotherapy. She has never required inpatient psychiatric care. In her 20s, she smoked cannabis recreationally as an "escape," but has reported cessation for several years. She does not use alcohol or other recreational drugs. She denies a history of trauma. Her mother also has been diagnosed with GAD and is treated with an SSRI. She does not report any other family psychiatric history.

KG's anxiety symptoms for the last several years include excessive worry most days of the week about her health, the security of her job and her family, and frequent apprehensive anticipation. She often experiences restlessness, irritability, and difficulty falling asleep and will spend hours at night reading internet forums about CF and lung transplantation. She does not experience panic attacks. For the last 5 years, she has been prescribed escitalopram 20 mg with improvement but not remission of symptoms. She is able to work part-time as a school librarian and enjoys spending time with her husband and other family members. She denies feeling debilitated by her anxiety symptoms but often appears to be under-reporting the effect that her excessive worry has on her daily life. Her care team has been concerned that on several occasions, she has postponed medical care for respiratory infections until very ill, with suspicion that she defers hospitalization due to anxiety. Despite the recommendation by her psychiatrist in the CF clinic, KG has declined change in her psychotropic medication and referral to psychotherapy.

Over the last several years, attempted discussions with KG about lung transplantation during her clinic appointments have been met with resistance. KG has often declined to discuss the potential indication for future transplant, stating that she feels healthy and does not think it is necessary. She has refused discussions about the referral process and benefits to early referral. When meeting with her CF social worker and psychiatrist, she at times has become tearful, stating that she "just can't think about it now."

At one of her most recent CF appointments, KG was told by her pulmonologist that her lung function had declined to the point that consideration for transplant listing was becoming medically necessary, with FEV1 25% of predicted. It was explained to her that if she did not wish to pursue lung transplant, her alternative goals of care needed to be more explicitly established. Her care team provided education about the risk of rapid decline with acute illness and encouraged her to begin to form her own advanced directives.

After this conversation, KG endorsed increased anxiety but was more forthcoming with her CF care team about some of her concerns related to transplant. Multiple themes arose including worry about the scrutiny involved in assessment for eligibility, concern about transplant assessment as a signifier of advanced illness, desire to avoid contemplation of her own mortality, and conflicting feelings about her worthiness of a limited resource that could help another person. She was also worried about potential negative transplant outcomes as she had read narratives of other CF patients' difficult experiences on the internet. KG expressed that she would be willing to think about a referral to a transplant center in the future but for now, she continued to decline the initial transplant assessment.

At this appointment, KG agreed to meet with the psychiatrist in the CF clinic more often (monthly rather than quarterly visits) to further explore her thoughts and feelings about transplant, but did not attend her scheduled appointments. When seen during her most recent quarterly CF visit, she

reported that she had been spending a lot of time alone, researching transplants and her anxiety symptoms online. She wondered whether cognitive behavioral therapy (CBT) might help her. She was disappointed to learn that structured CBT would not be available at the CF clinic due to staff availability. She expressed concern about ability to attend appointments at another clinic, but was agreeable to referral.

Clinical Questions

1. Could KG's anxiety have been better managed to improve her likelihood of transplant eligibility?
2. Should other interventions or treatment modalities have been attempted?
3. What is the role of the multidisciplinary care team in guiding discussion about organ transplant?

Discussion

KG's anxiety disorder is the main obstacle in her referral to a lung transplant center. While the decision whether to pursue transplant is her own, her anxiety symptoms interfere with her becoming educated enough to make an informed decision. Anxiety-related issues, including avoidant behaviors, catastrophic thinking, and fear of scrutiny, have profoundly shaped KG's experience of her illness and ability to consider treatment options.

In terms of avoidance, KG's anxiety disorder manifests as pervasive efforts to avoid worry-inducing situations and subjects of conversation. While she endorses spending hours worrying about topics related to her health and other aspects of her life, such as the security of her job, she tends to avoid confronting her worries and does not engage in proactive steps to address the causes. She worries about whether her job as a librarian is secure given her occasional absences due to illness, but avoids discussion with her employer about her attendance. She researches various illness symptoms she has on the internet, but does not make a timely medical appointment to be evaluated, and often perceives herself to be healthier than she is. She fears illness progression, but due to debilitating anxiety when imagining her health decline in the future, avoids discussion about interventions, including lung transplantation. Although aware that she has a life-limiting diagnosis, ultimately, she attempts to avoid contemplating her own mortality because of the heightened anxiety such explicit thoughts cause.

Although KG denied any specific history of childhood trauma, adverse early childhood experiences including experience of childhood chronic illness have been shown to affect psychosocial functioning in adulthood. Studies of young adults who survived pediatric illness into adulthood have demonstrated that childhood experiences with high disease burden, disrupted family dynamics, disclosure decisions regarding illness, and many other factors can affect illness cognitions and coping styles in adulthood [7]. In particular, avoidant coping strategies, such as those observed in KG, have been noted to develop in some patients with chronic diseases, and are associated with increased mental illness and decreased quality of life [8].

KG's concern that referral for transplant assessment is a signifier of advanced illness has led to her avoidance of discussions regarding lung transplantation. It is difficult to contemplate organ transplantation without thinking about one's own mortality, and for some patients, transplant referral suggests "the beginning of the end." Though survival rates after lung transplants have improved, predicting survival in patients with CF is difficult, and on average the median survival after lung transplant in patients with CF is about 8–9 years, significantly lower than other solid organ transplants, though higher than in patients with other chronic lung conditions [4]. Although transplantation has been shown to improve duration and quality of life (including physical symptoms, energy, sleep, and social functioning) [9], for a patient such as KG who has not fully accepted the extent of her illness, such survival statistics are a stark reminder of mortality. In some patients, cognitive distortions such as magical thinking may occur, with the belief that transplant evaluation itself decreases survival. In this way, anxiety related to death and dying may paradoxically contribute to earlier death due to excessive avoidance of indicators of serious illness.

The transplant assessment involves detailed evaluation of a patient's medical and psychosocial history. It includes imaging, bloodwork, and review of past participation in medical care. For patients with CF like KG, this includes assessment of past adherence with care, including frequent medical appointments and an intensive daily regimen including medications and chest physiotherapy multiple times per day. Assessment also involves evaluation of living environment, social supports, substance use, and other psychosocial factors. KG was able to verbalize that such scrutiny into her current and past choices—such as past drug use—exacerbates her anxiety about her self-worth and triggers self-conscious concerns about her deservingness for an organ transplant. The possibility of such a detailed assessment of the state of her illness, lifestyle choices, and adherence with care provoked intense anticipatory anxiety. Although KG did not deal with other difficult issues such as current homelessness, an active substance use disorder over the last 6 months, or the absence of any reliable social supports, which could be potential contraindications to transplantation [10], she worried about the presence of barriers to candidacy, such as past cannabis use, that would result in unbearable scrutiny.

By the time KG was receptive to discussion about organ transplantation, her referral had already been delayed by years, and her lung disease, by consensus guidelines and as

assessed by her CF care team, was advanced enough that a referral was "medically necessary." This means that her predicted survival from CF-related respiratory illness was less than her predicted survival with lung transplantation [4]. For her to be assessed for lung transplant, she would need to be referred to a transplant center located—as it is for many patients—in a different city (and in KG's case, a different state) from where her primary CF care is received. She would need to begin to build rapport with a new and unfamiliar treatment team, which is challenging for many patients but especially so for patients with anxiety disorders.

Due to her anxiety symptoms, KG was unable to experience the benefits of an early transplant referral, before acute need for listing was anticipated. With early referral, she and her family would have had more time to participate in education about the transplant process. In a transplant-focused psychosocial assessment, her psychiatric symptoms and potential need for treatment could have been identified, her understanding of the transplant process and motivation explored, and her ability to provide informed consent assessed. If potential barriers to transplant were identified, there would have been more time for treatable or reversible barriers to be addressed. For KG, declining referral to a transplantation center resulted in not having the opportunity to engage in this transplant-focused assessment.

One area for intervention is the optimization of KG's psychiatric care before any transplant referral occurred, such as through more frequent behavioral health assessments, optimization of medications, and earlier referral to psychotherapy. The Cystic Fibrosis Foundation provides guidelines for depression and anxiety screening and treatment, including the annual screening of all adult patients for depression and anxiety using standardized rating scales [6]. Treatment guidelines are tiered based on the severity of symptoms, ranging from psychoeducation for those with mild symptoms, psychotherapy (such as CBT or interpersonal therapy) for moderate symptoms, and exposure-based CBT for severe anxiety. Psychopharmacologic guidelines are also provided, with selective serotonin reuptake inhibitors (SSRIs) (i.e., citalopram, escitalopram, sertraline, and fluoxetine) recommended for patients with moderate to severe depression and anxiety for whom psychotherapy is not available or ineffective. The short-term use of lorazepam is recommended for moderate to severe anxiety related to medical procedures not responsive to behavioral interventions alone [6].

Given that KG's persistent anxiety symptoms were identified through screening as well as routine visits with her pulmonologist and psychiatrist, it would be ideal for her to engage in more frequent care with her CF psychiatrist to consider medication adjustments and other treatment strategies. Psychopharmacologic adjustments may be helpful, such as switch to a SSRI since KG has been treated with the same medication at a therapeutic dose for years. In our experience at our CF center, mirtazapine is also effective in treating depression and anxiety with associated insomnia and low weight and may be a reasonable option. Atypical antipsychotics can be useful for augmentation of SSRIs, with weight gain and sedation at times desirable side effects. While KG's renal and hepatic function were intact, dose adjustments need to be considered in CF patients with renal or hepatic impairment or in cases of drug–drug interactions, such as use of a CFTR modulator lumacaftor that increases hepatic metabolism of some SSRIs [6]. In addition to medication management, KG would also benefit from psychotherapy to explore maladaptive cognitions and behaviors contributing her anxiety.

An area important to highlight in psychotherapy is that some aspects of anxiety can be adaptive in chronic illness. In order to successfully manage her disease from childhood, KG needed to pay close attention to a rigorous daily schedule of medications, airway clearance, exercise, and appointments in addition to the usual activities of daily life. Apprehensive expectation promoted adherence, as variance from routine could lead to significant negative consequences. Hypervigilance about somatic symptoms was often reinforced, as infections could be caught early; in contrast, periods of care avoidance allowed for temporary escape from the burdens of chronic illness. Exploration of the ways in which previously adaptive anxiety can become detrimental—such as through the structured approach of CBT—may be an opening into KG's own understanding of her illness.

Access to mental health care is a historical barrier to care for many patients that has improved in recent years, but as KG's case highlights, has not been eradicated. With recent efforts to expand mental health services at CF centers (e.g., collaborative care model clinics, referral networks of community-based mental health providers, telehealth technology, and mental health coordinators within CF clinics), accessibility of mental health care has improved in some areas compared to decades ago. KG was fortunate to have a psychiatrist embedded in her clinic twice a month; however, the clinic did not have on-site psychotherapist available to see patients on a regular basis and the clinic had not yet trained other staff in providing CBT. Unfortunately, this meant that even as KG became motivated to participate in therapy, ease of access limited her ability to engage in care.

Given KG's early reluctance to engage in in-person conversations about transplant, use of alternative or supplemental media may be a way to meet her at her current level of engagement. One option is for her to be directed to reliable sources of information on the internet, such as the Cystic Fibrosis Foundation (CF Foundation) website and The International Society for Heart and Lung Transplantation, which maintains a list of educational resources for patients

on its website [11]. If attending traditional in-person psychotherapy is not feasible or desirable, use of other media, such as video therapy sessions, manualized therapy workbooks, or mobile device-based CBT, is an alternative that can provide effective treatment and may lower the barrier to entry into more traditional therapy [12]. Major internet-based companies as well as traditional clinics and individual providers are increasingly offering internet-based options for psychotherapy [13]. In addition, new modalities are being explored, such as a CF-specific CBT-based preventive intervention for depression and anxiety that can be administered in a number of modalities, such as in clinic, by phone, or on inpatient units, and that can be provided by multidisciplinary members of the CF care team rather than limited to mental health professionals [14].

The facilitation of peer connections is another way in which to improve KG's experience of illness. Notable in KG's case is her relative social isolation, with anxiety exacerbated by information gathering from internet sources of uncertain accuracy. By connecting KG directly to other patients with CF who have had experiences with lung transplantation, she would have the opportunity to learn from peer mentors and expand her perspective on what organ transplant can mean. For example, the CF Foundation provides a program called CF Peer Connect, which is a one-on-one peer mentoring program for adults with CF and their families, with support provided remotely by phone, video, email, and text [15]. Many other transplant support programs also exist through other professional organizations, hospital-based groups, internet support groups, and local groups for pre- and post-transplant patients and their families.

Finally, the role of the approach of care teams in discussing organ transplant before the time of referral should not be underestimated. CF Foundation Consensus Guidelines provide recommendations for lung transplant referral, including how to best address the topic with patients to optimize receptiveness. These guidelines note that "anticipatory guidance" provided to relatively healthy individuals is important in order to optimize the transplant referral process [16]. Normalization of the discussion of transplant during times of health can relieve anxiety. When such conversations begin outside the context of health deterioration, they are less likely to provoke negative reactions, such as fear, denial, or avoidance. The attitude of providers is also important and physicians perceived as having a negative bias toward transplant are linked to patients with increased anxiety and sense of personal failure [16]. Clinician avoidance may contribute to patient avoidance. For KG, perhaps if introduction of discussion of transplant had begun at an earlier age and with multiple members of the CF multidisciplinary team, the topic would not have held the same power to provoke anxious emotions and avoidant behaviors. Now that she is at a turning point and beginning to engage in discussion about transplant, attention should be paid by all care team members to the way the subject is discussed to promote informed, rather than anxiety-driven, decision-making.

Take Home Points

1. Anxiety disorders can interfere with patients' consideration of and eligibility for organ transplant.
2. Early steps should be taken to optimize treatment of anxiety disorders in patients with chronic health conditions prior to acute need for organ transplantation.
3. Potential areas for intervention, in addition to medication and traditional psychotherapy, include use of new media applications, enhanced peer support, and nuanced attention to the way organ transplantation is approached by care teams, ideally well before there is medical necessity for transplant.

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Panic Attacks in Transplant Recipients

6

Tsung Wai Aw

Introduction

Cardiopulmonary disease and panic attacks often co-occur and overlap significantly in clinical presentation and physiology. Patients with panic disorder have a higher risk of myocardial infarction under 50 years of age and a higher risk of cardiac disease at any age [1]. The point prevalence rate of any anxiety disorder in patients with cardiovascular disease is about 16%, increasing to 50% in patients with cardiovascular disease who are also suffering from depression [2]. The rate of panic disorders in post-transplant patients varies from 8% in post-heart transplant patients to 18% in post-lung transplant patients [3].

Both cardiopulmonary diseases and panic attacks can present with chest pain shortness of breath, palpitations, and diaphoresis and this can lead to difficulties in diagnosis. Even patients without any cardiopulmonary history who develop symptoms like chest pain or shortness of breath will tend to seek out general medical care prior to considering that their somatic symptoms might have a psychological explanation. Conversely, in a patient population prone to cardiac symptoms that are extremely similar to symptoms of panic attacks, mental health professionals may not initially consider a psychiatric cause when a patient complains of palpitations, shortness of breath, or diaphoresis especially early after transplantation. Misdiagnosis is possible, as illustrated by a case report of a patient complaining of dyspnea and paresthesia who was initially discharged home with a diagnosis of panic attacks, only to return to the emergency room 1 month later to discover the symptoms were unfortunately due to dilated cardiomyopathy [4]. In heart transplant recipients, cardiac arrhythmias are common: up to 60% of patients experience non-sustained ventricular tachycardia at some point post-transplant [5, 6]. Therefore, it is not surprising that in this group palpitations or chest pains will be first considered a manifestation of cardiac illness rather than an expression of anxiety.

Heart disease and anxiety share physiological changes that partially explain why two conditions frequently coexist, with increased level of catecholamines being at the center of this overlap [7–9] One theory described a possible link between panic disorder and idiopathic cardiomyopathy, but not other cardiac illness [7], postulating that the link between the two is likely due to the possible increase in peripheral catecholamine production during panic attacks, and/or dysfunction of the autonomic nervous system, specifically an increase in the centrally mediated cardiac sympathetic tone which could then cause idiopathic cardiomyopathy. Levels of plasma norepinephrine are shown to predict prognosis in congestive heart failure [10]. It is assumed that in patients with severe cardiac disease, the catecholamine levels are raised triggering panic attacks, with the relationship therefore being bidirectional.

Heart transplant recipients with panic attacks are particularly at risk of negative outcomes due to physiological and psychological factors. Depression and anxiety are risk factors of mortality for patients with heart disease, in particular to those with congestive heart failure [11]. Depressive, anxious, or panic states decreases heart rate variability [12] which is a predictor of worse cardiac outcomes [13]. In heart transplant recipients, heart rate variability is usually decreased post transplantation due to surgical loss of vagal innervation. This creates an unopposed sympathetic stimulation to the heart, which likely raises the risk of mortality if panic attacks were to occur unchecked [13].

Pulmonary diseases and panic attacks are highly comorbid as well. Prevalence rates of panic attacks in Chronic Obstructive Pulmonary Disease (COPD) patients can be as high as 67% [14]. Patients with panic disorder have an increased sensitivity to carbon dioxide [15], which could explain the increased comorbidity. The need to breath is also central to our ability to live, with ambiguous physical respiratory sensations causing catastrophic misinterpretations,

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leading to an episodes of panic [14]. Panic attacks have also been shown to produce a higher than expected levels of lactate [16]. Elevated lactate level can signal severe deoxygenation of tissues in which case, this could be impairing graft healing in a post-transplant patient or damaging the new graft the patients have just received [16].

Behaviorally, patients who are suffering from panic attacks in the hospital are less likely to participate in their care usually due to their avoidant behavior they develop in reaction to panic attacks. They may appear as less motivated for recovery than their peers who do not suffer from panic attacks, leading to a reduction in physical therapy sessions, less out of bed time, all of which would lead to poorer outcomes or delayed recovery. Occasionally, these patients may increase the burden on the nursing and ancillary staff, as they could present as being possibly more demanding than other patients on the unit, leading to staff consciously or unconsciously attempting to reduce their interactions with these patients [17].

Undergoing a transplant would be considered a significant life event for most patients, one that could negatively impact their psychological health despite improving their physical one. Despite the close association of symptoms between anxiety-related disorders and cardiopulmonary disorders, there is very little written about the rate of development of panic attacks or disorder post-transplant or its treatment. As mentioned above, one study found an 18% prevalence rate of patients with panic disorder about 2 years post lung transplant and 8% post cardiac transplant, only 2% of them with panic disorder pre-transplant [3]. A meta-analysis of the mental health literature in organ transplant recipients found while depression increases the risk of post-transplant mortality, anxiety did not significantly do so, although few studies examined the impact of anxiety on poor outcomes [18].

This overlap of symptoms and physiological mechanisms between anxiety and cardiopulmonary disease supports the multidisciplinary approach to the care of transplant recipients.

In this chapter, we will discuss one case in which the patient underwent orthotopic heart transplantation and developed panic attacks within the recovery period while still hospitalized. We will explore the possible differences in how we can approach evaluating panic attacks in patients who underwent transplantation.

Case History

Mr. A is a 65-year-old male with a history of generalized anxiety disorder (GAD) who prior to his cardiac transplantation was prescribed Paroxetine-CR 12.5 mg once a day, Alprazolam 0.5 mg three times a day as needed and Temazepam 15 mg as needed at night for sleep. His anti-anxiety medications had been prescribed by his primary care provider. He was also seeing a psychotherapist every 2 weeks for cognitive-behavioral therapy for anxiety. Prior to transplantation, he had been on the transplant waiting list for 2 years. During this time, he underwent several episodes of disappointment being alerted to the possibility of a potential transplant, but the surgeon rejected the donated heart due to the poor quality of the organ. In time, he had grown to expect these calls with a mix of hope not only about the possibility of getting a heart and anxiety about possible repeated disappointment but also about risk of dying waiting for the transplant or during surgery.

He underwent the heart transplant successfully, recovering well initially and was transferred out of the Cardiothoracic Intensive Care Unit (CTICU) within a week post-transplant. He reported that during this period, he did not have any difficulty with anxiety and had started ambulating around the CTICU. As he did not appear anxious, paroxetine and temazepam were not restarted post-operatively. Alprazolam was ordered as needed, however, patient used it sporadically (on average 0.5 mg every 48 h).

Psychiatry was consulted on day 7 post-transplant. Although he never had panic attacks prior to transplant, he now reports experiencing nocturnal panic attacks, waking up diaphoretic, with palpitations and feelings of discomfort and dread. This has been causing insomnia. He also reports worsening anxiety during the entire day, worse than pre-transplant with no clear precipitating event.

The medical team had performed initial laboratory work up prior to consulting us. His complete blood count, basic metabolic panel, liver function tests, and tacrolimus levels came back within normal limits. His electrocardiograph showed sinus rhythm. Telemetry monitoring showed no evidence of abnormal rhythm. A review of his medication list showed two possible contributors to his anxiety, tacrolimus and prednisone. He was on a prednisone taper, being on 25 mg twice a day at the time when the panic attacks started. Benzodiazepine withdrawal was ruled out, as his family and prescription records indicated he was not taking benzodiazepines daily and there was no indication of physical dependence.

He then developed difficulty with working with physical therapy due to anxiety of not being able to ambulate. He feels that he is taking "steps backwards" although his overall clinical status was improving. He became very irritable, being short with the nursing staff, and later feeling guilty about it. "I feel like I am getting depressed," "One step forward and four steps back."

Our team recommended olanzapine 5 mg once a night, switched his alprazolam to clonazepam 0.5 mg twice a day as needed, especially when working with physical therapy. His paroxetine was also restarted.

At follow-up visit 3 days later, he was sleeping well, without any nocturnal panic attacks, and had been able to work

with physical therapy. Seven days after the initial psychiatric consultation, patient no longer had panic attacks, he was sleeping well, his olanzapine was discontinued. He continued with paroxetine 10 mg once a day with the plan to only use clonazepam 0.5 mg twice a day as needed and taper down as an outpatient without restarting alprazolam or temazepam.

Clinical Questions

1. What elements of history or psychiatric interview help differentiating panic attacks from symptoms of cardiopulmonary disease?
2. Are there specific treatment approaches to consider for panic disorder in transplant recipients?

Discussion

What Elements of History or Psychiatric Interview Help Differentiating Panic Attacks from Symptoms of Cardiopulmonary Disease?

During the initial process of evaluation regarding panic attacks in this patient, it is important to elucidate the timeline between the sensation of anxiety or despair and the development of somatic symptoms, even though this might not be possible for some patients.

Creating a detailed timeline of how and in what order symptoms developed could potentially tell us if a patient has a specific precipitating factor for the panic attacks, or if a sense of dread or other cognitive distortions could have preceded the somatic symptoms. Telling the detailed story ("ICU diary") is not just helping the diagnosis, but it may have a therapeutic role in reducing the post-ICU anxiety [19].

A history of having panic attacks prior to the development of cardiopulmonary illness, a history of other anxiety disorders (in the case above, the presence of GAD), persistence of low to moderate anxiety even in between attacks, and family history of panic attacks are factors in patient's history that point toward a diagnosis of panic disorder.

Are There Specific Treatment Approaches to Consider for Panic Disorder in Transplant Recipients?

In the literature, there are only two case reports specifically addressing the treatment of panic disorder posttransplant, one from Germany [20] and another from China [21]. Both patients were both were successfully treated with Selective Serotonin Reuptake Inhibitors (SSRIs). In the first case report, the patient developed panic attacks months after transplant, and was referred to psychiatry only 9 months after transplant, which was then successfully treated with sertraline at a dose of 50 mg a day with significant decrease in symptoms after 6 weeks. In the second case report, the patient developed panic attacks 10 years after transplant attributed to her learning by happenstance about the average lifespan for cardiac transplant patients being 10 years. She was treated with citalopram at 10 mg a day with complete resolution of symptoms after 8 weeks. To date, there is no literature on diagnosis and treatment of panic attacks developed by patients during the immediate postoperative period after transplantation.

Do all postoperative panic attacks in transplant recipients require treatment? According to the fifth edition of the Diagnosis and Statistical Manual of Mental Health Disorders [22], the criteria for panic disorder require one or more panic attacks and persistent anticipation anxiety for a month. Some authors have suggested that anxiety returns to normal about 4 months after heart transplantation [23]. In the hospital setting, decisions must be made rather quickly, sometimes before a formal diagnosis is made. In clinical practice, we initiate treatment when the subjective distress is severe, patient is requesting intervention or when anxiety interferes with the overall functioning, with the medical care and the process of recovery.

The use of pharmacological agents after transplantation requires consideration to the pharmacokinetic and pharmacodynamic interactions with immunosuppressants and risk of exacerbating the symptoms of medical illness. A detailed review of psychopharmacology in organ transplant recipients is beyond the aim of this chapter. One excellent summary on this topic can be found in the chapter on Psychopharmacology in Transplant patients, published in Psychosocial care of End-stage organ disease and Transplant Patients, edited by Sher and Maldonado [24].

Selective serotonin uptake inhibitors are the main agents used in treatment of panic disorder. In general, they are easily tolerated; however, they carry the disadvantage of slow onset of effectiveness, which makes them impractical in the hospital setting, when immediate improvement is of essence. Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) are also approved by the FDA for treatment of generalized anxiety disorder and has been shown to be efficacious in treating panic disorders. There are not any studies specifically showing efficacy for SNRIs panic attacks in post-transplant patients, but it would be reasonable to assume that it would be useful as well [24]. SNRIs share the same disadvantage of the SSRI, of a delayed onset of efficacy.

For immediate anxiolytic response, antihistamine, benzodiazepines, and antipsychotics are typically used. Antihistamines have potential for contributing to delirium and there is concern for increased QTc interval, which may exacerbate the effect of some immunosuppressants.

Benzodiazepines are effective for short-term treatment of anxiety; however, they can worsen the postoperative delirium. Atypical antipsychotics are often used in post-transplant patients for treatment of delirium, and they have been reported to be effective in short-term treatment for panic disorder as well [25, 26].

Non-pharmacological interventions should also be considered. Cognitive Behavioral Therapy (CBT) has been shown to be likely the most efficacious psychosocial treatment for panic disorder, with up to 60% response rate [27]. Unfortunately, multiple factors make psychotherapy difficult for transplant recipients, especially early post-transplantation: their physical status, the need for multiple tests and medical treatments or nursing interventions, postoperative delirium or reversed sleep cycle. A recent study suggested that a 10-week self-guided help intervention was as helpful as CBT in treatment of panic disorder [28]. This approach, which allows the patient more flexibility in implementing, may be promising for transplant recipients early post-surgery; however, further studies are needed.

Take Home Points

1. In patients, post-transplant panic attacks may be difficult to distinguish from symptoms of cardiopulmonary illness, or side effects from medications. A prior history of anxiety disorder, cognitive distortions that preceded the onset of physical symptoms and a family history of anxiety disorder increase the possibility that symptoms are related to a panic disorder.
2. SSRI are the mainstay treatment for panic disorder post-transplantation. For immediate reduction of anxiety, atypical antipsychotics are a viable alternative to benzodiazepines or antihistamines which can be deliriogenic in the perioperative phase.
3. A quick response to reducing panic attacks in post-transplant patients would help with the process of recovery by increasing the patients' ability to participate in medical care and contribute to their overall well-being.

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Pre- and Post-Transplantation Post-Traumatic Stress Disorder (PTSD)

7

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Background

Post-traumatic stress disorder (PTSD) will affect 7–8% of the general US population during their lifetime [1–3]. The Diagnostic and Statistical Manual of Mental Disorders defines PTSD as a constellation of symptoms that can include flashbacks, hypervigilance, anger outbursts, and detachment from others [4]. Individuals suffering from PTSD are at substantially increased risk for other psychiatric disorders [3], as well as all-cause morbidity and mortality [5–7].

Relative to the general population, the medically ill are often at increased risk for PTSD. In particular, it has been estimated that up to 17% of solid organ transplant recipients will suffer from PTSD specifically associated with the transplantation process (PTSD-T); this is twice the rate of PTSD in the general population [8]. In transplant recipients who develop PSTD, the process of transplantation can be their first exposure to a traumatic event, or it can serve to "uncover" or "re-ignite" prior traumatic memories [9]. When the transplantation process itself serves as the nidus for post-traumatic stress symptoms (PTSS) or a PTSD diagnosis, the terms PTSS-T and PTSD-T are used.

The prevalence of PTSD-T appears similar across heart, lung, and kidney transplant recipients, but may be slightly lower after liver transplantation. An estimated 10–17% of heart recipients [10–14], 9–15% of lung recipients [15, 16], 15% kidney recipients [17], and 5–12.3% of liver recipients [18–20] will suffer from PTSD-T. Variation in the reported prevalence is likely due to many factors including significant variance among the screening and diagnostic measures used to detect PTSD-T in the transplant recipient population [21].

During the transplantation process, a variety of steps can serve as the inciting traumatic event leading to PTSD-T, including the diagnosis of organ failure [20, 22], the process of waiting for an organ [12, 13, 22], the transplantation surgery itself [20], treatment in the intensive care unit (ICU) during the post-operative period [20], delirium [8, 9, 23], and immunosuppression-related side effects [24].

Prior to transplantation, the psychological evaluation will often include questions pertaining to previous traumatic events. However, for a variety of reasons, patients will not always report prior traumatic experience to providers during the pre-transplantation evaluation. For some individuals, they may have repressed memory of the event, or do not find it salient to report, or they are trying to present themselves in the best possible light given the nature of the evaluation [25]. It does not appear that solid organ recipients are at increased risk for having experienced prior childhood trauma [26], but instead the transplantation process itself serves as a traumatic experience increasing the patient's risk for developing PTSD. A case series by Chernyak, et al. of three lung recipients highlights the challenge in identifying prior exposure to trauma pre-transplantation, but how enhanced methods to do so could improve recipients' outcomes post-transplantation [9].

Risk factors for transplantation-specific post-traumatic stress (PTSS-T or PTSD-T) can be categorized into three groups [8]: medical factors (such as need for extended ICU stay or delirium) [9, 15, 18, 23], sociodemographic factors [13, 18], and mental health factors [13, 15, 18].

Medical acuity at the time of transplantation, prolonged recovery following transplantation, and medical complications including acute organ rejection can increase the risk for PTSD-T [18]. During the immediate post-operative period, most transplant recipients require ICU level care. There is an extensive body of literature describing the relationship

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between care in the ICU and risk for PTSD diagnosis; patients admitted to the ICU have significantly elevated rates of PTSD relative to the general population. In fact, a recent meta-analysis and systematic review revealed that almost one in five ICU patients will develop PTSD within the first year following admission to the ICU [27]. ICU patients who received continuous moderate levels of sedation were more likely to have PTSS when compared to ICU patients who received light or no sedation [28]. Delirium, poor sleep, increased level of sedation (particularly with benzodiazepines), communication barriers, and traumatic memories from the ICU experience (nightmares, hallucinations, pain, and respiratory distress) have all been associated with higher rates of PTSS following discharge from ICU [23, 28–30]. Therefore, recipients who require ICU care, especially prolonged ICU admission, or who suffer from delirium, should be carefully screened for PTSD upon recovery. Following transplantation, acute organ rejection [18], the need for re-transplantation [31], and organ-specific conditions such as post-transplantation chronic dyspnea in lung recipients [15] have also been associated with increased risk for PTSD-T.

Certain sociodemographic variables appear to increase the risk for PTSD-T. Limited social support [13, 18] and female gender [13, 20] have been associated with increased rates of PTSD-T. In contrast, certain psychological traits such as a sense of mastery/control have been associated with a lower rate of PTSD-T [13].

Often described as the opposite of PTSD, post-traumatic growth (PTG) is characterized by positive psychological changes, such as improved interpersonal relationships, being open to new opportunities, an enhanced appreciation for life, an increased perception of strength and spiritual development following a trauma [32]. Factors associated with greater PTG in the solid organ recipient population include higher resilience [33], social support (especially friend support) [33, 34], better perceived health, and, surprisingly, post-transplantation panic disorder [34].

Several different comorbid psychiatric disorders have been associated with an increased risk for developing PTSD-T. In cohorts of heart and lung transplant recipients, a prior history of depression or anxiety has been associated with increased risk for PTSD-T [13, 15].

Solid organ transplant recipients can present with a unique subset of PTSD-associated symptoms. For instance, among heart and lung transplant recipients, two studies found that those experiencing clinically significant symptoms of PTSD were more likely to report hyperarousal and re-experiencing as opposed to avoidance. Of note, these studies did not restrict their investigation to PTSD-T, but instead investigated PSTD symptoms in solid organ recipients, no matter the inciting traumatic event [10, 35].

Following solid organ transplantation, treatment nonadherence is a critical issue, as it can lead to organ rejection, organ failure, and death. It is proposed that some symptoms of PTSD-T, such as avoidance, might increase the risk of nonadherence with the recommended treatment. Indeed, in other medically ill populations, such as survivors of a myocardial infarction, PTSD has been strongly associated with increased risk of nonadherence with medication regimens [36, 37]. In solid organ recipients, a diagnosis of PTSD has been associated with medical nonadherence in pediatric populations [38, 39], while data from adult populations have demonstrated an association between nonadherence and transplantation-related PTSD intrusive symptoms, but not the full PTSD diagnosis [10]. Of note, these studies were looking at PTSD, as opposed to transplantation-specific PTSD-T.

PTSD-T has been associated with lower overall quality of life [18, 20, 21] and decreased health-related quality of life [8, 18, 31]. Notably, Dew et al. demonstrated that PTSD-T was associated with significantly increased mortality after heart transplantation [11]. Patients that develop PTSD-T following transplantation should also be screened carefully for new onset anxiety and depressive disorders, as many patients with PTSD-T may also meet criteria for MDD and panic disorder [15].

There are limited data available regarding evidence-based treatment of PTSD or PTSD-T in solid organ recipients. Internet-based expressive writing has been explored for kidney recipients with associated improvement in transplantation-related QOL, but with limited impact on PSTD-T symptom severity [17]. Currently, providers tend to approach treatment of PTSD-T and PTSD in the transplant recipient population in a manner similar to treatment of PTSD in the general population.

In summary, it is challenging to predict which recipients will experience PTSD or PTSD-T. As is seen in the general population, only a portion of recipients exposed to a stressor will develop PTSD-T, while others can instead demonstrate PTG and resilience [8, 34, 40]. Unfortunately, when PTSD-T develops, only a minority of the patients received treatment for it [12, 15]. Increased awareness of the risk of PTSD-T following transplantation would hopefully improve recipients' ability to access care and, potentially, mitigate the negative effects of PTSD and PTSD-T in this population.

Case History

DN is a 57-year-old white female from rural Alabama. She had been healthy throughout her life, but at the age of 54, she began to experience difficulty breathing during routine tasks such as carrying groceries in from her car and walking to her mailbox. Her internist initially diagnosed her with bronchitis and treated her symptoms with inhalers and antibiotics for 6 months. Her pulmonary symptoms did not improve, and after 9 months she was referred to a local pulmonologist. At the age of 55, DN was diagnosed with idiopathic pulmonary fibrosis (IPF) and began using supplemental oxygen. She

recalled to being shocked by this diagnosis, and its poor prognosis, but denied any symptoms of depression or anxiety. Following the diagnosis, her health declined rapidly, and her pulmonologist referred her for lung transplantation.

DN was evaluated for lung transplantation candidacy by the multidisciplinary transplant team, which included the transplant clinical psychologist and social worker. It was only toward the end of the pre-transplantation psychological evaluation that DN shared some significant childhood experiences. When DN was 10, her mother had died unexpectedly, and the patient was sent away to live with her grandparents in another state. This move was challenging for her, as she was grieving the loss of her mother, did not know her grandparents well, and was struggling with the move from an urban to a rural setting. DN became pregnant in high school and dropped out before graduating. She married the father of her child, and at age 18 she moved with her husband and son to rural Alabama, where her second son was born. Over the years, her husband emotionally and physically abused her, and even tried to kill her by strangling her several times. DN said that he did not abuse her children. When he was incarcerated for trying to kill her, she divorced him at age 50. After her divorce, DN earned her GED and worked in a sewing plant and manufacturing mill.

During the psychological evaluation, DN denied any current symptoms of psychological distress, portraying herself as a resilient woman who coped via active problem solving and persevered in the face of adversity. Despite the physical and emotional trauma DN had experienced previously, she denied a history of any significant depression, anxiety, or PTSD symptoms, and had never received psychiatric or psychological (psychotherapy) interventions. The social worker calculated her Stanford Integrated Psychosocial Assessment for Transplant (SIPAT) score as 19, corresponding to low/medium psychosocial risk level. Scores on the Center for Epidemiological Studies Depression Scale (CES-D) and the General Anxiety Disorder (GAD)-7 did not indicate current psychological distress and supported her portrayal of herself during the interview.

The transplant team determined DN to be a good transplantation candidate from a medical and surgical perspective; however, the team was concerned she did not have adequate social support. Her children, who had remained close with their father, said they could not take time off from work to serve as caregivers. Her ex-husband was recently released from prison and offered to be her caregiver, but DN was not comfortable with that plan. Fortunately, DN had a close friend and a distant aunt who were willing and able to be her caregivers.

Two months after beginning the transplantation evaluation process, DN was contacted by her transplant team and was told had been listed for bilateral lung transplantation on the United Network for Organ Sharing (UNOS) list.

During that 2-month period her health had continued to decline, and she went from using 3 L of supplemental oxygen at rest to requiring 4 L. After being active on the UNOS list for 4 months, DN was called in for transplantation. She was anxious, but grateful. She came to the hospital with her two caregivers. After waiting for 18 h, she was told that the surgeons who went to procure the lungs had decided not to harvest them due to quality issues, so she was told she could return home. At a clinic follow-up visit, the transplant psychologist checked in with her to monitor her psychological functioning after the no-go transplantation, but DN denied any psychological distress, saying, "God has a better set of lungs for me." Three months later when she was requiring 6 L of supplemental oxygen at rest, DN was called in for transplantation again, and this time she received a bilateral orthotopic lung transplantation.

Her surgeons said the bilateral lung transplantation surgery went well and DN had minimal blood loss. However, she had a difficult post-transplantation course and remained intubated for 3 weeks post-operatively. She spent 2 months in the ICU. When the transplant psychologist visited her at 2 weeks post-transplantation, DN was still intubated, but could communicate by writing. DN's friend said that DN was afraid to be alone and was begging her to stay overnight in DN's hospital room. DN shared with the psychologist that she thought the transplant team and the ICU staff were planning to cut her open and remove all her organs. She thought the track on the ceiling of her room (which held the curtain around her bed) was for a saw that would be used to remove her organs. DN thought the transplant surgeons and the ICU staff were holding secret planning meetings to take her organs. Occasionally, DN saw men standing in the corner of her room watching her. DN indicated that she did not tell any of the other transplant team members or nursing staff about her beliefs because she thought "they were in on it." The transplant psychologist discussed her findings with the medical and surgical teams, and the inpatient consultation-liaison (CL) psychiatry service was consulted to evaluate the patient for new onset hallucinations.

The CL psychiatry service saw DN and found that she had mildly impaired attention, was oriented to self and hospital, but not to day of the week or year, and again was reporting perceptual disturbances, all of which were consistent with a diagnosis of delirium. As she had not demonstrated any agitation or other behaviors concerning for inadvertent self-harm, the decision was made to avoid standing antipsychotics, but as needed olanzapine was recommended for agitation or hallucinations. In addition, the CL psychiatrist recommended a thorough medical work-up for infections and other possible organic etiologies that might have been contributing to delirium. A urinalysis obtained at that time was concerning for a urinary tract infection, and a chest X-ray revealed possible aspiration pneumonia versus atelectasis. Antibiotics were started, and DN was successfully extubated a few days later.

As DN's physical status improved, her mental status improved as well. The psychiatrist and psychologist worked together to educate the patient and the patient's caregivers about delirium and validate her emotions. DN expressed embarrassment over the things she had seen and thought, and she was still somewhat afraid she was "crazy" despite education and reassurance from the transplant team.

At her first follow-up visit with transplant psychology, DN shared that although she knew the delusions and hallucinations she experienced in the ICU were "not real" they continued to cause her anxiety and embarrassment. She was also surprised that something that had seemed so "real" was actually not "real" at all. At least twice a day when alone, DN would see the same men that she saw standing in the corner of her ICU room. To avoid these experiences, DN begged people to spend time with her, or she avoided being alone. DN admitted to the transplant psychologist that she was afraid she had developed schizophrenia. She also endorsed trouble sleeping and difficulty concentrating. DN experienced increased anxiety when she had to return to the hospital for outpatient clinic visits, as these visits triggered more distressing memories of what she had experienced postoperatively. In pulmonary rehabilitation, DN had panic attacks on the treadmill and said she had forgotten "how to breathe." DN asked for a nasal cannula with oxygen despite the transplant pulmonologists reassuring her that she no longer required supplemental oxygen.

DN stayed in the area of her transplant center for 4 months to participate in pulmonary rehabilitation and have frequent follow-up visits with numerous members of the transplant team including transplant psychologist and transplant psychiatrist. After a few visits, due to persistent nightmares, irritability, and ongoing avoidance of reminders of her transplantation, the patient consented to starting low-dose sertraline; her symptoms slowly improved over the subsequent months and she continued to benefit from regular psychotherapy.

Clinical Questions

1. How can we improve our ability to predict who will suffer from PTSD-T?
2. Given patients' tendency to present themselves in an overly favorable light during the pre-transplant psychological evaluation, what strategies can be used to ensure we are gathering an accurate history and identifying patients at increased risk for developing PTSD-T?
3. What is the role of pre-transplantation trauma in PTSD-T post-transplantation?
4. What does PTSD-T "look" like in the transplant recipient population (a population who is already instructed to be hypervigilant for any sign of infection, organ dysfunction, and a population who is taking medications that can disrupt sleep, increase irritability, depression, etc.)?
5. What are the optimal treatments for transplant recipients who experience PTSD-T?

Discussion

As discussed above, it remains a challenge for clinicians to predict who will suffer from PTSD-T following solid organ transplantation. However, research has revealed certain risk factors for PTSD-T including demographic factors (female gender) [13, 20], limited social support [18], and prior history of depression or anxiety [13, 15]; while some psychological traits such as post-traumatic growth are protective [13, 32]. Accordingly, a pre-transplantation psychological evaluation can be a valuable resource for identifying individuals who may be at risk for PTSD-T.

Pre-transplantation psychological evaluations involve an assessment of a variety of psychological symptoms, including the presence (or history) of depressive, anxious, and PTSD-associated symptoms. Pre-transplantation psychological evaluations also include an assessment of situational and dispositional coping strategies and the extent to which these strategies are adaptive. This pre-transplantation evaluation can identify who may benefit from psychotherapy to address symptoms and/or provide treatment to maximize coping skills in anticipation of transplantation.

To reduce the risk of patients presenting themselves in an overly favorable light, providers explain the role of the psychologist(s) and psychiatrist(s) on the transplant team, inform the patient that the mental health team will be available for support pre- and post-transplantation, and then conduct a therapeutic interview to establish rapport. Being aware of a prior trauma history may help transplant team psychologists and psychiatrists more quickly identify patients who may develop PTSD-T surrounding transplantation. Even if a patient denies past trauma during the pre-transplantation evaluation, exploring the possibility of a patient having new PTSD symptoms related to a remote trauma is appropriate. Normalizing the possibility of PTSD-T to a patient by explaining the high prevalence of PTSD-T, as well as explaining the benefit of identifying these symptoms early can further improve the patients' willingness to be as open and frank as possible during interviews.

As the patients progress through the transplantation course, they will face certain challenges which can further increase their risk for PTSD-T [8, 9, 12, 13, 20, 23, 24]. Patients may be called multiple times to come in for transplantation, only to be sent home without an organ. Patients can suffer complications arising out of the transplantation surgery that result in prolonged ICU admissions or can suffer from delirium while in the ICU. Previous and current episodes of delirium may contribute to, or even cause, the patients' psychiatric presentation. Asking the patient and

their support systems about their understanding of delirium can provide the opportunity for psychoeducation, as well as a chance to evaluate for symptoms concerning for delirium. There can often be miscommunication regarding the etiology of delirium. Patients and family members will often reference the term "ICU delirium." It can be both relieving and helpful for patients and caregivers to understand that the actual ICU stay does not cause delirium, but instead infection, mechanical ventilation, electrolyte imbalances, nutritional deficiencies, sleep deprivation, lack of daylight and day–night reversal, among other etiologies, can cause delirium.

Providing education about the association between untreated PTSD-T and poor post-transplantation outcomes to family, caregivers, and patients is also important. This education, combined with knowledge that treatment is available, may allow for a more transparent dialogue to occur if a transplant recipient experiences psychiatric symptoms. When a diagnosis of PTSD-T is made, timely treatment can then be initiated to assist transplant recipients in their psychological recovery, as they make their physical recovery from transplant. Because PTSD-T may emerge at any time during the transplantation process, routine screening is indicated during and even well after transplantation, though the risk for PTSD-T declines over time [12].

There is limited research regarding treatment for PTSD-T specifically, so treatment of PTSD-T is similar to that for PTSD in the general population. While a full discussion of medications used for treatment of PTSD is beyond the scope of this chapter, a few key points are highlighted below. Pharmacotherapy treatments approved by the Food and Drug Administration for adults with PTSD are limited to two selective serotonin reuptake inhibitors (SSRIs), sertraline and paroxetine, though studies have shown effectiveness with other SSRIs, in particular fluoxetine [41–44]. However, in the transplant recipient population, fluoxetine and paroxetine are often avoided due to drug–drug interactions with immunosuppression regimens. Venlafaxine extended release, a serotonin norepinephrine reuptake inhibitor (SNRI), has shown similar efficacy to SSRIs [45]. Prazosin, a central acting selective alpha-1 antagonist, has shown to be an effective treatment for patients with PTSD, particularly when symptoms of altered arousal and reactivity are present, including nightmares and sleep disturbance [46–48]. A recent meta-analysis supported the use of exposure therapy, cognitive therapy, cognitive processing therapy (CPT), and cognitive behavioral therapy (CBT) to treat PTSD [49]. CPT and CBT may include aspects of exposure therapy and cognitive restructuring, both of which have evidence supporting their efficacy in patients with PTSD. While clinical trials have not shown combination treatment with psychopharmacology and psychotherapy superior to treatment with either as monotherapy [50], clinically, we have found patients have a robust response with combination treatment. Transplant psychologists understand that various stressors may occur at all phases of the transplantation process; this allows psychologists to provide appropriate therapy based on an individual patient's symptoms and preferences. Medication management by transplant psychiatrists with knowledge of and familiarity with adverse effects of immunosuppressants and possible drug–drug interactions (DDI) between transplantation-related medicines and psychotropics is imperative. Given the increased rates of PTSD among this vulnerable population when compared to the general population, the increased risk for delirium in the transplant population, and the numerous neuropsychiatric adverse effects of immunosuppressant medications, further research is indicated to help improve treatment for PTSD-T.

In summary, solid organ transplantation can be an extraordinarily stressful experience that is fraught with uncertainty. Prior to transplantation, candidates can suffer from anxiety over being deemed a good candidate, awareness of failing health, and fear about whether an organ will be found in time. Following transplantation, recipients must recover from major surgery, manage a complex medication regimen, attend a myriad of clinic visits, and adjust to new relationship dynamics with caregivers. Research indicates that transplant recipients are at elevated risk for PTSD-T [8]; this is concerning due to the suffering that PTSD-T brings, the large number of other psychological disorders that are comorbid with PTSD-T [3, 8, 15], and the negative impact that PTSD-T has on treatment adherence [10, 38, 39].

Take Home Points

1. Solid organ transplant recipients are at risk for the development of PTSD related to transplantation (PTSD-T); a high degree of suspicion on the part of the transplant team is warranted to ensure adequate screening, treatment, and follow-up.
2. Recipients experiencing post-traumatic syndrome symptoms must be identified, as both PTSS and PTSD are associated with decreased HRQOL, medical nonadherence, and decreased long-term survival.
3. Traumatic experiences reported by patients with PTSD-T include being informed they have organ failure, the transplantation surgery itself, delirium, and prolonged treatment in the ICU.
4. While a pre-existing psychiatric history is a risk factor for the development of PTSD-T, all recipients are at increased risk for PTSD-T when compared with the general population.

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Personality Disorders in Transplant Candidates and Recipients

8

Kristin K. Kuntz and Kristy L. Engel

Personality Disorders in Transplant

Personality disorders are characterized as a pervasive way of thinking, feeling, and behaving that cause distress or problems in daily functioning [1]. They impact the way individuals think about themselves and others, relate to others, respond to stressors, and behave [2]. Symptoms of personality disorders often appear by late adolescence. However, most personality disorders are diagnosed in adulthood because it often takes a review of long-term patterns of functioning to determine a clear diagnosis. Of particular diagnostic difficulty is that some individuals may not recognize a problem and may externalize their problems as originating with others in their life, not themselves. Personality disorders are difficult to treat, but without treatment, they can cause significant problems in an individual's life.

Ten different personality disorders are listed in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM 5) [1]. They are divided into Clusters A, B, and C. Cluster A disorders are considered to be "eccentric/odd" disorders (paranoid personality disorder, schizotypal personality disorder, schizoid personality disorder). Cluster B disorders are considered to be "erratic/dramatic" disorders (antisocial personality disorder, borderline personality disorder, histrionic personality disorder, and narcissistic personality disorder). Cluster C disorders are considered to be "fearful/anxious" disorders (avoidant personality disorder, dependent personality disorder, obsessive compulsive personality disorder) [1]. Some individuals are diagnosed with more than one personality disorder, often from the same cluster. About 9–13% of adults in the United States are estimated to have at least one personality disorder [3, 4].

Several studies have examined the prevalence of personality disorders in transplant patients. In a sample of cardiothoracic transplant recipients, 32% met criteria for a personality disorder, with obsessive compulsive personality disorder being most common [5]. In a sample of liver transplant patients with alcohol-related liver disease, antisocial personality disorder was the most common personality disorder diagnosed [6]. Individuals with personality disorders may face difficulty when in need of an organ transplant, both in coping with their underlying health problem and because of various psychosocial comorbidities associated with personality disorders. Common psychosocial contraindications to transplantation include active substance abuse, lack of social support, and psychiatric symptoms that interfere with their adherence to a medical regimen [7]. An epidemiological study of 40,000 individuals in the general population noted strong associations between personality disorders and substance dependence [3]. There were also strong associations noted between personality disorders and higher perceived stress, less social support, increased lifetime history of suicide attempts, increased interpersonal difficulties, and increased problems with legal authorities, all of which could prove problematic for patients post-transplant [3].

During times of increased stress, such as needing a transplant, those with personality disorders may revert to using maladaptive coping behaviors (e.g., acting-out, extreme dependence, impulsivity, and attempts to split the transplant team) [8]. Through the transplant process, patients are faced with the uncertainty of whether they will be approved for transplant, whether they will live long enough to receive a transplant, and the need to manage potential complications and a complex medical regimen if they do receive a transplant. There are multiple staff members and medical providers with whom they will need to interact, and there can be a great sense of loss of control over many aspects of their life. Thus, the presence of a personality disorder before transplant may lead to difficulty post-transplant with management problems, adherence to the medical regimen, or difficulty coping with unexpected complications [8].

The way in which a personality disorder might affect a patient's transplant experience is often determined by the

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specific disorder one has. For example, a patient who has obsessive compulsive personality disorder may do well with adhering to a daily structured medical regimen but may have difficulty adapting when aspects of the regimen need to be changed abruptly [5]. Often, as time passes after one's transplant surgery, the transplant team decreases the number of follow-up visits and contacts with the patient. This can make the average patient feel anxious and can be an especially difficult adjustment for patients with dependent personality disorder who may prefer close guidance and monitoring by their transplant providers. A patient who has borderline personality disorder may not adjust well when transplant providers change. In cases where a patient had a longstanding relationship with a provider that is no longer possible, this can trigger feelings of abandonment and mistrust. The ability to develop a trusting, collaborative relationship with transplant providers may also be a challenge for patients with other personality disorders (e.g., paranoid and narcissistic personality disorders) which could result in increased morbidity and mortality [8]. These factors are often considered by transplant teams when deciding whether or not to list a patient for transplant.

Case Histories

Case 1: Antisocial Personality Disorder

Antisocial personality disorder is broadly considered to be a pattern of disregarding or violating the rights of others. Often, those with antisocial personality disorder do not conform to social norms, may repeatedly try to deceive others, or may act impulsively [1]. These patients are prone to irritability and aggression and often disregard the safety of themselves and others. In the following case, this individual with antisocial personality disorder presented to the transplant center in need of a liver transplant.

Mr. D was a 67-year-old, divorced Caucasian male referred for a pre-liver transplant psychosocial evaluation. He presented with cirrhosis secondary to hepatitis C and hepatocellular carcinoma. His primary medical history was also significant for coronary artery disease, hypertension, cardiac arrhythmia, enlarged prostate with urinary retention, and gastroesophageal reflux disease.

Mr. D had a Bachelor's degree in political science and noted that he was accepted into law school but got caught up in "other things" (drug use). He reported an unstable work history and said the longest job he has ever held lasted about 6 months. He was on disability at the time of evaluation. Mr. D lived alone with two dogs. He had an adult son and adult daughter as well as two brothers, all of with whom he had strained relationships. Mr. D reported that his support after transplant would be a friend he had known for about 8 years. He reported that his son could provide secondary support but added that he had not told any of his family about "this liver stuff since it could take a while."

Regarding psychiatric history, Mr. D noted that he always worried about one thing—money. He shared that he has always liked to "be in control" and referred to always "hustling." He stated that he had a troubled relationship with his father growing up and noted that he felt like he was always trying to seek his father's approval but never felt he got it. Mr. D said that his father was "unfeeling" and that he never wanted to be "a corporate type" like his father. He got in trouble at school regularly and at an early age started abusing drugs. He said he had an aversion toward "following the rules;" however, he later realized that this only made his father (and brothers) want more distance from him. Mr. D endorsed symptoms consistent with conduct disorder when he was an adolescent and referred to himself as the "black sheep of the perfect family."

Mr. D said that he started using marijuana and psychedelic drugs (LSD and psilocybin mushrooms) in his mid-teens. He said he continued to use marijuana sporadically over the course of his life with his last use at age 57. At the age of 18, he started using cocaine and heroin. He described his first time using heroin as "a religious experience," and opiates became his drug of choice. He reported quitting cocaine and heroin at age 57 because he had an implantable cardioverter defibrillator placed, and his cardiologist told him "it would kill me if I kept it up." Mr. D had already started taking methadone by that time in addition to heroin. While he had gone to a methadone clinic for about 10 years, he eventually stopped going there because it felt like "too many hoops" for him to jump through to obtain it. He said as soon as he started at the methadone clinic, he would take a little of the methadone himself and sell the rest. Once he stopped going to the methadone clinic, he obtained and sold methadone illegally. He was taking 10 mg of methadone per day when he presented to his first transplant appointment and said it helped him "take the edge off" his stress. He was told he would have to stop using methadone illegally and stop selling it. He said he would do that and proceeded to have negative drug screens. Being focused on having more money, he discussed that he has been considering growing marijuana to sell, so time was spent explaining to Mr. D that he cannot be engaged in any illegal behavior if he wished to be considered for transplant given the potential for incarceration to impact his access to adequate post-transplant medical care. He laughed at the idea that he would ever get in legal trouble if he was caught selling methadone or marijuana. He reported a long history of criminal activity related to drug possession, drug trafficking, and theft. He bragged about being connected with powerful drug cartels and the amount of money he used to make selling drugs. Confirmation of his report through public records indicated he had eight prior arrests with his last one being 18 years before his transplant evaluation. Mr. D appeared keen to demonstrate his intelli-

gence and capability to the evaluator, commenting several times that he is very smart and can read people well. He was often tangential, sharing stories of how he has bested people and "the system." He noted that he could tell any doctors a story and convince them to give him opioids in the past.

He reported adequate adherence with his medical care, and chart review supported this. However, in response to questions about his past medical adherence and later his description of his criminal activity, Mr. D became frustrated and raised his voice, noting that the "transplant conglomerate" is "judging me and questioning my worth" and that "at least I am honest." He later apologized, noting that he has always had a problem with authority and that he has trouble filtering what he says even when it gets him in trouble. He gave several examples of this from when he was a patient at the methadone clinic ("I was always red-flagged there, they knew what I was about") and in prison ("I couldn't keep my mouth shut even when I knew the other guy would knock me out"). He shared that his impulsivity in such situations has been problematic in personal and professional relationships. Mr. D attributed the "triggered" feeling he got when he felt he was being judged to his family history, particularly his poor relationship with his father. He noted that he has not been satisfied with how his life has turned out and said, "but I don't know any other way."

Mr. D's presentation was consistent with antisocial personality disorder, as demonstrated by inflated self-esteem derived from personal gain, power and pleasure, and goal setting based on personal gratification. He also endorsed failure to obey laws, had a history of lying and deception, impulsivity, irritability, physical aggression (while incarcerated), disregard for others' feelings, and lack of remorse for his actions [1]. He also had a diagnosis of opiate use disorder, in early remission. Mr. D denied any history of suicide attempts, psychiatric hospitalizations, or taking psychotropic medication. He attended counseling "on-and-off" for over 10 years that started at the methadone clinic, and he was still seeing a licensed social worker periodically. A conversation between that provider and the transplant evaluator noted that their treatment goals were to help Mr. D with anxiety around his health and to stay sober. The counselor did agree that Mr. D had features of antisocial personality disorder but advocated for Mr. D to become a transplant candidate, as he felt he had friends who would support him and had been off methadone for several months. He reported a family psychiatric history of alcohol use disorder in an uncle. At the time of the transplant evaluation, Mr. D denied any current psychological distress.

The transplant team required Mr. D to demonstrate 6 months of negative drug screens and to bring his support person (friend) to the transplant clinic for education and evaluation. Mr. D completed both tasks successfully. It was noted to the transplant committee that his support system was small, and though Mr. D reported he was no longer selling methadone, there would be no way to know this for certain. The team was also informed of his antisocial personality disorder and the difficulty this could bring in caring for him after transplant. Nevertheless, the transplant team decided to list the patient for liver transplant.

Mr. D was successfully transplanted and has demonstrated adequate adherence with medications, follow-up appointments, and lab draws. Methadone was found in a follow-up toxicology screen about two and a half months after his transplant. When his transplant coordinator called him to ask him about this, he said he was surprised that it showed up as he had "only taken five milligrams" 3 days prior to the test. He stated he was having headaches that were not relieved with acetaminophen and that he was "going to do what I need to do to take care of myself" since the transplant office would not prescribe him anything for pain. He reported being able to obtain methadone from his acquaintances at the methadone clinic. He stated he had "nothing to hide" and if he was tested that day, it would be negative.

Patients with antisocial personality disorder can feel "above the law" when it comes to following direct orders from those in positions of authority. In Mr. D's case, his past experience of feeling like he could "get away with" not following the rules when he did not want to contributed to his return to use of illegally obtained methadone. It may contribute to nonadherent behavior in other ways in the future. By boasting about "being able to read" and manipulate others and by describing his past illegal exploits in a glamorous way, he appeared to naively think he was presenting himself as bright and charming. Some of his medical providers fell prey to this, while others felt uncomfortable around him. In the end, Mr. D's demonstration of pre-transplant ability to be adherent with managing a chronic illness contributed most significantly to his being listed for transplant.

Case 2: Narcissistic Personality Disorder

Narcissistic personality disorder is characterized by a pattern of feeling special (often grandiose) and needing admiration from others. Individuals with narcissistic personality disorder may have trouble experiencing empathy and often feel a sense of entitlement [1]. In the following case, this individual with narcissistic personality disorder presented to the transplant center in need of a second kidney transplant.

Mr. Z was a 62-year-old, divorced, Caucasian, male referred for a pre-kidney re-transplant psychosocial evaluation. Mr. Z presented with end-stage renal disease secondary to polycystic kidney disease and had received a deceased donor kidney transplant 4 years prior to the current evaluation with graft failure secondary to chronic antibody-mediated rejection. He had returned to dialysis 2 months

prior to the evaluation. His primary medical history was also significant for hypertension, supraventricular tachycardia, and anemia.

Mr. Z had a graduate school education and obtained his doctoral degree in chiropractics. He was self-employed as a chiropractor and had a strong identification as a medical professional. At the time of evaluation, he was on a COBRA plan from his ex-wife's insurance, which would expire in 6 months. Mr. Z described some urgency to receive the transplant while he was still covered under his current insurance but did not have a plan for insurance coverage after this expired and minimized this as a concern. He described a somewhat strained financial situation although he denied immediate concerns of affording housing or other essentials. Mr. Z and his wife divorced shortly after he received his first transplant. They had adopted two children together. His young adult son was staying with him and was reported to have unstable mental health with ongoing medication nonadherence, which resulted in frequent psychiatric hospitalizations. Mr. Z reported that his current significant other would be his primary support after transplant. However, despite communication to bring his support person to his psychosocial evaluation, Mr. Z presented alone and denied that such communication had occurred.

Mr. Z had a history of depression in the context of contemplated separation between him and his wife 5 years prior. He reported experiencing symptoms including anhedonia, fatigue, psychomotor slowing, and intermittent feelings of worthlessness and guilt at that time. He and his wife later sought counseling in the context of their divorce. He otherwise denied any mental health diagnosis, psychotropic medication, or psychiatric hospitalization and denied any biological family psychiatric history. He reported his current mood as "fine" with adequate and stable appetite and sleep and enjoyed recreational activities including hiking and camping. Mr. Z reported coping with stressors through exercise, maintaining good sleep, meditation, and spending time with family and friends. Mr. Z had no tobacco use history. He occasionally used alcohol but had no history of heavy or problematic use. He had a history of recreational marijuana use twice per year but had not used in several years and denied any symptoms of a use disorder. All toxicology screens had been negative.

Mr. Z's adherence history was thoroughly reviewed especially in the context of graft loss after only 4 years. Per chart review, Mr. Z had a long-standing pattern of concerning behavior including refusals, requiring multiple iterative conversations regarding how best to move forward with his care, and leaving the hospital against medical advice. His post-transplant nurse coordinator, who interacted with him most frequently, noted him to be friendly but also alluded to concern about Mr. Z making decisions regarding his own care which went against medical advice. Mr. Z did not deny these instances and cited his belief that it is his health and his body, so it is ultimately his choice. He voiced his identification as a medical professional who does his own independent "research" regarding his treatments and makes decisions accordingly. He presented several concerns regarding his post-transplant care following his first transplant including poor care coordination at important junctures in his care. His rationale for pursuing a second transplant at the same institution was explored. In a somewhat back-pedaling manner, he reflected that he was generally comfortable with his individual providers and that poor care coordination was a product of a large institution and that all large institutions were likely to have similar issues. Mr. Z stated that he felt comfortable with the reputation of this institution but qualified that he would pursue a second opinion about any major procedures. Per chart, it was evident that Mr. Z was more responsive when presented with a well-reasoned rationale and an exhaustingly collaborative approach from a physician. Mr. Z denied missing medications and had a history of obtaining consistent lab draws, which he would review himself and contact his providers if he had questions. There were an extensive number of telephone notes in his chart. He had canceled six appointments in the past year, which he reported were due to work conflicts. Mr. Z demonstrated an adequate understanding of transplant and was well aware of post-transplant procedures.

In summary, there were no absolute contraindications, from a psychosocial perspective, to Mr. Z's listing. It was observed that he strongly identifies as a health care professional and prides himself in reviewing research to be informed about his care. Although this behavior is not definitively problematic, it was noted that his approach to his own healthcare may be perceived as challenging to providers, as Mr. Z was not likely to simply comply with recommendations without a thorough rationale, and even then, may choose a different approach. Despite that, Mr. Z had historically engaged in such conversations and arrived at mutually agreed upon plans with his providers, albeit not always his providers' first preference of action. However, the problematic nature of Mr. Z's approach to his care became clear through the evaluation and selection process.

Mr. Z was presented to the patient selection committee shortly after his psychosocial evaluation was completed at which time he was required to complete further cardiac evaluation. His cardiology appointment was scheduled several months out, as was typical for that clinic, but Mr. Z voiced discontent with this, and his evaluation was expedited. He was again presented to the patient selection committee at which time his insurance coverage and historical interactions with post-transplant providers were discussed in greater detail. Multiple providers voiced concern about Mr. Z's resistance to following recommendations based on their personal experiences and interactions with him that were not necessarily

noted in his chart. Providers in the patient selection committee voiced hesitance about working with Mr. Z again given his historical behavior and difficulty following their instructions. At that time, Mr. Z was instructed to follow-up with urology (for native nephrectomy), to obtain insurance coverage once his current insurance expired, and to commit to adhering to the recommendations of his post-transplant providers. When he was contacted by his pre-transplant nurse coordinator to notify him of these recommendations, he became agitated and stated that he did not understand why the process was being prolonged. Despite multiple explanations regarding insurance, he refused to get additional coverage because he was currently covered, and he ended that call by hanging up on the coordinator.

Over the next several months, Mr. Z no showed to his appointment with the transplant finance worker and then called to state that he got married and would be covered under his new wife's insurance. During this time, he also called to complain about crossmatch blood work not being completed despite multiple documentations noting that the kit had been sent to him. He was re-presented to the patient selection committee after a hospitalization during which he was noted to have a type B aortic dissection. He was deferred for cardiac concerns along with his inability to follow successfully with medical recommendations. He contacted the transplant clinic a month later to re-initiate evaluation and was told that resolution of his aortic dissection would need to be verified before his referral could be processed. He was scheduled for re-evaluation several months out to allow for this verification about which he voiced discontent and stated that he would pursue transplant elsewhere which he did. He traveled to a transplant center out of state that he felt had a good reputation; however, he disagreed with a procedure they asked him to get, so he did not complete his evaluation there. Six months later, he again contacted this institution for a transplant evaluation and is scheduled to have another psychosocial evaluation before his physical evaluation is initiated.

Patients with narcissistic personality disorder often present as personable and charming in order to exploit those relationships to serve their own needs. In Mr. Z's case, his grandiose sense of self-importance and entitlement presented in his demands for expedited treatment and evaluation. His disregard for information presented by the nurse transplant coordinators was likely due to his belief that he should only interact with other high-status individuals (e.g., physicians). He also exhibited a lack of willingness to appreciate the needs (or expertise) of others by refusing to get additional health insurance coverage when that was posed as a requirement with which he did not agree. His more prolonged relationships with post-transplant providers proved to be difficult as they were able to see the ways in which his personality made performing their jobs more difficult. Thus, although narcissistic personality disorder is not an absolute contraindication to transplantation, it can have a significant impact on the patient's post-transplant care.

Clinical Questions

1. How can personality disorders be identified and addressed during the pre-transplant process?
2. What are some of the challenges that personality disorders can present for patients and the transplant team?
3. What steps should be taken by the transplant team to ensure the best outcomes for patients with personality disorders?

Discussion

Transplant teams have the goal of optimizing a patient's psychosocial functioning prior to transplant to decrease the likelihood that psychological or social factors contribute to adverse outcomes. During the pre-transplant psychosocial evaluation, a psychosocial provider (often a social worker and sometimes a psychiatrist or psychologist) sees patients to identify potential psychosocial challenges. Structured or semi-structured interviews are often used, but in the case of personality disorders, chart review, interview with a support person, and the patient's prior interactions with the transplant team are helpful to identify potentially problematic personality patterns. In some instances, the use of structured measures of personality, such as the Neo Personality Inventory Test (NEO-PI-R) (5) and the Personality Diagnostic Questionnaire-Revised (PDQ-R) (6) may be helpful to identify and clarify characteristics that are observed. Such measures can also be used to provide feedback to patients who may have limited insight.

It is also important to remember that, just like other mental health disorders, there are criteria for personality disorders specified in the DSM-5, and patients should not be characterized as having a personality disorder without proper diagnosis by a qualified professional. It should be noted that not all maladaptive behaviors are attributable to a personality disorder, so it is important to understand the driving factors behind patients' behaviors. There are cases where personality disorders are not identified prior to transplant, and the transplant team only sees the impact of this after the transplant.

As part of the pre-transplant assessment, it is important for the team to consider the potentially added challenges to transplant care that personality disorders can bring. Patients with personality disorders often have difficulty building trusting relationships with the transplant team which can increase the risk of nonadherence with medical instructions and lead to poorer post-transplant quality of life. Individuals with personality disorders may engage in splitting the medical team, may act out if they feel their needs are not being met, and they may be hypersensitive to feedback. They may simultaneously demand help and reject medical advice.

When it comes to mitigating risk of poorer outcomes in transplant patients with personality disorders, the transplant team may require patients to receive mental health treatment prior to being an accepted as a candidate. The type of treatment recommended often depends on the type of personality disorder, the symptoms experienced, and the patient's circumstances. No psychotropic medications specifically treat personality disorders, but antidepressants, anxiolytics, or mood stabilizers may help to treat some of a patient's symptoms [2]. Psychotherapy can help patients develop insight and appropriate coping strategies. Therapy may be focused on decreasing psychiatric symptoms, improving distress tolerance, and/or quitting substances of abuse. Cognitive behavioral therapy has been found to reduce distressing symptoms and to increase daily functioning in individuals with personality disorders [9]. Dialectical behavior therapy is commonly used in treating personality disorders to help increase distress tolerance and impulsivity [10]. In cases where the patient's personality disorder has caused strain with his or her support system, including the patient's family in therapy or encouraging family members to seek psychotherapy may be warranted.

Once a patient with a personality disorder has been transplanted, continued psychiatric care should be strongly encouraged. Transplant psychiatrists or psychologists may be asked to see patients whose problematic personality traits are interfering with their care. The transplant psychosocial team can help to provide education to medical providers about a patient's personality disorder to help foster better understanding and empathy for the patient's experience. They can facilitate an understanding that patients with personality disorders often do best with a consistent team of medical providers with whom they can establish rapport and trust. Teams should be educated about how to set firm expectations and boundaries with these patients to minimize the tendency to "split" or manipulate team members. These patients often consume a disproportionate amount of the transplant staff's time and may evoke negative emotions in team members, such as fear of physical violence or verbal harassment. In return, team members may resist confronting these patients about nonadherence or their inappropriate behavior [10]. Concerns about patients' threats of self-harm also elicit anxiety in many transplant team members. Demonstrations of how to de-escalate heightened emotional distress in patients and how to engage in safety planning can be helpful.

Take Home Points

1. A personality disorder is not, in itself, an absolute contraindication to transplantation but can contribute to unique management challenges such as: patient mistrust, splitting of staff, testing of boundaries, extreme rigidity with or self-management of the post-transplant regimen leading to additional time requirements and provider distress.
2. Those involved in the care of these individuals should be alerted to potential challenges, and transplant psychiatrists/psychologists should be prepared to educate providers and when necessary, provide intervention to the patient.
3. Maintaining a consistent team of providers and staff who set and endorse boundaries and with whom patients can develop a trusting relationship over time can be beneficial.

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Psychiatric Aspects of Obesity in Transplantation

9

Filza Hussain

Introduction

According to the World Health Organization (WHO), patients with a body mass index (BMI) of 25–30 are classified as overweight and those with a BMI of 30 or greater, as obese. The global prevalence of obesity tripled between 1975 to 2016 and 13% of the world's population qualified as obese in 2016 [1]. Obesity is on the rise in the United States as well, with the prevalence of obesity increasing from 30.5% in 1999–2000 to 42.4% in 2017–2018. This is a matter of significant concern given the prevalence of heart disease, stroke, type 2 diabetes, and certain cancers, which represent the majority of obesity-related causes of preventable, premature death [2]. While obesity is often attributed to lifestyle factors, the etiology of obesity is multifactorial (Fig. 9.1). Similarly, several serious comorbidities have been associated with obesity affecting multiple organ systems including cardiovascular, renal, and gastrointestinal complications (Fig. 9.1) [3]. The prevalence of non-alcoholic fatty liver disease (NAFLD) has also increased in parallel with obesity and metabolic syndrome, quickly becoming one of the major causes of chronic liver disease, prevalent globally in about 24% of the population [4]. It is no surprise that because of these trends, transplant physicians are evaluating an increasing number of patients with obesity. Given the multi organ effects of obesity, transplant outcomes for obese patients are fraught with challenges. Studies show increased rates of post-operative pneumonia, atelectasis, pulmonary embolism, portal vein thrombosis, atrial fibrillation and, a higher rate of infections and wound dehiscence as well as primary graft dysfunction [5, 6]. For the transplant psychiatrist, evaluating depression, anxiety, and psychosocial factors along with a nuanced approach to exploring the relationship with food and potential eating disorders is of utmost importance.

Binge eating disorder is the commonest eating disorder in the United States [7]. The majority of patients with binge eating disorder present with metabolic syndrome, obesity and all its end organ sequela including fatty liver disease. This chapter will discuss fatty liver disease, binge eating disorder, the connection between the two and nuances a transplant psychiatrist needs to be aware of when evaluating patients with obesity for transplant.

What Is Nonalcoholic Fatty Liver (NAFL) Disease?

An excess of carbohydrates, such as fructose and glucose as well as fatty acids in the diet, leads to overproduction of phospholipids and cholesterol with resultant lipid accumulation in hepatocytes. Progressive injury and inflammation secondary to lipid accumulation lead to fibrosis and eventually cirrhosis. NAFLD is an accumulation of hepatic fat in more than 5% of liver cells in the absence of excessive alcohol consumption, other liver diseases, or drugs promoting steatosis. NAFLD encompasses patients with simple steatosis, a reversible condition, to more progressive steatohepatitis, also called non-alcoholic steatohepatitis (NASH) [8].

Who is at risk and what is the progression of the condition? Overweight and obese middle-aged men with comorbid conditions such as diabetes mellitus type 2 and dyslipidemia, or metabolic syndrome are at the highest risk for developing NASH [9, 10]. Among men, there is a decline in the incidence of NAFLD noted after the age of 60. In contrast, women tend to be spared prior to menopause with a rise in incidence after 50 and, peaking at 60–69 years of age. NASH in women is histologically more severe compared to the same process in men [11]. Heritability and genetic variance in susceptibility has been shown in studies [12]. Hispanic patients appear to be at more risk than their white counterparts, while. Black individuals show the least susceptibility [13]. Genomic studies

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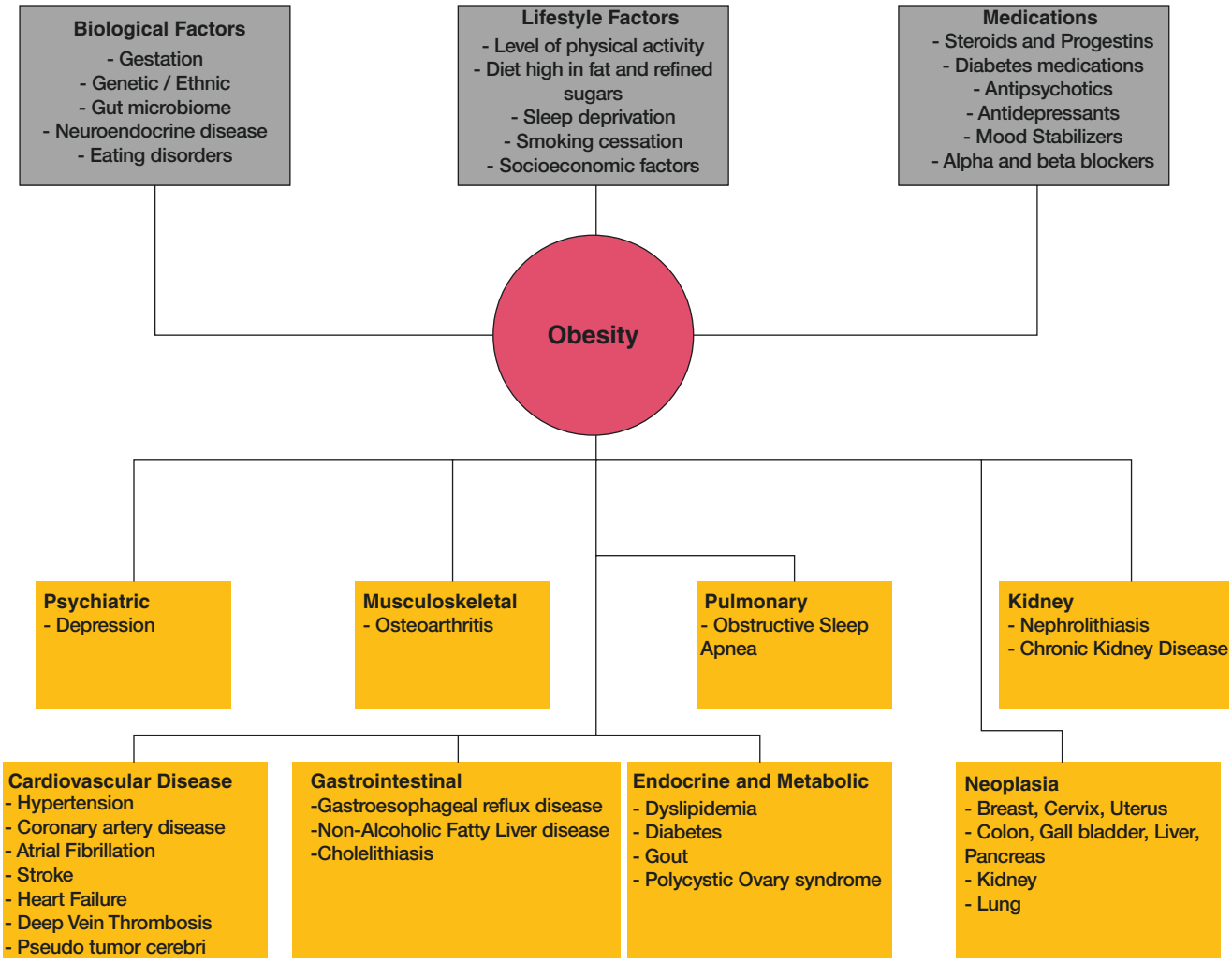

Fig. 9.1 Factors contributing to obesity and its downstream medical sequela

have identified patatin-like phospholipase domain-containing 3 (PNPLA3) gene variants as a key factor in individual and ethnicity-based differences in disease progression. This gene is involved in the secretion and remodeling of fat droplets in liver cells [14]. Patients with this gene have increased liver fat content, triglyceride stores, and inflammation with certain polymorphisms encoding more severe NAFLD [15]. Along with a sedentary lifestyle and a diet high in fats, smoking was found to be an independent risk factor for the development of NAFLD [16].

NAFLD is increasingly being recognized as a multisystem disease, associated with a two-fold increase in the risk of chronic kidney disease [17], endocrine disorders, obstructive sleep apnea (OSA), and colorectal cancer. Despite the effects on all different organ systems, much like obese patients with metabolic syndrome, cardiovascular disease is the most common cause of mortality amongst these patients [18]. The risk of liver-related mortality, including the development of hepatocellular carcinoma (HCC) in NAFLD patients increases by 5–10-fold, depending on the degree of fibrosis [4]. Approximately 3–13% of patients with NASH cirrhosis will develop HCC [19]. NASH cirrhosis is one of the top three leading reasons for patients to be listed on the transplant list [20].

How Is NAFLD Diagnosed?

Although there are no specific physical exam findings particular for NAFLD, a waist circumference of greater than 102 cm in men and greater than 88 cm in women, dorsocervical hump, acanthosis nigricans, hypertension and, hepatomegaly on the physical exam [21] and the presence of other risk factors for metabolic syndrome along with the family history of NAFLD can alert the physician to obtain liver function tests. Of note, these may or may not be elevated. The history and laboratory work should also evaluate for other causes of liver disease, such as alcohol

use, viral hepatitis and other metabolic issues. The presence of lipid accumulation and change in the texture of the liver in NAFLD can be diagnosed with imaging studies such as ultrasound, computed tomography or magnetic resonance imaging. However, a confirmed diagnosis of NASH requires a biopsy showing the presence of inflammation, hepatocyte ballooning, Mallory- Denk bodies[1] and fibrosis and other stigmata of steatohepatitis [8]. The NAFLD activity score (NAS) assesses the degree of steatosis, lobular inflammation, ballooning of liver cells, and fibrosis and is used for histologically diagnosing NASH [8].

How Is NAFLD Treated?

The cornerstone of NAFLD management is a lifestyle and dietary modifications, resulting in weight loss. When recommending healthy food choices, a Mediterranean diet is a good alternative to a Western diet [20]. A study of almost 300 participants following lifestyle modifications over 52 weeks showed NASH reversal in 25%, NAFLD activity score (NAS) improvements in 47% of the participants, and improvements in histological features of NASH in 39–50% of patients [22]. Clinicians frequently recommend a weight loss of 5–10% of total body weight to improve steatosis and inflammation of the liver [23]. For some patients, bariatric surgery may be an important step in their weight loss journey, resulting in additional improvements in insulin resistance, lipid levels and type 2 diabetes [7].

Medications that modify hepatic fat accumulation and alleviate oxidative stress on cells, anti-obesity medications, and those that affect insulin resistance can play a role in management of NAFLD. Metformin has been used in other diseases where insulin resistance plays a key role, such as polycystic ovary syndrome, yet data has not shown metformin to have a significant impact on liver function tests and histology and hence its use is not recommended [24]. The American Association for the Study of Liver Disease (AASLD) practice guidelines recommend use of pioglitazone in patients with biopsy-proven NASH, as it has been shown to improve steatosis [24]. Vitamin E has also been investigated due to its anti-oxidant properties. Studies demonstrate improved steatosis, liver function tests and reduced inflammation, however, due to concerns over an increased all-cause mortality and risk of prostate cancer, Vitamin E is only recommended for those without diabetes with biopsy-proven NASH [24].

[1]Mallory-Denk bodies: cytoplasmic hyaline inclusions in hepatocytes which can be found in various types of liver disease. *Jensen, K; Gluud, C (Oct 1994). "The Mallory body: morphological, clinical and experimental studies (Part 1 of a literature survey)". Hepatology.* ***20*** *(4 Pt 1): 1061–77. doi:*https://doi.org/10.1002/hep.1840200440. *PMID 7927209*

What NAFLD Specific Issues Should the Transplant Psychiatrist Be Aware of?

Much like the alcohol associated liver disease (ALD) population, patients with NAFLD need a nuanced approach to their care, preferably long before the onset of NASH. Given the growing prevalence of obesity and the metabolic side effects of some psychotropic medications, such as antipsychotics and mood stabilizers psychiatrists should be monitoring the weight and metabolic indices of their patients. NASH is a dreaded complication for patients who start taking psychotropic medications in their youth [25]. The joint consensus paper between the American Diabetes Association and the American Psychiatric Association delineates monitoring guidelines for patients on antipsychotics. They recommend obtaining baseline measurement of personal and family history, weight, waist circumference, blood pressure, fasting blood sugar or hemoglobin A1c (HBA1c) and a fasting lipid profile. It is also recommended to monitor weight every 4 weeks, the rest of the parameters annually and fasting lipids every 5 years [26]. When treating patients with NASH, psychiatrists should pay attention to body image issues and any symptoms of depression and anxiety stemming from them. Patients with NASH are at a higher risk of depression and anxiety compared to the general population [27]**.** Another important factor is to understand the patient's relationship with food, their daily eating patterns, and what, if any efforts they have made to lose weight.

Binge Eating Disorder (BED)

By definition, patients with binge eating disorder (BED) consume large quantities of food in a discrete period while experiencing a lack of control over their consumption. There are no accompanying compensatory behaviors to the binge episode, such as purging seen in bulimia nervosa [28]. These episodes of overconsumption are accompanied by at least 3 or more of the following: (a) consuming food much more rapidly than normal, (b) eating food until uncomfortably full, (c) consuming large amounts of food when not hungry, (d) consuming food alone to avoid embarrassment, and (e) feeling disgusted, depressed, or guilty after the eating event. Per DSM 5, the episodes must occur at least once a week over a 3-month period [29].

Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC-III) comprising over 36,000 respondents assessed with lay-administered diagnostic interviews revealed that BED is the most common eating disorder in the United States. According to the survey, lifetime and 12-month prevalence of DSM-5-defined BED as 0.85% and 0.44%, respectively [30]. Lifetime prevalence is 1.25% for women and 0.42% for men [30].

Although the neurobiology of BED is not completely understood, functional imaging and cognitive studies highlight attentional bias towards food-related cues, compulsive and impulsive behaviors, and impaired reward processing as key issues [31].

Obesity is a common co-occurrence in patients with BED due to the recurrent binge episodes and increased calorie consumption. In the NESARC-III data, 56% of people with lifetime BED had a BMI greater than 30 and qualified as obese, another 23% were overweight with a BMI between 25–30 and 20% of the populations with BED had normal weight [30]. BED is diagnosed with a clinical interview to assess for the criteria described above. The binge eating scale (BES) is a validated tool that can help determine the severity of binging and can be used both as a screening tool and to monitor treatment response [32]. A score of less than 17 indicates a non-binging pattern, a score of 18–26 is moderate binging and a score of 27 or greater indicates severe binging [32].

Patients with BED have concerns and distortions regarding food intake, body shape and weight. This usually results in a pattern of food restriction which in turn leads to a maladaptive and cyclical pattern of restriction and binging [33]. These patients show a general tendency towards overeating, have a more variable dietary pattern with frequent snacking, and report distress due to their eating patterns [33].

Cognitive behavioral therapy (CBT) helps patients to identify food and body image-related distortions. It has shown to be effective for reduction in binging frequency, decreasing the number of days with episodes, increasing the length of abstinence from binging behaviors, and reducing depression and concerns about weight and eating [34]. Interpersonal Psychotherapy (IPT) conceptualizes binge episodes as a coping mechanism in response to negative affect stemming from poor interpersonal social function. IPT is considered a good second-line option for treating BED [33].

Pharmacological interventions can also be helpful in promoting weight loss and treating comorbid psychiatric conditions. Common strategies include using selective serotonin reuptake inhibitors (SSRIs), anticonvulsants, and, stimulants. A meta-analysis [34] found pharmacological treatments to reduce the number of binge eating days and symptoms of depression and found a mild benefit for abstinence from binge episodes. Another meta-analysis found that treatment with lisdexamfetamine, the only treatment for BED approved by the US Food and Drug Administration (FDA), and SSRIs led to more days without binge eating and fewer eating-related obsessions and compulsions. Lisdexamfetamine and topiramate also showed reductions in weight [35].

Is There a BED and NAFLD Connection?

NAFLD is one of the most common liver diseases and BED is the most common eating disorder. There is a significant similarity in risk profiles for these two disorders. Most patients who have either condition are obese, with increased rates of metabolic syndrome, diabetes, and cardiovascular comorbidities. Zhang et al. studied 95 NALFD patients to evaluate overlap with BED in these patients and found 23% of their study population to have binge eating tendencies [36]. In fact, 6% of their sample scored high enough on the BES to suggest a severe eating disorder [36]. This is higher than the incidence of BED in the general population.

A recent French study of 388 severely obese patients with NAFLD referred for bariatric surgery 38% were found to have BED using the BULIT self-report questionnaire [37]. The authors hypothesized that NAFLD patients with BED would have histologically more severe NAFLD. Although there were limitations to the study, including using a self-report questionnaire based on DSM III, the authors could not demonstrate an association between BED and the severity of NAFLD. However, the high prevalence of BED in their sample of biopsy-proven NAFLD provides evidence for the intuitive association between BED, NAFLD and obesity.

What Are Some challenges Facing Both Physicians and Patients?

The cornerstone of treatment for both NAFLD and BED is lifestyle modification, identifying distortions in underlying habits, and targeted efforts at improved nutritional decision-making. It is recommended to lose 5–10% of total body weight to reverse the deleterious consequences of NAFLD [23]. This weight loss requires not only nutritional changes and exercise but also the use of behavioral strategies.

Obesity and its associated comorbid conditions are a public health concern requiring a systemic management approach. The micro- and macro-environments necessary to make and sustain such changes are widely lacking in the developed world. Unfortunately, there are few concentrated efforts on the government level to support healthy lifestyles, especially in rural settings and areas with lower socioeconomic circumstances. Access to recreational spaces and affordable healthy meals is limited. Lack of public transportation also adds to a sedentary lifestyle. The problem is made even worse by the lack of foresight in developing training curricula for physicians and other healthcare providers who rarely receive formal training in effective communication with patients to facilitate changes in lifestyle [38].

Case History

Mr. A is a 56-year-old, 5′9″ tall man with a premorbid weight of 250 pounds and a history of hypertension and hyperlipidemia. He was followed in a hepatology clinic for 8 years due to liver dysfunction secondary to NAFLD with a Model for End-Stage Liver Disease (MELD) score of 10. His Hemoglobin A1c levels had been within normal limits.

In his ninth year of follow-up, he developed stigmata of liver failure with ascites, mild hepatic encephalopathy (HE), jaundice and, varices which required banding. During his liver transplant evaluation, he denied a psychiatric history, and reported drinking alcohol only occasionally which he was asked to stop. He was not seen by the team psychiatrist at that point. He was seen by a nutritionist three times over the course of his nine-year follow-up and was given guidelines to lose weight.

Prior to his transplant, he developed nausea and anorexia and lost a substantial amount of weight in 6 months. His weight right before transplant was 200 pounds.

He was seen by psychiatry in the post-transplant period when he identified difficulties with unspecified anxiety. Careful history revealed that he met criteria for Generalized anxiety disorder (GAD) even before transplantation yet had never been treated for it. He was started on escitalopram, referred to therapy, and scheduled for a follow up with the psychiatrist.

On his return visit in a month, the patient had visibly gained weight and weighed 230 pounds. He described suffering from back pain, which he believed was secondary to being on the operating table for several hours. His transplant surgeon prescribed him gabapentin 600 mg three times a day for the back pain. The patient did not seem too bothered with his weight gain, despite knowing that he was now categorized as obese. He believed the weight gain was due to medications and acknowledged the need to be active and monitor his food intake and choices.

He subsequently missed two appointments with the psychiatrist, despite reminders and only came back in at his hepatologist's request. His hepatologist expressed alarm at his weight gain and was also concerned whether his medications led to the rapid weight gain.

When Mr. A finally returned to see the psychiatrist, 6 months after the transplant, he weighed 272 pounds. He noted he was no longer on prednisone and had discontinued gabapentin and escitalopram 2 months prior without informing his healthcare team as he wanted to reduce the medication-related weight gain.

The patient described overwhelming anxiety, debilitation by his back pain, and frustration at inability to return to work in construction. On probing further, he noted that his normal daily routine included getting up at 6 AM in the morning, walking his children two blocks away to and later from school, and then spending most of his day on the couch watching TV, except for walking his dogs twice daily for 15 min each. He described feeling embarrassed that his wife was the primary breadwinner and hence he did not expect her to do much else around the house. As a result, their family usually ordered out at least one meal a day.

A dietary recall revealed:

- Breakfast: two white bread toasts with butter at 7 AM.
- Mid morning Snack: grapes, peaches, nectarines and 1–2 full size candy bars at 10 AM.
- Lunch: burger, fries, a large shake, or a pizza (daily) at 2 PM.
- Dinner: rice and beans or spaghetti, occasionally steak, and 1–2 cans of regular Pepsi at 8 PM.
- After dinner snack: 2–3 regular sized candy bars plus occasional ice cream at 10 PM.

Clinical Questions

1. With hindsight, what additional information should have been part of the evaluation in a patient with NAFLD and obesity prior to listing for transplant?
2. What role can the psychosocial team play pre-transplant, to improve patient outcomes in NAFLD patients post-transplant?
3. What role can the family play in Mr. A's recovery and should providing balanced meals be one of the caregiver's responsibilities?
4. What should the post-transplant treatment plan for this patient include?

Discussion

Mr. A's case highlights the importance of multidisciplinary evaluation pre-transplant and coordination of care post-transplant. Liver transplant patients routinely see dieticians before transplantation for evaluation of sarcopenia, frailty, and malnutrition, which increase morbidity and mortality post-transplant. The dieticians also provide education about achieving adequate nutrition while maintaining specific dietary restrictions such as fluid volume and sodium levels.

The available dietician notes for Mr. A included frailty scores, but none of the three encounters had any documentation of his food recall or suggestions for improving his dietary habits. He had no scheduled appointments with the dietician post-transplant.

Screening tools such as the BES could be added to routine pre-transplant dietician visits in patients with NAFLD as well as other pre-transplant patients who suffer from obesity. Patients who screen positive can then be referred to psychiatry for further assessment. Mr. A's case highlights another important aspect of nutritional evaluation. A review of his food intake either via interview or with the use of validated

tools such as the Food Records (FRs), the Food Frequency Questionnaire (FFQ), and the 24 h recall (24 h.), would have highlighted his challenges with food and risk for weight gain much earlier [39]. These screening tools can be used even prior to visits with the dietician.

The psychosocial team is poised to play an important role in pre-transplant patients with obesity also. All transplant patients are routinely screened for depression, anxiety, and cognitive deficits, assessment for eating disorders with validated tools such as the BES and a clinical interview should also become routine.

After reviewing data from the dieticians' visit, the psychosocial team can explore the patient's relationship with food and assess their dietary knowledge, attitude and practices affecting the medical situation. They can then engage with the patient in a plan to modify behaviors towards a healthier lifestyle. This plan would involve a motivational interview, cognitive behavioral therapy and potentially medications. An important aspect of this plan would be relationship building and continuity of care. An organ transplant is an exceptionally stressful life event, patients who have engaged in disordered eating in the past to self-soothe are at risk of utilizing familiar ways of coping. Much like we recommend continued support and structure to our patients with alcohol use disorder, for post-transplant success in maintenance of sobriety, our patients with disordered eating will need the same structure and support to succeed.

Successful outcomes after transplant "takes a village" and the caregivers are an essential part of the team of people supporting the patient, before, during and after transplant. Transplant centers educate the caregivers on their set of responsibilities including bringing the recipient to medical appointments, learning all medications, ensuring the patient is taking them on a schedule, tracking progress and providing mental support to the recipient. The implicit message is that the caregiver will ensure the recipient is receiving adequate, balanced nutrition.

With the rise in obesity in the transplant patient population, providing detailed education to the caregiving team regarding nutrition, weight and BMI parameters is extremely important. The importance of balanced nutrition and weight monitoring needs to be stressed upon. Caregivers should contact the transplant team sooner if there are concerns the patient is becoming overweight. Mandating the provision of balanced meals as part of the caregiver's responsibilities may not be practical nor enforceable, yet frequent check-ins with the patient and the caregiver by the team's dietician and mental health professional can ensure support and early course correction.

Ideally, patients suffering from obesity, NAFLD and or BED need a comprehensive plan to help the patient pre-transplant and optimize outcomes post-transplant. For Mr. A, referrals to trained lifestyle modification counselors such as dieticians, physical activity supervisors, and case managers would be a reasonable next step to provide him with support and guidance to regain a healthier lifestyle. Providers trained in CBT would also be a valuable addition to the treatment plan to help him with his underlying feelings of guilt and anxiety, help him understand his coping mechanisms and address food-related distortions. Patients like Mr. A who also have other psychiatric comorbidities, including depression and anxiety, should have regular follow up with both the psychiatrist and the hepatologist. All clinicians working with this patient population should employ motivational interviewing to move the patient along the stages of change [34] and collaborate for optimized care and the best outcomes.

Case History (Continued)

Mr. A did not meet criteria for BED. He described being unaware of the importance of monitoring his diet after transplant and generally displayed poor awareness of the nutritional value of his food. He described eating when he was bored and when he felt stressed. During his appointment, he was provided education regarding food diaries and several app-based tools available on his phone to help him track his daily food intake. He described owning a fitness tracker and was encouraged to start utilizing it and gradually working on increasing his activity levels. Mr. A was referred again to a dietician with a specific question of creating a diet plan and attainable measurable goals. He was also referred to a CBT therapist close to home so he could start developing better coping strategies and start working on his underlying anxiety. With the education provided, he agreed to try a different antidepressant for pharmacological management of his anxiety. He was reticent to try another SSRI given his perceived experience with Escitalopram. He requested the use of venlafaxine as he had read online that venlafaxine may be neutral from a weight gain perspective.

Mr. A's case demonstrates a confluence of multiple risk factors for weight gain, including some of psychotropic medications. Much has been written about the weight and metabolic side effects of antipsychotics and some antiepileptic medications, such as valproic acid and gabapentin [40]. Meta-analysis of antidepressants and changes in weight show differences in short-term (4–12 weeks) and long-term treatment (more than 4 months). Over the short term, amitriptyline and mirtazapine cause weight gain up to 2 kg whereas most SSRIs are anorexigenic in the short term with fluoxetine causing a deficit of 1 kg. In the long term though all SSRIs contribute to weight gain especially paroxetine (3 kg) and to a lesser extent citalopram (up to 2 kg). There has been a dearth of data on SNRI Venlafaxine though Duloxetine follows a similar pattern of weight gain as the

SSRIs [41]. The only antidepressant to have sustained weight loss both over the short(1 kg) and long term(2 kg) is bupropion [41]. Interested readers are referred to a more recent meta-analysis with similar findings and a review of potential mechanisms of weight gain secondary to psychotropic medications [42]. Medication effects on weight gain should be considered when treating NAFLD and other transplant patients both pre and post-transplant and if a medication is suspected of contributing to weight gain, a switch to a different medication should be made.

Future Directions

Paying heed to the predictions that NAFLD will soon surpass other indications for liver transplantation, about it is important to consider how to provide comprehensive care to these patients. This will need planning at several different levels. From a public health approach, we need to advocate for policy directed toward healthier living. Improved access to parks, gyms and other fitness and recreational centers, the availability of subsidies to help drive down costs of healthy eating, and providing education to the population at risk will all enable individuals to take action.

Multidisciplinary models of care which include medical providers, dietitians, and mental health clinicians, similar to those often used in the care of bariatric surgery candidates, can be conceptualized for obese patients who become transplant candidates. In addition, health care curricula at all levels of training should evolve to include more education regarding lifestyle modification, nutritional needs, and exercise-based interventions for patients.

Finally, more research into obesity, NAFLD, BED and their relations to psychological or psychiatric factors is needed to further understand overlaps and develop better prevention and treatment strategies for these patients.

With regard to the evaluation and care of transplant patients with obesity, it should be a standard practice to involve dieticians early on, with continued and regular visits with both pre and post-transplant patients. These patients should be screened for eating disorders along with other psychiatric comorbidities by the psychosocial assessment team and routine questions should assess the role food and nutrition have played in the patient's life. It is important to note that due to prolonged illness, some transplant patients may present as being normal weight or even underweight with muscle wasting. A history of massive weight loss should trigger the team to inquire about proximal factors leading to obesity to make a comprehensive prevention plan for the patient. It is also extremely important to include caregivers in the education and planning to ensure support at home for a healthier lifestyle.

Take Home Points

1. Obesity and related comorbidities are on the rise. Obesity as a multisystem disease affects all organ systems in the body and transplant teams are seeing a rise in the number of patients with obesity in need of a transplant. As an example, NAFLD is expected to exceed ALD as the top reason for liver transplantation. Given the overlap in presentation including metabolic syndrome, it is reasonable to expect a higher prevalence of disordered eating in the obese NAFLD patient population.
2. There needs to be a coordinated multidisciplinary approach with the integration of dieticians and psychiatrists to assess these patients and devise realistic treatment plans.
3. Transplant psychiatrists should screen patients for eating disorders, use validated scales such as the BED, use simple tools such as food recall, explore the patient's relationship to food and evaluate for other proximal environmental factors impacting the patient's weight. The psychiatrist can also help demystify weight gain, evaluate medications that may be contributing and treat underlying conditions affecting weight gain, such as BED, employ CBT to address food-related distortions and educate the patient and encourage them to work closely with the nutritionist.

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Anorexia Nervosa in Solid Organ Transplantation

10

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Anorexia Nervosa in Solid Organ Transplantation
There is a paucity of published data on solid organ transplantation in the context of anorexia nervosa in terms of pre-transplant evaluation, post-transplant management, the development of eating disorders triggered by transplantation, and anorexia nervosa in potential living donors. This is somewhat surprising given the prevalence of anorexia nervosa and the myriad ways in which it can potentially interact with solid organ transplantation. This chapter will review the literature and report a case of successful transplantation in a patient with anorexia nervosa. Salient considerations in the evaluation of patients with anorexia nervosa who are being considered for solid organ transplantation and their management post-transplantation will be highlighted.

Introduction

Anorexia Nervosa: A Quick Review

Anorexia nervosa (AN) is part of the broader category of feeding and eating disorders in the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders fifth Edition (DSM-5) [1]. Two forms of AN are described—a restricting form and a binge/purge form where a variety of methods are used to purge calories including self-induced vomiting, vomiting, laxative abuse, ephedrine abuse, insulin omission in diabetics, or excessive exercise, AN typically begins in adolescence or young adulthood. The 12-month prevalence of AN is 0.4% in young females with a 10:1 female-to-male ratio [1]. The etiology is complex [2]. Common morbidities include bipolar, depressive, anxiety disorders, substance use, and post-traumatic stress disorder and these may antedate the onset of AN [1, 2].

There are a small number of evidence-based psychotherapeutic treatments for AN although none are effective in all [2]. While psychiatrists often have a very pessimistic view of outcomes, many individuals do improve or remit over time [3]. Poor outcomes do occur and there is a 5% per decade elevated crude mortality rate for AN and a lifetime early mortality rate of 10%—approximately half due to suicide and a half due to medical complications of the disorder [1].

What Might Anorexia Nervosa Contribute to Medical Illness, End-Stage Organ Disease Leading to Transplant and Poor Medical Outcomes with Transplant?

A wide variety of medical complications have been described [4]. Individuals with AN (AN) are in varying stages of starvation and protein malnutrition, both of which have important physiological consequences for major organ systems. Those with purging behaviors have additional risks related to metabolic disturbances [4, 5] End-organ failure, either acute or chronic, can occur secondary to AN. It can impact renal function in multiple ways including acute kidney injury, chronic kidney disease, electrolyte abnormalities, disorders of water metabolism, and nephrolithiasis with over 70% of AN patients having renal manifestations over their lifetime [6]. The binge-eating/purging subtype is associated with an increased risk of kidney failure potentially progressing to

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end-stage renal disease [6]. There are special challenges in diagnosing and staging chronic kidney disease in patients with AN [6]. Hepatic complications of AN are thought to be secondary to starvation autophagy, although acute liver failure is uncommon and the mortality rate from severe acute liver failure is low [7]. There are numerous cardiac complications of AN and these account for a significant number of sudden deaths in patients with AN [5].

End-organ failure may itself be associated with malnutrition, cachexia, and sarcopenia, and there is preliminary evidence of its negative prognostic implications for end-stage illness and for transplant outcome. There is evidence that malnutrition and sarcopenia independently predict poorer outcomes in liver transplantation [8], although assessment may be challenging [9]. Similar findings exist with respect to renal transplant [10] and lung transplant [11]. It is unclear how these data might inform risk assessment for low body mass index individuals secondary to AN given that the underlying pathophysiological mechanisms remain to be elucidated and likely differ from cachexia secondary to organ failure.

There is one recent publication showing poorer kidney graft survival in AN patients with a hazard ratio of 5.5 and a greater risk of cardiovascular complications [12]. This retrospective study from four French transplant centers compared patients with a diagnosis of AN at the time of transplant, with low and normal BMI controls. Graft loss had occurred in 7/19 (36.8%) by 5 years post-transplant. The study is limited in terms of the degree to which the AN patients were characterized.

What Factors Should a Mental Health Assessor Consider when Evaluating a Transplant Candidate with Comorbid Anorexia Nervosa?

Mental health assessment is straightforward when the potential transplant candidate describes a history of AN. The mental health assessor can obtain a history of the potential transplant candidate's experience with AN, clarify whether it has been restrictive or whether there have been periods of binge/purge, document what types of treatments they have had and what the outcome of the treatment has been. Collateral information can be obtained through medical records or contact with prior or current treating professionals. The situation is more challenging with occult eating disorders. As noted above, cachexia is a feature of many types of end-organ failure. Most patients with chronic conditions report poor appetite and differentiating this from a symptom of an eating disorder is not always straightforward. Our clinical experience is that most people respond to direct questions about consciously restricting their food for weight and shape concerns. Similarly questions about purging are more likely to be answered when they are framed in terms of identifying and helping to manage behaviors that put health at risk and may have fatal outcomes. Purging through omission of insulin must always be queried when insulin-dependent diabetes is present.

It is important to obtain a full psychiatric history and psychosocial assessment to identify other potential targets for optimization or treatment and to be able to risk stratify potential candidates for transplantation.

What Do we Know About How the Transplantation Process Might Impact Anorexia Nervosa?

There is a very limited literature about the impact of transplantation on AN. There is a single case report in the literature of a 40-year-old man developing an eating disorder pre-transplantation following recommended dietary restriction to lose weight (54 lbs.) to be eligible for lung transplantation [13]. Once he began restricting intake and losing weight, he could not stop severely restricting his food intake. He began vomiting and using laxatives. He lost 82 lb. in 7 months. He was referred to an eating disorder program. He declined to consent to communication between the eating disorder clinic and the transplant program. Interestingly, the transplant program did not insist on communication. He underwent transplantation and was readmitted to hospital at 7-week post-transplant with rejection likely related to the deleterious effects of vomiting his anti-rejection medications.

New-onset AN has been described after pediatric kidney transplant in a 12- [14] and a 16-year old [15] and living donor kidney transplantation in a 23-year-old young woman who had received a living kidney donation from her mother and weight went as low as a BMI of 10.8 [16]. Of note, the pediatric cases recovered after discontinuation of tacrolimus, while the young adult case remitted following psychotherapeutic treatment.

There are many aspects of life post-transplantation that may precipitate or exacerbate AN. Stressful life events are known precipitants of worsened status in AN and transplantation is well documented as being stressful for many recipients. Tacrolimus, one of the major immunosuppressants used post-transplant, may alter taste perception and lead to decreased food consumption, which in turn can serve as a trigger for further food restriction in individuals with AN. Bodily changes post-transplant secondary to prednisone and other commonly prescribed immunosuppressants such as calcineurin inhibitors affect many but not all transplant recipients. There is an undue influence on self-evaluation of weight and shape concerns in AN which can be exacerbated when prednisone side effects occur. These changes include

increased weight [17], changes in distribution of fat in some patients with Cushingoid changes secondary to prednisone, and hirsutism or hypertrichosis. All the aforementioned bodily changes may become a focus for vulnerable individuals and contribute to the reactivation of or new occurrence of eating disorder pathology. The one study that examined body dissatisfaction and concerns about body image post-transplant found that they are common in adolescent heart and lung transplant recipients [18], but disordered eating behavior was not increased in the sample of 25 heart and 3 lung transplant recipients.

Anorexia Nervosa and Living Donation

While most would agree that active AN would preclude someone acting as a living organ donor, the question of what to do about potential donors with periods of stability remains open. On an anecdotal basis, surgical interventions can reactivate symptomatology. Concerns about pain, nausea, and loss of appetite in the postsurgical period reactivating eating disorder symptomatology must be considered. There are no reports in the literature to date.

Case History

Nicholas was a 37-year-old single man when he was first seen in assessment in 2005 regarding his suitability for renal transplantation. He began dialysis in 2004 with CKD-5 secondary to a 35-year history of insulin-dependent diabetes mellitus. He had the additional complication of diabetic retinopathy with blindness in one eye and decreased vision in the other. He was supported by social entitlements and a small disability pension. He had completed a degree in kinesiology and worked as a personal trainer until dialysis sessions prevented him from maintaining a schedule that met his clients' needs. He "helped out" at the neighborhood gym a couple of days a week and in return he was given access to their aerobic exercise and weight-lifting equipment. During his initial medical appointment with the renal transplant program, there were concerns about his "very lean" body habitus as well as fluoxetine being on his medication list.

In 2005, during his initial assessment by transplant psychiatry, he endorsed a 20-year history of eating disorder symptomatology. He described having been diagnosed with bulimia nervosa although detailed history taking and review of collateral from his family physician suggested that a diagnosis of AN—binge/purge subtype was more appropriate. When this was explained to him, he sheepishly noted that he "liked the diagnosis of bulimia better" and commented that he saw AN as a more stigmatizing diagnosis as, "people think only women have it." He described restricting his daily food intake to 750–850 calories per day with gum chewing to help decrease his sense of hunger. His BMI had been as low as 15 in his late teen years but had stabilized at 17 for a decade. Prior to his kidneys failing, he drank 3–4 L of water a day to subdue his hunger. He described body checking on a daily basis. He denied chewing and spitting, laxative use, vomiting or other methods of purging although vomiting had been frequent at points in the past, sometimes in association with bingeing and sometimes on its own. He denied ever manipulating his insulin for weight management purposes and had a stable record of HbA1c levels. He acknowledged excessive exercise in the past (up to 4–5 h a day of running and 2 h a day of weightlifting) but was now too fatigued to exercise excessively. On inquiry, he reported a history of depression and generalized anxiety that was under good control with fluoxetine 60 mg and on which he remained symptom free with maintenance therapy. The psychiatrist consulting to his dialysis center had prescribed the fluoxetine for mood symptoms and had not been aware of his eating disorder.

His primary concern about pursuing transplantation was post-operative weight gain and Cushingoid features secondary to prednisone use. He described himself as being more comfortable with dialysis than significant weight gain. He understood that his long-term prognosis was likely to be better with transplantation, but he was adamant that he would not be tolerate weight gain should he suffer that side effect.

Five years later, he was re-referred to the renal transplant program. In the interval, there had been expansion of the program with the establishment of a kidney-pancreas program. He was interested in pursuing transplantation that would free him from both dialysis and insulin therapy and allow him to be more active in his daily life. His BMI was 17. He was medically stable apart from osteomyelitis secondary to a difficult to treat infection. He explained that his life situation had changed. He had met and married and was the father of a 6-month-old daughter. He had a strong desire to do "whatever was required" to ensure "a long marriage," enhance his ability to parent his child, to "dance at the father and daughter graduation dance" and to ensure his longest possible survival. He was reassessed by transplant psychiatry and transplant social work. Both evaluators commented on his strong motivation for transplant arising out of his status as a husband and father and the impression that he was now willing to trade potential increased weight for a greater longevity with his wife and child. A referral to an intensive eating disorder program was recommended to obtain an expert opinion with respect to the potential role of intensive eating disorder treatment in preparing him for transplant. He agreed to this referral.

The eating disorder expert opined that Nicholas had a severe and enduring form of illness and that given its duration, was unlikely to benefit from treatment. The expert noted that while Nicholas was significantly underweight, he had maintained a stable BMI of 17 for 15 years and was able to

be functional in his daily life. They noted that engaging him in an intensive eating disorder program would require that he gain to a BMI of 22 (typically the goal for males with anorexia rather than 20 as the goal for women) and that this was unlikely to be successful for him.

Extensive discussions with the kidney-pancreas transplant team occurred to consider the potential for a novel immunosuppressive protocol, which limited prednisone use. Ultimately, this was determined to be possible in the context of a kidney-pancreas transplant but would not have been possible for a heart, lung or liver transplant. After an informed consent discussion, he elected to go with a standard protocol as it offered him the lowest risk for rejection.

Nicholas' transplantation peri-operative course was smooth. He made a good recovery and tolerated a minimal 3 lb. weight gain. In the first 3 years post-transplant, he occasionally found himself "on a slippery slope down" but quickly reached out for help and stabilized increased eating disorder symptoms when they occurred. His symptoms were restricting his calories or increasing his time at the gym. His wife served as "an early warning system" for him. He reached out to his family physician who monitored him weekly, and his wife provided extra support until he could get back on track. Nicholas noted that his young daughter was "the motivation I need to be successful." He enjoyed being free of needing to take insulin. He went on to live a further 10 years before a tragic, unexpected death with a ruptured cerebral aneurysm despite longstanding normotensive blood pressure readings. His eating disorder remained stable throughout this period.

Clinical Questions

1. What are some common post-transplant concerns for individuals with pre-existing AN?
2. Are there risk mitigation strategies, which might be helpful in improving outcomes for individuals with pre-existing AN?

Discussion

What are some common post-transplant concerns for individuals with pre-existing AN?

The most common post-transplant concerns for individuals with AN that we have worked with have been the body image changes secondary to steroids which may interfere with medication adherence after transplantation. Our case demonstrates the importance of strong motivation to make the risk of bodily changes resulting from immunosuppressive medications more acceptable for individuals with a history of AN. The steroid sparing regimen agreed to by the transplant team was helpful. No doubt luck also played a role!

Are there risk mitigation strategies, which might be helpful in improving outcomes for individuals with pre-existing AN?

The most important mitigation strategies are to ensure a comprehensive assessment to allow the transplant psychosocial team to understand all the relevant risks for their patient and to be able to develop a management plan to mitigate these risks. For patients at higher risk, it is important that the transplant team collaborate with the patient's mental health providers and that good social supports are in place to support the patient across the transplant trajectory. When it has not been possible to put these safeguards in place, we have turned down individuals for transplantation. The greatest worries are with patients with high-frequency purging symptoms where a period of symptom control would be mandated before transplant. For those with longer periods of stability and few if any psychiatric comorbidities, we have found that psychoeducation of the patient and their support network has been helpful. The transplant team monitors weight at routine follow-up visits and asks about changes in eating behaviors as a routine part of follow-up. Community providers are encouraged to contact the transplant team at any point that they are concerned.

Take Home Points

1. Individuals with pre-existing AN require careful evaluation prior to solid organ transplantation. Close communication between transplant psychiatry, community providers, eating disorder experts and the transplant team provide the scaffolding for successful transplant outcomes. The importance of realistic expectations and a strong motivation for transplantation are clear. Mitigation strategies, including potentially novel immunosuppressive regimens, should be considered when possible.
2. There is still much to be learned about the reciprocal impact of AN and solid organ transplantation and there is value in publishing cases and case series to help the transplant community increase their collective experience with the intersection of these two conditions.

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Body Image and Facial Transplantation

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Introduction

Even before the first partial facial transplant (FT) in 2005 by Dubenard, there were concerns about psychological issues related to body image with transplantation of an organ that is visible. Brill et al. remarked that the advent of FT presented a new opportunity to study models of body image. The concepts of body image and body schema have begun to diverge, and have relevance with transplantation of visible organs such as face and hand. Cash described body image as deriving from both the individual's self-concept and societal perception [1]. Thus, the concept of body image is thought to be multidimensional [2]. The hypothesis that the psychological impact of FT will be different for every patient was true. Even if patients do not return to an independent life, their quality of life can be significantly improved by FT [2, 3]. In contrast, predictions about self-esteem and social functioning made by Brill et al. were not completely true, in that self-esteem does not increase significantly after FT, although social functioning does improve [3].

Review of the Literature on Body Image

Body image is a multidimensional construct involving perceptions of the appearance and function of the body, which may not correlate with the objective assessment of disfigurement or alteration in function [4–8]. Body image refers to the cognitive perception of one's own body as well as attitudes and beliefs about one's body. This concept was first described by Paul Schilder in 1935 in " The Image and Appearance of the Human Body" [9].

Price conceived of body image as being composed of three elements: body ideal, body reality, and body presentation. The three elements are in equilibrium forming a satisfactory body image which people attempt to maintain. Price's hypothesis was that a change in body reality would force a change in either the body ideal or body presentation. The person must either adjust their idea of what was ideal, or present the body in such a way as to compensate for the change in body reality. There are no systematic empiric investigations of Price's model [10–12].

However, observations of FT recipients seem to confirm Price's model. Prior to face transplant, one candidate whose reconstructive surgery left her with a single large ventilation space but no nose, attempted to conform by wearing a nasal prosthesis. Ultimately, she abandoned this as uncomfortable and unnecessary for her body presentation and acceptance by others. Another candidate did wear a nose prosthesis, as he felt this was important for a more normal body presentation. Another FT candidate always wore a hat with a veil in public, adjusting her body presentation which after facial injury did not conform to her body ideal. Although her garb garnered notice, the veil minimized comments that would highlight her body reality. One male FT candidate likewise changed his body presentation by wearing dark glasses and a bandana-tied pirate-style around his head to disguise his missing eyelids and damage to his scalp. After the transplant, he prized his hair, as he had received facial tissues and scalp as well. He grew his hair hoping to donate this to children with cancer for wigs (Coffman unpublished).

For one FT recipient, the change in the face to a more acceptable body image allowed her to then focus on her body which was altered by steroid-related weight gain in the first 3 months after transplant. She began riding an exercise bicycle to slim down to re-conform her body image to her body ideal [3].

Another model, the fear-avoidance model postulated by Newell, could also be used to explain the alteration in body presentation through camouflage [12]. Newell proposed that damage to the body image results in fear of the changed body as well as fear of the reactions of others to the altered appearance. Activities that were associated with the lost or damaged body part(s) are avoided to minimize anxiety. Dysfunctional

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thoughts may also result in avoidance of activities that remind the person of the loss. Such body image coping strategies that result in avoiding stressful situations may become reinforcing. Personality traits such as introversion/extroversion may determine whether the person with facial disfigurement reacts through avoidance or confrontation and mastery of the situation. Newell's ideas are related to the fear avoidance model of exaggerated pain perception of Lethem and the model of body image in eating disorders put forth by Slade [12–14].

Body image has been described as formed by the accumulated beliefs, emotions, expectations, memories, and prejudices of the person, as well as the internalization of cultural ideals of desirable features and comments of parents and peers [15, 16].

In contrast, body schema is the awareness of the position of the trunk and limbs in space, and their relationship to one another, as well as the length of the limbs, and the shape of the surface of the body [17–20].

Pitron postulates the co-construction model, in which body image and body schema are functionally distinct but each construct is influenced by the other. Sensorimotor processing developed body schema first related to predatory behavior, and body image arose later with the capacity for recognition of one's own image. As such, body schema may influence body image more than vice versa. One demonstration of this principle is the observation of the exploratory behavior of infants involving visual and proprioceptive integration [21, 22].

This exploratory behavior was observed with the first FT recipient in the United States, who was legally blind. She repeatedly touched her new face incorporating the dimensions of her new body surface, observing her upper lip (donor tissue) was fuller than her original upper lip. She stated, "Now I have sexy lips!" (Coffman unpublished).

Adaptation of body awareness was viewed by Kinsbourne as a dynamic process throughout the lifespan [23].

Evidence that cortical processes mediate the sense of embodiment or body image emerged in the early twentieth century [24]. Over 10 years ago, evidence was published demonstrating that the central nervous system reorganizes the graft after successful transplantation of the upper limbs in humans [25]. The acceptance of the hand graft though MRI cortical feedback and improvements in sensation and function were taken as support for Kinsbourne's idea that body image could be updated by cognitive relabeling through incorporation of new information [26].

Facial trauma involving muscles, nerves, bone, and skin results in reorganization of the primary motor and sensory cortex [2, 27]. Functional EEG has demonstrated that FT helps restore the sensorimotor abilities with cortical reorganization up to 5 years following the original trauma. This finding suggests plasticity in representation of the body schema in the brain [3, 28].

Body Image in Craniofacial Conditions

The psychological issues related to body image in face transplant candidates before the transplant are the same in many regards to those in patients with craniofacial conditions. Chen observed that clinical causes of changes in body image can include amputation or injury including medical procedures (catheterization, punctures) or natural processes such as pregnancy [29]. Hair loss, loss of body parts, and scarring due to cancer have been investigated as causes of changes in body image. Head and neck cancers differ from other cancers due to the change in appearance, speech, swallowing, and personal identity [30]. This is analogous to face transplant bringing visible change in contrast to other solid organ transplants. The degree of emotional reaction of community observers to facial disfigurement from head and neck cancer correlates with perception of severity of disfigurement [31]. Ratings of disfigurement measured by medical professionals positively correlate with patients' self-perceived body image [32]. The repair of self-concept after surgery for head and neck cancers is lengthy, and involves body image reintegration through reorganizing one's perception of self [32].

Body image flexibility plays a part in acceptance or dissatisfaction with the body. Schilder stated that our body image is formed by interactions with others, as we are social entities [9]. Cash observed that the life we lead is influenced heavily by the body we live in [33]. Therefore, it is not surprising that people strive to maintain their body image intact, as changes in function or parts threaten our bodily functions, social relationships, self-concept, and self-esteem [29].

Structural instruments that measure body image in general may not be specific enough to pick up concerns about facial features, and use of condition-specific rating scales may limit comparisons with control groups and possibly over pathologize appearance and psychosocial issues.

Emerson's group identified three components of body image [34] as detailed in Table 11.1.

The goal in gaining a better understanding of body image is to be better able to identify who is at risk for psychosocial problems and to develop targets for interventions. In exploring the factors determining quality of life in head and neck cancer patients with facial disfigurement, Davidson and Williams found four main themes: changes within the self, help from healthcare professionals, social reintegration, and social support [38].

Patients with craniofacial (CF) injury have reported three main themes in their psychological adjustment: they no longer felt like themselves, they had lost part of who they were, and their values had changed. They reported negative emotions including self-consciousness, loss of self-esteem, and loss of control [39–46]. The patients often felt they did not receive timely information specifically about how greatly the CF surgery would affect them [39, 42, 43].

Table 11.1 Components of body image and structured measurements

Component of body image	Structured instrument	Significance
Investment in appearance (the importance of appearance to self-worth)	Multidimensional body-self relations questionnaire appearance scales (MBSRQ-AS) [35]	
Body image disturbance, meaning appearance	Body image disturbance questionnaire (BIDQ) [35]	Related anxiety or distress Higher scores with preoccupation with appearance concerns and interference with daily activities
	Satisfaction with appearance scale (SWA) [36]	Indicates satisfaction with facial features First developed for burn patients
Impairment in functioning (for example, due to avoidance of social interaction)	Derriford appearance scale (DAS) [2, 37]	Higher scores indicating higher distress and dysfunction

Social integration was desired by patients, but they dreaded the reactions of others [41–43]. Gradual exposure to others to build confidence was suggested [39]. Konradsen suggested that reintegration could start by socializing in the hospital. In order to cope and accept their disfigurement, the patients sought social support from various people, including family and friends. Peer support from others with similar experiences was helpful [41, 43–45]. The reactions of people closest to the patient provided a gauge of their disfigurement [47]. Social situations can provoke anxiety and phobic reactions in those with facial disfigurement [48]. Social rehabilitation through graded exposure that is not overly protective, but characterized by benign neglect has been found to reduce stigma and foster social integration [39, 43, 49, 50].

When patients received support through psychosocial interventions by health professionals, quality of life improved. Being able to talk and ask questions impacted recovery in a positive way [51]. Receiving adequate and appropriate information tailored to the patients' needs improved satisfaction with their care [46, 51].

Crerand et al. studied body image in adolescents with craniofacial conditions compared with adolescents without CF conditions. The adolescents with CF conditions reported significantly less appearance investment ($p < 0.001$) and were more likely to report concerns about facial features ($p < 0.02$) compared to the control group who was more preoccupied with weight and shape. Females were more invested in appearance overall with greater body image disturbance and lower satisfaction with weight than males in both groups ($p < 0.01$).

The adolescents with CF conditions did not significantly differ from control group on measures of body image disturbance, satisfaction with appearance, or quality of life [47]. A review of body image articles in patients with head and neck tumors showed that 75% of patients felt embarrassment at some point after their diagnosis [48]. Men reported distress with dysfunction versus disfigurement [43]. Many FT candidates struggle with the same issues prior to transplantation: two studies found that the strongest predictor of altered body image and appearance dissatisfaction were depressive symptoms [7, 52, 53]. The use of camouflaging with accessories, bandages, or clothing served to reduce embarrassment. Others gained confidence from their change in appearance, viewing their scars as reminders to be grateful for surviving cancer [54].

One study described a cosmetic rehabilitation program addressed body image concerns by teaching camouflaging techniques and showed higher scores on the Multidimensional Body-Self Relations Questionnaire-Appearance Scales (MBSRQ-AS) on perceived attractiveness and satisfaction with appearance after the 12-week intervention [55].

Specific changes in body image in head and neck cancer patients include alopecia due to chemotherapy or radiation, cranial deformity, or scars, Cushingoid facies and neurological deficits. Effects of corticosteroids on the skin include bruising, scars from tears due to fragility of thin skin and red striae, [56, 57] similar to what is often seen in transplant recipients.

Self-concept is related to the concept of body image, as both convey an idea of the self based on one's perception of oneself in addition to the responses to oneself from others [58]. However, self-concept incorporates other qualities of the self beyond mere appearance, such as sense of humor, intelligence, compassion, or artistic or musical talent. As seen with kidney donors, cosmetic appearance may be judged to be different than body image. The literature on facial disfigurement often links appearance with self-concept [59].

The face plays a key role in identity among humans, allowing recognition and social interaction with one another. The importance placed on facial appearance results in biases affecting choice of a life partner, [60] hiring decisions, [61, 62] as well as the odds of justice in legal proceedings. Even outcomes in political elections are affected due to inferences drawn about competence from facial appearance [63].

The effects of facial disfigurement on self-confidence, social anxiety, and avoidance due to fear of negative social evaluation are well known, though these are not universal [64]. Children with cleft lip may have higher risk for anxiety,

self-doubt in interpersonal relationships, and unhappiness [65]. Even after surgery, lower self-confidence may persist throughout adolescence [66]. One paper presented over 20 years ago reported double the risk of suicide in those with cleft lip [67]. Although younger patients adjust better than those with facial disfigurement occurring later in adulthood, [68] studies have not shown any correlation between age, sex, or severity of injury and psychosocial distress [5, 53, 69, 70]. Adults do express more of a sense of discordance between their "real selves" and their "new faces," and are acutely aware of the difference in how they are now perceived by society [71].

Identifying factors that predict successful adaptation to facial disfigurement are worthy goals of future research. With facial paralysis, factors that have been found to be protective include determination, faith, family support, humor, networking, social skills, and a strong sense of self. Desire for an improved appearance drives patients seeking orthognathic surgery to correct dentofacial abnormalities [72]. Corrective surgery can result in improvements in many areas including self-concept, self-conflict, self-esteem, self-identity, and even on measures of neurosis and psychosis [72–78].

The psychological burden of adjusting to a new face due to corrective surgery is described as significant due to a rapid change in facial features, requiring incorporation into the self-concept which can be confusing and frightening. Family and friends also may struggle in the beginning to adjust to the patient's new appearance [79]. In FT, the adjustment after facial injury appears to be more difficult than the adjustment after the transplant.

Psychosocial Rating Scales for Facial Transplantation

Although developing reliable and validated instruments for psychosocial assessment for facial transplantation is a worthy goal for ongoing evaluation of outcomes, the sample size at any institution is likely to be too small for generalizations. Instruments do exist for measuring quality of life, anxiety, depression, and self-esteem, though rating scales for body image are generally adapted from instruments for other conditions, such as eating disorder instruments.

Various instruments have been proposed and used to assess the psychological impact of FT including changes in self-esteem, body image, and quality of life. Only two rating scales have been validated in transplant patients: the Adult Self Image Scale used in heart transplant recipients [80] and the Body Awareness Scale used in heart transplant recipients [81].

The most used scale is the Body Image Questionnaire, (BIQ) [82]. Zimbrean used the Body Image State Scale and the Body Dysmorphic Disorder Evaluation-Self Report in liver transplant recipients [83]. Other rating scales that can be used that include questions regarding body image, include eating disorder questionnaires, sexual functioning questionnaires, sickness impact rating scales, or other quality of life rating scales.

The instruments used determine whether change is observed, as some instruments are not able to detect the change we are interested in as well as others. Rating scales used in plastic surgery patients included the Acceptance of Cosmetic Surgery Scale (ACSS) [84], the Fear of Negative appearances evaluation Scale (FNAES) [85], and the Multidimensional Body-Self Relations Questionnaire [86]. Development of instruments specific to FT based on reported concerns of patients themselves can be useful. The Psychosocial Adjustment to Illness Scale-Self-rated (PAIS-SR) has useful domains, addressing areas such as the relationship with doctors, immediate and extended family, partner, and neighbors as well as information about self-care, sexual functioning, social and vocational activities which may reflect reintegration into society [87].

More so than the Short Form 36 Health Survey Questionnaire (SF-36) or World Health Organization-Quality of Life instrument (WHO-QOL) which focus mainly on physical feats such as walking distances or climbing stairs, the PAIS-SR has utility in helping understand the changes these patients are negotiating in making the transition from facial disfigurement to post-transplant life. The Facial State Anxiety scale was adapted from a body image rating scale, the Physical Appearance State and Traits Anxiety Scale (PASTAS) with questions about specific facial components or facial functions reported to be of concern by FT candidates [88, 89].

Body Image and FT

The concepts of body image and personal identity have given rise to two camps. The body camp opined that personal identity resides in the continuity of the body, and concludes that the FT recipient acquires a new identity and loses the old identity. The mind camp suggested that personal identity is composed of psychological components such as memories, personality, and spirituality; therefore, FT does not impact one's personal identity [90, 91].

Narrative ethics, or the development of personal identity through life story, is embodied in FT in that the new face has the status of "transplanted face," expressing not the restoration of the natural face, but a face that encompasses a self that experienced both the accident and the therapy [91].

This could also apply to those with FT due to congenital conditions such as neurofibromatosis or acquired facial difference due to cancer, who also learn to adapt to changes in the body due to life history. The life history of FT recipients is still being written, the longest survivor to date having survived 11 years, succumbed to multiple infections in 2020.

Whether or not the benefits of FT are worth the risk of immunosuppression has generated controversy. Unfortunately, transplantation of any kind does not lead to perfect health, but is a tradeoff. Although Rivkin draws a distinction between the FT and solid organ transplants stating that FT does not prolong survival, this is not entirely accurate. Solid organ transplants differ in their ability to prolong life. For solid organs such as liver and lung, patients are trading certain death for a chance to live longer, hopefully with better quality of life, but this is not a guarantee. For heart, kidney, and pancreas transplant recipients, the bargain is not necessarily trading death for another chance at life, as left ventricular assist devices, dialysis and insulin offer other alternatives to transplantation.

Likewise, hand transplantation does not prolong life, but is done for a sense of wholeness. Uterine transplantation is done to fulfill one's concept of womanhood through carrying a life within oneself. Likewise, penile transplantation restores the sense of manhood and sexual functioning which facilitates social integration and reproduction. The risks of infection, skin cancer, metabolic disorder, and post-transplant lymphoproliferative disorder (PTLD) due to ongoing steroids are risks that not all candidates with facial disfigurement are willing to accept after evaluation and education are completed. Many patients would prefer to live as they are and work on self-acceptance rather than risk their lives with a yet experimental procedure. Of the first 12 FT candidates evaluated at our center, six (50%) decided against transplantation. Three underwent FT at our center, and three received FT at other centers.

Furthermore, FT cannot guarantee improved quality of life. The possibility exists that the outcome will not provide the benefits the patient envisions; therefore having clear and realistic goals and providing patient education to enable true informed consent is essential. As the longest survivors of FT are now years' post-transplant, the long-term psychosocial effects will be discerned over the next 5–10 years and provide data on the risk–benefit ratio of this procedure. With FT, the gamble is for improvement in quality of life versus quantity of life.

One research group used utility scores for facial disfigurement involving a visual analogue scale, time trade-off and standard gamble to answer that question. The sample included 307 subjects including both the general population and medical students. Results showed that if subjects suffered facial disfigurement, they would be willing to give up 12 years of life, and take a risk of 34% mortality to undergo facial transplantation and attain perfect health [92].

The issue of identity was key for 200 subjects in a survey asking whether they found facial transplantation acceptable. Both for the scenario of donation and receiving facial transplants, there was an inverse relationship between willingness to participate and resemblance to the donor. More were willing to donate or receive a facial transplant (81% and 83.5%, respectively) if there was no resemblance to the donor than if there was a strong resemblance to the donor (41.5% and 43.5%, respectively). The compromise in identity was of concern to this group of 200 composed of 30 doctors, 30 plastic surgeons, 30 medical students, 30 nurses, 30 renal transplant patients, 30 lay people, and 20 patients with facial disfigurement. However, acquiring some superficial facial characteristics of the donor, such as eyebrows, is inevitable [93].

Adjusting to disfigurement is more difficult than adjusting to a new face after a transplant, perhaps because the disfigurement meriting transplantation is extreme and the social reaction to extensive facial disfigurement is so intense. Family members may find it difficult to look at a loved one with an extensive injury even after the initial surgery to cover defects with flaps and grieve the lost appearance of their loved one. Brill et al. were correct that after FT, the source of information about facial appearance was key to forming a new body image, including information from the image in the mirror for those that had vision, and the appraisal of the new appearance from medical staff, as well as family members [2, 3].

Brill et al. pointed out that although the new body image is acquired from the donor, this was portrayed in the literature as negative, whereas when a likeness is noted in families, this is generally considered as positive and reassuring. Indeed, with one face transplant recipient, the patient's daughter felt the recipient looked more like the daughter after the face transplant as compared to before her disfigurement, so the perceived resemblance reinforced family bonds, as predicted by symbolic interaction theory [94].

Members of the public have commented on one face transplant recipient's appearance asking, "Why didn't the surgeons make you pretty?" The lack of understanding of the procedure and difficulty of obtaining donation for facial tissue can result in criticism of the aesthetic result. Function also may not be perfect with speech impediments remaining or worsening due to a hole in the hard palate requiring an obturator to prevent breathy speech and lodging of food in the nasal cavity.

Patient satisfaction with postoperative outcome is favored by a positive self-concept prior to the surgery [95], and a realistic rather than idealized mental image of their facial appearance [96]. Determining patient goals and expectations is paramount pre-transplant.

Brill et all did not imagine the extent of tissue that could be involved in a face transplant as the first partial transplant was thought by those authors to involve only skin. Although subsequent facial grafts have involved other tissue components besides skin including bone, ligaments, muscles, nerves, parotid glands, scalp, tendons, and vessels as well as functional units including ears, eyelids, lips and nose, the outcomes have not always resulted in a natural looking face. Siemionov noted that many face transplant recipients still

carry the stigma of "past deformity" with unnatural shape or mismatch in skin color [97, 98].

Controversy has arisen over whether the FT candidate should have already undergone conventional reconstructive surgery, or whether FT should be done emergently within weeks of the facial trauma, as was done in France, with the first FT recipient, and in Poland [99–102]. Siemionow raised the question of whether FT is indicated in patients with localized defects involving eyelids, mouth, or nose with the risks of lifelong immunosuppression. Siemionow also raised concerns about surgical removal of normal tissue to perform a FT that would better accommodate the aesthetic units of the face [103–107].

Deciding how extensive a facial graft to use can be affected by family members wish to hold onto the remnants of a familiar face, rather than using a graft involving the whole face. Final acceptance of the new appearance occurs after approximately 2 years with stabilization of body image and self-esteem in studies of surgery for facial disfigurement [108]. By comparison, psychological integration of a hand graft requires about 1 year after the transplant [26, 109, 110].

There may also be a period of adjustment with FT, which varies with the individual. As further procedures may be done after FT to refine the appearance, the adaptation may be a work in progress as well with each new step toward the end result. It remains to be seen whether the psychoanalytic approach or the cognitive behavioral approach is more effective in helping patients adapt to composite facial allografts. In France, the adaptation to hand graft was discussed in psychoanalytic terms. The Chinese team took a cognitive behavioral approach to preparing recipients for the hand transplant [26, 109].

Due to the recipient's refusal to accept hand grafts, extensive pre-transplant conditioning was done to encourage management of the emotional response before the transplant, with both positive labelling and reappraisal of the graft postoperatively [109]. Patients with extensive composite tissue defects, such as mid-face injuries, may not have acceptable aesthetic or functional restoration with conventional reconstructive surgery, particularly with the structures most important for self-concept: eyelids, lips, and the nose [110]. Attempts to create competent oral closure may lead to complications including microstomia or leakage, both of which impact eating and drinking. Severe tissue deficits may be covered with free flaps to close nasal cavities and sinuses, but these interventions compromise the sense of smell. Patients may feel more self-conscious wearing nasal prosthetics than having only a nasal opening, which at least preserves sense of smell.

Replacement rather than attempting to reconstruct complex structures such as eyelids, nose, and lips restored function and, in many cases, provided acceptable aesthetic results as well [100, 111]. Initial fears that there would be difficulty adapting to a new facial identity were unfounded as the previous transition from facial normality to facial disfigurement is a much more difficult adjustment both psychologically and socially. Additionally, in our experience when donor family members have met two of our FT recipients, they have been proud of the tremendous difference their donation made in the recipient's quality of life. They have not been disturbed by similarities between the recipient's face and that of their loved one. Some teams have performed a rhinoplasty to foster a different appearance from the donor. Also, due to differences in bone structure, the donor and recipient do not appear to bear a strong resemblance to one another.

The recipients' faces do not resemble their former faces. This blending of appearances was predicted by mock transplantation and computer simulation exercises [112, 113]. Therefore, rather than regaining their personal identity through FT as described by Rivkin, patients are gaining a unique new facial identity; no longer a nonentity socially due to the lack of a socially acceptable face. As many are legally blind due to their injuries, they take their cues about their appearance from those around them. The ability to function in a social capacity due to improved speech, ability to eat with family in a restaurant without leaks or food falling out of their mouths, and improved sexual function are some of the gains reported by FT recipients. Similarly, plastic surgery patients have reported an increase in self-confidence and better interpersonal relationships [114, 115]. Some transplant teams have reported that recipients with certain personality traits, particularly a strong self-concept, have fewer problems adjusting to the change in physical appearance and fewer negative psychosocial consequences [116, 117].

Emotional acceptance of the new face is thought to be critical for self-concept adaptation, whole-body reintegration and greater adherence with postoperative care [118, 119]. The aesthetic changes from FT resulting in an improved body image and facial image have resulted in a more accepting reaction from the public; rather than being reviled, verbally abused or attracting unwanted attention, the FT patients can now function without attracting undue negative attention [3, 120]. This is consistent with the idea that patients undergoing plastic surgery are seeking to heal both their bodies and minds.

Emotional and psychological factors that correlate with better outcomes are becoming known. In addition, new information about how neural underpinnings of self-recognition function to gradually form a new facial identity [121–123], through altering body image and body schema is emerging. Facial transplant recipients often experience many challenges preoperatively including gastric or jejunal feeding tubes, skin grafts, and multiple eyelid surgeries. FT recipients may undergo orthopedic adjustments to bone alignment after the FT to improve speech by assuring the proper tongue position in proximity to the teeth, and some may require

tooth implants to replace missing teeth due to jaw damage sustained in the original injury.

Data have shown that the concern about body image shifts from the face after FT to the body in the first 3 months after FT due to weight gain and impact of steroids on muscle strength [3]. Fatigue and weight gain can affect body image and self-concept over time as shown on the SF-36. Eyelids may invert over time, cause irritation due to eyelashes scratching the cornea. Several months after the FT patients are transitioned from tube feeding via J-tube to oral feeding. The tracheostomy tube and Passy Muir valve are removed leaving a scar on the neck.

Dental issues due to loss of native teeth or loss of donor teeth may require dentures. Some recipients may have obturators made by dentistry to plug a hole in the hard palate to prevent food from entering the sinuses. Patients may feel that the obturator changes their normal speaking and singing voice as, preventing family and friends from recognizing them on the telephone. This also involves a loss of identity if the patient prized his or her voice. One recipient felt he sounded as though he had a speech impediment as in cleft lip or cleft palate, which was upsetting to him (Coffman unpublished). In general, among our FT candidates, women have expressed more concerns about body image then men, but this was individual.
One female recipient, indicated that her self-esteem depended more on her skills than her appearance, and one male recipient prized his appearance as he fancied himself a ladies' man. However, he was motivated for transplant not mainly due to appearance, but for function in hopes of improving his vision and returning to work (Coffman unpublished).

Pre-Existing Psychiatric Conditions and FT

Controversies remain about FT candidates with mood disorders and addictions. Many of the FT candidates around the world were injured due to self-inflicted gun shot wounds, and one had an electrical burn injury due to jumping onto the subway tracks [97, 104]. Therefore, the ethical issue of whether suicide attempts are an absolute or relative contraindication to FT is a relevant question. Many FT candidates have alcohol or substance use disorder (4/10 candidates for FT seen for evaluation by our transplant team had alcohol use disorder), so addressing the issues of addiction is important. Several of the suicide attempts occurred during alcoholic blackouts. Patients may arrive dependent on opiates due to multiple surgical attempts at reconstruction. If addiction is not addressed by improving coping skills, the FT recipient is in danger of either returning to alcohol in response to life events, or may substitute another addiction that can also endanger life, such as overeating to the point of morbid obesity or using other substances, such as cannabis. In our experience, this has been true in FT as for other organ recipients [124]. The first FT recipient in France had a history of alcoholism, but died due to lung cancer as she relapsed to smoking after the transplant. No intervention was proposed for smoking cessation due to feelings of the transplant team that this would infringe on her freedom. New risks have appeared with regard to smoking. To date, in the US, there have been over 2500 hospital admissions and more than 50 deaths due to vaping nicotine or THC oil [125–127].

Case History

An 18-year-old female with self-inflicted gunshot wound underwent 3 years of recovery after sustaining severe neurological consequences, including seizures and trephine syndrome.[1] The trephine syndrome resulted in cognitive impairment and spastic gait, and the patient was underweight. She was initially not listed for transplant due to debilitation because FT surgery can last more than 24 h. Over several years, she gained weight and worked with physical therapy to overcome her frailty. The patient initially had many episodes of delirium following each reconstructive surgery. She had little recall of her first year after her injury. Through ongoing education in stages with increasing complexity appropriate to her improving level of cognition, she gradually acquired the information needed to demonstrate capacity for informed consent for FT. Due to her age, the team initially questioned her maturity and ability to make such a difficult decision regarding an experimental procedure.

Clinical Questions

1. Considering that patient's injury had been self-inflicted, should FT be considered in this patient?
2. What are the ethical principles behind the concept of substituted judgement?

Discussion

One transplant team had lost a patient to suicide 3 years after transplant who was injured due to self-inflicted gunshot wound and decided that FT for self-inflicted injuries in the future would not be considered. In Sweden, an large demographic study had been done to determine whether those that had attempted suicide would attempt again in the future. The data did not support that repeat suicide attempt was very likely [128]. This patient had experienced a single episode of

[1]Trephine syndrome: cluster of neurological symptoms following a depressed skull. Annan M, De Toffol B, Hommet C, Mondon K. Sinking skin flap syndrome (or Syndrome of the trephined): A review. Br J Neurosurg. 2015 Jun;29(3):314–8. doi: 10.3109/02688697.2015.1012047. Epub 2015 Feb 27. PMID: 25721035.

depression, with impulsive behavior under extreme stress without history of substance abuse.

There was no indication of a personality disorder. She had excellent family and social support. She demonstrated good coping skills despite many painful procedures and long hospitalizations. She had not had a recurrence of depression over 3 years of follow-up, and was engaged in learning Braille, working actively on speech therapy and intensive physical therapy. Other than one serious attempt, she did not have the risk factors associated with adolescent suicide, namely: current suicidal ideation (none in the 3 years since the attempt), exposure to suicidal behavior, lack of family support, male gender, mood disorder, psychopathology, or psychosis [129–131].

The decision was made by the selection committee to list the patient for FT. The patient waited for a year for a donor to be found. The patient had one "dry run"[2] with an unacceptable donor. After an excellent donor was found, the patient was prepped for surgery. After inspection of the donor, there was enough congruity between the bone structure for either of two procedures to be done. As the patient was already under anesthesia by the time of this determination, her parents were approached to make the decision whether to do a limited procedure to replace the midface structures of nose, lips, and chin, including bone, muscle, and skin. Alternately, a larger procedure could be done to replace the total face including forehead, part of the skull, and all bony structures including maxilla, mandible and carry the incision for about 1 inch behind the hairline as the hair color of the donor and recipient were a near perfect match, to give a more normal facial appearance. In the event of loss of the facial graft, a smaller procedure would allow more possibility for a second procedure. Both had the possibility of restoring speech and sense of smell. The less extensive procedure might offer a better possibility for another transplant in the future, due to the youth of the recipient and potential for chronic rejection after 8–10 years.

What are the ethical principles behind the concept of substituted judgement? Should the parents decide based on what they think is best for their daughter, or based on what they believe she would decide if she was making the decision? Knowing their daughter had always been a competitor both academically and athletically, who believed in "going big or going home," they decided on a more extensive procedure as they felt she wanted the best result for social reintegration. They were torn as they would have liked to retain some features of her remaining face, but the larger procedure precluded this option. The decision they made involved the endorsed life approach to substituted judgement, promoting the life the patient valued, rather than the family interests [132]. After the transplant, the patient agreed with the decision to pursue a more extensive FT to allow for a more normal appearance and function.

[2]Dry run in transplantation typically defines when patient is called to the hospital when a graft becomes available, only to find out the graft is not suitable and the surgery will not occur.

Conclusions

Body image is an important construct for investigating the psychological impact of composite organ grafts, whether visible such as hand, face, or penile transplants or invisible such as uterine transplant. Due to many FT recipients having lost their vision in the injury resulting in the facial disfigurement, they may not be able to resume their previous lives or employment. However, if improvement in communication and interaction with family members and friends are the goals, this is realistic. For some with severe facial injuries, the injury changes their goals completely.

The bigger adjustment is from a normal appearance to being disfigured, rather than from being disfigured to having a new face through FT. Body image changes initially when focus shifts from the face to the body due to steroid-related weight gain. Over time, steroids may cause weakness and fatigue, greatly impacting the quality of life, even in younger FT recipients. Chronic immunosuppression can predispose to cancer and potentially life-threatening infections. Humoral rejection can cause large lesions on the face and scalp, as seen in one FT recipient 6 years after transplant. He has been treated with IVIg and Rituximab, but may need re-transplantation if the graft cannot be salvaged. Ultimately, between years 8 and 10 after FT, chronic rejection can threaten the survival of the facial graft with the appearance of large ulcerated areas. These wounds can show remarkable healing with hyperbaric oxygen treatment over several months if immunosuppressant interventions are not effective.

Substitute addictions such as overeating can alter body image and function, and vaping can have unintended consequences and be potentially life threatening. In summary, there is much still to learn regarding body image and FT which will become more clearer with time as more recipients reach the 10-year survival mark.

Take Home Points

1. A history of psychiatric disorder, including suicide attempt with disfiguration, should not be an apriori contraindication to FT, provided that remission is achieved. Emphasis needs to be placed on strengthening coping skills, maintaining motivation and

realistic expectations regarding the post-transplant outcomes.
2. Body image in FT depends on many factors, including extend of the facial trauma, scope of the surgery, prior psychiatric history and psychological status, and post-transplant medications side effects.

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Part II

Cognitive and Neuropsychiatric Disorders

Delirium in Organ Transplant Recipients

12

Jose R. Maldonado

Introduction

Delirium is the most common neuropsychiatric syndrome encountered by clinicians dealing with older adults and the medically ill, with a prevalence ranging from 10% in general medicine to 85% in advanced cancer and critical care [1, 2]. When it relates to organ transplantation, the incidence of delirium is high. There appear to be three peaks of delirium around organ transplantation: the first is caused by progressive end-organ failure immediately before transplantation (e.g., encephalopathy due to hepatic, renal, pulmonary, or cardiac dysfunction). The second occurs during the acute post-transplant period. For example, delirium in the immediate post-transplant period has been described to be between 2 and 13.8% of renal transplant recipients [3], between 34 and 44% of lung transplant patients [4, 5], between 26 and 52% among heart transplant recipients [6, 7], and between 26.4 and 47.4% of liver transplant recipients [8, 9]. The third is usually associated with immunosuppressant medications (i.e., medication toxicity or medication-mediated side effects, as in the case of posterior reversible encephalopathy syndrome [PRES]) [5]. Of note, the development of post-transplant delirium has been associated with significant negative outcomes. For example, among renal transplant recipients, those who developed delirium were at a 5.42-fold higher odds of ≥2-week length of stay (LOS), 22.41-fold increased risk of institutional discharge—as opposed of going home, 2.73-fold increased risk of death-censored graft loss, and 3.12-fold increased risk of mortality [3, 4, 10]. Among older adults, delirium is considered to be the most common surgical complication after transplantation [11], occurring in up to 50% of older surgical patients [12, 13].

Delirium is an acute or subacute disorder, usually developing within hours to days. It represents a change from the patient's baseline cognitive functioning, characterized by disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness, with impaired orientation to the environment (criterion A), with additional disturbances in cognition (e.g., memory deficit, disorientation), language, visuospatial ability, or perception (e.g., hallucinations or delusions; criterion C) [14]. Available data suggest that numerous pathological factors may serve as precipitants for delirium, each having differential effects depending on patient-specific physiological characteristics [15, 16].

The clinical features of delirium include a prodromal phase, usually marked by restlessness, anxiety, irritability, and sleep disturbances, which usually develop over a period of hours to days. There are five delirium phenotypes: [1] subsyndromal delirium, often under-recognized as it presents with partial diagnostic criteria; [2] hypoactive delirium and its extreme manifestation, the catatonic subtype; [3] hyperactive delirium and its extreme form, the excited subtype; [4] mixed delirium, which often exhibits alternating characteristics of both hypoactive and hyperactive types, and likely gave rise to the classic description of delirium as waxing and waning in nature; and [5] protracted or persistent delirium [2]. Finally, though the DSM suggests delirium is an acute and transient syndrome, chronic forms may be seen in several scenarios, such as those with baseline cognitive impairment or experiencing delirium as sequelae to new intracranial processes, or the effects of acute substance intoxication or withdrawal, or to the long-term effects of organ failure and the chronic use of immunosuppressant agents commonly used among patients experiencing end-stage organ disease and organ transplant recipients.

The most likely predisposing factors include the patient's age, baseline cognitive level of functioning, and frailty. Contributing factors include the patient's illness severity, comorbid medical and psychiatric conditions, end-organ dysfunction, and the use of pharmacological agents [2, 15]. Among medications, opioids, benzodiazepines, and medications with high anticholinergic load appear to be the main offenders. A systematic review among intensive care unit

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(ICU) patients revealed the following: age, dementia, hypertension, pre-ICU emergency surgery or trauma, Acute Physiology and Chronic Health Evaluation (APACHE) II score, mechanical ventilation, metabolic acidosis, delirium on the prior day, and coma as strong risk factors for delirium, whereas multiple organ failure was a moderate risk factor [17, 18]. The data indicate that in older adult patients, the probability of developing delirium increases by 2% per year after age 65 [19].

Vigilance and a high level of suspicion may be the most important tools for the timely diagnosis of delirium, particularly in patients at higher risk, such as in the case of transplant recipients. The DSM-5 [14] and the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [20] are considered the diagnostic gold standards. In addition, there are many validated instruments to screen for the presence of delirium, with the Confusion Assessment Method (CAM) [21] most widely used in the general medical setting. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [22] and the Intensive Care Delirium Screening Checklist (ICDSC) [23] are the most commonly used screening tools in the critical care settings. Newer delirium surveillance and diagnostic tools include the Rapid Assessment Test for Delirium (4AT) [24] and the Stanford-Proxy Test for Delirium [25, 26]. Some of these tools are best for surveillance as they provide a binary result (i.e., delirium or no-delirium), such as the CAM and CAM-ICU. However, some tools provide a severity score (i.e., the ICDSC and the S-PTD) and can be utilized to monitor the patient's progress (i.e., assist in determining whether the implemented treatment intervention is having the desired effect; that is, the score should improve as the patient is getting better). In our facility, nursing staff performs the S-PTD at the end of every shift and that information is conveyed to the ICU team during daily rounds. The CLP Team performs the ICDSC on every visit for consult cases in the ICU or when the diagnosis of delirium is suspected, in non-ICU cases, to assess the patient's progress and response to treatment. Despite its high prevalence, delirium remains unrecognized by most ICU clinicians in as many as 66–84% of patients [27, 28]. There are two likely reasons for the lack of recognition. The first has to do with the fact that most diagnostic tools require patient's participation. Patients at the extreme of symptom presentation (i.e., too agitated or those exhibiting the extreme of psychomotor retardation) might not be able to adequately participate or respond and thus are considered "untestable." The other reason is lack of recognition by medical personnel [2, 15]. When we think of delirium as a form of confusion, agitation, and psychosis (i.e., hyperactive delirium), we probably will recognize those patients. Unfortunately, that constitute only about 10% of cases. On the other hand, the most common delirium phenotype (67%) is that of hypoactive delirium. Patients with hypoactive delirium might be suspected to be experiencing depression, demoralization, dementia, or just to be a "natural part of the patient's illness," so a surveillance test might not be administered due to lack of suspicion.

The Transplant Psychiatrist should be aware of the possibility of delirium given the significant potential consequences of its development. The data show that after controlling for demographics, apparent illness severity, age, and medical comorbidities, patients who develop delirium fare much worse than their non-delirious counterparts [2, 29–32]. In addition to causing distress to patients, families, and medical caregivers, the development of delirium has been associated with increased morbidity and mortality, increased cost of care, increased hospital-acquired complications, poor functional and cognitive recovery, decreased quality of life, prolonged hospital stays, and increased placement in specialized intermediate and long-term care facilities [1, 2].

In general, the management of delirium includes the following interventions [2, 33]:

1. The primary intervention and thus the treatment of choice is the recognition and correction of the underlying and contributing medical problems causing the syndrome of delirium. In the transplant patient population, common medical problems that may contribute to delirium include: electrolyte imbalance, dehydration or fluid overload and other metabolic derangements, acute neurologic injuries; nutritional deficiencies; age; baseline cognitive deficits; toxic effect of medications including immunosuppressant agents; anemia, anoxia and low cardiac perfusion states; infectious processes; pain and the use of opioids; isolation and immobility; disturbance of the patient's circadian rhythm and sleep deprivation; and of course, organ failure.
2. Surveillance and, accurate, timely diagnosis of delirium (e.g., hypoactive delirium vs. depression, hyperactive delirium vs. alcohol withdrawal or drug intoxication) is imperative—as the development of delirium usually indicates a decompensation of the patient's overall medical condition.
3. Monitor for the development of delirium as a side effect of therapeutic agents or drug–drug interactions. Conduct an inventory of all pharmacologic agents and discontinue any medications known to cause delirium (e.g., opioid, benzodiazepine, steroidal, and antihistaminic agents), including those with high anticholinergic potential.
4. Timely implementation of non-pharmacological prevention and management strategies to minimize the risk of development and facilitate rapid resolution and minimizing the long-term sequelae of delirium. Non-pharmacological strategies include: minimization or removal, if possible, of immobilizing lines and devices

(e.g., chest tubes, intravenous [IV] lines, and bladder catheters) and physical restraints; correction of sensory deficits (e.g., provide eyeglasses or hearing aids to facilitate the patient's integration with the treatment environment); minimize environmental isolation; involve the patient's family members and loved ones and educate regarding the nature and long-term consequences of delirium and enroll them in assisting in the patient's recovery; restore a normal circadian rhythm, by controlling nighttime noise and light variables; and providing a protected sleep block to allow for the patient to naturally sleep and rest; and provide appropriate orientation and cognitive stimulation.

5. Consider pharmacological management of the behavioral and psychiatric manifestations and symptoms of delirium for improved patient and staff safety [2, 33].

Case History

Mr. X is a 67-year-old married man diagnosed with emphysema 7 years prior to his presentation for lung transplant. The emphysema was associated with severe airway obstruction, likely secondary to prior tobacco dependence (70-pack-year history, which ended 13 years earlier) and alpha-1 antitrypsin deficiency. He had been oxygen dependent for 7 years with increasing requirements even at rest. Medical evaluation for transplant included cardiac studies, which confirmed diastolic dysfunction and concentric left ventricular hypertrophy. Despite this, he was deemed a suitable candidate for lung transplantation from a medical standpoint.

As part of the pre-transplantation process, the patient underwent a comprehensive psychosocial evaluation. Although no major psychiatric disorders were identified during the evaluation process, it was noted that he had experienced anxiety related to his medical condition with depressive features, and had Post-traumatic Stress Disorder (PTSD) related to his service during the Vietnam War, aggravated by experiences in the complicated medical setting of pulmonary failure (e.g., admissions to the critical care units, intubations, delirium). He had been prescribed citalopram for anxiety and, trazodone and alprazolam for insomnia by his local pulmonologist. A history of organic cognitive psychopathology was identified, presumably associated with his underlying chronic hypoxemic respiratory failure and episodes of mild delirium during previous hospitalizations. He also had a remote history of alcohol use, not meeting criteria for an alcohol use disorder.

Upon review of his medical history, this patient had several risk factors for developing delirium. He had been on long-acting anticholinergic agents, bronchodilator agents, and inhaled corticosteroid therapy. Medically he suffered from severe airway obstruction and chronic hypoxemic respiratory failure, along with pulmonary scarring, with associated chronic hypoxemia. Due to his chronic illness, he had also experienced severe physical deconditioning, moderate to severe weight loss, and significant frailty. At the time of transplantation, he required 5–6 L of supplemental oxygen at rest and 8 L with activity.

The patient underwent a single-lung transplantation 2.5 years after he was initially evaluated and listed for transplantation. On the first post-operative day (POD#1), extracorporeal membrane oxygenation (ECMO) was initiated to compensate for increasing oxygenation requirements, presumed to be due to primary graft dysfunction. As part of ECMO and ventilation management, the patient was initiated in intravenous (IV) sedatives (i.e., propofol and fentanyl).

On POD#2, the patient experienced periods of desaturation overnight, with significant increase in oxygen requirements and ventilator settings. Due to concerns of primary graft rejection, IV Solumedrol was started. Given concerns for increased anxiety, the Consultation-Liaison Psychiatry (CLP) team was consulted to [1] evaluate for the possibility of benzodiazepine withdrawal (given years of alprazolam use) and [2] non-benzodiazepine anxiety management. The ICU team wanted to avoid benzodiazepines, given their potential negative effect on respiratory drive and hence time to extubation. The team found the patient to be anxious, he described previous PTSD symptoms and having a hard time currently in the ICU. The CLP team agreed with continued cessation of alprazolam and recommended use of dexmedetomidine (DEX) instead of propofol. Additionally, guanfacine was recommended to decrease sympathetic overdrive and hence facilitate extubation, minimize delirium, and allow for ease of transition off DEX, when appropriate. Recommendations were also made to switch from fentanyl to hydromorphone (given data demonstrating that the risk of delirium appeared to be lower and pharmacokinetics preferable with hydromorphone, compared with other opioids, including fentanyl) [34, 35] and to continue citalopram for anxiety and trazodone for sleep. Melatonin was added for its chronobiotic effects to restore the sleep–wake cycle. Finally, the CLP team recommended an aggressive non-pharmacological delirium prevention protocol.

Over the next several days, the patient received increased doses of methylprednisolone due to ongoing concerns with graft rejection. The team observed an increased level of anxiety especially around the timing of his spontaneous breathing trials and at bedtime. In an attempt to further avoid benzodiazepines, the transplant team added gabapentin POD#2. The CLP team subsequently signed-off on POD#6, as there were no concerns for delirium and his anxiety appeared well under control. His mental status remained clear, with no evidence of confusion and no episodes of agitation. He was successfully extubated yet remained on ECMO.

On POD#10, the patient became delirious overnight, for which the transplant team started him on low-dose haloperidol. By POD#11, the patient continued to experience progressive deterioration on pulmonary function, confirmed by chest X-ray on POD#12, which revealed "near complete white out" of the new graft lung. A bronchoscopy performed latter that day revealed considerable burden of clot and secretions, raising concerns of primary graft dysfunction with diffuse alveolar damage. His pulmonary decline was accompanied by progressive confusion and nighttime agitation, leading to an upward titration of haloperidol and gabapentin. Unfortunately, a few days later, the team noted the patient to be demonstrating "muscle twitching." Concerned that these may be caused by haloperidol, they immediately discontinued it and reconsulted psychiatry on POD#15.

The CLP team was reconsulted for the management of delirium and "concerns with tardive dyskinesia (TD)" due to worsening delirium, ongoing "muscle twitching" and what the team thought was akathisia. The CLP evaluation concluded that the motor symptoms demonstrated by the patient were more likely due to the presence of gabapentin, in a patient with relatively impaired renal function, rather than true extrapyramidal symptoms secondary to exposure to antipsychotic agents. In fact, the use of gabapentin, especially in a patient with compromised renal clearance, has been associated with the development of multiple motoric side effects including tremors, asterixis, chorea, stimulus-sensitive and spontaneous myoclonus, painful muscle spasms, and myokymia (i.e., a simultaneous or sequential spontaneous contractions of multiple motor units that cause a rippling of muscle) [36–38]. Gabapentin was discontinued at that time.

Due to ongoing pulmonary deterioration, on POD#16, the patient was re-intubated and continued on ECMO. Psychiatry recommended switching from propofol to a DEX-cycling mode and adjusted dosage of guanfacine to help with restlessness and anxiety. No other psychotropic agent changes were made. By his third post-operative week, his respiratory function had improved, and he was decannulated from ECMO and underwent a tracheostomy. Given corresponding improvements in his anxiety and mental status, psychiatry signed off again on POD#21.

A few weeks later, POD#37, the patient became confused and restless overnight, requiring restraints, yet his mental status was rather clear, and he was fully oriented the next day. This cycle repeated itself for the next 3 days. On POD#40, the CLP team was reconsulted due to worsening sleep and a sun-downing pattern. On exam, the patient was calm at the time of evaluation, yet the CLP team uncovered worsening confusion, disorientation, hallucinations, reversed sleep–wake cycle, restlessness/agitation requiring PRN medications, soft restraints, and a bedside sitter for redirection. His Intensive Care Delirium Screening Checklist (ICDSC) score was 6/10, which along with the history and clinical picture, were consistent with a hyperactive type of delirium. Noting that the patient had previously responded to the use of haloperidol, we recommended restarting this agent for management of delirium with sundowning pattern. In addition, suvorexant was started and trazodone was discontinued as it had not proven effective in managing his insomnia. On POD#42, the patient still exhibited significant confusion, intermittent agitation, and continued reversal of his sleep–wake cycle. The haloperidol dosage was then increased (from 2 to 5 mg/d in divided doses) to address the agitation given the absence of rigidity and extrapyramidal symptoms.

By POD#44, there were significant improvements in mentation and no further complaints of agitation, yet he was still demonstrating reversal of sleep–wake cycle with sundowning pattern. His ICSDC score improved to 4/10. Unfortunately, on POD#47, the patient experienced hypotension and hypoxemia, along with an episode of atrial fibrillation (AFib) and new episode of pneumonia was identified. This was associated with a parallel worsening of mental status and associated agitation, requiring increasing sedation with DEX and propofol.

On POD#49, after aggressive treatment of his Klebsiella pneumonia and fluid resuscitation, and overall improvement in pulmonary functioning, the patient's delirium picture seems mostly resolved. Haloperidol was discontinued at this time. Nearly a week later, on POD#56, the patient experienced yet another episode of nighttime delirium, with acute agitation, restlessness, and pulling on intravenous (IV) lines. He was found to have urosepsis. Antibiotic treatment was initiated; and for his agitation, haloperidol was restarted at previously effective doses. On POD#58, 2 days after identifying and starting treatment for sepsis and the addition of haloperidol and guanfacine, the patient demonstrated significant improvement of his mental status. On this day, his ICDSC score was 1/10. By the next day (POD#59), his delirium had resolved. In fact, he continued to do well for the next 3 weeks.

On POD#80, the patient was found to be withdrawn, apathetic, and uncooperative with physical therapy (PT) staff, which was unlike him. PT notes documented that at one point, the patient reportedly stated "you should let me die." The CLP team was reconsulted for "treatment of depression with suicidal ideation." On exam, the patient was very somnolent, required much stimulation to stay awake, and was unable to fully cooperate with the bedside neuropsychiatric assessment. He also exhibited multiple primitive reflexes, not previously observed, including grasp and palmomental reflexes bilaterally, as well as positive snout and sucking reflexes. We concluded the patient as being delirious again, hypoactive type rather than being depressed. We noticed the

team had added hydroxyzine for the management of "anxiety," with escalating doses in the past few days. We recommended discontinuing hydroxyzine given its anticholinergic burden and his impaired kidney function. Instead, we recommended an increase in nighttime guanfacine, and recommended adding modafinil in the morning to promote wakefulness.

Two days later, on POD#82, there has been only minimal response to the use of modafinil. The dose was increased twice in the morning, doses at 0600 and 1100. In an effort to optimize his nighttime regimen, we asked the team to include full dose of melatonin and suvorexant, which had been decreased over the course of his hospital stay. We also recommended a strict sleep protection regimen whereby nursing care-related interruption to sleep at nighttime was minimized. By POD#83, the patient's sleep–wake cycle appeared to have been restored. He was awake, alert, and oriented during the daytime, participating in aggressive PT. He was reportedly sleeping 6 h each night. A week later, he displayed no deterioration in his mental status, had a normal circadian rhythm, and no evidence of sundowning or frank delirium. After 3 months in the hospital, he was transferred to a long-term acute care hospital, for further rehabilitation.

Clinical Questions

1. What are specific risk factors and what is the role of immunosuppressant agents in the development of delirium?
2. What should clinicians be aware of with respect to the various manifestations and causes of delirium during a prolonged hospitalization?
3. What is the best treatment for delirium among patients with end-organ disease and after transplantation?

Discussion

Cognitive impairment, including delirium, are commonly found in patients with end-organ disease and failure, as well as during the immediate post-transplant period [4, 39–44]. The overall incidence of delirium among organ transplant recipients varies according to the degree of end-organ failure and the organ transplanted. For example, the incidence of delirium was 2–20% among kidney transplant recipients [main pre-operative risk factors included: older age, frailty] [3]; 18–34% among heart transplant recipients [40, 45–48]; 17–45% among liver transplant recipients [main pre-operative risk factors included: preoperative ammonia; higher Model for End-Stage Liver Disease (MELD) score, presence of hepatic encephalopathy; higher APACHE II scores, and need for re-intubation] [9, 49–53]; and 36–44% among lung transplant recipients [main pre-operative risk factors included: obesity, pre-transplant benzodiazepine prescription, total ischemic time, duration of time with intraoperative mean arterial pressure < 60 mmHg, post-operative benzodiazepine use, and Grade 3 primary graft dysfunction] [4, 10, 44]. Invariably, research data have found that post-transplant patients experiencing post-operative delirium (POD) had longer ICU and hospital stays, increased ventilator days, and shorter survival time, as well as an increased frequency of hospital acquired infections [10, 43, 50, 51, 54].

1. This case is an excellent example of how delirium manifests itself in the clinical setting, its pattern of presentation, and the fact that the primary step in the management of delirium is the identification and aggressive correction of the underlying causes contributing to its development [2, 55]. In fact, on POD#2 the patient first demonstrated mental status alteration, consistent with a post-operative delirium pattern (usually arising within the first 72 h after surgery).
2. Notice that we recommended the use of DEX and guanfacine, over more classic, GABAergic type of sedatives such as propofol or midazolam, as GABAergic agents' use has been associated with an increased incidence of delirium [19]. There are also data suggesting that DEX use is associated with lower incidence of delirium, a shorter length of intensive care (ICU) stay, shorter ventilation duration, and lower overall ICU mortality [56–62]. There is even more recent data suggesting that the use of DEX-cycling, (i.e., relatively low dose administered in the daytime with higher dose at night to maintain circadian rhythm), rather than a continuous infusion, has been specifically beneficial in the prevention of post-operative delirium among transplant patients [63, 64].
3. As is often the case, the ultimate cause of delirium in this case was multifactorial, including: chronic hypoxemia, respiratory failure; post-surgical state; multiple hypoxemic episodes; the use of multiple immunosuppressant agents, including high-dose steroids; a baseline history of PTSD; a pre-operative history of chronic benzodiazepine use; and multiple episodes of infection, including pneumonia and urosepsis. These episodes of delirium resolved quickly, after the team swiftly addressed the precipitants of delirium, treated agitation and restlessness with relatively low doses of haloperidol, and restoration of his sleep–wake cycle.

   Notice that the patient was started on gabapentin on POD#2 and haloperidol was started on POD#3. When the patient experienced restlessness (akathisia) and muscle twitching, the primary team immediately blamed the classic psychotropic agents (i.e., haloperidol), which resulted in its quick discontinuation. Yet, the abnormal neuromuscular symptoms persisted, leading to a second CLP consultation, and the identification of gabapentin as

the rightful culprit. In fact, gabapentin use has been associated with the development of dysphagia due to gabapentin-induced jaw myoclonus, as well as myoclonus, asterixis, akathisia, and even acute dystonic reactions [65–74].

On POD#38, the patient experienced a second episode of hyperactive delirium. Again, immediate work-up of his medical status identified the presence of pneumonia, AFib, and hypoxemia as likely causes and these were corrected, along with a brief course of haloperidol. As we suspected, when re-exposed to IV haloperidol, the patient experienced no signs or symptoms of acute dystonia or other forms of extrapyramidal symptoms. These interventions resulted in a complete resolution of delirium.

4. Of interest, on POD#80, the CLP team was consulted again, this time for the management of "depression with suicidal ideation." This presentation, sudden onset of suicidal ideation in a medically ill patient with no prior history of a mood disorder, should always prompt us to consider delirium in the differential. In fact, on exam, the patient exhibited the classic symptoms of hypoactive delirium, when patients often present as "apathetic, somnolent, and quietly confused" [33]. Also of importance is the fact that nearly 40% of the time, a psychiatry consultation called for the treatment of "acute depression" in the medically ill, the underlying diagnosis for the presenting symptoms is hypoactive delirium [75–77]. In addition, the sudden presentation of multiple primitive signs has been described, particularly in the case of patients experiencing hypoactive delirium [2, 33, 78–81]. Although a very low dose of haloperidol was used in this instance, the main component of this episode's treatment included restoration of his sleep–wake cycle, aided with the use of psychostimulants in the morning and agents to assist in promoting of sleep at night, along with aggressive physical therapy and other forms of non-pharmacological techniques.
5. Finally, it is important to know that nearly one-third of transplant recipients experience clinically significant neurologic alterations [82, 83], with immunosuppressant agents related neurotoxicity been one of the earliest complications after organ transplantation [84], including delirium [85]. For example, calcineurin inhibitors (CNI) (i.e., cyclosporin A and tacrolimus), have been associated with the development of delirium and posterior reversible encephalopathy syndrome (PRES), which itself has delirium as a presenting symptom [86–89]. Some side effects are dose dependent and may respond to CNI dose tapering, with an increased risk of subsequent transplant rejection [90]. Yet, there are cases when CNIs must be stopped due to cerebral complications and replaced by a non-CNI immunosuppressant agent (e.g., mTOR inhibitors or belatacept) [86]. Similarly, steroid agents have long been linked to transitioning to delirium [91]. In fact, evidence suggests that every commonly used immunosuppressant agent has been known to cause delirium as potential side effect [83, 85]. Similarly, many of the common early complications of organ transplantation, including infection, pain, opioid use for pain management, renal insufficiency, hypertension, hypokalemia, severe metabolic alkalosis, fever, graft rejection and graft failure, and coagulopathy may lead to the development of post-transplant delirium [2].

Take Home Points

1. Delirium is the most common neuropsychiatric syndrome found in the general hospital setting. As such, transplant candidates and patients are liable to suffer from this complication.
2. There are three, well-described forms of delirium: hyperactive, hypoactive, and mixed type. Hypoactive delirium is the most common, has the poorest outcomes, but it is the least likely to be recognized and addressed. All forms of delirium can occur in transplant recipients and sometimes pose significant diagnostic challenges.
3. In the pre-transplant period, the specific risk factors for delirium in organ transplant recipients include: the patient's age, degree of frailty, baseline level of cognitive functioning, overall level of health, fluid/electrolyte balance, the patient's overall nutritional status, and the effects of end-organ disease and failure (which could lead to hepatic or renal encephalopathy in the case of liver and renal disease, or hypoxemia/anoxia in the case of heart and lung failure). The level of organ dysfunction may be further associated with the need for extreme rescue methods, such as the need for cardiorespiratory support in the form of ventilators or extracorporeal membrane oxygenators, which might be associated with drastic changes in oxygenation levels, rapid fluid shifts, and the need for CNS-pharmacological agents in order to facilitate treatment (i.e., the use of high-dose opioids and GABAergic agents to facilitate ventilatory compliance, minimize metabolic needs, and prevent accidental dislodging of lines). During the post-transplant period, contributing factors include: graft function versus rejection, previous episodes of delirium, physical and cognitive stimulation (including mobility), and more importantly medication use. Unfortunately, most immunosup-

pressant agents cause some degree of neuropsychiatric side effects, from tremors, to headaches, post-transplant cognitive impairments, PRES, and delirium.

4. Effective interventions for delirium in transplant recipients include: minimizing the use of agents known to cause delirium (such as opioids and benzodiazepines), be mindful of the psychoactive effects of immunosuppressant agents, which could cause CNS toxicity even at therapeutic levels in sensitive individuals (usually managed by changing agents or decreasing to the lowest effective dose), monitoring for the possibility of drug–drug interaction (usually manifested by one agent interfering with the metabolism of an immunosuppressant leading to toxicity), but there are some agents (e.g., various antibiotics, antifungals, antivirals, and steroids) that might cause delirium on their own. When correction of metabolic dysfunctions, resuscitation with fluids, correction of electrolytes, management of infections, and restoration of the sleep–wake cycle do not resolve the problem, the judicious use of antipsychotic medications and mood-stabilizing agents might be required. Sometimes, the selection of the least offensive agent is required. For example, among opioid agents, hydromorphone and oxycontin are the least deliriogenic. Similarly, among the sedative agents, dexmedetomidine is preferable to propofol, which itself is less deliriogenic than midazolam. When an antipsychotic agent is required, usually a shorter half-life, least sedating agent such as haloperidol, risperidone, or aripiprazole is preferred. Be mindful that the toxic side effects of many antipsychotic and immunosuppressant agents can be similar and the use of one agent can worsen the effects of the other.
5. In general, we should avoid or minimize the use of opioids, benzodiazepines, first-generation antihistaminergic agents, and any agent with high anticholinergic potential—the main problem is not a single agent, but the additive antimuscarinic effect of all the medications the patient is receiving.
6. Nothing seems to work better for delirium prevention than early mobility. Getting the patient out of bed, then up and walking as soon as it is medically appropriate is among the best delirium prevention techniques.

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Cognitive Impairment in the Pre-Transplant Setting

13

Jorge Luis Sotelo and Alejandro Enrique Rodulfo

Introduction

Patients who present for organ transplantation evaluations experience a variety of symptoms and changes that limit their ability to function. End-stage organ disease brings with it a constellation of new challenges to the successful performance of activities of daily living. Not least among these is the extent to which cognitive functioning is impacted in the pre-transplant patient population. CI, even when relatively mild and not easily detected in a routine clinical evaluation, can affect the extent to which patients can progress successfully from the pre-transplant phase, through the surgery, and to post-transplantation recovery. CI identified in the pre-transplant setting can be perceived as a barrier to active listing due to concern for adverse post-transplant outcomes. Its early detection can timely identify patients who might need additional support or a different management approach. It could also shorten the time to listing, thereby facilitating access to transplants for many patients with the end-stage illness.

In this chapter, we briefly review the literature on cognitive limitations in patients with advanced kidney, liver, and heart disease and the extent to which such limitations can impact their likelihood of receiving a transplant. A clinical case is used to highlight some of the challenges inherent in the evaluation of cognitively impaired patients who present for pre-transplant psychosocial evaluations.

Cognitive Impairment in Kidney Disease

Overall, 14.9% of US adults surveyed in 2015–2018 had chronic kidney disease (CKD) and over 780,000 of them have end-stage renal disease (ESRD), many of them were older adults (over 7000 cases per million people for both the 65–74 and 75 and older age groups) [1]. In patients with renal disease, CI increases in prevalence and severity with declining kidney function [2–9]. Individuals with CKD are at significantly greater risk for CI than the general population, with a prevalence of 10–40% [10, 11], while those with ESRD have twice the prevalence of moderate to severe CI [12, 13]. The prevalence of CI is highest among dialysis patients: 50–87% [11, 12, 14]. Patients on dialysis have a high burden of CI even at younger ages [14–16] and HD patients of all ages have worse cognitive functioning than their general population counterparts [17, 18]. Many patients have compromised cognition when they begin HD [19–21] and it declines further while undergoing such treatment [15, 22–24].

Older age and disproportionately greater level of cerebrovascular disease contribute to cognitive dysfunction in patients with CKD. This patient population has a high prevalence of cardiovascular disease risk factors (e.g., diabetes, hypertension, and dyslipidemia) [25, 26], with a high prevalence of strokes and transient ischemic attacks as well as increased findings of subclinical cerebrovascular disease on imaging [27, 28]. Moreover, mortality rates post-stroke are approximately threefold greater in patients with HD compared to the general population [29]. As a matter of fact, there is increasing evidence that both initiation of [30] and exposure [31, 32] to HD is associated with stroke. Rapid fluid shifts during HD lead to wide blood pressure variations [33], and such hemodynamic instability has been associated with cerebral ischemia, hypoperfusion, cerebral atrophy, and brain injury [34–38]. Cerebral microbleeds are also common in HD patients and may increase the risk for intracranial hemorrhage [39]. Other risk factors for CI in patients on dialysis include reduced creatinine clearance, elevated homocysteine levels, and arteriosclerosis [40, 41]. Previous studies have identified an association between dialysis initiation and its duration with progressively worsening cognitive function [13, 16, 42, 43] through the buildup of uremic toxins, inflammation, and cerebral hypotension and hypoxia

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during dialysis sessions [44, 45]. It has recently been demonstrated that cerebral blood flow declines during dialysis, correlating with a measurable decline in executive function and progressive white matter hyperintensity burden [36].

In ESRD, failure to recognize CI could perpetuate future cognitive decline, as those with CI are less likely to adhere to fluid restriction recommendations leading to an increase in ultrafiltration volumes, compromised cerebral circulation, worsening cognition and, in turn, adherence. Cognitively impaired dialysis patients spend more time in the hospital, are at higher risk for all-cause mortality, and are more likely to have poorer adherence to treatment, including dialysis withdrawal [18, 42, 46–50].

The cognitive domain most affected in patients with CKD and ESRD is executive functioning [11, 14, 51, 52] and it is the domain most impacted by vascular disease and HD initiation [16]. Severe executive dysfunction impairs ability to comply with the dialysis schedule, maintain complicated medication regimens, retain capacity for independence and self-care, make informed decisions, and adhere to fluid and dietary restrictions. On average, HD patients suffer from a threefold higher rate of executive function impairment than same-age general population individuals [14, 53]. In one study, ESRD patients with higher MoCA (Montreal Cognitive Assessment) scores were listed earlier than those more cognitively impaired (median time to active listing of 10.6 months vs. 6.3 months). Cognitively impaired patients were also declared ineligible for transplant sooner (8.6 months vs. 15.4 months). By the end of 1 year, 23.3% of patients with CI were listed or transplanted versus 41% with no CI, whereas 43% of patients with CI were declared ineligible versus 32% of those without CI [54].

Strategies for prevention and treatment of CI in this population should aim to control the previously mentioned cardiovascular risk factors to prevent or limit cerebrovascular disease. In patients with CKD not on dialysis, reduction of albuminuria with either angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers may be associated with a slower cognitive decline. In one study, participants who were able to either reduce or eliminate albuminuria had 20–40% lower odds of having a decrease in Mini-Mental State Examination (MMSE) score of 3 or greater compared with those who had increase/no change in albuminuria [55]. In addition, intensive blood pressure control has been associated with lower incidence of mild CI compared to standard blood pressure control [56]. Exercise training has been reported to improve cognitive function in patients on dialysis [57–59] presumably by enhancing the basilar maximum blood flow velocity [59].

Cognitive Impairment in Liver Disease

Up to 50% of patients undergoing liver transplant suffer from hepatic encephalopathy (HE) at transplantation and between 35 and 45% have a history of HE episodes [60]. The 1-year mortality after the first bout of HE has been reported to be as high as 50% [61]. Assessing the extent to which CI is caused by liver disease can be difficult, as not only can factors such as infection, renal failure, medications, or preexisting cognitive/ psychiatric disorders contribute to and exacerbate HE, but causes of underlying liver disease such as alcohol [62], obesity [63], and hepatitis C [64] may also lead to CI.

Cognitive performance in patients with cirrhosis has been negatively correlated with severity of liver disease [65]. In HE, CI spans the range from persistent and progressive deficits fully appreciated only with psychometric testing (minimal hepatic encephalopathy, mHE) to rapidly developing acute confusion and coma. Minimal hepatic encephalopathy is characterized by a subcortical pattern of CI with impairments in attention, immediate memory, visuospatial construction, motor speed, vigilance, response inhibition, and affective and executive functioning [66–71], which impact upon the safety and quality of life of patients with cirrhosis and can reduce their chances of obtaining a favorable pretransplant evaluation. In addition, hepatitis C infection and alcohol use, conditions commonly present in liver transplant candidates, are also each independently associated with cognitive decline. Viral CNS involvement in hepatitis C may play a role in the observed subcortical pattern of neuropsychological impairment [72, 73]. Alcohol use, long implicated in CI independent of liver disease, can cause brain atrophy affecting preferentially the frontal lobes and cerebellum. Patients with alcoholic liver disease perform more poorly on cognitive testing than patients with liver disease due to other etiologies [70].

Individuals with mHE are at risk for developing overt HE [74, 75] and exhibit increased mortality and accelerated progression to liver failure [76–78]. In one study, patients with mHE had a 3.7-fold increased risk of developing overt HE, compared with their counterparts without mHE, and 56% of the patients with mHE developed overt HE within 3 years versus only 8% of those patients without mHE [79]. Episodes of overt HE have clinical relevance as they are frequently followed by declines in neuropsychological functioning [80]. In another study, patients with mHE were more likely to have experienced previous episodes of HE [81]. These are important findings since overt HE can prevent a patient from listing for a transplant, especially when social support is marginal.

The effects of mHE on quality of life and outcomes in patients prior to transplant are significant, though not always readily apparent to the clinician since domains such as language and delayed memory are relatively spared. Minimal hepatic encephalopathy can contribute to depression, apathy, and fatigue and result in delays in endorsement of patient's psychosocial readiness for transplant until these symptoms have responded to treatment. Patients with mHE are more likely to have trouble driving (e.g., speeding tickets, automobile collisions, difficulty following map directions, and fatigue while driving) [82–86], to fall [87, 88], and to have trouble sleeping [89–91]. Minimal hepatic encephalopathy has also predicted disability independent of liver disease severity [70, 92].

Effective treatment of mHE improves psychometric function and quality of life [93–96]. Lactulose and rifaximin improve cognition in patients with HE [93–97]. Rifaximin can improve driving performance on cognitive tests and health-related quality of life scores [97, 98]. Probiotics have shown promise in patients with mHE [94, 99–102], as demonstrated by a 2011 Cochrane review that showed an advantage of probiotics in all-cause mortality, number of adverse events, and quality of life [103]. Several agents including new antibiotics, ammonia scavengers, and brain steroid modulators are currently investigated for treatment of HE with promising results [104]. Among psychotropic medications, memantine was reported to help behavioral problems in HE [105].

Cognitive Impairment in Heart Disease

Individuals with heart disease often suffer from comorbidities that can increase the likelihood of CI (obesity, cerebrovascular accidents, hypertension, diabetes, and hyperlipidemia, for example). There is strong evidence to suggest that heart failure is an independent risk factor for CI and the combination of heart failure and CI is associated with increased mortality, repeat hospitalization, and poor quality of life. Consequently, CI in patients with heart disease could negatively impact their chances of receiving a heart transplant.

In one study of outpatients 65 years and older with heart failure, over 70% scored below the MoCA cutoff score of 26, suggesting the presence of CI [106]. In this cohort, the presence of CI (MoCA score < 26) was significantly more common in patients with advanced heart failure symptoms (91% of patients with New York Heart Association classes III to IV vs. 52% of patients with classes I to II) or a recent hospitalization (89% of patients with recent hospitalization vs. 62% without). The MoCA cognitive domain subscores showing significant differences were short-term memory, visuospatial function, executive function, and language.

A study of 207 candidates for heart transplant revealed pathological scores in one or more of the cognitive tests conducted in 86% of the patients, while 36% performed within the impaired range on five or more tests, indicating poor performance across a broad range of cognitive domains [107]. Executive functions were the cognitive domain most impaired (70%) in this patient population, followed by perception, memory, attention, and praxis abilities. Poor performances were not related to the etiology of heart disease, but rather to cerebral dysfunction secondary to hemodynamic impairment and to other medical comorbidities.

Mild CI was also highly prevalent in a cohort of 176 patients with advanced heart failure who were being assessed for LVAD implantation, with 118 (67%) scoring <26 [108]. Significant improvement in overall MoCA score was noted after LVAD implantation.

CI is therefore the rule in patients with advanced heart disease, as it has been observed in a variety of patient populations. Minimizing its impact on patients' understanding of the pre-transplant process and their adherence to pre-transplant recommendations is essential in ensuring successful clinical outcomes.

Case History

Mr. Y is a 62-year-old widowed retired carpenter with a history of end-stage renal disease due to previously poorly controlled hypertension and type 2 diabetes mellitus who is accompanied by his 37-year-old daughter to a pre-transplant evaluation appointment. He is adherent to thrice a week dialysis sessions. His hypertension and diabetes have been well controlled since he started dialysis, as his daughter has become more actively involved in his care, often providing transportation to dialysis sessions. Even though he does not have any identified potential living donors, Mr. Y is hopeful that he will be given a favorable evaluation because he does not miss dialysis sessions and does not have a history of substance misuse, factors which have delayed the listing of some of the individuals who dialyze on the same shifts that he attends. During cognitive testing, it becomes apparent that Mr. Y exhibits deficits in visuospatial and executive functions, attention, and delayed recall. His score on the Montreal Cognitive Assessment test (MoCA) is 20 out of a possible maximum 30 points. His daughter confirms that she prepares his medications for him and accompanies him to his medical appointments because she realized several years ago that he could no longer reliably inform her of what transpired during these meetings. Initially, Mr. Y becomes demoralized when he realizes how poorly he performs on the MoCA. As the assessment progresses, he becomes increasingly more anx-

ious and tearful, admitting that dialysis has taken a toll on his mood. Later, he apologizes for having become emotional during the assessment and blames his outburst on recent trouble sleeping and the "stress" of the assessment. Daughter confirms recent challenges with sleep and energy. Mr. Y fears that he may not live long enough to see his 12-year-old grandson graduate from high school unless he receives a transplant and is concerned that he may have ruined his chances as a result of his struggles on the MoCA screening instrument.

Clinical Questions

1. Does Mr. Y have dementia (major neurocognitive disorder)?
2. Do his cognitive limitations preclude him from receiving a kidney transplant?
3. Could depression be contributing to his cognitive limitations?
4. What intervention can improve his cognition to increase the likelihood of a successful pre-transplant clinical course?

Discussion

It is reasonable to consider a diagnosis of dementia as we consider Mr. Y's case, given his age and the results of cognitive testing. After all, CKD is an independent risk factor for CI [109] with prevalence of CI and dementia in ESRD more than double that in the general population [4]. It is important to ascertain if his cognitive limitations support the diagnosis of dementia since, when diagnosed before initiation of dialysis, dementia is an independent risk factor for subsequent death with 2-year survival for patients with dementia of 24% vs. 66% for patients without dementia [110]. Among dialysis patients, dementia predicts poor outcomes, such as disability, hospitalization, and death [42, 110]. The Renal Physicians Association has recommended forgoing dialysis for patients with very poor prognosis or for whom dialysis cannot be provided safely, including those who have a non-renal terminal illness [111]. It could be argued that patients with advanced dementia belong to this category, and hence, by forgoing dialysis, become poor candidates to ever receive a transplant. A diagnosis of dementia could jeopardize his chances of receiving a kidney transplant. The MoCA test, validated in dialysis and chronic kidney disease patients [112], is not sufficient to diagnose dementia, but it does identify him as a patient who will need cognitive monitoring throughout the pre-transplant process. Since he is attending dialysis sessions and medical appointments without difficulty, it is safe to conclude that the CI that he exhibited during the assessment is not keeping him from meaningful participation in treatment. Since he was able to participate in the evaluation and his cognitive deficits were only identified when the MoCA was administered, it could be argued that he is able to understand important clinical information (including asking pertinent questions and answering them logically). Moreover, his daughter is providing the necessary assistance to make sure that he attends pre-transplant appointments and takes his medications correctly and her help is instrumental in improving his chances of receiving a kidney.

Pre-transplant cognition may not be a true reflection of post-transplant cognition or medication adherence. CI alone should not be a criterion or absolute contraindication for kidney transplant eligibility and future studies could determine if there is a cutoff MoCA (or other cognitive evaluation tool) score for which post-transplant outcomes are poor or identify a subset of patients whose significant CIs affect post-transplant outcomes. Yet, Mr. Y still exhibits significant cognitive limitations that warrant investigation. Although they may not disqualify him from being listed at this time, they could eventually prove to be too large an obstacle to overcome. In the pre-transplant setting, patients with CI may have difficulty completing the pre-transplant evaluation and provide informed consent about transplantation [54]. If clinical evaluation and history suggest a history of cognitive impairment of functional decline that preceded the chronic kidney disease, a full workup for major neurocognitive disorder should be considered, which would include ruling out additional reversible causes of cognitive impairment (hypothyroidism, vitamin B12 or thiamine deficiency) and brain imaging. In addition, Mr. Y's decision-making could be compromised due to CI. More conservative management would be the most appropriate option if he were to be found to lack capacity to consent to kidney transplant surgery.

For patients with CI pre-transplant, serial cognitive assessments with reproducible tests, such as the MoCA, should now be incorporated into his pre-transplant evaluations even after he is listed in order to determine the level of family and/or social support that he requires or is no longer a viable candidate due to further cognitive decline. Fortunately, at this time, he has a support system in place that would ensure adherence to medications and post-transplant follow-up and his cognitive dysfunction should not automatically preclude kidney transplant surgery.

Patients with CKD are at increased risk for psychiatric disorders, including anxiety and depression, and these syndromes can contribute to CI. Mr. Y's emotional state warrants further exploration. Administration of items such as the PHQ-9, the GAD-7, and HRQOL could help identify symptoms that need to be addressed through full clinical evaluation and interventions. These measurements should be performed serially if they were to reveal the need for intervention. It is quite possible that the stressful nature of the pre-transplant process is resulting in clinical anxiety or depression and affecting his quality of life, but it is also pos-

sible that he is having an understandable and appropriate emotional reaction to not doing well on the MoCA, particularly if in the moment he is concerned that this could diminish the likelihood of being listed. Obtaining collateral information from his supportive daughter and other close contacts would be necessary to establish if the affect observed during the interview reflects symptoms that are more pervasive and relevant. If symptoms of clinical anxiety or depression are identified, Mr. Y would need to be referred for treatment. If severe enough, such symptoms may delay his being listed until he responds to interventions such as psychotherapy and/or psychiatric medications. Patients with chronic kidney disease and depression frequently exhibit suboptimal adherence with pre-transplant treatment recommendations and poor health-related quality of life, both of which improve with successful treatment [113–115]. As symptoms of anxiety or depression decrease, Mr. Y's cognition and quality of life would be expected to improve, if psychiatric conditions are contributing to cognitive limitations identified in pre-transplant assessments. Such improvement would then support the notion that psychiatric conditions were responsible, to some extent, for his poor performance on the MoCA. It is also possible that, even with optimal treatment of underlying psychopathology, Mr. Y may continue to exhibit CI that could jeopardize his chance at a kidney transplant unless other interventions are implemented.

While there may not be treatments that specifically target CI in pre-transplant patients, certain interventions could result in improvement of cognition and prevention of further cognitive decline. We have already emphasized how important is to screen for and adequately treat depression and anxiety, both of which could contribute to CI in Mr. Y's case. In addition, treating sleep disorders, which are common in patients with ESRD, could also improve cognition by reducing daytime fatigue [116]. A positive correlation between depression, sleep disorders, and fatigue (characterized by difficulties with concentration, reduced motivation and physical activity) has been demonstrated in patients with kidney disease [117]. Since medications that induce sleep could negatively affect cognition, they are not ideal first-line treatments for insomnia. Fortunately, mindfulness meditation strategies have effectively improved sleep, as well as anxiety and depressive symptoms with improvements maintained at 1-year post-intervention [118]. Bright light therapy has also been demonstrated to be effective in improving sleep timing in this patient population [119]. Finally, it is important that Mr. Y continues to have the social support necessary to optimize adherence to pre-transplant treatment recommendations and to augment it as needed. These interventions would not only mitigate cognitive decline and improve the likelihood of being listed, but they would also prevent complications that could jeopardize his standing and improve Mr. Y's quality of life while he waits for transplant surgery.

Conclusion

Patients with end-stage disease, as has been highlighted in the populations discussed in this chapter, are at increased risk of CI. Such impairment is not always readily apparent during pre-transplant evaluations as it can be subtle or not apparent until psychometric testing is conducted. Patients with more severe impairment and dementia are typically not given strong consideration for transplant surgery because of concerns that lifespan and quality of life may not improve sufficiently because of this intervention. Consequently, the transplant psychiatrist is often tasked with having to decide if cognitive limitations warrant further testing or interventions. If found to have mild or moderate CI, patients should have more detailed neurocognitive testing, if possible. If psychiatric conditions (depression, anxiety, insomnia) are contributing to CI, it is imperative that comorbid mental illness be treated. It would also be important to avoid sedating medications and polypharmacy, improve sleep hygiene, optimize social support, and encourage exercise and mental stimulation. Often these interventions will be sufficient in preventing further cognitive decline and improving the chances of a successful transplant.

Take Home Points

1. CI is common in patients with end-stage organ disease.
2. It is important to address the psychiatric factors that may impact cognitive function: mood disorder, anxiety, and sleep disturbances.
3. Family and social support are key factors in assisting the patient to complete the pre-transplant evaluation.

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Intellectual and Developmental Disabilities in Transplant Patients

14

Joy J. Choi and Rubiahna L. Vaughn

Introduction

Transplant centers have historically considered intellectual and developmental disabilities (IDD) a contraindication to transplant due to concerns that the disability would adversely impact an individual's ability to follow the complex self-care routine required of transplant patients. According to the fifth Diagnostic Statistical Manual (DSM-5), individuals with IDD are characterized by "developmental deficits that produce impairments of personal, social, academic, or occupational functioning" [1]. It is not unreasonable to anticipate that individuals with such deficits may have difficulty engaging in complex medical care. However, over time, studies have demonstrated that with adequate support, individuals with IDD can successfully undergo transplant with outcomes comparable to individuals without IDD [2–6]. Unfortunately, despite the growing evidence, individuals with IDD continue to experience challenges in obtaining access to transplant. This chapter begins with a review of the historical relationship between the IDD and transplant communities, followed by an illustration of how functional deficits secondary to IDD impact a patient's ability to participate in pre- and post-transplant medical care through two real-life cases. Additionally, we focus on the role of transplant psychiatrists in identifying the deficits and formulating strategies to mitigate some of the challenges faced by transplant patients with IDD.

Medical History of Intellectual and Developmental Disabilities

In the 1920s, intelligence quotient (IQ) testing provided an objective way of diagnosing IDD and became the pillar of IDD diagnosis for the following several decades. Psychiatry did not differ from the rest of medicine in its delay in recognizing IDD as more than simply deficits in IQ scores. In 1952, the American Psychiatric Association (APA) published its first Diagnostic and Statistical Manual (DSM-I) and it defined intellectual disability based on IQ range. However, in the 1960s, the medical community began to pivot from solely relying on IQ to determine one's intellectual or developmental disability. Adaptive behavior, such as ability to care for oneself, socially engage with others and navigate the world, was incorporated into medical understanding of IDD. Almost 60 years later, in the DSM-5, the APA finally eliminated IQ from the diagnostic criteria for intellectual disability, pivoting toward the use of adaptive function levels for diagnosis [1].

Although healthcare guidelines have improved with each decade to expand access to care and quality of care, their implementation and provider education on these guidelines lag behind [7]. In fact, large disparities in health status between individuals with IDD and without persist. Research has shown that individuals with IDD have less access to preventative care, thereby suffering from higher rates of preventable comorbidities and mortalities. The problem with access lies on the side of both the healthcare recipients and providers. Individuals with IDD may have cognitive impairments which limit their ability to assess their health, recognize need for care, and navigate the healthcare system. On the other hand, the medical providers may not be trained to care for the specific needs of individuals with IDD [8].

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Approaches to Intellectual and Developmental Disabilities in Solid Organ Transplantation

The transplant world's evolving stance toward intellectual and developmental disabilities mirror that of the general medical community. In the United States, each transplant center adheres to its own internal guidelines for absolute and relative contraindications for solid organ transplantation. Transplant programs' concern that intellectual or developmental disabilities may negatively impact an individual's transplant outcome is not completely unfounded. Many individuals with IDD in general have limited access to healthcare, depend on caregivers for self-care, have limited comprehension of medical recommendations, and have difficulty scheduling and following through with appointments and procedures [9–11]. Receptive and expressive communication deficits secondary to IDD, both verbal and non-verbal, can cause communication failures between patients and providers [8, 12–14]. Furthermore, aggression, impulsivity, and self-injurious behaviors associated with IDD is seemingly incompatible with transplant which involves a high level of compliance and patience [14, 15]. However, considering IDD an absolute contraindication is problematic as it assumes that all individuals with IDD do not have the capacity to comprehend and comply with the complex post-transplant care regimen. By making such assumptions, the field failed to acknowledge the diversity of etiologies and functioning among patients with IDD [2, 16]. Such generalization of IDD, especially as it relates to organ transplantation, was considered biased and discriminatory and ultimately sparked a nation-wide debate in 1995 when a woman named Sandra Jensen made national news headlines.

Sandra Jensen was a 32-year-old woman with Down syndrome, who was initially declined a heart–lung transplant in 1995 at two major hospitals in California. The New York Times reported at that time that the "hospitals argued that the mental limitations of Down syndrome could affect a patient's ability to follow a post-operative regime in which mistakes can mean death, and so organs in short supply would do more good if they were given to others" [17]. However, further investigation by the reporter revealed that "Ms. Jensen, unlike many people with Down syndrome, had lived on her own for years and had held various jobs" [17]. After months of advocacy and growing public support, Sandra Jensen finally received a heart–lung transplant in January 1996. Unfortunately, she died 18 months later due to side effects from immunosuppressive medications. In an interview, Dr. James Theodore, who supervised the transplant team who initially rejected then later accepted Sandra Jensen, acknowledged that, "we rejected her out of hand, based on a label … That was wrong, and I'm willing to admit that" [18].

The case of Sandra Jensen persuaded the medical community to acknowledge that IDD should not be considered an umbrella category under which all conditions are contraindicated for transplantation. However, in a 2004 survey of the members of the Arc of the United States, one of the largest organizations for individuals with IDD and their families, 80% of responders believed that individuals with IDD are discriminated against regarding access to transplant [2]. Another survey found that only about half of people with IDD who requested a specialist referral regarding an organ transplant received a referral. The same survey also showed that 35% of individuals with IDD for whom a transplant had been suggested never received an evaluation [19]. In 2019, the National Council on Disability published a report that the "assumption that people with disabilities will not be able to comply with post-operative care has caused disability to be considered a contraindication to organ transplant at many transplant centers, despite the fact that people with disabilities, when provided with necessary supports, are no less likely to comply than people without disabilities." Furthermore, the Americans with Disabilities Act and Section 504 of the Rehabilitation Act prohibits transplant centers from declining an individual access to transplant solely on the basis of disability [19].

Transplant Organ Types and Intellectual and Developmental Disabilities

Medical care required post-transplant is complex with some variations among organ types. All transplant recipients regardless of organ type initially undergo frequent blood draw (i.e., initially 1–2 times a week) to check for immunosuppressant level, organ function, and signs of infection. Owing to their immunosuppressed state, transplant recipients take precautionary measures to avoid infection such as frequent hand washing, cooking food thoroughly, avoiding travel to regions of high infectious disease prevalence, and staying away from sick individuals. Many patients require rehabilitation or physical therapy post-transplant. Examples of organ-specific requirements include daily oximetry and spirometry for lung transplant recipients, and weekly biopsy in heart transplant recipients in the first month to monitor for rejection.

Despite the variations in post-transplant care, the practice guidelines for determining transplant candidacy for individuals with IDD are similar among professional organizations for solid organ transplantation. The International Society for Heart and Lung Transplantation previously listed IDD as a relative contraindication in its 2006 guideline. In the updated 2018 guideline, it cites a small body of literature that suggests individuals with IDD do not differ in medical outcome compared to those without IDD with adequate necessary social support to enhance treatment adherence [20]. The 2013 practice guidelines by the American Association for the Study of Liver Diseases and the American Society of Transplantation state that individuals with IDD "with proper

evaluation and preparation, as well as adequate social support can have successful long-term outcomes" [21]. Similarly, the 2020 Kidney Disease: Improving Global Outcomes clinical practice guideline recommends against excluding individuals with "non-progressive intellectual, developmental or cognitive disability" from renal transplant candidacy [22].

While the guidelines are consistent across organ types, there is a wide variation in their implementation among transplant centers [2]. A study published in 1993 explored this practice variation among cardiac, liver, and renal transplant programs in the United States [23]. This study found cardiac transplant programs were most likely and renal transplant programs were least likely to consider intellectual disability as a contraindication to transplant. For example, 74.4% of surveyed cardiac transplant centers considered IQ < 50 as an absolute contraindication, while 24% of renal and 45.7% of liver transplant programs considered it an absolute contraindication. In a more recent study of pediatric patients with IDD, a survey of solid organ transplant programs in the United States found that 39% of the programs "rarely" or "never" factor IDD into their candidacy evaluation, while 43% of programs "always" or "usually" do [24]. Such discrepancy among programs in candidate selection process is not unique to IDD and occurs with other medical and psychiatric factors such as age, body mass index, social support, and substance use history. While this warrants a more in-depth discussion, a transplant psychiatrist should at least be aware of the existence of such practice variations and familiarize oneself with their respective program's guidelines.

The Role of Psychiatrists

Psychiatrists are uniquely positioned to consider the patient's medical needs as well as their developmental history and intellectual, cognitive, and behavioral functioning when assessing a patient's psychiatric risk level as a transplant patient. This is a labor-intensive task including an exhaustive review of the patient's psychiatric history, substance use history, medical history, social history, and the patient's relationship with and behavior toward healthcare providers and the transplant team. Collateral information from caregivers and medical providers can aid in a comprehensive understanding of the candidate's current and future needs with respect to self-care and adherence to medical directives. Another essential task is the assessment of the unique risks associated with transplantation in persons with IDD that may include challenges related to their cognitive or behavioral deficits that make adherence more difficult. As noted above, each type of organ transplant has unique post-transplant care demands and how a patient may adjust to or manage these specific demands needs to be considered. The creation of thoughtful and individualized risk mitigation strategies is crucial for each step in the transplant process.

However, it must be made clear that the evaluating psychiatrist's role is not to determine whether IDD is a contraindication to transplant. Rather, the psychiatrist must consider IDD like any other psychiatric disorder and provide diagnostic clarification and/or confirmation, assess the adequacy of current psychiatric treatment, potential challenges in adhering to post-transplant care, adequacy of social support to assist with provision of care, and subsequently provide recommendations to mitigate these challenges. We will elaborate on the role of the evaluating psychiatrist further in the concluding section of this chapter after the case discussions.

Our chapter will discuss two cases, one of a patient with Autism Spectrum Disorder and another of a patient with Danon disease.

Case Histories

Case 1: Autism Spectrum Disorder—Developmental Disability

The patient is a 36-year-old single man, living in a group home and unemployed, who is admitted to a cardiac care unit (CCU) for worsening heart failure. He had been in psychiatric treatment most of his life for self-reported bipolar disorder and had been hospitalized four times for depressive mood. At age 20, his diagnosis was changed from bipolar disorder to autism spectrum disorder after over a decade of longitudinal monitoring by his outpatient psychiatrist at a large academic center.

Two years ago, the patient was diagnosed with heart failure. A year ago, he was psychiatrically hospitalized for depressed mood in the setting of poor psychotropic adherence, triggered by difficulty coping with worsening symptoms of heart failure. During the admission, it was noted that the patient had difficulty following lifestyle changes necessary for heart failure management, including dietary changes, fluid restriction, and adherence to heart failure medications. He also missed heart failure clinic appointments due to worsening shortness of breath and fatigue. At that time, the patient was residing in a group home for adults with mental health needs with no supervision for medical and self-care. The patient's case manager referred the patient to a nursing home to increase the level of supervision but the patient was not accepted. For 6 months preceding the current admission, the patient was hospitalized for heart failure associated with non-ischemic cardiomyopathy of unknown etiology so frequently that he had not been able to make it to his outpatient psychiatric appointments. Consequently, his case at the clinic had been closed. During his numerous hospitalizations for heart failure exacerbation, cardiac transplant was considered but he was never referred to a transplant center due to his history of mental illness. His psychiatrist made efforts to

refer him to another hospital's transplant center but the patient was declined based on his history of treatment non-adherence.

Serendipitously, he was brought by EMS to a completely new hospital after a fall at his group home and was found to be in severe heart failure in need of advanced cardiac therapy. During this hospitalization, Psychiatry was consulted to evaluate the patient for capacity to consent to a ventricular assistance device (VAD) implant or cardiac transplant. The CCU physicians explained, "Medically, he is a good candidate for advanced heart therapy. But we are not sure about his psychiatric status." Further discussion with the CCU team revealed that they were holding off any discussion about VAD or transplant with the patient because they were not sure "if he would understand." This was further complicated by the fact that the patient disclosed to the CCU team that he had a diagnosis of bipolar disorder but did not mention ASD. The CCU team found the patient to be "oddly related" and questioned if his bipolar disorder was well managed.

The psychiatric assessment was notable for a psychiatric history which was not consistent with bipolar disorder but possibly clinical or subclinical episodes of depression in the past. The mental status exam was notable for poor eye contact, reduced social reciprocity, odd relatedness, concrete thought process, and limited ability to provide complex answers. He was also obese, disheveled, wearing a pair of broken glasses, and played games on his phone during the entire duration of interview. At this time, the diagnosis of ASD was suspected. Collateral from the patient's brother and outpatient psychiatrist confirmed that the patient in fact did not have bipolar disorder but ASD. The brother denied history of intellectual disability in the patient. He also stated that the patient will only do what interests him and that it is otherwise difficult to get his attention. He expressed concerns that if the patient's interest cannot be piqued by the idea of transplant, it would be difficult to engage him in any conversation about it. Fortunately, the patient was able to state that his "heart is failing" and that he would be willing to "do anything to live." The evaluating psychiatrist recommended that the CCU team offer advanced cardiac therapy evaluation to the patient. The psychiatry consult team continued to build rapport with the patient by bringing in his favorite candy (with the permission of CCU staff) and offering bedside art therapy to reduce his boredom and restlessness during the prolonged hospital course.

The patient was eventually transferred to an affiliated transplant center. There, Psychiatry was consulted for a formal transplant evaluation. Neuropsychological evaluation performed at the transplant center had already confirmed the absence of intellectual disability with full-scale IQ of 105, which is within normal range. The PhD neuropsychologist reported that the patient had the cognitive ability to understand and retain directions, reflective of intact intellect, but that his behavioral delays and impairment in higher-order deductive reasoning may present a challenge for the patient in understanding the gravity of his medical situation and therefore comply with recommended procedures and instructions. However, the transplant team still had concerns about the patient's ability to understand and consent to the transplant process, as well as his ability to adhere to post-transplant care. The patient was "annoyed" about the evaluation but answered questions appropriately. He shared that his "heart is dying and weak as hell." He knew that the "heart transplant is the only way and the final solution." He commented that the "Impella and the mechanical heart and lung (in reference to the extracorporeal membrane oxygenation machine) is maintaining my old heart." He had difficulty expressing his emotions about his current circumstance but stated that he felt "angry" and "irritable." He expressed a full understanding of need to wait for a matching organ, plan for an orthotopic cardiac transplant, need for lifelong immunosuppressant, and lifestyle changes. However, when asked about his current lifestyle in terms of diet and exercise, he answered, "Well that's not important right now. What's important is what's going to happen next. And that's what matters."

A normal social response to a psychiatrist who is requesting an interview would be to stop other activities and focus on the interview. Failure to do so may be interpreted as a lack of interest or wish to avoid the interview. For example, the patient from the case played video games on his phone during the entire duration of the initial psychiatric evaluation. However, it was clear from the answers he gave that he was very interested in transplant and wished to comply with the interview as much as possible. To the evaluating psychiatrist, it was obvious that the discrepancy between the patient's intention and actions was due to his social communication and interaction deficits secondary to ASD. Without psychiatric training, it is easy to understand why the CCU team had difficulty gauging the patient's understanding of the severity of his medical condition.

The patient in the case also demonstrated difficulty with abstract thinking. Although he was able to state the importance of lifestyle changes in the future, he could not understand why discussing his current lifestyle was relevant to the interview. This could also be misunderstood as being defensive or avoidant of an important subject. However, the patient may simply need extra explanations to help him appreciate the importance of discussing his current health status.

Both the evaluating psychiatrist and PhD neuropsychologist confirmed that the patient had cognitive and behavioral deficits secondary to ASD including limited language skills, behavioral delays, and higher-order deductive reasoning deficits. The psychiatrist assessed the patient to be at a moderate-to-high-risk candidate for transplant from a psychiatric perspective, largely driven by history of treatment non-

adherence secondary to symptoms of ASD. It was recommended that a higher level of social support (i.e., living at home with a care provider, supervision with medications and appointments, transportation assistance, care management, etc.) would largely mitigate the risk.

The psychiatric assessment and recommendations were discussed in person with the transplant surgeons, cardiologist, and social workers. The transplant team expressed concerns that the only available care provider was the patient's brother, and ideally the patient should have more support. The transplant social workers, who take on a large part of the responsibility to monitor and provide post-transplant care to the patients, were frank about the possibility of "other patients falling through the cracks" should this patient require additional time and effort to maintain his health due to his ASD symptoms. Psychiatrist validated the team's concerns and fears and offered support. Psychiatrist presented the plan to help reconnecting the patient to his outpatient psychiatry clinic, through which he could receive additional social work and care management support. This recommendation was well received by the transplant team and alleviated their anxiety. Ultimately, it was unanimously determined that the patient's medical need for transplantation was greater than any challenges his psychiatric illness may present to the patient and the transplant team.

After the transplant, the patient participated in inpatient rehabilitation and was discharged home. The patient is living with his brother, who is providing housing and supervision with medical visits, medications, and lifestyle changes. Symptoms of ASD at times continue to interfere with care. For example, the patient has difficulty breaking the routine of taking medications and at times forgets to hold tacrolimus the morning of blood draw to check levels. However, his brother can intervene and remind him as needed.

Psychiatrically, the patient's outpatient psychiatry clinic, which was initially eager to reopen his case became hesitant after the patient's heart transplant stating the patient was too medically complex. The transplant team and transplant psychiatrist reassured the outpatient provider that the patient's mental status is unchanged from before and that he is now physically healthier and able to regularly attend appointments. Afterwards, the outpatient psychiatrist agreed to reconnect with the patient to assess his needs in person with the plan to refer out, if appropriate.

Autism Spectrum Disorder: A Brief Review

The number of individuals diagnosed with Autism Spectrum Disorder (ASD) is growing rapidly. In the United States, its prevalence has risen 600% between the 1960s and 1980s, and there has been another 600% increase in the past two decades [25]. ASD is a neurodevelopmental disorder defined by "persistent impairment in reciprocal social communication and social interaction" and "restricted, repetitive patterns of behavior, interest, or activities." These symptoms are present from early childhood and limit the individual's daily functioning [1]. Severity of these impairments can vary. As indicated by its name, ASD is a spectrum illness with a wide variety of clinical presentations. Statistics regarding the heterogeneity of intellectual disability, as defined as IQ below 70, vary across gender, state, and age. For school-age children with ASD, it is estimated that 11–65% have intellectual disability [26]. The range also varies for adults; it is estimated that 10–33% of adults with ASD have verbal and non-verbal IQs consistent with intellectual disability [14].

However, even in the absence of intellectual disability, individuals with ASD still find navigating social roles and meeting social expectations difficult. According to one study, only 13% of individuals with ASD with average intelligence, defined as IQ $\geq$ 70, are living independently and only 25% are employed [27]. Additionally, even in the absence of intellectual disability, long-term, intimate relationships remain rare with people with ASD.

Currently, there is little published literature on how these social and behavioral deficits of ASD impact the transplant process. In the following sections, we explore how ASD may impact an individual's candidacy for transplant evaluation, extrapolating from existing information on the impact of ASD on general medical care and health of these individuals. The following sections are also applicable to other developmental disorders with overlapping symptoms.

Autism Spectrum Disorder and Transplantation

Individuals with IDD face challenges in obtaining referrals to transplant centers in part due to the existing bias that they are poor transplant candidates simply based on their disability. These challenges are no exceptions to individuals with ASD as evidenced by this case. The patient from the case was declined transplant due to his mental illness at an outside hospital. Even at the institution where he eventually received a heart transplant, the CCU team initially hesitated to initiate transplant evaluation because they were unsure of the patient's intellectual functioning. Only after the psychiatrist advocated on behalf of the patient to overlook his disability but to consider his medical needs, they offered him the option of referral to a transplant center.

Restricted, Repetitive Patterns of Behavior, Interests, and Activity

In the introduction to this chapter, we reviewed that individuals with IDD suffer from higher rates of preventable comorbidities and mortalities partly due to limited access to healthcare. It is important to highlight that ASD itself can negatively impact physical health. Individuals with ASD have restrictive and repetitive patterns of behavior, interests, and activity. This often translates to decreased physical activ-

ity and poor dietary habits, such as rigid, unhealthy food choices [14, 28].

A pre-transplant psychosocial evaluation includes a thorough evaluation of one's lifestyle pertaining to the affected organ system. It assesses the patient's current lifestyle, their understanding of necessary changes in their lifestyle in anticipation of transplant, as well as their readiness to make the changes. Therefore, an individual with ASD who leads a sedentary life with an unhealthy diet presents a higher risk as a transplant candidate. Additionally, it is difficult to mitigate adverse lifestyle habits because change can be very difficult and psychologically distressing to individuals with ASD, who have a strong preference for set habits and routines.

The patient in the case presentation had a sedentary lifestyle with poor diet and a strong preference for candy which resulted in obesity. Fortunately for him, he had insight into the need for a lifestyle change. However, we see in his post-transplant treatment course that having insight does not always translate to behavioral changes. For example, the patient knew that on the morning of getting blood drawn to measure tacrolimus level, he was supposed to hold the medication; however, despite having this knowledge, he was unable to break the routine of taking medications daily without interventions from his caregiver.

Not seen in this case, but relevant to this characteristic of ASD, is the symptom of hyper-reactivity to sensory input such as pain, temperature, texture, light, sound, and scent. Individuals with ASD may have difficulty tolerating the unfamiliar sensory input of being in a hospital such as constant, loud noises from medical equipment, bright and harsh white lights, new smells, unfamiliar taste and texture of hospital meals, and unfamiliar textile input from medical equipment such as stethoscope, intravenous lines, and hospital gown. Medical teams should be made aware of these potential difficulties with individuals with ASD and accommodate as much as possible by proactively and gradually introducing any new sensory experience for the patient and attempting to create a familiar environment with items from home. This is especially important given the potential for long-term hospitalization.

Deficits in Social Communication and Interaction

Individuals with ASD have varying degrees of communication deficits as manifested by deficits in social-emotional reciprocity such as inability to maintain normal back-and-forth conversation, and inadequate response to and misunderstanding of social, verbal, or affective cues [14]. As a result, individuals with ASD may have difficulty relaying their thoughts and feelings and therefore be misunderstood by healthcare providers [28]. It is easy to see how these deficits would be barriers to reporting essential information, such as symptoms, to the healthcare team.

Case 2: Danon Disease—Intellectual Disability

The patient is a 21-year-old single man domiciled with his great aunt, unemployed, enrolled in community college part time with a history special education, and no formal psychiatric history. His medical history was notable for non-ischemic cardiomyopathy (ejection fraction 25–30%) in the context of being diagnosed with Danon disease at age 15. His medical history was also notable for stage D systolic heart failure, Wolff–Parkinson–White Syndrome status post ablation and implantable cardioverter defibrillator (ICD) with multiple recent admissions for chronic heart failure exacerbation.

Given the severity of his disease, preliminary heart transplant evaluation was initiated during an admission for right heart failure. The transplant social worker found the patient to have an adequate understanding of his medical issues, the transplant, and appropriate concern for potential complications, especially in light of his mother's death status post heart transplant. Likewise, Neurology, who was consulted to rule out skeletal myopathy that might preclude transplantation also found him to have a "good understanding" of his medical status. However, the initial transplant committee meeting documented its doubt that the patient would be able to independently manage the complex tasks (e.g., medication management, wound care, etc.) required following transplant surgery given his cognitive limitations. The committee documented that substantial social support would be required for further consideration of transplantation. Furthermore, the committee also raised questions of whether the patient would be able to provide full informed consent for the transplant given his intellectual limitations.

As part of the work-up for heart transplant, he was referred for pre-surgical neuropsychological testing to determine if there were neurocognitive challenges that could impact his eligibility for heart transplant. The patient's social and educational history bears noting here for context. The patient was raised by his mother until the age of 9 months when she passed away from complications just months after a heart transplant for peripartum cardiomyopathy. While further details of his mother's medical history were unknown by the patient, it was presumed that she had Danon disease. The patient's great aunt, who was his primary social support, raised him after the death of his mother. The patient was first diagnosed with learning disability in elementary school and was in special education until tenth grade. He reported graduating high school in regular education but with continued academic accommodations. He was enrolled part time at a community college working toward an associate degree in information technology before having to leave school due to worsening heart failure just prior to transplant evaluation.

The PhD neuropsychologist's report indicated that his general intellectual functioning was estimated to be in the

impaired range with a Full-Scale IQ score of 63 (cut-off scores for intellectual disability (i.e., ≥2 SD below the mean, or a standard score of ≤70) [29]. His Verbal Comprehension Index score 74 was in the fourth percentile and his Perceptual Reasoning Index of 53 was less than first percentile. In summary, his standardized scores were low, very low, and extremely low, respectively. His performance indicated marked impairments in attention, immediate learning, memory, visuospatial processing and construction, language, and executive functioning (e.g., cognitive flexibility, problem-solving, reasoning). The patient was reported as meeting the criteria for Intellectual Disability without a specifier. His widespread low scores across cognitive domains were consistent with known significant academic difficulties and reflect his history of developmental and neurocognitive delays. The neuropsychologist noted that the patient had great difficulty articulating key concepts involved in transplantation (e.g., confirming the idea that his heart would be removed and replaced with another person's heart). The report ended by commenting that it was unclear if the patient would be able to fully consent to transplant given the aforementioned deficits.

Considering the formal diagnosis of intellectual disability and concern for his ability to consent, Psychiatry was consulted for capacity to consent to heart transplantation. The transplant and primary teams had no other concerns for psychiatric disturbance on the part of the patient which was also corroborated by his great aunt. Based on extensive discussions between the consulting psychiatrist and the transplant team, especially in the context of recent extensive cognitive testing and the neuropsychologist's concern regarding his ability to consent, it was determined that the patient lacked capacity to consent due to concerns that he had a limited understanding and appreciation of multiple critical components of transplantation and post-transplant care. It was then documented that he lacked capacity to consent due to well-described cognitive deficits in the setting of a formally diagnosed intellectual disability. The patient was made aware of this, and assented to transplant. The patient's great aunt, his healthcare proxy, consented for heart transplant in his stead.

At this juncture, the transplant committee found him medically appropriate for transplant and planned to follow-up with him as an outpatient to fully assess compliance. The transplant social worker determined his great aunt to be an adequate social support for the transplant and post-transplant process. The patient was discharged following a 14-day admission with his symptoms having improved significantly on milrinone.

Twenty-two days later, he was readmitted with acute on chronic systolic heart failure, despite milrinone. At that time, the transplant committee approved the patient to be listed as status 2 by exception on the United Network for Organ Sharing (UNOS) heart transplant list. During the admission, the patient quickly clinically deteriorated to end-stage cardiogenic shock and 6 days after listing, the patient received a heart transplant from a high-risk donor (CMV+). His post-operative and rehabilitation course was uneventful, and he eventually returned home with his great aunt. To date, the patient, with maximum support of his great aunt, has been fully adherent to his post-transplant regimen.

Danon Disease: A Brief Review

Danon disease is a rare X-linked dominant metabolic disorder, characterized by a triad of cardiomyopathy, intellectual disability, and skeletal myopathy [30, 31]. Further case studies have demonstrated that people with Danon disease also often have hepatic disease, respiratory muscle weakness, and loss of retinal pigment leading to vision loss [32, 33]. The exceptionally high mortality of Danon disease is worth noting. Men with Danon disease are likely to die before age 25 without cardiac transplantation as compared to women who live to an average age of 34.6 years without transplantation [32]. The prevalence of Danon disease is unknown, however, observational studies found patients with Danon disease in 4–33% of patients with hypertrophic cardiomyopathy [34–36].

Evaluation for early transplantation is a mainstay of treatment for Danon disease. This is especially true for young men, who are at highest risk of sudden cardiac death [37]. Cardiac ablation is considered only a temporizing measure for arrhythmia because progressive cardiac fibrosis often outpaces continued ablation [30]. Genetic counseling is also warranted given the X-linked pattern to help patients and families understand the reproductive risks associated with the disease [30].

Intellectual Disability in Danon Disease

Historically, formal psychometric testing was generally not done in Danon disease patients, which has severely limited our understanding of this dimension of the disease. A relatively recent observational study of 82 patients with Danon disease demonstrated that 100% of males had intellectual disability [32]. Notwithstanding, in a small observational study of 12 people with Danon disease, 75% had a normal IQ (5 males and 8 females) and the mean FSIQ score did not differ significantly from males to females [31]. What is notable from this small study is that in-depth cognitive testing demonstrated widespread difficulties with executive functioning in both men and women with average and below average IQs. This study suggests that even in patients with Danon disease with normal IQ, there may be deficits in executive functioning that raise important questions about fitness for cardiac transplantation. This is consistent with the modern conceptualization of intellectual disability as simply more than below average IQ.

Psychiatric Disorders and Danon Disease

It is also important to assess for co-morbid psychiatric disorders in individuals with IDD as these may require additional mental health treatment. A small study that systematically assessed the psychiatric and cognitive components of patients with Danon disease [31] found 69.2% of patients were diagnosed with a mood disorder (major depressive disorder $n = 3$ and dysthymic disorder $n = 3$) and 46.15% met criteria for an anxiety disorder (generalized anxiety disorder $n = 3$, social anxiety disorder $n = 2$, panic disorder $n = 1$, specific phobia $n = 1$). As of 2018, there were only two case reports describing psychiatric illness in Danon disease patients with one described mood symptoms and the other with post-transplant psychosis and suicidal ideation [31].

Clinical Questions

1. What are the unique considerations a psychiatrist must consider when evaluating IDD transplant candidates?
2. What are the functional and behavioral needs of patients with IDD and how might this affect their ability to follow transplant directives?
3. What constitutes an adequate care supervision for patients with IDD after transplant? Does their behavior interfere with the ability of caregivers to provide such assistance?
4. What issues might the transplant team need to consider in evaluating the appropriateness of care provision in a residential setting?
5. What are the implications of lack of capacity to consent to transplant surgery in a patient with IDD?

Discussion

Patients with intellectual and developmental disabilities are at an increased risk of not being referred for transplant evaluation due to their disability. The case of ASD reflects both the delay in referral to the transplant center as well as delay in listing due to the medical providers' limited understanding of his diagnosis and intellectual functioning. In this case, Psychiatry's role extended beyond just providing a pre-transplant psychosocial evaluation to advocating on behalf of the patient to receive a transplant referral, as well as providing psychoeducation to the transplant committee about symptoms of ASD and how they may impact the transplant process.

In the case of Danon disease with intellectual disability, while neuropsychological testing was completed beforehand, the psychiatrist guided the transplant committee through the process of obtaining consent for transplant in a patient who did not himself have the capacity to consent due to intellectual disability. The documentation of lack of capacity and recommendation to involve the healthcare proxy by Psychiatrist, when the transplant team is unfamiliar or uncomfortable with the process, can remove a large barrier to receiving transplant for individuals with intellectual disability.

The two patients discussed were fortunate to have transplant teams who prioritized their medical needs over their psychosocial limitations. Not all patients are fortunate to receive this type of consideration and have been denied on the basis of inability to participate in informed consent or presumed inability to comply with post-transplant care [38]. It bears noting that provider bias toward individuals with IDD may impact their decision to list them for transplant. These biases include belief that transplant would not improve the quality of life for individuals with IDD as much as it would for those without IDD [39]. Furthermore, the idea of "social worth" or "social value" that individuals with IDD have less to contribute to society is a precarious one but persists in some transplant centers [40]. The idea of social value stems from the need to balance the principals of utility and justice when performing transplant evaluations. This means that the scarce, precious organs should go to those who can maximize its benefits [40]. However, what constitutes maximization of benefits is highly debatable and remains an ethical dilemma. We must all remember that centuries of bias against individuals with IDD as "mental defectives" who were ostracized and locked away from society still permeates the medical field. Psychiatrists must stay vigilant to any explicit or implicit biases in themselves and others to provide fair assessments of individuals with IDD.

The psychiatrist's role in transplant evaluation is crucial in differentiating such bias from valid concerns that intellectual, cognitive, and/or behavioral deficits of a specific individual with IDD may jeopardize post-transplant health. We achieve this goal by taking the time to review not just the general diagnostic criteria of a specific IDD illness but educating the transplant committee on how these symptoms manifest in each transplant candidate under consideration. Based on a thorough review of the unique risks related to transplantation of some individuals with IDD, psychiatrists should make recommendations to the transplant committee on how to mitigate those risks throughout each step of the process. An in-depth understanding of each patient's intellectual deficits, behavioral challenges, and psychosocial milieu will allow the transplant psychiatrist to create individualized behavioral and contingency planning to ensure the best health outcomes.

This is no different from making recommendations for harm reduction, abstinence, and monitoring as part of substance use treatment for patients with alcohol use disorder under consideration for a liver transplant. For example, the transplant committee was highly appreciative of the psychiatrist's offer to connect the patient with ASD to outpatient mental healthcare management programs, to increase his community support for treatment adherence. Other

approaches to risk mitigation may include pharmacological treatment, behavioral planning, and referral to neuropsychological evaluation when appropriate. It is crucial to acknowledge and validate the perceived challenge and burden transplant committees may feel with regard to patients with IDD. By bringing these feelings to the conscious level, psychiatrists can actively intervene and prevent them from manifesting as an implicit bias against the patient.

Psychiatrists must also work with transplant teams to appreciate the nuances of the consent process in an individual who may not have capacity to consent. Ensuring that assent from the patient is obtained free of coercion and duress is a primary role. And, clear documentation of both assent from the patient and consent from the healthcare proxy accompanied by a thorough explanation to the transplant team on the rationale for this unique process can help ease any ethical and legal concerns. Another unique feature of transplant evaluation in individuals with IDD is the scrutiny given to the quality of care giver support and their ability to aid the patient in the provision of daily activities for transplant living. Developing contingency plans for behavioral disruptions on the part of the patient to the care givers' ability to perform these tasks or caregiver burnout can reduce concerns for non-adherence.

In some situations, individuals with IDD may not have adequate support from existing care providers to successfully adhere to post-transplant care. The case of patient with ASD highlights this problem as his group home staff was not equipped to monitor and implement lifestyle changes and medication adherence. While it requires further research, Woodman et al. have suggested that individuals with IDD may fare better in terms of health when residing with relatives instead of community residences [41]. Transplant recipients whose behavioral health is critical to sustaining their life, alternative housing and supervision level options should be considered, if their current level of housing and supervision is assessed to be inadequate.

Conclusion

In this chapter, we reviewed the historical backdrop for the ongoing challenges and discrimination against individuals in IDD who need solid organ transplant. Psychiatrists are uniquely positioned to provide advocacy for patients with IDD who have been historically disenfranchised in the transplant arena. They are also tasked with characterizing the individual's cognitive and behavioral deficits and recommend an individualize plan to address any symptoms which may interfere with successful transplant. We hope that this chapter and the aforementioned take home points will empower psychiatrists to play a more active role in the care of patients with IDD.

Take Home Points

Individuals with IDD can have post-transplant outcomes as successful as other transplant patients without IDD with adequate caregiver support to overcome challenges associated with their cognitive and behavioral impairments. Unfortunately, individuals with IDD still face barriers to solid organ transplant. With this in mind, psychiatrists should:

1. Encourage transplant committees to offer transplant evaluations to individuals with IDD when medically indicated.
2. Consider individual symptomatology and level of functioning in assessing transplant eligibility in the pre-transplant psychosocial evaluation of individuals with IDD, rather than declining evaluation solely based on the diagnosis of IDD.
3. Recommend neuropsychological evaluation in patients whose strengths and deficits have not been characterized recently.
4. Assess the risks that may be unique to persons with IDD and develop risk mitigation strategies and behavioral plans to support the patient through the process of the transplant evaluation through post-transplant care.
5. Educate transplant committees not only about IDD but also about the diversity of presentations of IDD that can lead to good transplant outcomes. When necessary, provide a background on how patients with IDD were treated historically and the consensus with regard to these patients now. Do not assume that transplant committees have any familiarity with IDD.
6. Help the transplant committee identify and process any biases, implicit and explicit against individuals with IDD.
7. Guide the transplant team in creating a treatment plan tailored to the patient's particular strengths and weaknesses.
8. Assist in evaluating and, if needed, strengthening the social support/caregiving provision to the patient necessary for a successful transplant outcome.
9. Bolster the transplant care provider's comfort level with individuals with IDD by providing patients with referrals to appropriate psychiatric care and social services.
10. Reinforce the patient's understanding of the complex information presented to them using language and an interpersonal style tailored to their specific needs.
11. Facilitate the patient's comfort throughout the process by being attentive to their verbal and non-verbal cues and educating other team members on how to do this as well.

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Post-Operative Seizures in Transplantation

15

Mira Zein and Yelizaveta Sher

Introduction

Seizures, are sudden, uncontrolled, electrical disturbances in the brain, that lead to changes in a person's behavior, movements or feelings and in their levels of consciousness. They occur in 2–42% of transplant recipients [1–3]. Adult patients tend to experience seizures in the early postoperative period within the first 2 weeks [3]. One study demonstrated two peaks, one within the first week and then from the fifth to sixteenth weeks after surgery [4]. Another study found the majority occurring in the first 4 weeks post transplant [1]. Post-transplant seizures cause psychological distress to the transplant recipients as well as to their caregivers and can mimic or exacerbate post-transplant delirium. They most frequently are generalized tonic-clonic seizures, but focal seizures, convulsive, and non-convulsive presentations have also been reported. Non-motor seizures are often mistaken for delirium [3, 5, 6]. While post-transplant seizures are usually time limited and cease after the reversible, underlying cause is treated, status epilepticus can occur [3, 5]. Post-transplant seizures, particularly if status epilepticus occurs, can lead to prolonged hospitalization and recovery time, persistent delirium and cognitive changes, and poorer overall outcomes [5, 7, 8].

Risk Factors for Post-Transplant Seizures

General preoperative risks for post-transplant seizures include age, hypertension, and pre-transplant seizure history [3, 6, 9]. In patients who receive a liver transplant for fulminant liver failure the incidence of post-transplant seizures is 30% [due to metabolic derangements, hyperammonemia, inflammation, and oxidative stress] [9]. For heart transplant recipients, risk factors for postoperative seizures include a history of kidney dysfunction, history of diabetes, etiology of the underlying disorder [such as mitochondrial disease], and underlying atherosclerosis [3, 10]. Diabetes, kidney dysfunction, and atherosclerosis are also pre-operative risk factors for seizures after renal transplantation [11]. Patients with chronic kidney disease (CKD) and End-Stage Renal Disease (ESRD) on dialysis are also at increased risk for neurological disorders, including an increased incidence of seizures, due to accumulation of uremic toxic, metabolic, and hemodynamic dysregulation, oxidative stress, inflammatory cascades, and changes in the blood–brain barrier [12]. These pre-operative changes can increase the risk of post-renal transplant changes including seizure [11]. The literature on pre-operative risk factors in lung transplant recipients is limited: complex pre-transplant course and patients with cystic fibrosis who have severe multi-systemic pre-transplant metabolic disturbances have been posited as risk factors due to an increased correlation of post-surgical neurological complications [including seizures] in this population [13].

The transplant surgery itself conveys additional seizure risk through increased risk of cerebrovascular events; in fact, all solid organ transplant surgeries (especially cardiac) are correlated with increased risk of major cerebrovascular events, such as stroke and hemorrhage [10, 14]. Surgical risk factors for seizures include prolonged ischemic times and hemodynamic instability which can lead to diffuse anoxia or watershed regional infarction, anticoagulation leading to intracranial hemorrhage, and cardio-embolic events [10]. In one study looking at neurologic complications after lung transplantation, risk factors for seizures included a longer time in the operating room, blood transfusions during surgery, and ischemic times in the 303.10 ± 76.1 min range [8]. Factor VIII Inhibitor Bypass Activity (FEIBA) infusion, a pro-coagulant used frequently during transplant operations to limit bleeding, carries a risk of seizure, potentially due to cerebral thrombotic and embolic events [15].

Focal seizures are associated with structural abnormalities that can develop intra- or post-operatively, such as intra-

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cranial hemorrhage, stroke, cerebral abscess, meningitis, encephalitis, malignancy [i.e., post-transplantation lymphoproliferative disorder], and central pontine myelinolysis after liver transplantation [2, 6]. Generalized seizures are due to sepsis, or metabolic derangements, such as hypoglycemia, uremia, hyponatremia, hyperammonemia, hypernatremia, and hyponatremia [3]. Generalized seizures can also be precipitated by certain drug toxicities, including calcineurin inhibitors, penicillin, beta-lactam, cephalosporin, and fluoroquinolone antibiotics [16]. The use of calcineurin inhibitors in particular [i.e., tacrolimus and cyclosporine] is a common risk factor for post-transplant seizures; in fact, reported incidence of tacrolimus-related seizures ranges between 5 and 11% [3]. Immunosuppressive drug-related seizures may occur independently or in association with posterior reversible encephalopathy syndrome (PRES)], even in patients with low or normal drug levels [1].

PRES is associated with calcineurin inhibitor use after transplantation and, in addition, is correlated with hypertension, hypomagnesemia, and to a lesser extent, corticosteroid use and hypercalcemia [17]. Seizures are a frequent clinical presentation of PRES [5, 17], with one study finding 77% of patients with PRES suffering at least one seizure [17]. Of importance, PRES due to calcineurin inhibitors does not correlate with supratherapeutic serum levels of medications and can occur with levels in the therapeutic range. Furthermore, though hypertension is a common cause of PRES [17], Dhar noted that most transplant recipients who develop PRES are normotensive [5]. One exception was kidney transplant recipients, who may develop a delayed PRES with associated hypertension [5]. PRES-related seizures are usually generalized tonic-clonic seizures, but they can also present as various focal seizures and convulsive status epilepticus [17].

Treatments for Post-Transplant Seizures

When treating seizures in post-transplant patients, the transplanted organ, interactions with the anti-rejection medications, and underlying causes must be taken into account to minimize risk to the transplant recipient and the transplanted organ [16, 18]. Management approach will also be determined by whether the underlying causes are reversible derangements versus structural damage (i.e., a cortical stroke) which may have more permanent consequences. Most seizures are self-limiting and cease spontaneously within 3–5 min. These seizures do not require acute management. Seizures lasting longer than 5 min, recurring in a clustering pattern, or associated with prolonged periods of altered behavior or unresponsiveness are treated as evolving status epilepticus and should be terminated using intravenous [IV] antiepileptic medication [AEDs] [16, 18]. Benzodiazepines such as IV midazolam and lorazepam are the most common AEDs used to abort seizure, with IV levetiracetam utilized as the next line agent. If seizures do not subside, then guidelines for status epilepticus management are followed [19].

Once initial seizures are controlled or completed, the subsequent treatment will depend on identification of precipitating factors. Reversible derangements such as metabolic abnormalities, infection, or iatrogenic toxicity should be promptly addressed to prevent seizure recurrence. For recurrent seizures or a seizure with an epileptogenic abnormality on imaging such as a stroke or hemorrhage [], AED therapy is initiated in addition to interventions for the underlying seizure focus. Duration of AED therapy depends on the presence of an epileptogenic brain lesion, whether control of reversible derangements is achievable and whether a recurrent seizure may cause significant morbidity for a frail patient [16, 18]. If investigations do not reveal the cause and the patient is clinically stable, patients do not require continuous AED initiation [18].

Choosing AEDs with minimal protein binding and minimal hepatic enzyme interactions is preferred in the post-transplant setting to limit interference with immunosuppressants and other medications [i.e., infection prophylaxis]. Phenytoin and phenobarbital were previously the first-line therapy for post-transplant seizures due to IV formulation and physician familiarity. However, both carry a risk of hypersensitivity reactions such as fever, rash, eosinophilia; both stimulate hepatic enzyme systems and thus can decrease effectiveness of other seizure and non-seizure medications; and both have demonstrated interactions with calcineurin inhibitors and corticosteroids [18]. Levetiracetam is now a widely used first-line agent for continued AED management of post-transplant seizures due to its limited hepatic and drug–drug interactions and its flexible formulation availability, including IV and oral solution [18].

For patients with renal impairment or failure after transplantation, levetiracetam is less optimal as it is predominantly renally excreted with clearance directly correlated with creatinine clearance. Hemodialysis removes about 50% of the body's levetiracetam pool, requiring supplemental doses after hemodialysis and otherwise decreased doses [16, 18]. Valproic acid was previously recommended for non-liver transplant patients, but has fallen out of favor given its risk of hepatotoxicity, leukopenia, and thrombocytopenia as well as hepatic enzyme interactions [18]. However, it may be used with caution as an alternate agent in patients with significant renal impairment [16, 18].

Case History

Mr. K was 67 years old at the time of his bilateral lung transplantation. He had a past medical history of interstitial lung disease with concomitant chronic-obstructive pulmonary disease diagnosed 7 years prior to transplantation. He had a

psychiatric history of anxiety with panic attacks and mild depressive symptoms that developed after the worsening of his pulmonary disease, and he was receiving treatment with the transplant psychiatrist liaising with the transplant program. He had no history of neurologic disease. Prior to transplantation, he had been discussing with his psychiatrist his concerns about a long recovery period. He and his wife of 30 years were both retired. While he hoped that the transplant would allow him to live longer, to spend more time with his wife during their retirement, and to travel together, he was also clear that he did not want his wife to be burdened with "waiting on him hand and foot."

Mr. K received a bilateral lung transplant 5 months after being placed on the transplant list. During his surgery, he received propofol, fentanyl, and dexmedetomidine drips, had a total bypass time of 234 min, ischemic time of 283 min, and received multiple blood products as well as FEIBA. He also was administered two 500 mg doses of methylprednisolone. Two hours after surgery, the intensive care unit [ICU] team attempted to extubate Mr. K, but he became acutely and severely agitated upon decreasing propofol dose, leading to retitration of propofol after multiple boluses of medications were unable to control his agitation. During his period of agitation, his systolic blood pressure increased up to 250 mmHg. Additionally, he was started on tacrolimus and mycophenolate for immunosuppression. His initial tacrolimus levels were low at 1.5 and 1.8 ng/mL. His sodium levels were within normal limits and he had mild hyperglycemia controlled with an insulin drip. He had an isolated aspartate aminotransferase elevation and an increase in his total and direct bilirubin, as well as a new leukocytosis from 8.8 to 12.7/μL.

When first assessed by the inpatient consult liaison psychiatry [CLP] team for agitation management, Mr. K had was unarousable even after the propofol drip was held for 20 min, but later became agitated again. Scheduled haloperidol 1 mg three times a day [TID], guanfacine 1 mg TID, and gabapentin 300 mg TID [Mr. K's home dose] were started to control his agitation. Later that afternoon, Mr. K developed intermittent leftward gaze deviation and continued to be unresponsive to commands. The head computed tomography [HCT] scan was as negative for acute changes and the consulting neurocritical care team postulated that encephalopathy/delirium was more likely than seizures, given there were no clear seizure activity on their exam. On the CLP team's follow-up assessment, Mr. K was staring unresponsively with his head turned to the left and was moving his left leg and arm intermittently. At that time, the CLP team encouraged the ICU team to further investigate seizures as a possible etiology of Mr. K's altered mental status. Continuous EEG was started and subsequently showed discharges concerning for non-convulsive status epilepticus [NCSE].

Over the next 6 days, Mr. K received a loading dose of levetiracetam 4.5 g and titrated up to 2 g twice daily [BID]. Midazolam drip was titrated up to 4 mg/h, lacosamide up to 200 mg IV BID, and ultimately phenobarbital 100 mg TID was added to control seizure activity even after tapering off propofol. Finally, after no seizure activity for 48 h, the midazolam, then phenobarbital, then lacosamide were all tapered off, and levetiracetam was decreased to 1.5 g BID over the next 12 days without any seizure recurrence. However, Mr. K continued to have a persistent, poor mental status exam [i.e., staring, not following commands, not regarding or tracking] with minimal to no movement. Amantadine was started at 100 mg BID to encourage neurocognitive recovery. Five days later, he had only a limited response [intermittently shook his head and followed a simple command], therefore methylphenidate was started and titrated ultimately up to 20 mg TID in the first half of the day to promote wakefulness and alertness. During this time, Mr. K experienced medical complications including failed extubations requiring tracheotomy, atrial fibrillation with rapid venous return requiring amiodarone, febrile spikes, critical illness myopathy, elevated ammonia, and renal insufficiency.

One month after his initial transplant surgery, Mr. K finally began to demonstrate responsiveness and followed one-step commands. He progressed over the next two weeks to mouthing answers to orientation questions, following multiple commands, participating with physical therapy, and speaking with passy-muir valve trials. He demonstrated symptoms of hyperactive delirium in the afternoon and evening [e.g., agitation, visual hallucinations, disorientation, and confusion] requiring titration of risperidone up to 3 mg daily. Methylphenidate was tapered to 20 mg and 10 mg given at 6 am and 10 am with good effect on his mental status, however, when risperidone was decreased and discontinued his delirium recurred, especially in the evening. While Mr. K was initially discharged to a long-term acute care facility more than 2 months after his initial surgery, he returned less than 1 month later with a respiratory decline and associated worsening of his mental status.

Mr. K's recovery included two subsequent prolonged hospitalizations, lasting five then two months, during which time levetiracetam was tapered without further seizure events. Patient had lasting cognitive changes including sundowning with agitation and confusion and deficits in attentional and other executive function, especially triggered by any medical complications and/or lack of sleep. He also struggled with demoralization, depression, and anxiety over his prolonged treatment and his dependence on others, and especially his wife, for his care. The CLP team worked with him throughout his hospitalizations, and he continues to follow with his psychiatrist to the present day. He has been maintained on a lower dose of risperidone in the evening for sundowning, methylphenidate and amantadine, and rivastig-

mine (started during his second hospitalizations) for neurocognitive support. Twenty months after his transplant surgery, the patient had sustained cognitive and emotional improvements and was able to live at home with continued support from his wife.

Clinical Questions

1. Given the patient's concerns prior to transplantation, should the potential neurological complications, including seizures, have been discussed as part of the transplant education process?
2. Based on the patient's risk factors, were there symptoms or concerns that could have led to earlier intervention and decreased severity or even prevention of his seizures? How would one be able to differentiate delirium from a non-convulsive seizure presentation?
3. How much did the patient's NCSE contribute to his prolonged recovery?

Discussion

Lung transplant recipients often have complex metabolic disturbances before and after transplantation and require high immunosuppressant levels to protect their lung allograft, putting them at higher risk of neurologic complications [13, 20]. In one study, 6-month prevalence of neurologic complications was 68% [13], with another study demonstrating 92% prevalence over a 10-year period [20]. Evidence suggests that neurological complications, including seizures, increase median length of ICU stays by 28.4 days, and double the overall hospital length of stay [8]. Critical illness neuropathy [CIN] was found to increase ICU days even further by a median period of 35.5 days [8]. Due to Mr. K's protracted seizures causing extra weeks of being bedbound, Mr. K developed CIN, which further prolonged his recovery. His increased ICU stay left him susceptible to additional complications. The impact of neurological complications on survival rates is less clear, with one study finding no significant difference in 1-year survival rates [8], but another study reporting a drop in 5-year survival rates from 57.1 to 32.6% [7]. Another study posited that survival outcomes of patients post transplant who had seizures was not contingent on the seizures themselves but on the underlying causes of the seizures [21]. In their study, patients with seizures secondary to immunosuppressants had better survival outcomes than patients with seizures due to cerebrovascular disease, sepsis, or rejection [21]. There is a paucity of data looking at quality of life in post-transplant patients who have seizures, with one study noting that "preventing complications can boost quality of life of patients [22]." Certainly, Mr. K identified his quality of life during his hospitalization and afterwards as poorer due to the physical limitations he experienced, his prolonged hospital stays, and the related demoralization and anxiety he experienced due the complications his post-transplant seizures precipitated.

As delirium and post-transplant seizures often occur simultaneously, it might be difficult to distinguish between the two without the patient exhibiting obvious epileptic movements [5, 6]. Yet, it is very important for CL psychiatrists to be familiar with the phenomenon of post-transplant seizures, its presentations and risk factors, as they will likely be the physicians consulted for changes in patients' mental status. NCSE is a common occurrence in ICU patients, but it is often underrecognized as it is mistaken for delirium [23]. What might be helpful is for physicians being aware of any minor movements concurrent with mental status changes as well as having high suspicion for NCSE. NCSE, though not as damaging as convulsive status epilepticus, is far more common and there is growing evidence that NCSE can contribute to additional brain injury in the hippocampal region, prolong ICU length of stay, and increase healthcare costs [23]. If a patient has persistent mental status alteration after surgery, an EEG should be done to evaluate for seizures. Additional investigations, including laboratory tests, lumbar puncture, and/or brain imaging should also be considered [3, 18]. Mr. K had elevated seizure risk due to multiple contributors, including surgical risks [i.e., prolonged ischemic time, use of multiple blood products, use of FEIBA], spikes of his blood pressure in combination with a calcineurin inhibitor, leading to the risk of PRES and intracranial hemorrhage, potential infection, and the use of large doses of corticosteroids. Immediate initiation of continuous EEG and earlier seizure termination may have helped decrease his recovery time and lessen the risk of other complications. Evidence indicates that transitioning from calcineurin inhibitors to another immunosuppressant will lead to cessation of seizure activity when medication is the clear inciting factor; thus, medication change should be explored if seizures recur despite control of other factors or if the medication is the clear cause of the seizures [3, 5, 24, 25]. It is possible that transitioning Mr. K from tacrolimus to a different calcineurin inhibitor may have helped end his NCSE earlier, although protection of the lung allograft is also an important consideration. There have been no studies assessing neurological risk pre-transplant and choosing different immunosuppressant regimens and/or starting AEDs prophylactically to prevent seizures.

Mr. K. had ongoing cognitive problems throughout his post-transplant recovery; while part of his cognitive deficits were due to repeat episodes of delirium, some parts may have been attributable to remaining on anti-epileptic medication for months. Multiple studies have found an association of different anti-epileptic medications with cognitive side effects [CSE] [26, 27]. One review of 2860 patients noted that 15% of patients had intolerable CSEs attributable to an AED, which was correlated with decreased quality of life [26]. AEDs also have associated psychiatric/behavioral side

effects [PSEs] such as increased aggression, anxiety, mood changes, and suicidality [28, 29]. Levetiracetam—the AED Mr. K was taking for months—has one of the highest rates of PSEs [28]. Thus, it is unclear how much Mr. K's psychological sequelae were due to iatrogenic effects from his AED, from iatrogenic effects from other medications, and from his prolonged and complicated recovery.

While Mr. K was titrated on mirtazapine to address his changes in mood and anxiety post transplant, other transplant patients who suffer post-transplant seizures may have their psychiatric medication discontinued due to concerns that the medication lowers seizure threshold. Due to the generalizations that all psychotropic drugs worsen seizure frequency, psychiatric comorbidities in patients with seizures often are untreated or undertreated [30].

Risk of seizures with anti-depressants is overall low, with increased incidence occurring largely in overdose or in reduced drug clearance leading to higher plasma concentrations [30]. Bupropion, particularly its immediate release formulation, and the tricyclic antidepressants imipramine, clomipramine, and maprotiline have higher risk of seizures at therapeutic doses and are thus not recommended in populations of patients with seizure activity [30]. For antipsychotic medications, typical antipsychotics have higher pro-convulsive risk than atypical antipsychotics; of the atypical antipsychotics, clozapine and then olanzapine have elevated risk when used at higher concentration [30, 31]. In particular, risperidone and aripiprazole have been shown to have no significant impact on seizure incidence across studies [30, 31]. These data suggest that patients with comorbid psychiatric disorders both before and after transplant can safely be titrated on medication to address their symptoms, even after the occurrence of post-transplant seizures.

There is limited literature on how transplant teams communicate the risks of post-transplant complications or on the process of obtaining informed consent for organ transplantation. Similarly, there are limited available resources on the internet that educate patients about the risks of the post-transplant period despite evidence that the internet is the most common source of transplant information for patients and their families [32]. In the United Network of Organ Sharing's document of "What Every Patient Needs to Know," post-transplant complications are not addressed [33]. On the United States' website for Organ Donation and Transplantation, risk of infection and prolonged illness recovery is briefly mentioned [34]. The Epilepsy Foundation does have an online article detailing the risks of seizures after transplantation, but it is under their section for professional learning [35]. Transplant teams have an ethical obligation to balance patient autonomy in their desire for information and choices around transplantation while practicing beneficence and non-maleficence while educating patients about the benefits and consequences of choices during the transplant process [36]. Discussion around specific complications should be a joint decision between patients and their transplant teams.

Transplant psychiatrists are uniquely situated to help patients understand the potential neuropsychiatric sequelae of transplantation, assess for pre-transplant risk factors, and help monitor the patient after transplant surgery. In Mr. K's case, the involvement of the CLP team helped assess and diagnose his post-transplant seizures by picking up on initial mental status changes. Afterwards, the team helped manage protracted symptoms of delirium following the seizures, helped manage his protracted cognitive changes following both seizures and delirium, and managed other mood and anxiety symptoms associated with his prolonged recovery and multiple complications.

Take Home Points

Seizures are a common complication after transplantation linked to surgical risks such as ischemic time, hemodynamics, and thrombotic risk, as well as post-surgical risks including metabolic derangements, risk of infection, and use of immunosuppressant medications such as calcineurin inhibitors and corticosteroids. During the pre-transplant education process, transplant teams should explore with patients their treatment preferences and discuss potential neurological complications as a part of the informed consent process, particularly if patients have pre-transplant risk factors such as pre-existing seizure disorders, hypertension, and metabolic disturbances.

While most seizures self-resolve and do not recur if underlying issues are addressed, status epilepticus is a risk that has been documented in post-transplant patients. Seizures in addition to other neurologic complications carry risk of prolonging the recovery time of transplant recipients, and status epilepticus carries additional risk of cognitive damage as well as increasing risk of mortality if left untreated [37]. Given that NCSE is difficult to distinguish from delirium, continuous EEGs should be pursued early after alteration in mental status. Data from non-transplant populations suggest getting an urgent continuous EEG under the following circumstances [37, 38]:

1. Prolonged postictal period [30 min] where patient does not awaken after a convulsive seizure.
2. Altered mental status associated with twitching or blinking and/or fluctuating mental status.
3. Altered mental status of unexplained etiology, especially in patients with a history of seizures.
4. Unexplained altered mental status in the elderly.

5. Stroke patients who look clinically worse than expected.

Seizure contributors should then be identified through laboratory and imaging investigation and addressed. Levetiracetam is the AED of choice for patients who require ongoing AED treatment, given its minimal hepatic metabolism and drug–drug interactions. However, it should be used with caution in patients with renal impairment after surgery. Prompt seizure identification and intervention will help optimize patient's post-transplant recovery and decrease overall burden on patients and their families.

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Post-Transplant Cognitive Impairment

16

Yelizaveta Sher and Jose R. Maldonado

Introduction

Cognitive impairment (CI) is common in solid organ transplant recipients. In fact, given that organ transplantation is performed as a treatment of end-organ disease, sometimes it is difficult to differentiate how much of the witnessed cognitive disorder is due to residual symptoms of the organ failure, the trauma of the surgery (e.g., post-transplant delirium), the side effects of immunosuppressant agents, or a combination thereof. Another possibility of newly diagnosed or appreciated CI is that patient might not actually have a new decline in cognition after transplantation, but rather they did not experience the improvement in cognitive functioning after transplantation.

In patients with end-stage liver disease (ESLD), hepatic encephalopathy (HE) is an expected complication of progressive liver failure, which is often associated with CI. The available evidence suggests that the prognosis of patients with HE is not uniform [1]. Advanced HE is a marker of the severity of liver dysfunction and of the presence of intracranial hypertension. Severe HE (grade 3–4) upon admission and during hospitalization is a significant determinant of poor outcome [2]. A study of patients with cirrhosis ($n = 226$) demonstrated that there are residual effects on cognitive function, especially executive functions that result in learning impairment and working memory problems in patients with overt HE, even after adequate therapy and the attainment of clinical "normal mental status" [3]. Furthermore, the psychometric performance deterioration continues and expands to the more basic cognitive domains of psychomotor speed, set shifting, and divided attention with increasing numbers of episodes and hospitalizations for overt HE [3]. Despite previous thoughts that HE is a neuropsychiatric syndrome fully reversible by liver transplantation, an increasing body of data demonstrated, which is not uniformly the case [4–7]. Some studies have found that patients with a history of HE are at higher risk of developing neurological complications following liver transplantation [8], while others have found evidence for a "dementia like" parameter of minimal HE that is irreversible following liver transplantation [7]. Some have found that global cognitive function after liver transplantation was poorer in patients with a lower educational level, alcohol etiology, diabetes mellitus, or a history of HE prior to liver transplantation, and that recipients with prior HE had persistent impaired cognitive and motor function after LT [3, 9].

Similarly, cognitive impairment is very common in chronic kidney disease (CKD). For example, the prevalence of cognitive impairment ranges from 10 to 30%, rising to 30 to 55% in patients older than 75 years [10]. In fact, compared to age-matched controls, the prevalence of cognitive impairment is increased threefold in end-stage kidney disease (ESKD) [11]. It is believed that contributors to cognitive impairment among ESKD patients include (a) the negative effects of various uremic toxins (e.g., uric acid, indoxyl sulfate (IS), p-cresyl sulfate (PCS), homocysteine, interleukin-1β, interleukin-6 and TNF-α) [12], (b) hyperparathyroidism, (c) chronic inflammation associated with ESKD, and (d) the direct negative effects of dialysis (e.g., osmotic shifts, hypotension) [13]. Among kidney transplant recipients, available data reveal that the prevalence of CI was 58.0% [14]. Multivariable linear regression demonstrated that older age, male gender, and absence of diabetes were associated with lower Montreal Cognitive Assessment (MoCA) scores ($p < 0.01$ for all) [14]. After renal transplantation, there are many factors that might further contribute to CI, including (a) ischemia-reperfusion injury causing upregulation of pro-inflammatory neurotoxic molecules (e.g., IL-1β, IL-6, and TNF-α); (b) the direct effect of immunosuppressive medications; and (c) secondary

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complications, such as infections and post-operative delirium [13].

Among heart transplant candidates, studies have found that cognitive impairment occurs in up to 40% of patients [15, 16]. The post-surgical data suggest that although there might be improvement in some transplant recipients, not all subjects return to a normal level of cognitive functioning [17]. It is also important to consider the fact that in recent years, there has been an increased use of left ventricular-assist device (LVAD) as a bridge to transplantation. The use of this device has been associated with an increased risk for CI, thus, potentially increasing the risk of poorer cognitive outcome after successful heart transplantation [18, 19]. As in other solid organ transplant recipients, a number of factors might contribute to cognitive dysfunction among this patient population, including recipients' age, immunosuppressant side effects, altered cerebral blood flow and cerebrovascular pathology, post-surgical complications (e.g., delirium, seizures), and residual effects of pre-transplant decline [16].

Whatever the cause, the presence of CI after organ transplantation is distressing to patients and their loved ones, impairs their quality of life, makes taking care of oneself and adherence to complex post-transplant regimen more challenging, and can worsen post-transplant outcomes [20, 21]. Yet, it is not discussed enough among transplant recipients and transplant care teams. Thus, frequently, providers are not sure when and how to evaluate it and what interventions they can offer to their patients.

Case History

Our patient is a 65-year-old man who underwent lung transplantation for interstitial lung disease (ILD) 2 years ago. His transplant course was complicated by delirium, which resolved prior to discharge from the hospital with the assistance of short-term use of risperidone. He was followed by a transplant psychiatrist for depression after transplantation and was treated with sertraline 100 mg daily. Now he presents 2 years after transplantation with a complaint of memory problems. The patient expressed concerns that he might be developing "early dementia". He notes that he is forgetful about names of new people he meets, it is harder for him to concentrate when he is reading books, and that overall, he just feels "duller." The patient described that after transplantation, it has just been "harder for him to make cognitive connections and be quick in his thinking, the way it felt before."

Of note, the patient lives with his wife of 35 years. She manages their finances, as she has done since he became ill before transplantation. The patient takes medications on his own, but wife helps him to arrange them into his weekly pill box every Sunday. He is taking care of all his activities of daily living (ADLs) on his own. Family history is significant for a mother who was diagnosed with Alzheimer's type dementia at the age of 72. The patient has a college degree.

During the initial psychiatric evaluation, the patient was awake, alert, and overall attentive. He was oriented fully. Montreal Cognitive Assessment (MoCA) was performed, revealing a score of 25 out of 30 with patient losing 2 points within the visuospatial/executive domain, 2 points on language, and 1 point on his recall. He was evaluated for depression and anxiety using the Patient Health Questionnaire (PHQ)-9 and Generalized Anxiety Disorder Scale (GAD)-7, obtaining a score of 5 (points for poor sleep and increased fatigue) and 5, respectively. His medication list was reviewed for psychoactive meds. He was asked about alcohol, tobacco, pain medication, and recreational drug use, which he denied, except for a glass of wine twice per week.

Recent laboratory values were reviewed, and they were significant for renal impairment, with creatinine clearance of 54. Tacrolimus levels were reviewed, and while he had several elevated levels throughout the years, they were within therapeutic range in the last half a year. Additional laboratory work-up for reversible causes of dementia, including thyroid studies, vitamin levels, and screening for HIV and syphilis were done.

He was then referred for a neuropsychiatric evaluation, which revealed that the patient performed "at or near expectation in almost all domains during the current evaluation, however, demonstrated mild weaknesses in working memory and processing speed that are possibly related to reported sleep problems/fatigue and medication side effects."

The patient was, thus, further referred to sleep clinic where he was diagnosed with obstructive sleep apnea (OSA), and the use of continuous positive pressure airway (CPAP) was recommended. The patient was also started on melatonin and suvorexant for sleep. He was reassured about his overall functioning. The transplant team and patient/family were encouraged to use written documentation to convey clinic recommendations. The patient was also educated about the effects of sleep deprivation and cognition and instructed to increase his exercise to help with sleep, energy, and perceived cognition. A scheduled follow-up with neuropsychological evaluation was scheduled in a year to evaluate for any progression of the symptoms.

Clinical Questions

1. What is the frequency and what are the possible etiologies of cognitive impairment in transplant recipients?
2. What should an evaluation of cognitive impairment entail in transplant recipients?
3. What are potential treatment options for cognitive impairment in transplant recipients?

Discussion

Epidemiology and Etiologies of Post-Transplant Cognitive Impairment

Post-transplant cognitive impairment is common in all solid transplant recipients. Based on several studies, it is prevalent in lung transplant recipients. For example, a study of 42 patients up to 64 months after lung transplantation demonstrated that mild cognitive impairment with a MOCA score of 18–25 was observed in 67% of post-transplant patients, while moderate cognitive impairment (score 10–17) was seen in 5% of patients [22]. Similarly, in a study of 124 lung transplant recipients, transplanted between 1 and 264 months (mean 60.1 ± 44.1 months) prior to detailed neuropsychological assessment, 70% of patients demonstrated cognitive impairment in at least one domain [23]. Out of 4 tested domains (executive functioning, verbal memory, visual memory, and concentration/attention), the most frequent impairment was noted in executive function (78% of recipients) followed by verbal memory impairment (72%) [23]. Of note, the cognitive deficits in this study were not correlated with age, gender, education, particular immunosuppressive medications, or time since transplantation.

In another study of 49 lung transplant recipients, at least 20% of individuals exhibited at least one impairment on the test battery at their 6-month neurocognitive assessment [20]. Of significance, during a 13-year follow-up, better neurocognition was associated with longer survival (hazard ratio [HR] = 0.49 [0.25–0.96], $p = 0.039$), with strongest association for tests assessing processing speed and executive function [20].

Cognitive impairment has also been evaluated in heart transplant recipients. In a study of 37 patients, comparing 20 patients on everolimus and 17 patients on calcineurin inhibitors (CNIs) (i.e., tacrolimus and cyclosporine), 40% of subjects had cognitive impairment in at least one domain, defined as performance at least 1.5 standard deviations below normative mean [24]. Of note, there was no statistically significant differences between immunosuppressant groups across cognitive domains, but some postulated predictors of cognitive impairment in this group included estimated premorbid IQ, age of donor, cold ischemic time, creatinine at time of cognitive assessment, and lifetime cerebral bleeding/infarction [24].

Similarly, cognitive impairment has been identified in up to 50% of liver transplant recipients [25] and in more than 50% of kidney transplant recipients [14]. In general, overall cognitive function may be impaired after liver transplantation in the absence of major neurological complications related to the surgical procedure or the postoperative management, due to evidence of central nervous system damage [9, 26]. There are also data to indicate that patients suffering from HE at the time of liver transplantation may be more vulnerable to the metabolic stresses of surgery and the neurotoxicity of the drugs used, and were at highest risk for such complications [27]. In fact, in a study of perioperative neurological complications after liver transplantation, 90% of HE recipients experienced neurological complications, compared with 6.5% of recipients without HE prior to liver transplant [27]. In this study, logistic regression identified active preoperative HE as the strongest predictor of postoperative morbidity (OR 10.7, 95% CI 3.8–29.9) [27]. Others have found that patients with a history of overt hepatic encephalopathy (OHE) before liver transplantation had worse cognitive performances ($p < 0.001$) and EEG performances in comparison with their counterparts with a negative history [28]. The same study showed significant cognitive improvement after liver transplantation ($p < 0.01$); however, their global cognitive performance remained slightly impaired ($p < 0.01$), even though electroencephalograms (EEGs) normalized for 98% of the patients ($p < 0.01$).

The etiology for post-transplant cognitive impairment is likely multifactorial, including various pre-operative, peri-operative, and post-operative factors. The pre-operative factors comprise pre-transplant cognitive impairment and frailty. Pre-transplant cognitive impairment is common in patients with end-stage disease as discussed above and can be due to brain hypoxia in patients with end-stage lung or heart disease, uremia in patients with end-stage kidney disease, and hepatic encephalopathy in liver patients. Pre-transplant frailty has been shown to predict eventual worsening of cognition in kidney transplant recipients [29].

Peri-operative factors contributing to post-transplant cognitive impairment include allograft ischemic time, primary graft dysfunction, time spent on mechanical ventilation, intraoperative hypoxia, micro-emboli, and length of intensive care unit stay [20, 22, 30, 31].

Finally, postoperative factors include development of delirium, physical functioning after transplantation, presence of acute rejection, and immunosuppressive medications. Delirium is common after organ transplantation with up to 40% of lung transplant recipients [32, 33], up to 25% of heart transplant recipients [34], and up to 47% of liver transplant recipients affected by this neuropsychiatric complication [35]. Post-operative delirium has been associated with worsened cognition in transplant recipients and other critically ill patients [20, 36].

In addition, drug neurotoxicity can influence cognition in transplant recipients. The most likely medications to contribute to neurotoxicity in this patient population include corticosteroids and CNIs. Prolonged exposure to endogenous cortisol levels is associated with decreased hippocampal volume on magnetic resonance imaging (MRI) and results in memory impairment [13]. In fact, it has been demonstrated that kidney transplant recipients treated for rejection with

high doses of prednisolone experience memory impairment. Mild calcineurin neurotoxicity (e.g., tremor, neuropathies) occurs in about 40% of kidney transplant patients, while severe toxicity (e.g., psychosis, seizures, posterior reversible encephalopathy) affects up to 5% of patients [13]. While CNIs do not readily cross the blood–brain barrier (BBB), in the presence of underlying comorbidity (such as neurodegenerative disease, systemic infections or hypertension), the BBB can be disrupted. Once CNIs have entered the brain, they might lead to altered neurotransmission via calcineurin inhibition, further leading to changes of calcium homeostasis and gene expression [13]. This can in turn affect memory and other aspects of cognition.

Evaluation

The evaluation of post-transplant cognitive impairment follows the general guidelines (Please see Table 16.1 for full suggested work-up). It is important to carefully review the patient's history to understand potential risk factors, potential etiologies, and contributors of CI, and to identify any reversible factors. The patient's medication list should be carefully evaluated for the presence of any psychoactive medications, both prescribed and over the counter which could further impair the patient's cognition (e.g., anticholinergic medications, antihistaminic agents, benzodiazepines). We should also evaluate for the presence of any mental health contributors, such as depression and anxiety. The patient should be questioned about the use of any psychoactive substances that might affect cognition (e.g., alcohol, cannabis). The laboratory work-up should include a complete metabolic and blood count panel, as well as evaluation of thyroid tests, vitamin levels (thiamine, B12, D), RPR, and HIV. Imaging, such as head CT scan and/or brain MRI might be important to evaluate for volume loss, ischemic events, or trauma sequalae. Neuropsychiatric testing might be helpful to further identify and specify cognitive deficits, query the etiology, and help develop strategies for better patient functioning and communication between the team and the patient. There is no specific neuropsychiatric battery for transplant recipients. Most commonly in clinical practice, neuropsychologists choose tests that allow a detailed assessment of various cognitive domains: visuospatial function, memory, attention, executive function, language, and praxis. Neuropsychiatric testing also allows for more detailed behavioral observations which are not always overt during the psychiatric encounter (e.g., dependent traits, poor effort, sensorial deficits).

Table 16.1 Work-up and differential of cognitive impairment in transplant recipients

Neuropsychological testing • Bedside cognitive tests (e.g., MOCA and MMSE) • Detailed neuropsychological testing • Screening tests for depression and anxiety (e.g., PHQ-9, GAD-7, HADS, GDS)
Laboratory work-up • Complete metabolic panel, complete blood count, thyroid tests, vitamin levels (thiamine, B12, D), RPR, HIV
Imaging • Head CT scan • Brain MRI
Review of medications • Review of any medications for potential sedating and anticholinergic effects
Discussion of psychoactive substance use • Alcohol • Benzodiazepine agents • Antihistaminic agents • Pain medications • Nicotine • Recreational drugs (including THC) • Caffeine
Consideration of sleep/energy/exercise patterns
Consideration/evaluation of underlying organic factors • Obstructive sleep apnea

Treatment

The appropriate treatment of course will depend on the identified etiology of the CI, understanding that some deficits might be irreversible. In addition to addressing the underlying contributors (e.g., sleep disorders, anxiety, depression, medication side effect), the treatment of cognitive impairment in transplant recipients can consist of both pharmacological (if available) and non-pharmacological interventions, including improvements in the psychosocial support of both the patient and his/her caregivers. If identified, the underlying etiology should be addressed.

Pharmacological

There are no studies evaluating the use of cognitive enhancers (e.g., rivastigmine), NMDA antagonists (e.g., memantine), or psychostimulants (e.g., methylphenidate, modafinil, dextroamphetamine) in the management of transplant-related cognitive impairment. However, in our clinical experience, these agents can be useful in carefully selected cases.

Contributors

Depression is a significant comorbidity after transplantation and can affect cognition, quality of life, and outcomes. Thus, depression should be evaluated for and treated in all organ transplant recipients, especially when patients present with cognitive complains [37]. If depression is identified as a contributor, psychotherapy and/or medications can be helpful. If medications are

considered, the clinician can select among SSRIs with the lowest degree of sedation and minimal drug–drug interactions. Thus, sertraline, citalopram, and escitalopram are the preferred agents, when depression is associated with significant symptoms of anxiety. On the other hand, bupropion, a dopamine-norepinephrine reuptake inhibitor, might be the preferred agent when major symptoms are associated with symptoms of impaired attention, concentration, low energy, and/or amotivation.

Substance Use

In the case prescribed or over the counter medications with adverse effects on cognition are identified, these should be tapered off and adequate treatment substitution should be provided. When opiates or benzodiazepines are identified as potential culprits, these should be cautiously tapered off to minimize the possibility of substance withdrawal or symptom rebound, and when indicated, these agents should be substituted, as appropriate, with appropriate alternative agents with no effect in alertness and cognition. In the case, a substance use disorder is identified, and patients should be provided necessary resources, referrals, and treatment—this might include medication-assisted treatment or psychotherapeutic interventions for addictive disorders such as cognitive behavioral therapies or 12-step programs.

Non-pharmacological

Exercise and Diet

Available research data suggest that exercise can improve cognition in patients with end-stage organ disease and transplant recipients. In particular, the literature in kidney recipients suggests that exercise and cognitive exercises can improve cognition and decrease the risk of developing dementia [38]. Among lung transplant recipients, post-transplant exercise and improved physical functioning have been associated with better neurocognition [22].

Social Support

It is important for the team to provide the patient and his caregivers with the necessary psychoeducation regarding the changes patients might experience. Some patients might need more assistance with working on adherence to their complicated medication regimen. Family members can help patients with filling out the medication boxes and setting the reminders to take medications at the right time on alarms or smart phones. A variety of apps are available to help patients with adherence to medications. While the evidence for the overall effectiveness of these apps varies, some patients, such as those with CI, might benefit from such interventions. Moreover, the team should be sensitive to modes of communication that work best for the patients.

Take Home Points

1. Cognitive impairment is common in transplant recipients and can affect patients' quality of life, ability to adhere to their complex post-transplant care, and mortality. Pre-transplant, pre-surgical, and post-transplant factors can contribute to such impairment.
2. It is important to further evaluate and to investigate treatable and reversible causes of CI in transplant recipients, including medical contributors, medications that can impair cognition, substance use, and psychiatric disorders.
3. Treatment of CI in transplant recipients can include treatment of medical contributors (e.g., OSA); tapering off medications that can worsen cognition (e.g., benzodiazepines); treatment of contributing substance use or psychiatric disorders; use of cognitive enhancers; and psychoeducation and team support.

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Part III

Addictive Disorders in Transplant Candidates and Recipients

Alcohol Use Disorders in Organ Transplantation

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Introduction

Drinking is implicated in 1 in 20 global deaths [1]. Its medical disease burden on society is enormous [2, 3] and alcohol associates with myriad mental health problems (suicide [4], anxiety [5], depression [5] as examples) each of which adversely affects the health, wellness, and adherence of transplant candidates and recipients. Perhaps the quintessential intersection of alcohol-related complexity is liver transplantation (LT), where alcohol is both a primary and adjunctive etiology of organ dysfunction. Alcohol recently became the leading cause for LT in the United States [6].

While we will discuss various challenges in the evaluation and treatment of alcohol use disorder (AUD) in transplant patients in this chapter, we also note that these same patients are highly, and uniquely, motivated to change based on their health [7]. This means that amidst the challenges and complexity, there are also opportunities for mental health (MH) clinicians to leverage this distinctive momentum toward AUD treatment engagement and favorable clinical outcomes before and after transplant.

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Case Histories

Case 1: Alcohol Use Disorder in a Transplant Candidate

"Becky" is a 30-year-old female with a history of decompensated alcohol-related liver cirrhosis complicated by varices, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, and end-stage renal disease secondary to hepatorenal syndrome requiring intermittent hemodialysis. She is admitted emergently to the hospital for worsening symptoms of decompensated cirrhosis. The medical team requests a consult with transplant psychiatry to evaluate the Becky's candidacy for simultaneous liver and kidney transplant as her clinical condition is steadily worsening and a decision about her candidacy must be made imminently.

Becky had previously undergone transplant evaluation at an outside center and her evaluation at that center was closed for psychosocial reasons. The team does not have the details of this decision. Becky's transplant evaluation at our center began outpatient 3 months ago, and at that time, hepatology documented her stating that she did not have an alcohol problem. While alcohol biomarkers were positive several months ago during outside transplant evaluation (serum phophatidylethanol 632 ng/mL, urinary ethyl glucuronide 912 ng/mL), these have remained negative with our center's monthly rechecking. Transplant social work evaluated her alongside hepatology and found her to be a high risk candidate with a Stanford Integrated Psychosocial Assessment for Transplant (SIPAT) score of 52 and they referred her, for logistic reasons, for a substance use disorder (SUD) evaluation in Becky's local area. Those community SUD clinicians, in turn, recommended that Becky attends an intensive outpatient program (IOP). Initially, Becky declined to follow on the recommendation for IOP. After it was clarified that attending the recommended treatment is required for transplantation listing, she acquiesced.

As she grew increasingly ill in the ensuing weeks, her insight and motivation shifted and, between frequent hospi-

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talizations and dialysis, she courageously attended five full days of IOP. Her providers gave encouraging clinical reports to the transplant team and strongly advocated for Becky's listing. She had also attended two sessions of individual psychotherapy. She was unable to attend recommended local Alcoholics Anonymous meetings due to medical limitations.

Given the need for imminent decision making, transplant psychiatry evaluated Becky at bedside while she is admitted to the medical service where essential additional details of her psychiatric and SUD history were elicited. Becky first drank during adolescence with resultant legal charges. She had a child pass away unexpectedly 6 years ago and her drinking sharply increased to at least a pint of liquor (roughly 11 standard drinks) daily. Her severe AUD subsequently went untreated until her more recent decompensation and worsening health. She has a remote history of cannabis and cocaine use and recreational prescription psychostimulant use which resulted in clinically significant hypertension. There is a robust family history of alcohol problems including her father and mother. Becky is a survivor of domestic violence with longstanding trauma-related symptoms consistent with post-traumatic stress disorder. She had previously undergone several trials of selective serotonin reuptake inhibitors (SSRI), benzodiazepines, and sleeping medications though each overlapped with periods of heavy drinking and their effects are unclear. Over several years, multiple primary care and other medical providers had unsuccessfully referred her for psychiatric and SUD treatment. Three years prior, she had been discharged from an outside family medicine clinic due to poor follow-up and frequent no-shows. Becky exhibits current and evident commitment to long-term sobriety and a current acceptance of her AUD. She reflects on her drinking history and discusses new coping strategies to manage distress. Her trauma symptoms have been treated in recent months with escitalopram and have improved significantly.

Clinical Questions

1. Which factors place this patient in a higher risk category for LT?
2. Does the length of sobriety before transplant matter?
3. How should teams conduct pre-transplant AUD evaluation, treatment, and monitoring?
4. How should transplant teams interact with patient and families regarding AUD?
5. What should transplant teams do to facilitate their own productive AUD discussions and decision making?

Discussion

Which Factors Might Place this Patient in a Higher Risk Category for Transplant?

The literature contains a variety of risk factors for returning to drinking after transplant including severe psychiatric comorbidities, suicidal ideation and attempts, younger patient age, absence of children, poor social support, first-degree relatives with SUD, treatment non-adherence, shorter sobriety periods, polysubstance use, and prior unsuccessful SUD treatment [8–11]. While high-fidelity prediction of relapse is impossible given this wide variety of dynamic risks, clinical judgment and risk stratification using an accumulation of factors and careful follow-up treatment planning are paramount.

Does the Length of Sobriety before Transplant Matter?

There is no interval of pre-transplant sobriety that reliably predicts post-transplant sobriety but each month of pre-transplant sobriety confers less risk to drink [9, 12]. Transplant psychiatrists commonly evaluate candidates with prolonged sobriety who lack AUD insight constituting a high risk for transplant. Similarly, there are newly sober candidates who are so ill that they will never survive to attain longer periods of sobriety who are favorable transplant candidates. Length of sobriety is one factor of an AUD patient's candidacy considered alongside other risk factors mentioned above and should be verified with toxicology whenever possible to verify patients' reports. Although it is more concrete and numerical, sobriety duration should not eclipse other more abstract and subjective markers of behavior change and insight as discussed below.

How Should Teams Conduct Pre-Transplant AUD Evaluation, Treatment, and Monitoring?

The stakes of a transplant AUD evaluation cannot be overstated: definitive medical treatment, improved quality of life, and longevity on one hand with death, morbidity, and disability on the other. Yet there is no widely accepted protocol as to the precise approach to AUD in transplant and between policies and practices are often heterogeneous. The LT community desires more standardization [13] given changes in the field resulting in transplanting more patients with acute alcohol-associated hepatitis (AAH), a topic covered in another chapter.

During evaluation, patients desire to make a good first impression just as they would during other important evaluative situations. As such, patients may be motivated consciously or subconsciously to conceal or minimize aspects of their history including substance use. Especially in alcohol-related liver disease (ALD), the underlying AUD is often severe [14] meaning that clinicians face uniquely steep challenges in speaking openly with patients about their drinking alongside the task of providing adequate SUD treatment in the context of end-stage medical disease.

The transplant psychiatry environment is different from traditional psychiatric settings in several important ways. Transplant clinicians must maintain equipoise between patient advocacy and stewardship over precious donor organs. Therapeutic alliances can be difficult to build and maintain since psychiatric evaluations often arise from transplant team insistence rather than from treatment-seeking patients; clini-

cians are often perceived as obstacles rather than advocates. Some patients are unaware that they are seeing a psychiatric clinician. Such early confusion and defensiveness impacts rapport. Typical parameters of confidentiality are compromised given the need for psychiatric clinicians to communicate thoroughly with transplant colleagues along with the likelihood that documentation will be accessed by other transplant centers.

Given the prevalence of AUD in general and transplant populations, transplant teams should regularly screen for alcohol use at least once during all candidate evaluations. In many programs, AUD evaluations are initiated by transplant social workers who refer patients to transplant psychiatrists or psychologists as needed. Cross-training and interprofessional collaboration refine these workflows.

The timetables of end-stage disease progression and transplant logistics often demand rapid AUD evaluation. In patients with more available time in their pre-transplant course (i.e., patients on dialysis, with left ventricular assist devices, or those with milder disease), teams may require evidence of AUD treatment engagement and response along with negative toxicology *before* listing and transplant or as a requirement to keep their listing active. Transplant centers may need to collaborate with community clinicians, with varying transplant-specific expertise, given the broad geographic dispersal of patient populations. Patients may be motivated to attend AUD treatment only to fulfill a requirement rather than to gain insight, develop coping skills, deepen understanding of their drinking, maintain lifestyle changes, prevent relapse, and rebuild social support networks. Clinicians must balance advocating for patients in their AUD recovery while not colluding with those who are not developing insight and moving through stages of change.

Observing treatment response is often not feasible, however, in severely ill patients with high short-term mortality or those likely to be transplanted quickly once listed (i.e., certain blood types). In acute settings, a single evaluation of patient AUD insight and treatment commitment may be all the team has, along with collateral information from family and medical records, to make clinical decisions. Prioritizing psychosocial interviews ahead of likely patient mental status changes (i.e., hepatic encephalopathy) is often prudent given this paucity of data.

Serial clinical and toxicological evaluations are prudent for monitoring at-risk patients. Psychometric instruments like the Alcohol Use Disorders Identification Test (AUDIT) [15] can be useful in detecting and stratifying risk. Clinician-rating scales like the SIPAT [16] can be helpful in synthesizing a patient's overall psychosocial risk but should not replace clinical judgment. Serum phosphatidylethanol (PEth; indirect marker of alcohol exposure with a detection window of 2–4 weeks [17] and urinary ethyl glucuronide (uEtG; direct, minor ethanol metabolite which turns positive after a single drink and remains positive for up to 80 h [18]) used together can provide valuable information about recent drinking. Patients who drink right before their evaluation may have a positive uEtG and a negative PEth. Conversely, drinking patients who stop days before their evaluation can be PEth positive and uEtG negative. The therapeutic alliance may be adversely affected by use of toxicology which patients often interpret as intrusive and evidence of provider mistrust. On the other hand, some patients in recovery may find the knowledge they are subject to testing an additional motivating factor to maintain abstinence.

How Should Transplant Teams Interact with Patient Families Regarding AUD?

Family support systems are vital to both AUD recovery and successful organ transplantation. Transplant psychiatry clinicians often reinforce education about the unique transplant process, gather collateral clinical histories, and recruit family to support patients' transplant courses and AUD recovery. A warm practical, de-stigmatized, and non-judgmental approach facilitates working with families of AUD patients. Families commonly have strong and sometimes contradictory emotions regarding patients' medical illnesses and their AUD. Clinicians must be prepared to mediate difficult and complex discussions. A patient, teach-back method of information transfer can assist clinicians in ensuring families build understanding amidst such strong feelings. Due to concealment or unawareness, family members may not fully understand AUD and the nature of their loved one's drinking at the time of transplant evaluation. Key teaching points include the role of alcohol in liver disease, clear need for complete abstinence, relapse potential and associated risk factors, and the need for candor and alliance. Particularly during urgent presentations (i.e., fulminant liver failure secondary to acute decompensation), families may occupy a strong advocate role which could place them at odds with the transplant team's goals. Families rightly desire to save their loved one and may distort or filter important information fearing the effects of full disclosure. The team's recommendations for ongoing AUD treatment may seem unnecessary, irrelevant, unwelcome, judgmental, paternalistic, or impossible given the challenging circumstances.

What Can Transplant Teams Do to Facilitate Productive Pre-Transplant AUD Discussions and Decision Making?

Patient outcomes are affected by how members of a medical team perceive one another [19]. Transplant teams are large amalgams of diverse specialties and disciplines and composed of individual clinicians of varying levels of AUD experience and understanding. The composition of centers' psychosocial teams varies and may include many clinicians fully embedded within the transplant workflows or only a few clinicians completely unaffiliated with the center.

All clinicians have individual experiences and opinions about AUD from their training, clinical work, personal lives,

and communities which colors how they understand AUD. AUD information is largely subjective, unlike the more objective lab and imaging data that the team uses elsewhere in their work. Given this multilevel complexity, selection conferences are unlikely to be an ideal venue for *initial* AUD discussions. Just as meetings exist for other aspects of transplant (i.e., tumor boards, donor evaluation meetings, morbidity, and mortality), psychosocial meetings running parallel to selection conferences are optimal places for careful discussion and vetting of AUD cases. This ensures that AUD presentations for the transplant selection meetings will be focused and standardized facilitating more efficient discussion with medical and surgical colleagues. For centers without embedded clinicians, cordial and bidirectional correspondence between the transplant center and unaffiliated colleagues is optimal to ensure that AUD evaluations and treatment are sufficiently thorough and aligned with transplant-specific goals.

Case 1 Outcome

Becky's case was discussed at length during each of the transplant team's weekly selection conferences over the course of her month long inpatient stay. Some team members strongly advocated for the patient given Becky's young age, life stress, and her observed admirable changes in her insight and commitments to treatment. Her depression and anxiety had been treated with medication and psychotherapy and her clinicians provided favorable reports. Other team members were concerned about the chronicity and severity of her polysubstance use and her history of medical and psychiatric treatment nonadherence. Her sobriety was short, much of it comprised by the controlled hospital inpatient environment. Team discussions surrounding Becky's case were lengthy and contentious. In the end, the committee decided that the patient was not an appropriate candidate and Becky died during that hospitalization.

Case 2: Alcohol Use Disorder After Liver Transplantation

"Craig" is a 35-year-old male with a history of alcohol-related cirrhosis complicated by ascites, hepatic hydrothorax, and encephalopathy first diagnosed 2 years while drinking a fifth (750 mL, 17 standard drinks) of liquor per day. Psychiatric history is significant for chronic disorders of generalized anxiety disorder and major depression disorder, recurrent. He transferred care to the transplant center from an outside center after experiencing dissatisfaction with that center's clinicians.

Over Craig's year of pre-transplant affiliation with the current transplant center, he successfully engaged with and maintained local AUD treatment and followed regularly with transplant psychiatry. He continued taking venlafaxine for anxiety and depression and gabapentin off-label for AUD which were helpful and well tolerated. Serial alcohol biomarkers have been consistently negative and reassuring pre-transplant. His last drink was 1 year prior to his liver transplant which eventually came from a deceased cardiac donor.

Two months post-liver transplant, Craig's transaminases, alkaline phosphatase, and total bilirubin trended upward. Ischemic cholangiopathy was diagnosed, and re-transplant was considered. Also, around this time, Craig unexpectedly discontinued AUD treatment and all transplant psychiatry follow-up and, unbeknownst to the team, severely relapsed to drinking (sharing a fifth of liquor with a new girlfriend 3–4 days per week over 2 months). Positive phosphatidylethanol (PEth) testing in transplant surgery clinic (70 ng/mL) eventually revealed alcohol exposure and allowed the team to clinically detect and address his drinking. The team acknowledged that his elevated liver enzymes might have come from drinking in addition to ischemic cholangiopathy. Craig's mother had been aware of the relapse and did not notify the team.

After several ensuing transplant psychiatry visits addressing alcohol use though motivational interviewing, patient restarted medications, reconnected with local AUD therapy (including completing an intensive outpatient program), attended local 12-step meetings and obtained sponsorship, and followed up regularly. AUD medications included naltrexone and gabapentin while his anxiety and depression were treated with regular and frequent psychotherapy, mirtazapine, and buspirone. Transplant psychiatry is asked at 6-months post-transplant whether Craig should be re-transplanted. Craig's local therapists and recovery meeting group leader wrote letters documenting treatment response.

Clinical Questions

1. What kind of post-transplant AUD follow-up and monitoring should teams implement?
2. How should teams respond to post-transplant drinking?
3. Are AUD and other psychiatric medications safe to use in post-transplant patients?
4. How should teams collaborate with mental health providers not affiliated with the transplant center?

Discussion

What Kind of Post-Transplant AUD Follow-Up and Monitoring Should Teams Implement?

Alcohol use is less likely to occur in the peri-operative phase of transplant care [20] which can lead to its inadvertent deprioritization in post-transplant encounters due to myriad other pressing issues. Patients' post-operative recovery may not allow return to AUD care right away, but inpatient teams should be assertively discussing the need for the patient to recommence AUD treatment promptly after hospital dis-

charge as medically appropriate. When AUD information comes from medical and surgical providers and is presented as integral to graft health and clinical outcomes, the post-transplant need for AUD treatment uniquely solidifies in the minds of patients and families. Teams should avoid clinical approaches which foster antagonism or shame.

Consistent monitoring of AUD patients is essential and includes in-person evaluations including questions about drinking, urges and cravings, near misses, triggers, changes in support, or other new stressors. Medical and surgical clinicians may elect to defer some of these in-depth and nuanced questions to psychosocial colleagues, but patients' AUD care should remain prominent in all medical charting and clinic conversations as a permanent, relevant element of the patient's ongoing care. Validated psychometric questionnaires are useful post-transplant tools in detecting mental health changes and other factors related to alcohol relapse risk alongside toxicological biomarkers (serum phosphatidylethanol, urinary ethyl glucuronide, urine cotinine, and urine drug screens) querying recent substance exposure. Such monitoring can foster patient accountability as patients realize transplant teams are dedicated to ongoing monitoring. Teams will need to individualize their own use of toxicology based on cost, feasibility, and availability.

How Should Transplant Teams Respond to Post-Transplant Drinking?

Post-transplant drinking negatively affects transplant outcomes [21] and follows different trajectories with earlier drinking portending more severe relapses [20]. It is challenging to predict which patients will relapse as the literature, as mentioned above, is heterogeneous as to which factors might associate with relapses after transplant.

Teams, while striving to apply thoughtful and equitable selection criteria, must prepare themselves for an inevitable frequency of AUD recurrence post-transplant and ensure they have adequate procedures and personnel to detect risk and clinically respond. This involves thoughtful drinking-related questions during clinical encounters, long-term use of biomarkers, and collateral updates from family. Teams must also be cautious about new or resumed use of other addictive substances (i.e., chronic benzodiazepines, protracted opioid regimens). Addressing anxiety, sleep, or pain post-transplant should involve medications with low or no addictive potential when possible. Psychotherapy can be effective as adjuvant and as monotherapy for these conditions. If opioids must be used, standard precautions aimed at tapering medication should be in place.

Post-transplant patients can get mixed messages from clinicians who may inadvertently lead patients to believe that resumed moderate drinking is safe and permitted. If teams check in less and less over time about drinking, it may inadvertently signal to patients and families that alcohol abstinence and AUD treatment is unimportant. Transplant clinicians truthfully respond to questions like "will alcohol hurt my organ?" by stating accurately that small and infrequent amounts of alcohol, in and of themselves, may not necessarily be dangerous to the transplanted organ. However, if they are speaking to an AUD patient unable to regulate their drinking, then any implicitly permissive statements may, in the end, collude with a patient's AUD and cause negative outcomes. If transplant teams do not have their own understanding of AUD or if they lack embedded mental health providers with whom they regularly collaborate, then the likelihood of consistent AUD follow-up may be reduced. Teams not using toxicology to verify what patients are reporting may be erroneously complacent about the status of the patient's AUD when in fact patients need help.

Transplant recipients commonly have a unique psychology regarding post-transplant alcohol ideation, cravings, or slips/relapses. Some patients experience potent shame when they experience any alcohol-related cue or urge after transplant. Urges are expected given the nature and chronicity of AUD, but patients often fear disclosing their occurrence to their team or family. Their gratitude for substantial transplant resources and effort can limit their candor and ability to access needed support; they do not want to disappoint their care team. When patients slip or relapse, shame often only fuels ongoing concealed drinking risking a spiral of deception and drinking that can have disastrous consequences.

Teams must accept and prepare for the fact that alcohol relapse *will* occur in some proportion of transplant patients and understand that AUD by definition is a chronic, relapsing condition. When relapse happens, transplant teams should expect to experience strong emotions themselves: betrayal, anger, or disappointment that a patient would drink. These feelings are natural given the amount of work that goes into transplant, the pricelessness of donor organs, and the singular relationship between transplant clinicians and patients. Patient families commonly have similar strong reactions toward relapsing patients. If unchecked, however, these feelings can lead to clinician and family detachment and a sense of futility which may only worsen a patient's shame and concealment and reduce engagement and disclosure. Transplant psychiatry clinicians must be liaisons between patients and their medical teams and families given the importance of these relationships. Importantly, relapses can also be reframed as learning opportunities through which patients can recommit to abstinence and AUD treatment, particularly with support from transplant teams and families.

Are AUD Medications Safe to use in Transplant Patients?

AUD medications can be effective and well tolerated in transplant patients. They require attention to drug interac-

tions, physiological changes affecting drug metabolism and clearance, and general risks and benefits in the context of end-stage disease and ongoing transplant care. Transplant pharmacy colleagues are invaluable in exploring AUD medication options.

Benzodiazepines may have an important and limited role in acute alcohol detoxification. Given the pharmacologic similarities between alcohol and benzodiazepines, AUD patients may be susceptible to using and misusing these medications. Due to the preponderance of hepatic encephalopathy and SUD in liver patients, benzodiazepines are commonly avoided altogether except in medical necessity since medications that depress the central nervous system can worsen hepatic encephalopathy.

Transplant psychiatry clinicians affiliated with liver teams tend to avoid disulfiram due to toxicity risks [22] and are similarly cautious with naltrexone use, particularly when it comes to the injectable long-acting depot formulation, due to possible risks of hepatotoxicity and metabolite accumulation [23] though such concerns are waning. Given naltrexone's opioid receptor antagonism, it can interfere with peri-operative pain control. Renally cleared AUD medications are good treatment options for patients with adequate kidney function, like acamprosate, which has Food and Drug Administration approval for AUD treatment, or gabapentin, topiramate, or baclofen, which are used off-label for AUD treatment [24–26].

An important aspect of AUD care, pharmacologic treatment of comorbid psychiatric conditions, and other substance use disorders are discussed elsewhere in this book and in the literature [27]. Active collaboration with medical and surgical colleagues on pharmacologic planning and monitoring is essential to maintaining a favorable risk–benefit balance. Teams who retain psychosocial personnel who administer psychotherapy ensure that their patients will have access to a wider array of psychiatric treatments, especially important when AUD medications are not tolerated or indicated.

How Should Teams Collaborate with Mental Health Providers Not Affiliated with the Transplant Center?

There are many reasons why connecting transplant AUD patients with treatment is challenging. Transplant centers accept patients over large geographic areas lowering the likelihood that they can provide long-term AUD care patients require. AUD treatment providers to which the center refers may be few in number, reticent to take such complex patients, and already saturated with other chronic and severe psychiatric and SUD problems. Transplant teams often have little to no information about the quality of care provided or the methods or philosophies outside providers use in AUD treatment. Insurance companies may also not reimburse providers in the patient's local area or may impose visit limits.

Unaffiliated providers may have never evaluated a transplant patient before and often advocate for their patients, whether or not they are good candidates, not wanting to impede the transplant process or contribute to a patient's disqualification, suffering, and possible death. They may not have ready access to the transplant team and be unsure about transplant-specific treatment objectives or timetables. Some defer or decline treatment because medically ill transplant patients may frequently miss appointments because of hospitalizations, clinic visits, or dialysis. Such lapses in treatment can be interpreted as poor engagement and motivation, and their treatment may be terminated. Patients who are intermittently altered in their mentation can be deemed inappropriate for treatment.

Communication between transplant centers and local AUD treatment providers is paramount and is facilitated by personalized and collegial correspondence. Written and verbal methods may work to introduce transplant team members, offer expertise, build collaborative and ongoing relationships, and orient non-transplant mental health colleagues on some of the unique features of post-transplant patient life (chance of protracted post-operative recovery, adjustment from chronic illness to wellness, psychological challenges of medical complications and other clinical setbacks, importance of post-transplant medication adherence and side effects, risks of recurrent psychiatric symptoms, and alcohol relapse to transplanted organ and future chances of re-transplant, etc.).

Case 2 Outcome

Craig's case was discussed at length in multiple selection conferences as he underwent treatment for ischemic cholangiopathy. Team members advocating for him stated his liver function was primarily affected by ischemic cholangiopathy rather than AUD and that the question of re-transplanting is a parallel issue and does not necessarily rest on drinking. They also referenced Craig's exemplary communication with team, treatment reengagement, toxicology, testimonial letters, and adherence over time across multiple tiers of AUD care (intensive outpatient, outpatient, and recovery support groups).

Concerns raised by team members included Craig's prompt alcohol relapse and full discontinuation of AUD treatment and transplant psychiatry visits post-transplant. His deception and the absence of disclosure from his

mother caused deep concerns about the nature of their alliance with the team. Worried team members asked how the team could interpret his new AUD adherence given that he already demonstrated such dedication before liver transplant, and he still relapsed. They also referenced the many other candidates waiting for their first liver, let alone a second.

As of this writing, Craig remains sober and clinically stable and regaining function post-operatively. He continues to follow with local and transplant psychiatric providers and has not been listed for a second liver transplant.

Take Home Points

1. Teams should be cautious transplanting patients with severe psychiatric comorbidity; polysubstance use; shorter periods of sobriety; poor social support; poor insight; previous episodes of medical, psychiatric, and SUD non-adherence among other potential factors.
2. While increasing sober time pre-transplant correlates with lower post-transplant relapse, there is no agreed-upon or literature-based period of sobriety time that has been identified as a reliably predictor. AUD treatment can mitigate risks in patients with shorter sobriety.
3. Psychometric instruments, DSM-5 criteria and AUD severity categorization, clinician rating scales, and biomarkers do not replace clinical judgment but augment transplant psychiatry evaluations, AUD treatment, and eventual candidate selection.
4. AUD monitoring and treatment should be conceptualized as integral as any other facet of post-transplant care.
5. Alcohol relapse will occur in some patients regardless of team efforts, social support, and length of sobriety. Teams must be aware of their own potential for strong emotions and approach the patient empathically with the goals of clinical stabilization and attaining new sobriety via appropriate levels of AUD care.
6. AUD medications are important tools though psychiatrists should consult transplant physicians and pharmacists when considering their use.
7. Proactive communication and collaboration with community colleagues who treat transplant recipients with AUD is essential. Outreach will ensure ongoing collaboration and transplant-specific treatment goals.

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18 Psychiatric Evaluation of the Liver Transplant Candidate with Alcohol-Associated Hepatitis

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Introduction

Transplant professionals face profound ethical and clinical dilemmas when they are asked to evaluate a patient with alcohol-associated hepatitis (AAH) and short sobriety, once considered absolute contraindications to liver transplantation.

The primary impetus for early liver transplantation in such a high-risk population is that the risk of death with medical management alone in such patients approaches 70%, mostly within 2 months of completing a failed trial of glucocorticoid therapy [1]. By contrast, more recent studies have demonstrated that liver transplantation for AAH results in 1-and 3-year survival rates of 94% and 84%, respectively [2].

The standard of practice for the majority of liver transplant programs in the United States has been to require at least 6 months of sobriety and some form of addiction treatment or attendance at Alcoholics Anonymous or similar 12-step support meetings to be eligible for placement on the liver transplant waiting list [3]. Historically, this so-called "6-month rule" was discussed at the National Institutes of Health consensus conference concerning the management of patients with alcohol-related liver disease, last held in 1996. The rationale for this rule was derived from the belief that a minimum of 6 months of pre-transplant sobriety was a predictor of post-transplant sobriety. Moreover, it was thought that 6 months of sobriety would allow some patients sufficient time to improve and avert the need for liver transplantation. Consequently, the "6-month rule" was universally implemented by the majority of liver transplant programs and mandated by most insurance providers. Unfortunately, the "rule" was not based on controlled studies, but rather early observational data obtained from highly selected samples of ostensibly sober liver transplant candidates. A few years later, Beresford and Everson published an editorial in which they explained that despite the lack of supporting evidence, utilization of the "6-month rule" was so prevalent that it was once under consideration by the United Network of Organ Sharing (UNOS) for application across all transplant centers [4]. However, it was never implemented because UNOS attorneys considered it "indefensible." Subsequent research has shown that 3 months of sobriety can adequately differentiate patients needing transplant from those whose livers will recover [5], and that a 6-month duration of pre-transplant sobriety is a weak predictor of post-transplant sobriety [6].

In spite of all of the aforementioned data to the contrary, the "6-month rule" has continued to be a requirement for liver transplant eligibility by the majority of transplant programs and insurance providers in the United States, until very recently. At the time of this writing, expert guidelines now exist in Europe, but not in the United States, stating that a fixed period of abstinence is no longer recommended prior to being waitlisted for transplant [7].

In 2011, a landmark study published by Mathurin and colleagues described the success of early liver transplantation for acute alcoholic hepatitis. Patient data were combined from seven centers comparing 26 highly selected patients with AAH to 26 matched controls, of which none responded to medical therapy [8]. Controls were selected non-randomly and matched to cases on age, sex, and severity of disease. Selection criteria consisted of four components: (a) severe AAH as the first liver-decompensating event; (b) presence of close supportive family members; (c) absence of severe coexisting substance or psychiatric disorders; and (d) agreement by patients and family members to adhere to lifelong total alcohol abstinence. Transplant selection teams were grouped into four "team circles" composed of an inner circle of caregivers closest to the patient (such as nurses, residents or fellows), followed by an addiction specialist, a senior hepatologist, and finally an outermost circle of the surgeons and the anesthesiologist. Team members had to reach complete

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agreement for a patient to be selected. Cumulative 6-month survival rates were 77 ± 8% for patients receiving early liver transplantation vs. 23 ± 8% for those who did not, and survival rates were maintained through 2 years of follow-up. Three patients returned to drinking, all at 720 or greater days post-transplant.

Subsequent to publication of this study, many transplant centers in the United States have become interested in exploring early liver transplantation for AAH, and transplant psychiatrists are increasingly being asked to evaluate these patients. In the following paragraphs, we will describe clinical and ethical dilemmas faced by transplant professionals tasked with evaluating critically ill patients with AAH and describe a clinical case of a patient with AAH for whom a psychiatric evaluation was requested to determine eligibility for liver transplantation.

Clinical and Ethical Dilemmas

The choice between deciding whether or not to deny a dying patient a life-saving procedure may be viewed in terms of a pragmatic and/or emotionally based perspective. From a pragmatic standpoint, if survival is the goal, a transplant will provide the patient with AAH the best chance of attaining excellent survival rates compared to the inevitable consequences of denying a transplant, which is very likely to result in the patient's imminent death. From the emotionally based perspective, these decisions weigh heavily on all members of the transplant team, but also on the non-transplant professionals caring for the patient in the hospital setting. Negative countertransference feelings toward the patient are likely to be high, and treatment team members must be cognizant of how their emotional reaction to the situation could affect their clinical judgment. For example, if a transplant surgeon or hepatologist has a close relative with an Alcohol Use Disorder, depending on whether that relationship is favorable or not, the doctor's feelings about their relative may unconsciously affect the objectivity of their decision to transplant the patient. Likewise, psychiatric consultants should be aware of the potential to formulate their opinion about whether to transplant the AAH patient based on the unconscious desire to agree with other members of the transplant team, even if they have a different opinion. Finally, all transplant team members should be careful not to base their opinion about the probity of transplanting the patient they are currently evaluating upon the outcome of their last patient. This is especially important if the outcome of the most recent patient was unfavorable.

When considering a patient with AAH for transplant, most transplant programs adhere to the same selection criteria as in the Mathurin study [8]; however, some programs continue to evaluate patients on a case-by-case basis. In concert with recently published guidelines from the Dallas Consensus Conference held April 5–6, 2019 [9], many programs agree that gravely ill hospitalized patients with AAH should only be selected for transplant if they were never previously made aware that alcohol was the cause of their liver disease. This is because a patient with AAH would presumably have stopped drinking if they were informed of the risks of ongoing alcohol consumption to their survival.

Case History

A 36-year-old mother of three young children was transferred from a local hospital to the Intensive Care Unit of a large tertiary care hospital for a liver transplant evaluation. She was diagnosed with alcohol-associated hepatitis (AAH) and hepatorenal syndrome that was not responsive to medical management. The patient and her husband denied being told that she had alcohol-related liver disease by any healthcare provider prior to this hospitalization. Her most recent use of alcohol had been 3½ weeks prior to her admission. Although gravely ill, at the time of the evaluation, she did not demonstrate signs of hepatic encephalopathy.

The patient reported she had been increasing the quantity of her drinking over the past 2 years and was up to two standard sized 750 mL bottles of wine daily (about 10 glasses). Over those 2 years, her husband and her employer had both advised her to stop drinking due to poor performance at work as well as frequently requiring her husband or other family members to assume responsibility for attending to the needs of her children. She tried to stop drinking at least three times on her own without a medically supervised detoxification, and as a result, suffered from coarse shaking of her hands, nausea, sweating, and insomnia, which led her to relapse in order to relieve these classic signs of alcohol withdrawal. The patient and her husband told members of the liver transplant team that she briefly attended an Intensive Outpatient Program (IOP) to address her Alcohol Use Disorder about 6 months prior to hospital admission, but ultimately dropped out after a relapse. Instead, she periodically attended a local faith-based recovery group. She acknowledged hiding her drinking from her husband and indicated that groups were hard for her because she was so "introverted." Her longest sobriety was reported to be less than a month. She denied any history of tobacco or illicit drug use and comprehensive psychiatric evaluation did not reveal any concurrent psychiatric diagnosis. The patient was determined to have met the DSM-V criteria for Alcohol Use Disorder, Severe.

Consistent with the Dallas Consensus Conference on Liver Transplantation for AAH guidelines, the patient described above was evaluated by an experienced transplant social worker and psychiatrist [9], and their findings were presented at the weekly transplant team selection committee meeting. The committee determined that the patient was an appropriate candidate for liver transplantation, and she was placed on the waiting list.

Clinical Questions

1. What is the role of the transplant psychiatrist in the evaluation of transplant candidates with AAH?
2. Within the psychiatric evaluation of AAH, what areas are specific to this category of patients?
3. What are the treatment options aimed at reducing the risk of alcohol relapse available to AAH patients after transplantation?

Discussion

In the following sections, aspects of this patient's presentation will be explored, and the role of the transplant mental health professional will be described regarding some of the unique barriers encountered when evaluating patients with AAH. Given the short window of time and limited access to information the examiner often faces when evaluating hospitalized and/or critically ill patients, useful strategies to compensate for these shortcomings will also be illustrated.

The Role of the Transplant Psychiatrist in the Evaluation of Transplant Candidates with AAH

The psychiatric consultant should be open with the patient and their family about their role on the transplant team before beginning the examination. Patients and their significant others must know that information gleaned from the psychiatric examination is shared with the transplant team. It is important to explain to patients and their supports that the psychiatrist's role is not to "rule in or rule out" the patient for transplant, but, if appropriate, to develop a psychiatric treatment plan to mitigate any challenges that could adversely affect the health of the patient and graft. Explaining this to a prospective transplant candidate can allay some of their fears that the psychiatrist will be the sole decision maker about whether they will live or die. It is essential to explicitly inform patients that listing decisions are made by the entire team and that listing is determined by the strength of a patient's support network, the severity of their medical and surgical risks, and the treatability of their psychiatric and substance use disorders. Whenever possible, it can be helpful to patients if the impressions and recommendations the psychiatric consultant intends to share with the transplant team are also shared with the patient and their support network at the conclusion of the interview.

The Psychiatric Evaluation of Patients with AAH

While a comprehensive psychosocial evaluation is optimal, when time is limited and not all sources of information are available, the mental health evaluator may need to focus on the most relevant parts and often make do with incomplete data. Ideally, the examiner should attempt to obtain as much information as possible pertaining to the following three relevant areas of inquiry:

Evaluate for the Presence and Severity of Psychiatric and/or Substance Use Disorders

In the context of a transplant evaluation for AAH, significant emphasis should be placed on addiction and alcohol use history, which may prove difficult for some patients, especially when the patient is meeting the psychiatrist during their first lifetime episode of medical complications secondary to drinking. Examiners can start the interview by seeking to obtain the alcohol history by asking the patient about the quantity and frequency of their drinking; however, a more open-ended strategy can improve rapport with some patients. An alternative approach may begin with a statement such as "tell me when alcohol started to play a role in your life," eliciting a reverse chronology of use and prompting the patient to provide a narrative of how their addiction has progressed over time.

Important components of an alcohol use history include age of first use, a description of the time in their life they consider their heaviest drinking period, current level of consumption, quantity and frequency of intake (including fluctuations over the lifespan), the presence of physiological dependence, withdrawal history, and treatment history. Triggers for drinking and the circumstances surrounding periods of sustained sobriety are important to discuss, but an essential component of the pre-transplant evaluation requires exploration of the medical and psychosocial consequences of alcohol use. This information is meant to allow the interviewer to gauge a patient's insight as well as motivations for a liver transplant and their willingness to seek treatment for their Alcohol Use Disorder.

Assess whether the Patient Possesses any Risk Factors Associated with an Increased Likelihood of Post-Transplant use of Alcohol, Drugs, or Tobacco

When one is assessing for a patient's insight and motivation to accept addiction treatment, there are very little data published on patients with AAH. In contrast, much has been

written about predictors of relapse in non-AAH liver transplant candidates with ARLD[10]. However, because it does not seem unreasonable to attribute what is known about the risks of post-transplant drinking from studies in Non-AAH transplant patients to AAH patients, some of that data will be described here. More broadly, these studies have demonstrated that poor insight and low motivation to engage in addiction treatment are risk factors associated with a greater likelihood of relapse to post-transplant drinking and harmful drinking compared to patients with high insight and strong motivation for alcohol treatment [10, 11].

Specific to patients with AAH, Lee et al. examined patient outcomes from the American Consortium of Early Liver Transplantation for Alcoholic Hepatitis (ACCELERATE-AH) study. In their 2019 paper, a tool developed by the investigators was intended to assist in prediction of sustained post-transplant alcohol use (distinguished from recovered sobriety or a "slip," as greater than 100 days). This new instrument, the Sustained Alcohol Use Post-LT (SALT) Score, ranges from 0 to 11 points and incorporates four pre-transplant variables considered to be relatively objective in nature and routinely obtained from a patient's substance use history. These included: greater than 10 drinks per day at initial hospitalization (4 points), multiple prior rehabilitation attempts (4 points), history of alcohol-related legal issues (2 points), and prior illicit substance abuse (1 point), with a total score of <5 having a 95% negative predictive value [12].

More recently, risk factors shown to be associated specifically with harmful post-transplant drinking were published in a retrospective study of non-AAH patients [13]. They included

1. Alcohol relapse after attempt at sobriety prior to transplant,
2. The inability to engage in recommended addiction treatment,
3. Continued drinking after the diagnosis of liver disease. In their paper, Deutsch-Link et al. also showed associations between the SALT Score and another previously validated tool, the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) [14]. The authors found that a SIPAT score ≥ 21 and a SALT score ≥ 7 were associated with alcohol relapse that resulted in harm to the liver graft.

In AAH patients with a relatively clear mental status, assessing motivation and insight can be challenging because of the subjective nature of these terms. When asked how patients with AAH in critical condition feel about getting treatment for their Alcohol Use Disorder, understandably, most of them say they will "do whatever you tell me." This tacit agreement may be interpreted as a lack of insight, but it is not known whether this kind of conciliatory promise is any more or less likely to result in an adverse outcome for the potential liver transplant recipient. Therefore, at the time of this writing, using the SALT and/or the SIPAT in addition to assess for the presence of the risk factors listed above appears to be the most objective approach to assessing insight and motivation in this population of patients. As for assessing for the risks of return to smoking or drug use in patients with AAH post-transplant, data to guide the mental health professional in this population are lacking.

It should be mentioned that patients who are unable to be interviewed directly eliminate the examiner's ability to hear in the patient's own words their degree of insight into the effect of addiction on their lives, or whether they agree to participate in addiction treatment. These are critical elements of the evaluation and results in the need to rely on collateral informants who know the patient well, such as family members, primary care, and mental health providers, and if available, their community gastroenterologist. Unfortunately, it is not known to what extent collateral informants provide transplant teams with an accurate version of the patient's own opinions.

Estimate the Likelihood of Adherence to Post-Transplant Medications, Follow-Up Visits, and Addiction Treatment

The importance of assessing a patient's insight and motivation to be adherent to post-transplant medications and follow-up visits cannot be overstated. Many transplant professionals believe that the strength of a patient's social support network is essential, particularly in the early phases of transplant surgery recovery when medication and follow-up requirements are at their most complicated and patients require significant physical and emotional support. Given the importance of maintaining patient engagement in post-transplant medical care and addiction treatment, any obstacles or notable barriers to care such as lack of local providers, resources, or transportation should be addressed prior to transplant, when feasible. Post-transplant, exploring issues with medication or treatment adherence, should be a multidisciplinary endeavor, incorporating transplant team physicians and nurse coordinators, social workers, mental health providers and addiction specialists, primary care physicians, and insurance providers, among others. Furthermore, clearly communicating expectations for post-transplant follow-up can provide the necessary structure to maintain regular contact with patients, such as meeting with a mental health specialist from the transplant team on a twice monthly basis for the first 3 months, then monthly for 3–6 months, then quarterly and so on. Finally, serial lab monitoring with biomarkers such as urinary ethyl glucuronide (EtG) or serum phosphatidylethanol (PEth) testing is recommended for corroboration of alcohol use history, both pre- and post-transplant. In the post-transplant period, these biomarkers

were emphasized by the 2019 Dallas Consensus Conference as an important means of monitoring for alcohol slips and/or relapse, with recommendations of routine monitoring for a minimum of 2 years, with further requirements tailored to the individual patient [9]. While a multitude of additional biomarkers for alcohol use is available or currently being studied, they should always be used in combination with regular follow-up visits and guide ongoing addiction treatment as necessary [15].

Barriers and Solutions Encountered in the Psychosocial Interview of Patients with AAH

Impediments to the psychiatric interview that may be encountered in AAH patients include symptoms of alcohol withdrawal, varying degrees of hepatic encephalopathy (HE), gastrointestinal bleeding, renal complications, sepsis, or the intubated and sedated patient [16]. Thus, before getting too far into the interview, it is useful for the examiner to conduct a brief mental status examination. Clinicians can rely upon administering the Mini Mental Status Evaluation (MMSE) or the Montreal Cognitive Assessment (MOCA) to a patient who can communicate in order to have a quantitative baseline of the patient's cognitive status [17, 18]. When it is not possible to interview the patient, the transplant psychiatrist and social worker will need to rely upon information obtained from interviewing multiple collateral informants, as described above. However, obtaining the aforementioned information from collateral informants can also be challenging. One commonly encountered obstacle is that people in the patient's support network may not feel comfortable sharing the whole truth with the examiner because they worry that information will interfere with the patient's chances of being accepted as a transplant candidate. It is often helpful to emphasize to patient's family that the primary use of the information remains planning the best comprehensive care possible, pre and post transplantation. In addition, members of the support network can be reminded that the decision to place a patient on the transplant waiting list relies on multiple sources of information such as the severity of the patient's medical illness, the ability to tolerate the surgery, and potential limits set by the patient's insurance coverage. Accordingly, the psychiatric interview is just one aspect of the various components that contributes into the decision-making process.

Post-Transplant Treatment of Alcohol Use Disorders

Little has been written about the optimal way to treat Alcohol Use Disorders in this specialized population of patients with AAH. While there are a number of useful studies evaluating the treatment of AUDs in non-AAH liver transplant patients, there remains a paucity of randomized, controlled studies to guide the field. A thorough review of behavioral interventions for the treatment of AUDs in patients with alcohol-associated liver disease is beyond the scope of this chapter, but interested readers are encouraged to explore the 2016 paper by Khan and colleagues [19], and more recent publications by Weinrieb et al. [20] and Luchsinger et al. [10].

Nonetheless, the choices of treatment for AUD in patients with AAH in the community are limited. Traditional treatments for AUD (12-step programs or formal substance abuse programs, either inpatient, residential or outpatient) typically focus on patients actively drinking or very early in recovery. Many AAH patients, by the time, have received a liver transplant and are stable enough to attend such a program, and they no longer qualify as they have already been abstinent for a significant amount of time. In addition, patient's physical conditions or the logistic of post -transplantation medical care with multiple clinic visits and tests are additional barrier to AAH transplant recipients attending traditional addiction treatment programs. There is limited information about the role of medications in preventing relapse in this group, with a high refusal, as patients are adjusting to the lifelong need for medical follow-up after transplantation ("I am already taking so many pills"). Many transplant recipients do not feel they need alcoholism treatment [21]. While there are some addiction treatment facilities that offer ongoing weekly groups for patients who are sober, very few of them are available. Finally, patients can attend Alcoholics Anonymous meetings in the community free of charge as often as they like. However, it should be noted that AA is not professional addiction treatment, which in contrast is delivered by a Certified Addiction Counselor, with increasing numbers who hold a Masters or PhD degree, and information related to relapse or increased risk of relapse discussed during AA meetings is rarely available to the medical providers and, therefore, cannot be used in guiding the treatment.

While patients with AAH face many obstacles in receiving treatment for AUD, particularly if critically ill, the following paragraphs briefly describe some of the innovative research that seems promising in patients with AAH. Of note, all studies mentioned below include patients with ARLD, not AAH. These studies were designed to address some of the difficulties described above that patients can encounter when seeking to obtain treatment for their AUD in the community.

Text-Messaging Pilot Study

In their pilot study, DeMartini et al. published the first RCT-evaluating text messaging as a relapse prevention intervention in patients with ARLD [22]. The authors assessed the feasibility and efficacy of text messaging in 15 pre-transplant patients who drank at least once in the past year. The investigators and research assistants were blinded to the randomiza-

tion which was used to assign one group to standard care only ($n = 7$), compared to another group receiving both standard care and text messaging ($n = 8$). The majority of the text message group reported high satisfaction, responded to 81% of the messages, and had zero positive alcohol tests vs. the non-text message cohort, in which two patients drank.

Randomized Controlled Trial (RCT) of Telepsychiatry in the Post-Transplant Phase

This pilot study is currently in progress at the time of this writing [23] and is timely given the burgeoning use of telepsychiatry due to the SARS COVID-19 pandemic. This study seeks to evaluate the effectiveness of Symptom-Targeted Intervention (STI), which is a combination of Motivational Enhancement Theory (MET), Cognitive Behavioral Therapy (CBT) and Mindfulness Meditation, all administered via telemedicine, compared to a Treatment as Usual group receiving routine social work monitoring and care coordination, also via telemedicine. Measures of anxiety, depression, stress, and alcohol use will be assessed in 50 post-liver transplant patients with AUDs. STI is delivered to patients recruited within 2 months of liver transplantation over 6 weeks by trained social workers.

Multidisciplinary, Co-Located Alcohol Treatment Programs

A recent publication by Winder et al. [24] described their experience in developing the first multidisciplinary, alcoholism treatment program in the United States, co-located in a liver transplant clinic. The impetus for this unique conformation stemmed from the disparate nature of how and where addiction treatment is provided, i.e., not in hospitals, relative to hepatology, surgery, and other subspecialties that practice in a tertiary care hospital setting. The authors point out that care coordination is difficult to achieve and community providers, whether they are psychiatrists, social workers, psychologists, or certified addiction counselors, have little or no experience with the complexities inherent to transplant patients' medical disorders. Winder et al. explained how they were able to obtain support from every stakeholder who provides care to liver transplant patients at their institution and created a system combining that care in the liver transplant clinic. This is similar to the embedded Alcohol Addiction Unit developed by Addolorato et al. [25] that demonstrated such significant gains for their patients, and is also representative of "alcohol care teams" and integrated treatment pathways in the United Kingdom. Winder, et al. described their experiences with the first 51 patients they treated in their first year of operation. They provide demographics, costs, clinic visit details, workflow diagrams, and psychological instruments used for longitudinal measurements of their patient's outcomes. Research design and communication strategies for continuity of care are also described. It will be exciting to see the results of their efforts from the longitudinal measures of the patient outcomes they are tracking.

The primary purpose of this chapter is to provide health care professionals with a working knowledge of the psychiatric interview as it pertains to patients with short sobriety being evaluated for early liver transplantation due to alcohol-related liver disease. A historical view of how and why patients with AAH could benefit from early liver transplantation was included as was a case example of a young woman with severe Alcohol Use Disorder and short sobriety. The following chart shows characteristics of the patient in the case example associated with higher vs. lower risk of post-transplant relapse.

Higher risk	Lower risk
Short sobriety (weeks)	First presentation with decompensated AAH
Presence of family history of AUDs	Availability of a functional social support network
Presenting at a relatively younger age	Absence of comorbid substance use disorders
Female gender	Self-referred to a faith-based recovery group
Failed alcohol rehabilitation program	Absence of legal problems
Consumed > 10 drinks/day	

The patient in the case example's SALT score was 4, which is indicative of a potentially lower risk for post-liver transplant alcohol use. After a comprehensive, multidisciplinary assessment, the transplant team ultimately reached a consensus to place the patient on the liver transplant waiting list, citing not only the objective criteria above, but many members of the team expressed a desire to give a mother with multiple young children another chance at life.

Transplant providers and the people who make up the patients' support network need to understand that Alcohol Use Disorders (AUDs) are chronic, relapsing conditions that are genetically and environmentally influenced, and though there are no cures for AUDs, effective treatments do exist. If this sounds familiar to the reader, it may be because the same can be said for other chronic medical conditions such as diabetes, hypertension, and asthma [26].

Physicians do not treat asthma, diabetes, or hypertension one time and expect their patients to be well managed. Similarly, a person with an alcohol use disorder should also receive a longitudinal plan of care to address the natural history of the disorder as well as any underlying issues such as psychiatric disorders, trauma, or learning disabilities, thus, acknowledging the fact that some of our patients are chronically at risk of relapse. Hence, it is advisable for transplant teams to plan for some degree of adverse outcomes in the AAH population, such as post-transplant drinking, and accept that effective management of these adverse outcomes takes time, social support, and money. Bangaru et al. found that although most transplant cen-

ters offered social work follow-up, less than half offered support group therapy or even encouraged patients to attend external support groups [27]. Alcoholics Anonymous (AA), the best known support group for people seeking help for their AUD, will provide AAH patients with the opportunity to be connected to a highly effective support system, but AA is not meant to provide professional treatment and may not meet the complex needs of many patients with AAH.

Transplant patients are unique in the world of surgery as conveyed by the viewpoint "once you are our patient, you are always our patient." This practice is advantageous for a longitudinal plan of care, and transplant teams would do well to provide ongoing surveillance and targeted interventions to their patients with AUDs, just as they do for the ongoing care of their patient's new livers and other medical co-morbidities. After all, if transplant teams accept a patient for transplant, it seems logical that they be ethically bound to accept the responsibility of adequately treating the disorder that caused their patient's liver to fail.

Take Home Points

1. The role of the psychiatrist or mental health professionals in evaluating patients for liver transplant with short sobriety and AAH is above all, to be transparent with the patient and family about their role on the team and to inform them that what transpires in the interview is shared with the transplant team.
2. Recognize that despite the existence of predictors for return to drinking after transplant, in reality, relapse cannot be predicted, but risk factors for relapse may be identified. Once the risk factors have been identified in a given AAH patient, members of the transplant team should work together toward a plan to mitigate the identified risk factors in concert with the patient and their support system.
3. Liver transplant patients with AUDs are probably best served if they can be treated by a multidisciplinary team of transplant professionals that work side by side in the same location, usually in a hospital-based liver transplant clinic.

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Opioid Use Disorders in Organ Transplantation

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Introduction

Opioid Use Disorder (OUD) is a serious condition affecting more than 16 million people worldwide and over 2 million people in the United States [1]. Diagnosis of the specific use disorder can be challenging as opioid-based pain medications continue to remain a mainstay of treatment for both acute and chronic pain complaints, despite conflicting evidence regarding their benefit. Vowles, in a 2015 study estimated that 21–29% of patients prescribed opioids for chronic pain misuse them; of those with misuse, 8–12% will develop an OUD, and 4–6% will eventually transition to the use of heroin [2]. Like other substance use disorders, Opioid Use Disorder is characterized by a combination of symptoms related to tolerance, psychosocial impairment, misuse, and withdrawal; with increasing symptoms leading to a higher severity of the disorder rated from mild to severe [3].

Patients abusing and misusing substances of abuse may develop end-organ damage from the direct toxicity of the substance, contaminants in substances they are using, comorbid infectious complications relating to route of use as well as life-style issues placing them at high risk for trauma and infectious diseases. In patients where opioid use involves the use of intravenous drug, there is a significant risk of both bacterial and viral infections, including HIV, viral hepatitis, and systemic introduction of staphylococcal and streptococcal skin flora [4, 5]. These infections can result in end-organ damage that may require eventual transplantation. In patients with other causes of end-stage organ disease, concomitant OUD presents a particular challenge in being listed for transplant, even if these individuals are able to maintain sobriety or are receiving medication-assisted treatment (MAT), which will be described later in this chapter. Post-transplant opioid misuse may result in increased morbidity and mortality depending upon the substance used and route of administration. Opioid misuse may result in direct organ damage, infections, overdose, and non-adherence to medications and medical care.

Despite the growing number of people affected by OUD and its sequelae, this population remains underrepresented in transplant. A 2017 survey of 61 liver transplant centers, collectively responsible for almost half of all liver transplantations in the United States, found that two centers listed current opioid use or opioid substitution therapy an absolute contraindication to transplantation. Thirty-nine centers (64% of centers surveyed) listed chronic opioid use and 23 centers (38%) listed opioid substitution therapy as relative contraindications to transplantation [6]. Individuals requiring transplantation may find policies restricting access to listing despite relative sobriety or stability on opioid substitution therapy based on their unique psychosocial situation, making nuanced psychological and psychiatric evaluation a necessary component in the process.

Other frequently unforeseen challenges in these cases include ethical questions regarding the requirement to either decrease or discontinue chronic opioid or opioid-substitution medications, issues related to not listing individuals who have demonstrated ongoing sobriety and stability, and adequate treatment of post-transplantation pain in patients that may have cross-tolerance and hyperalgesia from long-term exposure to opioids. Requests from post-operative patients for improved pain control may be misconstrued as medication seeking behavior despite an increased tolerance, especially in those patients on partial-agonist opioids who may require a full-agonist medication for adequate relief. In addition, a comprehensive psychosocial assessment may help to identify and mitigate risk factors for relapse or misuse of opioids in the long term post-operatively.

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Background

Medication-assisted treatment (MAT) combined with psychosocial interventions are the mainstay of management for patients with OUD. There are currently three FDA-approved medications for the treatment of OUD: naltrexone, methadone, and buprenorphine. Selection of appropriate treatment should be evidence-based and should factor in patient preference, characteristics of the disorder, and risk factors. Opioid substitution therapy is well supported by the literature as both safe and effective by blocking euphoria caused by illicit opioid use, reducing cravings, preventing withdrawal, and reducing risky health behaviors and criminal activity associated with opioid abuse [7, 8].

Naltrexone is a non-opioid mu-receptor antagonist with no analgesic properties. It is available in oral and monthly intramuscular depot formulations. It does not have any clinically relevant interactions with immunosuppressants but does render most opioids ineffective at their usual doses. A single oral dose of naltrexone can block the effects of opioids for 24 h. Meta-analysis of oral naltrexone did not find it to be superior to placebo for OUD maintenance due to poor adherence [9]. Retention in treatment with naltrexone intramuscular injections is about 57% and seems to diminish over a 6-month period [10, 11]. Long-acting formulations, while helpful for adherence, can be problematic when a patient will be unpredictably called in for transplant. Without sufficient time for planned washout, overcoming opioid receptor blockade may be difficult, even in a hospital setting. If a patient relapses and attempts to overcome the blockade by injecting increasing amounts of opioids, they are at risk of death by inadvertent overdose. Unless a patient has a high burden of risk factors or expresses a strong preference to avoid opioid-agonist therapy, the evidence to support the efficacy of naltrexone for OUD is currently limited. Currently, there do not appear to be any published studies regarding the use of naltrexone for OUDs in the transplant population. Many practitioners are reluctant to prescribe naltrexone for treatment of OUDs because of the reported risk of hepatotoxicity. However, hepatologists often prescribe naltrexone for the treatment of pruritus associated with hyperbilirubinemia.

Methadone is a synthetic mu-opioid agonist that also has weak NMDA antagonism. It is available in oral formulation and is usually administered once daily at a treatment program. Peak effect occurs within 2–4 h. Methadone has a long and variable half-life, which ranges from 24–55 h, therefore reaching steady state takes approximately 3–5 days. Retention in treatment with doses greater than greater than 60 mg daily is approximately 67% at 6 months [12] but has been reported to be as high as 80% [13]. At doses of 80 mg or greater, retention is about 72% at 2 years [14]. Methadone is metabolized primarily through CYP3A4, 2B6, 2C19 and, to a lesser degree, 2D6 and 2C9. It can interact with many medications, including immunosuppressants. Cyclosporine, an inhibitor of CYP3A4, can increase methadone levels, resulting in oversedation, respiratory depression, and QTc prolongation. Glucocorticoids are CYP3A4 inducers and can precipitate opioid withdrawal symptoms by decreasing methadone levels. QTc prolongation is another clinically relevant side effect of methadone. QTc prolongation is dose dependent and can increase risk for arrhythmias due to torsade de pointes. Other QTc prolonging drugs, such as tacrolimus, can result in synergistic QTc prolongation when added to a regimen containing methadone [15]. Patients with end-organ disease on methadone should be monitored closely for oversedation, respiratory depression, and mental status changes; methadone doses should be adjusted appropriately in these patients. Following transplantation, methadone should be restarted carefully and slowly titrated as tolerated keeping in mind the potential for oversedation and respiratory depression during titration. The QTc interval should be monitored during methadone titration with serial EKGs, particularly in patients receiving other QTc prolonging medications.

Buprenorphine is a partial mu-opioid agonist and mixed agonist-antagonist with high binding affinity for the receptor. It is often provided as a sublingual combination of buprenorphine/naloxone in an office-based setting. Peak effect takes about 1–2 h and half-life ranges from 24–42 h. Sublingual bioavailability of buprenorphine exceeds that of naloxone. However, if the medication is crushed and insufflated or dissolved and injected, withdrawal may occur since bioavailability of naloxone is higher by these routes. This deters misuse and diversion. At doses of buprenorphine of 16 mg or greater, retention in treatment and suppression of illicit opioid use is comparable to high-dose methadone [16]. Buprenorphine is metabolized by CYP3A4. There are fewer drug—drug interactions with buprenorphine in comparison to methadone. There is a ceiling effect for respiratory depression, but combination with strong CYP3A4 inhibitors can increase the risk of respiratory depression, as can combination with benzodiazepines. Buprenorphine poses minimal risk of QTc prolongation. There are case reports of hepatotoxicity in patients with Hepatitis C on buprenorphine [17] but these cases did not progress to liver failure. There are also case reports of buprenorphine maintenance therapy in both liver and cardiac transplant patients without any adverse effects [18, 19]. For patients who have stabilized on sublingual buprenorphine, monthly buprenorphine long-acting injectable was approved by the FDA in 2017.

There is a paucity of literature specifically examining opioid substitution therapy in transplant populations. This patient group is underrepresented despite the growing numbers of individuals affected by OUDs. The existing evidence for opioid substitution therapy in transplant comes primarily

from liver transplant populations. Evidence indicates that methadone maintenance does not affect graft survival [20–25]. In these studies, patient survival of patients on opioid substitution therapy was similar to the general liver transplant population and relapse rates to opioid use was low [20, 23].

The evidence is mixed about general opioid use in transplant populations, with some literature suggesting increased risk of graft failure in renal and liver transplant [26–29], but no association with graft failure in lung transplant [30]. In several studies, patients with high levels of opioid use had increased clinical complications and increased all-cause mortality post-transplant [26–29]. These studies addressed prescription opioid use for pain management and did not include data regarding patients with OUDs treated with methadone or buprenorphine.

A significant proportion of transplant programs deem OUD a relative contraindication to transplant [6]. More than 30% of programs that accept patients with an OUD require patients to decrease or stop opioid substitution therapy before being listed [6, 31]. The evidence indicates that patients on methadone doses of 80–100 mg remain in treatment and use illicit substances less often compared to those on moderate and low doses [32]. Relapse occurs more commonly when treatment is tapered and discontinued, so a clear rationale for doing so is necessary. Following transplant, maintenance doses should be reassessed to ensure that opioid cravings are being adequately controlled.

Evaluating the risk of relapse in patients with OUD is an important component of the transplant assessment. Risk factors for relapse include family history of substance abuse, undesirable life events, and non-adherence to opioid replacement therapy [33] as well as co-occurring alcohol use disorder, other substance use, and severe mental illness [34]. Injection opioid use is predictive of shorter time to relapse, as is benzodiazepine use and older age at onset of first use [35]. Older age, social support, stable relationships, and employment are predictive of retention in treatment [7, 34, 35].

Pain management for patients on opioid agonist therapy requires special attention. Intraoperative anesthesia and postoperative pain control needs are significantly higher in patients on methadone maintenance than control groups during and after liver transplant [23]. This is due to cross-tolerance. For patients on maintenance with either methadone or buprenorphine, another opioid can be added for acute pain control. Buprenorphine is a high-affinity partial agonist at the mu opioid receptor, so an opioid with a greater affinity, such as hydromorphone should be chosen for acute pain control. Alternatively, the usual maintenance dose of methadone or buprenorphine can be divided and scheduled at regular intervals to align with analgesic duration of each respective medication. Weinrieb noted that some post-transplant patients on methadone maintenance required up to a 60% increase in methadone dose although all patients in the study were on doses of methadone under 100 mg per day and some patients continued stable doses. Patients may require increased methadone dosing post-transplant to address issues with pain, drug–drug interactions, and with normalized metabolism of methadone [23]. Though the analgesic effects are relatively short-lived, other adverse effects of these opioids are not; caution must be exercised.

Case History

The patient is a 25-year-old woman with a psychiatric history of depression, alcohol use disorder in early remission, severe OUD in sustained remission, on maintenance therapy, and a medical history of end-stage liver disease secondary to autoimmune hepatitis, untreated hepatitis C, and alcohol use of unspecified severity, presenting for an evaluation for liver transplantation. Her liver disease was diagnosed by routine laboratory studies obtained at the age of 18 after she consulted her family physician for assistance with birth control. She was advised at that time to avoid drugs, alcohol, and potentially hepatotoxic medications. Despite counseling, the patient did not complete a thorough evaluation of her liver dysfunction, did not initiate treatment, and eventually was lost to follow-up. Six years later, she experienced sudden weight gain and peripheral edema, prompting her to again seek medical care. End-stage liver disease was diagnosed at that time and her Model of End-Stage Liver Disease (MELD) score was calculated at 18.

Her substance use started at age 11, shortly after her parents divorced. She began "running around with the wrong kids," started using alcohol and then marijuana by age 12. By the age of 15, she was consuming marijuana daily, reporting weekend "binges" of alcohol, and at the age of 16 she was consuming up to "a fifth" of hard liquor each weekend. During these years, she admits to experimentation with "everything else," including intravenous heroin, cocaine, and inhaled methamphetamines on a few occasions. The nature of her pattern of substance abuse changed for the worse after she began to misuse prescription opioid pain medications following an ankle fracture at the age of 17. By the age of 18 her use had progressed to both inhaled and intravenous heroin, as she could no longer afford to buy prescription opioids on the street. At 23, she met her current boyfriend, residing with him and his family on the condition of her seeking treatment for her substance use. Initial treatment plan included methadone and was dosed up to 90 mg daily prior to an eventual switch to buprenorphine 6 months prior to the evaluation for listing for transplantation. Her current dose of buprenorphine is 16 mg daily. She has since abstained from all street drugs, aside from a single relapse on heroin 1 year ago, lasting 2 weeks. She continues to smoke "medical" marijuana 1–2 times per month for "liver pain" and states she has used no alcohol for the last 6 months. She does not use tobacco.

The patient has a history of depression and has been receiving psychotherapy for the past year with moderate success. She is not prescribed psychotropic medications. She has no history of psychiatric admissions, suicide attempts, or self-harm behaviors. Family history is significant in that her biological father uses recreational marijuana daily and that her mother drinks alcohol socially. Both her brother and her sister are actively using illicit substances and alcohol daily. She sees her parents about once per month and reports that their relationship is "strained," but that they are interested in helping her at this time. She personally identifies that her main support remains her boyfriend and his family as they have "taken her in" and are supportive of her recovery. They describe themselves as "religious people" who do not drink, use drugs or tobacco, and do not allow such substances in their home. She is a high school graduate and has completed 2 years of college. She worked as a waitress until 3 months ago when fatigue and edema began limiting her activity. She would like to complete a business degree and go into accounting. Despite her previous lapse in medical care, review of records indicated that the patient has been routinely adherent to treatment recommendations for her current liver disease for the past 4 months.

Clinical Questions

1. Should this patient be accepted for transplant at this time?
2. What is this patient's risk of relapse in the future to alcohol, opioids, or other substances of abuse? Should she be required to stop the use of marijuana?
3. Should opioid maintenance treatment be continued? If so, are any modifications recommended? Are there additional recommendations for addiction treatment?
4. How should this patient's pain be managed pre-, peri-, and post-operatively?

Discussion

The patient in this case raises several questions. The patient's younger age, lack of comorbid medical illnesses, and potential for better medical outcome must be balanced with the obvious risk factors for substance abuse relapse and non-adherence to medical care. Both relapse and non-adherence to medical care contribute to poorer transplant outcomes. Addiction is known to be a chronic illness with a complex etiology that disrupts the functioning of the brain and the ability of the individual to modulate and control cognitive, emotional, and social behavior. Remissions and relapses are part of this chronic illness. Relapse is a major concern in organ transplant candidates as the recurrent use of substances may result in direct or indirect damage to the transplanted organ. In addition, graft rejection, medical complications resulting from substance use, poor adherence, and difficulty with patient management may result from relapse after transplant. There are many studies that address relapse risk, mostly in the population of patients using alcohol. Traditionally, factors that appear to predict higher relapse risk include use of alcohol plus other substances, shorter periods of sobriety prior to transplant, multiple episodes of failed addiction treatment, a strong family history of addiction, comorbid psychiatric illness, and lack of stable social support, among others. In addition, substance use in the face of severe medical complications is a concern among transplant professionals [36–50].

This patient's relapse risk factors include her history of both alcohol and polysubstance use, a strong family history of substance use disorder and comorbid psychiatric illness [36–51]. She has relapsed once while on opioid substitution therapy and did continue to use alcohol until 6 months ago. She has known about her liver disease for the past 7 years but did not heed advice to avoid alcohol and drugs. This ignoring of advice may partially be attributed to her young age at that time. She did continue alcohol use for several months after the diagnosis of end-stage liver disease. Her ongoing marijuana use must be further evaluated but given her report of infrequent use it may not be a significant risk factor at this time. These risk factors are mitigated by her recent success with sobriety, involvement in addiction treatment, adherence with opioid substitution therapy, success with MAT, and the presence of a strong clean and sober support system. Her recent adherence to medical treatment recommendations also mitigates her future risk. The strength of the relationship with the boyfriend and his family as well as the degree to which her recent sobriety and adherence to treatment is dependent upon these relationships must be further explored. Further information from her addiction and mental health treatment providers should be obtained. It would be important to ascertain this patient's insight into her addiction, her motivation for future sobriety, her treatment adherence, and her work in the area of relapse prevention. In addition, her primary support person(s) should be interviewed in depth regarding their commitment to assisting the patient. Most programs would recommend continuation of MAT, continuation of both mental health and addiction treatment, ongoing random urine drug screening, and ongoing evaluation of adherence to medical treatment for this patient. Ongoing success with medical, addiction, and psychiatric treatment along with proven social stability may predict a successful outcome but episodes of poor adherence, relapse, instability in social relationships and worsening of psychiatric illness would be relative contraindications to proceeding with transplant in this patient [36, 39, 42, 43, 48, 49, 51, 52].

Transplantation of patients with OUDs, particularly, those on medication-assisted therapies such as methadone and buprenorphine remain controversial. Some programs do not accept patients on opioid maintenance treatment and require

tapering and discontinuation of these medications, despite recommendations to the contrary [6, 31, 52, 53]. Limited studies indicate good outcomes of patients on opioid substitution therapies, particularly, those patients with long periods of abstinence from non-prescribed opioids, alcohol and other substances, good social support, adherence with medical care and factors indicating psychosocial stability [20–24]. Those studies mainly address methadone maintenance but several published cases addressing buprenorphine maintenance also report good outcomes. Currently, most addiction specialists working with transplant programs recommend continuation of opioid substitution therapies in transplant patients [18, 19]. Dose changes may be medically necessary because of sedation, QTc prolongation, or other dose-dependent adverse effects.

Evaluation of patients, particularly, those with comorbid psychiatric and substance use disorders focuses on risk of relapse to use of non-prescribed substances. Patients with OUDs together with alcohol and/or other substance use disorders are at higher risk for relapse to substance use post-transplant. Patients with long periods of sobriety from non-prescribed opioids and other substances are likely an exception. In addition, patients with comorbid psychiatric disorders are also at higher risk for relapse and poorer outcomes. Relapse and poor outcome may be mitigated by ongoing addiction treatment. In addition to continuing medication-assisted therapies, addiction specialists recommend continuation of psychosocial therapies, establishment of clean and sober social support systems, and creation of relapse prevention plans [36, 46, 48, 49, 52].

Several additional challenges exist with patients on methadone maintenance treatment. Drug—drug interactions with methadone are common and the practitioner must keep these in mind. These drug interactions may be either pharmacokinetic (altering metabolism of methadone) or pharmacodynamic (additive side effects) [54]. In addition, methadone does cause QTc prolongation and combination of methadone with other medications known to cause QTc prolongation can be challenging [55]. Opioid receptors are found extensively in the lungs and tolerance to effects of opioids in patients with lung disease is predicted. There is little experience with the use of opioid substitution therapies in lung transplantation, but careful management of pain, post-operative confusion, and respiratory depression is advised [56, 57].

Pain management of patients with OUDs is challenging. These patients may have higher tolerance to opioid pain medications and require higher than usual doses for post-operative pain. Patients on MAT represent a particularly challenging population. The pharmacology of methadone and buprenorphine must be considered carefully when planning surgical pain management in these patients. Patients on methadone can be managed with the addition of short-acting opioids or use of methadone in divided and/or higher doses to treat pain. Careful monitoring is certainly necessary to avoid unintentional excessive sedation and respiratory depression. The pharmacology of buprenorphine does pose unique challenges. Buprenorphine binds more tightly to opioid receptors than other opioids, addition of short-acting opioids may be ineffective in treating pain. Use of buprenorphine itself for intraoperative and post-operative pain management is limited by the "ceiling effect" at higher doses and may be ineffective for pain management. The literature does recommend several different approaches depending upon the situation. Buprenorphine can be tapered in anticipation of surgery which may be a feasible approach in the case of living donation. Short-acting opioids can then be used peri-operatively and post-operatively and the patient transitioned back to buprenorphine after pain management is no longer an issue. In cases where surgery cannot be planned, several approaches are possible. Buprenorphine can be abruptly discontinued, and short-acting opioids can be used for pain. This may or may not be successful for several reasons. The short-acting opioids may be ineffective because they do not displace buprenorphine from the receptors. Similar to methadone, care must be taken to avoid excessive sedation and respiratory depression. Buprenorphine patients may also consider a temporary transition to methadone maintenance therapy closer to the anticipated time of transplant which may simplify the pain management issues. A full discussion of this subject is beyond the scope of this chapter [58, 59].

This patient's current MELD score and the anticipated time to potential surgery are important considerations. If transplant is not expected for months to years, then current MAT management should continue. Once transplant appears to be more imminent, consideration can be given to either continuing buprenorphine and abrupt discontinuation of buprenorphine at the time of surgery or a change back to methadone which may be easier to use for both treatment of the OUD and pain management. Currently, there is no consensus on the approach.

Conclusion

In summary, OUDs are common, and it is expected that patients with these disorders will increasingly present for organ transplantation. Patients with opioid use disorders and those on medication-assisted treatments should be considered similarly to other patients. Medication-assisted treatments should not be discontinued but doses may need adjustment depending upon the patient's medical status and need for other medications. Risk for relapse in this patient population needs to be carefully evaluated as patients with comorbid other substance use disorders, alcohol use disorders, psychiatric illness, history of failed addiction treatment, a strong

family history of addiction, a history of poor medical adherence, and lack of stable social support may be at higher risk for relapse. Pain control is complex but can be managed with thoughtful planning and careful monitoring. Patients should be tapered off short-acting opioid pain medications after surgery and transitioned back to MAT as soon as practical. If a longer period of pain management is needed, it is recommended that consultation be obtained from both pain and addiction specialists. In these situations, MAT should be continued, and doses adjusted as appropriate. Drug—drug interactions may occur, especially with methadone; careful monitoring and consultation with experts in transplant drug—drug interactions may be helpful.

Take Home Points

1. Complete a thorough evaluation of the patient pre-transplant assessing stability of remission of their OUD, adequacy of their current treatment and supports, and potential risks factors for relapse.
2. Recommend treatment, including medication-assisted treatment as indicated.
3. Continue medication-assisted treatment, adjust doses as needed pre- and post-transplant.
4. Be aware of drug–drug interactions, particularly with methadone.
5. Careful planning for post-operative pain management in consultation with the patient's outpatient MAT program and pain experts if needed.
6. With expert management patients with OUD can have successful outcomes post-transplant.

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The Transplant Patient with Cocaine Use Disorder and Attention Deficit/ Hyperactivity Disorder

20

Sarah Ramsay Andrews

Introduction

Psychiatry is often asked to provide clinical assessments regarding candidacy of patients undergoing organ transplantation. Psychiatric disorders such as substance use disorders or severe mental illness can interfere with transplantation. Treating psychiatric comorbidities in transplant candidates can assist in improving a patient's candidacy.

According to SAMSA, 2% of the US adult population has used cocaine in 2019 [1]. More than 900,000 American met criteria for Cocaine use disorder in 2014 based on data published by National Institute of Drug Abuse. https://www.drugabuse.gov/publications/research-reports/cocaine/what-scope-cocaine-use-in-united-states (accessed February 25th, 2021).

There are significant medical consequences of cocaine use, including heart disease, hypertension, increased pulmonary hypertension [2], increased risk of thrombosis [3], increased risk of traumatic death and death by infectious diseases [4], increased rate of cardiovascular and respiratory disease [5], ketoacidosis in patients with diabetes [6], increased risk of sudden cardiovascular death [7], and stroke [8]. In a study examining the factors associated with recipient survival in lung transplant, donors with a history of cocaine use demonstrated decreased lung functioning [3]. Growing research has also demonstrated that cocaine use is associated with pulmonary hypertension [4]. In addition to medical risks, cocaine use is associated with significant psychiatric risks, including development of mood disorders [9], other addictive disorders, increased risk of suicide [10], post-traumatic stress disorder [11], and psychosis [12].

A significant number of cocaine users develop chronic, recurrent cocaine use disorder [13]. The rate of relapse of cocaine use can be as high as 86.4% [14]. Increased risk of relapse of cocaine use has been associated with impulsivity [15], unemployment [16], being married, African-American or having antisocial personality disorder [17], a history of childhood trauma [18], and cravings [19]. There is no FDA-approved pharmacological treatment for cocaine use disorder. Over 60 agents have been studied including include long-acting amphetamine formulations, antidepressants, modafinil, topiramate, doxazosin, and combined topiramate and mixed amphetamine salts extended release [20, 21]. More recently, transcranial brain stimulation [22] and cannabinoids [23] have been studied. Psychosocial interventions such as contingency management, cognitive behavioral interventions, and 12-step programs remain the main tool in treating cocaine use disorders [24].

There is no systematic literature on the impact of cocaine use upon transplantation outcomes nor on the predictive factors for relapse of cocaine use after transplantation. Due to the extensive, direct, and severe health risks of cocaine use, active users tend to be excluded from transplantation listing until they become abstinent [25]. There is no literature to guide about the optimal length of abstinence from cocaine or other protective factors that would predict a good outcome in the transplantation setting. Given cocaine's short half-life of a few hours, monitoring abstinence relies both on the patient's report and frequent blood or urine screens, which is often difficult to coordinate and obtain in transplant centers.

Case History

A 38-year-old man with stage-IV kidney failure secondary to polycystic kidney disease presented to the kidney transplant evaluation clinic for a preemptive kidney transplant with a potential living donor. Based on the social worker's evaluation, which revealed prior substance use as well as prescribed stimulants for attention-deficit hyperactivity disorder (ADHD), the patient was referred for further evaluation with the transplant psychiatrist. The transplant psychiatrist completed a full psychiatric interview and reviewed patient's prior psychiatric records. Direct conversations were also held between the transplant team and the patient's current

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substance abuse program and community or treating psychiatrist for further collateral.

The patient had no known complications at birth or during his development. Despite receiving a graduate degree, he described his school performance as average with ongoing difficulty in concentration and attention. He has a history of a prior assault charge in his early 20s for assault at a bar while intoxicated. Family history was significant only for mother with depression.

Regarding his substance use history, he first started smoking cigarettes in late middle school and had been smoking up to two packs daily for approximately 10 years. With the assistance of nicotine patches and lozenges, he was able to decrease his smoking significantly to one pack per week for 3 years and ceased smoking 1 year ago without any further nicotine replacement. He tried marijuana several times in high school but found that it led to increased anxiety and paranoia. He drank heavily during college with frequent binge episodes over the weekends, ranging from ten to 20 standard drinks on each weekend day.

Following college, patient's focus switched from alcohol to other illicit drugs. He had started using intranasal cocaine intermittently during high school over the weekends, but then increased his use in post-graduate school to several times per week. While in college, he would also buy prescriptions stimulants from friends, using them at appropriate doses to help him study and focus. After graduate school, the patient switched from using intranasal cocaine to inhaled cocaine due to cost and began using it daily, despite still being able to maintain employment. In his early 20s, patient had 1 year of opioid misuse for which resolved with 2-months course of buprenorphine followed by taper done in the outpatient setting. His drug of choice remained cocaine. Although the patient met criteria for several different substance use disorders during his lifetime, his most severe disorder was cocaine use.

When the patient reached his late 20s, he found it more and more difficult to function at work due to his ongoing cocaine use. His relationships with his parents and siblings also began to become strained. Patient's parents, who were partially financially supporting the patient at this point, encouraged him to seek residential treatment for 3 months in an out-of-state facility, to which the patient agreed a and eventually completed. He was in transitional housing for 1 month until he relapsed. He returned home to live with his parents since he had no source of income. Over the next few months, the patient was in and out of outpatient substance abuse programs without any significant periods of abstinence and did not want to return to residential treatment.

In his early 30s, the patient's drug use continued to escalate and led to a substance-induced psychosis which required inpatient psychiatric admission. His psychosis improved shortly after admission, and the remained of his psychiatric admission was focused on substance abuse education and preparing the patient for appropriate aftercare.

Upon discharge from the inpatient psychiatric unit, the patient, now 34 years old, was referred to both a psychiatrist for medication management, as well as an outpatient substance abuse treatment with the plan to return to his parents' home. The day following discharge from the inpatient unit, the patient presented for intake at the intensive outpatient substance abuse program. The comprehensive structure of the program provided a strong foundation for patient to begin building his recovery network. Patient's illicit substance use significantly decreased as he continued at the intensive outpatient program. After 6 months of sobriety, the patient relapsed with a 3-day binge on cocaine. Patient continued to engage in group therapy and weekly therapy with his addictions counselor at the program. Patient began to attend extra non-required group therapy sessions on his own for additional support, as well as narcotics anonymous meetings in the evening.

During the first year after hospital discharge, the patient began working a few hours per week providing consultation services within his field. He continued living with his parents and had maintained his prior romantic relationship with a woman, who, of note, had no prior substance abuse history. His parents, two siblings, and girlfriend continued to be a strong support network for the patient.

In addition to his substance abuse treatment, the patient had also begun care with a local psychiatrist and therapist. The patient, who had been started on a neuroleptic during his inpatient psychiatric admission for psychosis and aggression, exhibited no further signs of psychosis, while continuing his sobriety from all substances. As such, his neuroleptic was tapered off without ill effect and he was started on a selective serotonin reuptake inhibitor for generalized anxiety disorder. Given patient's prior report of difficulty with concentration and attention during childhood, which had continued into adulthood, the patient's psychiatrist had performed a comprehensive evaluation for attention-deficit hyperactivity disorder (ADHD). His cognitive deficits were not believed to be secondary to chronic kidney disease given the chronicity of his symptoms dating back to childhood. Based on the psychiatrist's evaluation as well as both the patient's self-report and his parents' collateral, the patient was formally diagnosed with ADHD. Initially, the patient was started on non-stimulant medications for treatment of ADHD, which were minimally effective. After extensive discussion with the patient, his parents, as well as his substance abuse program, the patient was started on a stimulant approximately 1 year after last use of any illicit substance. Although the patient had been abstinent from all substances prior to starting the stimulant, he continued to endorse cravings to use, specifically for cocaine. Shortly after starting treatment with a stimulant, the patient's cravings for cocaine diminished significantly. The

patient and his family members notice improvements in his attention and concentration, with a significant decrease in his overall impulsivity and emotional dysregulation.

At the time of the initial transplant evaluation, the patient had been abstinent from all illicit substances for 3 years, while continuing his substance abuse treatment program, now in the outpatient level of care. He had been on a stimulant, renally dosed, for ADHD for 2 years with no concerns of diverting or overusing. His anxiety was also well managed on both an antidepressant as well as weekly psychotherapy. His adherence with mental health care and substance abuse treatment was very good. He had moved out of his parents' home and was living with his girlfriend while working full time.

Regarding his renal functioning, the patient had been diagnosed with polycystic kidney disease while in college. His kidney functioning had slowly deteriorated over the years and, although his medical treatment was limited during his 20s and early 30s secondary to his substance use, over the last 3 years, he had been consistent with medical care, specifically improved blood pressure control, which required even closer monitoring due to his stimulant use. Given concerns of end-stage kidney disease, the patient presented for a preemptive kidney transplant with a potential living donor, his brother.

During the kidney selection committee meeting, several considerations were raised about the patient's candidacy for transplant, focused on his history of substance abuse, risks of relapse, and ongoing use of controlled substances, although prescribed. Despite the patient's increased risk of complications post transplant, including how a relapse could directly and indirectly impact the transplanted organ, it was evident that patient was highly committed to his recovery and to substance abuse treatment and mental health treatment. Despite having intermittent cravings to use substances, patient had developed strong coping skills and a comprehensive support network, including his mental health providers, substance abuse treatment program, and family, all of whom were invested in the patient's ongoing recovery. He viewed his recovery as a life-long journey and acknowledged his triggers for relapse and strategies to prevent a relapse. Ultimately, the patient was deemed an appointment candidate for transplant and his brother was cleared as a donor. As a part of his recovery, the patient had put a lot of effort in improving his relationships, which most likely contributed to several family members and friends coming forward as potential donors, as they were also in support of his candidacy and were confident in his active dedication in his recovery.

Patient was successfully transplanted 6 months after his initial presentation to the kidney transplant clinic. During his acute hospitalization for transplant, he did well with standard pain management without any evidence of misuse of narcotics. His stimulant was momentarily held at the time of surgery but resumed on discharge. Patient returned to work 2 months post surgery and continued in regular follow-up with his outpatient providers. He remained abstinent of all illicit substances throughout his follow-up visits post transplant and has since transitioned to a local nephrologist for the last 2 years and has had no relapses and continues to be actively engaged in his addiction recovery. His renal functioning has been stable since transplant.

Discussion

Reflections on the Case Presentation

Transplant psychiatrists are responsible for evaluating the patient's psychiatric history including substance use, and how these factors may influence post-transplant course. This case illustrates many dilemmas that we constantly face regarding patient selection, specifically the fallacy that we can predict outcomes. We are only able to evaluate the protective and risk factors a patient exhibits and then render an opinion regarding the potential future impact.

The patient above had many strengths including his strong familial support and connectedness with his outpatient providers, but most importantly insight into the negative impact his substance use has had on his life and his inability to manage it alone. Despite his ongoing use of multiple substances from adolescence and then into his early 30s with several failed attempts at sobriety, he was eventually able to find success in a comprehensive substance abuse program in conjunction with mental health treatment. Even despite his successes, he will always remain at risk for relapse post transplant and part of the pre-transplant evaluation was focused on how to assess his ability to manage a relapse if it were to occur.

This case also illustrates that stimulants can be used successfully in patients with substance use disorders, which can lead to a strong positive impact on functioning: the ability to manage medical care and maintain sobriety post transplant. Any potential risks of prescription stimulant use in the long term, such as cardiac [26] and renal [27], should be weighed against the functional impact on the patient, which can influence post-transplant success. This patient continued to have close monitoring of his cardiac and renal functioning, which remained stable while on prescribed stimulants. In addition, his substance use was monitored with toxicology screens and through the state prescription monitoring program and medical providers routinely communicated between them, which allowed for the patient to be prescribed a controlled-substance despite his prior substance abuse history.

Relapses: Not the If but the When

Transplant centers typically require abstinence, although the varying time-frames, from illicit substances prior to transplantation with the expectation of ongoing abstinence post transplant [28], while active substance use is often a contraindication for organ transplant [29]. Limited evidence exists that demonstrates "the six-month rule" predicts outcomes post transplant [30].

The amount of abstinence time may be less important as compared to other factors such as the patient's personal insight and active engagement in recovery. Relapses are a normal part of recovery for those treated for substance use disorder, which has shown to be similar to other chronic conditions, such as asthma and hypertension [10, 31]. Nearly half of all patients treated with alcohol or other drug use return to active use within 1 year following treatment [32]. While relapses are a part of recovery, it is the preparation and insight into the likelihood of a relapse that can help evaluate a patient's success post transplant.

In the case study above, although the patient had several failed attempts at abstinence prior with prolonged periods of use, once he was actively engaged in recovery and demonstrated insight into his illness, his relapse 6 months into treatment lasted only 3 days until he re-presented to treatment. Although the patient had been abstinent of all substances 3 years prior to transplant, it was not the 3 years of abstinence that made him an appropriate transplant candidate, but rather his ability to manage a relapse when it occurred. He exhibited ongoing commitment to improve his coping skills and was not naive to the notion that relapses occur.

Cocaine Use Disorder and ADHD

ADHD and substance use disorders are highly comorbid conditions with ADHD increasing the risk of drug use [33]. Among adults with ADD, 10% meet criteria for cocaine use disorder [34]. Treatment of ADHD can decrease the risk of developing substance use disorders [35, 36]. Stimulant use has not been shown to increase risk of relapse, but rather a decrease in substance-related events [37]. Moreover, medical treatment of patients with both cocaine use disorder and ADHD has shown a reduction in substance use and improvement in ADHD symptoms [38].

Despite stimulants having an abuse potential, patients who are appropriately treated for ADHD with stimulants have shown to have positive outcomes, specifically in those with concurrent substance use disorders. In the patient above, treatment of his ADHD positively influenced his level of functioning—improving relationships with others, increasing attention and concentration, decreasing impulsivity, and reducing drug use.

Conclusions

In our case above, the patient's kidney failure was secondary to polycystic kidney disease, although other factors most likely also contributed such as poor medical follow-up in the setting of substance use and any potential direct damage of cocaine as a vasoconstrictor on the kidney. Despite the potential negative effects of a relapse on the transplanted organ, this patient demonstrated the importance of evaluating his candidacy on his readiness to manage a relapse through ongoing engagement in substance use recovery, as well as optimal management of his co-occurring ADHD. We cannot predict with certainty a patient's post-transplant course, but we can optimize modifiable risk factors pre-transplant to help best prepare a patient post transplant.

Take Home Points

1. Heavy prior substance abuse should not exclude any patient from being considered for transplant. The transplant evaluation should focus on the patient's insight into the negative effects of ongoing use and strategies to focus on recovery, as well as relapse prevention.
2. Cocaine use disorder can significantly impact post-transplantation outpatient if the patient resumes use post transplant, but ongoing engagement in substance abuse treatment and strong insight into the triggers of relapse can help prepare patients for ongoing recovery post transplant.

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Cannabis Use in Transplantation

21

Jorge Luis Sotelo and Melanie Bilbul

Background

Candidates for organ transplant surgery undergo a psychosocial evaluation to identify risk factors for potential complications after transplant, which includes an in-depth review of their substance use history. The use of cannabis, the most used "illicit" drug in the world, has historically been of interest to transplant teams when they consider which individuals to list for surgery. In the United States, the use and possession of cannabis has remained illegal under federal law via the Controlled Substances Act of 1970 and the Food and Drug Administration has classified it a Schedule I drug. Nevertheless, as of June 2020, the time we started writing this chapter, cannabis is legal for medical use in 33 states and the District of Columbia and legal for recreational use in 11 states [1]. A 2017 survey found that cannabis is used by nearly 4% of the global population [2]. The prevalence of use varies widely depending on legalization status, age group, and availability. In 2018, the prevalence of cannabis use in the US was 16% (with 22% of individuals ages 18–25 reporting past-month use) [3], and is comparable to that observed in Canada, where cannabis use has been legal since October of 2018 [4]. Some countries, such as the Netherlands and Spain, have adopted a policy of limited enforcement. In Europe, rates of use from 2017–2018 varied widely by country, with the lowest in Malta (0.9%) and the highest in the Netherlands (9.2%), France, and Spain (11% each) [5].

A systematic review of the literature on medical benefits of cannabis is beyond the scope of this chapter but it is worth noting that cannabis has been used with favorable results in a variety of medical conditions, including chronic pain [6], nausea [7], epilepsy [8], and glaucoma [9]. A National Academy of Sciences-commissioned report concluded that there is substantial evidence for the use of cannabis or cannabinoids in chronic pain, but study methodologies were flawed with considerable variability in the quantity, quality, and type of cannabis product between studies and laboratories [10]. However, there is also evidence that long-term use of cannabis can produce pulmonary disease [11, 12], and consistent use is associated with pulmonary complications, increased nausea and emesis (the cannabinoid hyperemesis syndrome) [13], myocardial infarction, stroke [14], membranous glomerulonephritis [15], opportunistic infections [9, 16–18], schizophrenia [19], as well as vehicle crashes, emergency department visits, cannabis withdrawal and, of course, cannabis use disorder [20]. Additionally, addiction is more common in those who start smoking cannabis as adolescents and these early users are more vulnerable to cognitive impairment and forgetfulness [21], using illicit drugs [22], developing a lower IQ and dropping out of school [23], factors which can represent obstacles to optimal adherence with posttransplant treatment recommendations.

Still, there is no clear consensus among transplant centers and within the transplant community regarding whether patients who actively use cannabis, medicinal or recreational, should be eligible for transplant listing. Contributing to the confusion is a paucity of data on the outcomes of patients who use cannabis before transplant or safety data for cannabis use after transplantation. A 2016 international survey of heart transplant centers revealed that a majority of respondents (64.4%) support listing patients who use legal medical cannabis but only 27.5% support listing of patients using legal recreational cannabis [24]. Most providers in this survey (68.3%) still recommend a period of abstinence prior to

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listing. In another survey of heart transplant centers, most providers (73%) considered illegal cannabis use an absolute or relative contraindication to transplant [25]. Legal recreational use and legal medicinal use were less controversial, with 57% and 21% of providers, respectively, considering such use as a contraindication to heart transplant. A 2014 survey of policies regarding cannabis use, either recreational or medicinal, among liver transplant program in the US found that 19 out of 47 programs (40%) would not accept any cannabis use—recreational or medicinal [26]. Seven programs would accept either *medical or recreational* cannabis use. Eight programs would consider patients using medical cannabis but not recreational cannabis. Eighteen programs would consider patients using *medical* cannabis, but in 13 programs patients were required to discontinue use and test negative on drug screen for cannabis before transplant. Thirteen programs would accept patients who used *recreational* cannabis, although five would allow this on a case-by-case basis, and one required that the patients quit cannabis use at least 3 months before transplant and to complete a 12-step program. In this survey, 16% of programs would transplant patients who used cannabis, whereas 14% of programs would categorically reject such candidates. The remaining 70% of programs viewed patients who used medical cannabis more favorably than recreational users. Furthermore, a national Web-based survey of US liver transplant providers revealed that cannabis use was one of the top three most controversial characteristics among transplant candidates by 46.7% of the providers [27]. Finally, a survey sent by the Infectious Diseases Community of Practice Executive Committee to the membership of the American Society of Transplantation discovered that most respondents had concerns about cannabis use [28]. Fifty percent were from centers allowing medical cannabis use and 10% from centers who permitted both medical and recreational use. Twenty-eight percent rejected all candidates who used cannabis, irrespective of organ. No significant difference was identified regarding screening mandates between states with and without some form of legalized cannabis. Thirty-four percent of respondents practicing in states with no legal form of cannabis reported that their program declined transplantation to all cannabis users, compared to 25% in states with some form of legal cannabis. Further complicating the evaluation of some transplant candidates is the fact that seven US states (California, Delaware, Arizona, Illinois, Minnesota, Washington, and New Hampshire) recently introduced legislation explicitly prohibiting denial of transplant listing based on medicinal cannabis use [29]. Consequently, it is imperative that the transplant psychiatrists become familiar with their transplant program policies, their state legislation as well as thepotential risks and benefits of cannabis use in patients who are being considered for solid organ transplant surgery.

Potential Risks of Cannabis Use

There are several considerations when evaluating a person with regular cannabis use for organ transplant. Such considerations include potential effects of cannabis use on adherence, mortality or graft loss, infection and cancer risk, psychiatric illness, and other substance use.

Non-adherence

One consideration is whether cannabis use can lead to suboptimal adherence to treatment recommendations, namely medications and/or follow-up appointments. In general, impairments in cognitive domains associated with cannabis use, especially with chronic use, are feared to affect an individual's ability to take medications in a timely fashion, to understand instructions, and to schedule and attend medical appointments. Forgetfulness and carelessness have previously been identified as significant barriers to medication adherence [30] and cannabis use may have a dose-related effect on cognitive distortion and memory impairment [31]. Cannabis use has been correlated with non-adherence to medical regimen in other medical conditions, such as HIV [18, 32], systemic lupus erythematosus [33], psychosis, and bipolar disorder [34, 35]. However, some studies did not find an association between cannabis and non-adherence in HIV patients [36] or inflammatory bowel disease [37].

Studies examining the impact of cannabis use on transplant patient adherence have not consistently shown an association. In a survey of transplant centers, only 9 of 225 reported difficulties with adherence to medications and/or monitoring recommendations in their patients who were using cannabis [28]. On the other hand, an investigation of over 50,000 national kidney transplant records found that cannabis use disorder in the year before transplant was associated with non-compliance, as well as posttransplant alcohol and drug abuse, schizophrenia, and depression [17]. Concern for non-adherence to immunosuppressants in cannabis users has also been reported due to potential concomitant use with other habit-forming substances [16, 38]. The transplant literature has not differentiated between non-adherence *associated with* cannabis use and non-adherence *due to* cannabis use. Therefore, it is difficult to conclude to what extent cannabis use in transplant recipients will directly affect adherence, as the evidence about this relationship is not conclusive, and in many cases, other non-cannabis substance use may be contributing to non-adherence with treatment recommendations.

Patient and Graft Survival

Another important concern is whether cannabis use is associated with poorer survival outcomes in transplant patients. A study of 1489 patients (155 cannabis users and 1334 non-users) who were evaluated for liver transplant found no dif-

ference in posttransplant survival between the two study cohorts, but non-users were more likely to be listed (44% vs 27%) [39]. In this study, cannabis users did not have a significantly higher hazard of mortality, but they were more likely to test positive for illicit substances including narcotics, cocaine, amphetamines, and barbiturates on toxicology screens. Another retrospective review of liver transplant candidates revealed no statistically significant association between the risk of waitlist removal or death and a history of cannabis use [40]. Similarly, a retrospective analysis of liver transplant patients found an overall 5-year survival of 75% and no significant difference in 5-year survival between current or former and never cannabis users [41]. In contrast, tobacco users were over 3 times as likely to die within 5 years as never users of tobacco. A common limitation of these studies is that the data on cannabis use are often historical or from retrospective chart review. Thus, a direct association between active cannabis use and the outcomes or behaviors of interest cannot be firmly established. Additionally, the potential contribution of non-cannabis substance use to outcomes in these patient populations is often not considered.

There are similar findings in kidney transplant populations. A retrospective study of kidney transplant recipients found that diagnoses of cannabis dependence or abuse in the year before transplant were not associated with death or graft failure in the year after transplant [17]. However, cannabis use in the first year of posttransplant was associated with an approximately twofold increased risk of death-censored graft failure, all-cause graft loss, and death in the subsequent 2 years. Another retrospective review of 56 recreational cannabis users and 1169 non-users found that survival was no different between the two groups and the proportion of failed renal allografts at 1-year posttransplant was similar between them, as well [42]. Cannabis use was not associated with the combined outcome of death or graft failure in this study, although this review examined data on individuals without pathological cannabis use. While there is no evidence from the literature that recreational cannabis use impairs kidney allograft function or threatens kidney transplant survival, many transplant centers consider any cannabis use as an absolute contraindication to kidney transplantation. Whether active recreational use also is associated with inferior outcomes in graft and patient survival after renal transplantation remains to be seen. The overall survival rates in kidney and liver transplant patients using cannabis do not appear to be different than non-users [29], however, rigorous data on the timing and duration of use (pretransplant and/or posttransplant exposure), amounts of cannabis exposure, and outcomes have not been examined.

Infections and Cancer

Impaired lung defense mechanisms from chronic inhalation of cannabis have been linked to infections and cancer, the risks of which would be enhanced in the immunocompromised posttransplant patient [43]. Cannabis products may be contaminated with aspergillus [44], legionella [45], and mucor [46], which can lead to invasive infections in immunocompromised transplant recipients, especially if they have a tenuous respiratory status [44, 47–50]. Invasive aspergillosis associated with cannabis use has been described in a renal transplant recipient [47], as well as in patients with cancer [51, 52] and AIDS [53]. While these fungi pose a potential risk in immunocompromised patients who smoke cannabis, the risk of contamination is low and may not be, in and of itself, reason enough to recommend against cannabis use in the posttransplant population. This risk appears to be specific to smoked cannabis. In addition to fungal contamination, a case report of lipid pneumonia attributed to smoking cannabis oil was described in a kidney transplant recipient [50]. Infrequent reports such as these have been the basis for policies in many centers to deny transplantation to potential recipients who use cannabis [16, 38, 54, 55].

A survey of 225 transplant centers revealed that 72% of respondents had concerns about fungal complications in their transplant patient populations with 43% having observed fungal infections (aspergillus and zygomycetes) they believed were associated with cannabis use [28]. Of those reporting fungal infections associated with cannabis use, 89% reported infection associated with smoking of cannabis, 15% with vape pens, and 4% with edible cannabis. Medicinal cannabis, which is not sterilized and does not have FDA oversight, is not immune from infection risks. In a survey of California medicinal dispensaries, multiple fungi (e.g., Cryptococcus, Mucor, Aspergillus), as well as bacteria that would typically be attributed to hospital-acquired infections rather than exposure to cannabis (e.g., E. coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, etc.) were cultured from dispensary samples [56].

Inhaled cannabis may also carry carcinogenic potential [57], which is obviously a concern in transplant recipients, who are already at a risk of developing cancer due to immunosuppression and oncogenic viral infections [58]. However, the epidemiologic data correlating head and neck squamous cell carcinoma risk [59] and lung cancer [60] development with cannabis are inconsistent. Other studies have linked cannabis use with an increased risk of prostate and cervical cancer, malignant primary gliomas, bladder cancer, and testicular germ cell tumors [57], but the effects overall have been small and the studies are heterogeneous.

Psychiatric Illness

Cannabis use has also been linked with psychiatric conditions such as psychosis and depression. It is becoming clear that cannabis particularly increases the risk of psychosis independently of confounding and transient intoxication effects. There is evidence for an additive interaction of genetic risk for schizophrenia with lifetime regular cannabis

use, suggesting that the etiopathogenesis of schizophrenia involves genetic predispositions that may result in vulnerable individuals being more sensitive to the effects of what is described as regular cannabis use [61]. A 2007 systematic review found an increased risk of any psychotic outcome in cannabis users of approximately 40%, with greater risk in people who used it most frequently [62]. In addition, compared to never users, the daily use of high-potency cannabis increases the odds nearly five times of a psychotic disorder in first-episode psychosis [63] and of individuals with a substance-induced psychosis, the conversion to schizophrenia is highest for cannabis than other drugs or alcohol [64–66].

So far, the literature on cannabis and depression suggests more evidence for harm than good. A meta-analysis found an association between cannabis use during adolescence and a moderately increased risk of depression and suicidality in young adulthood [67]. In a 40-year study that analyzed over 400 individuals across several time points, cannabis use was correlated with an increased risk of receiving a diagnosis of major depressive disorder, and earlier onset of use was correlated with a shorter time to presentation [68]. Other studies have shown similar results, with a positive correlation between cannabis use and depression, with chronic use further strengthening this association [69–71]. Cannabis use has also been shown to promote depressive symptom progression [72, 73]. Other studies have found no correlation between cannabis use and later diagnosis of major depression or symptom severity after controlling for other illicit drug use, education, and childhood upbringing [74–76]. Nonetheless, to date there have been no randomized, clinical trials for the use of cannabinoids in depression. There are, however, studies that have analyzed depression symptoms as secondary outcome measurements in individuals with other conditions (e.g., chronic pain) and no significant therapeutic benefit has been found in association with administered cannabinoids, including nabiximols and dronabinol [10].

Other Substance Use

In liver transplant cohorts, cannabis use is closely associated with other substance use, alcohol-related cirrhosis, and hepatitis C cirrhosis. In the previously cited retrospective cohort study of 1489 patients with chronic liver disease, cannabis users were more likely than non-users to test positive for other substances, such as narcotics, benzodiazepines, barbiturates, amphetamines, and illicit drugs (such as cocaine and opioids), and to smoke tobacco, and they were, not surprisingly, less likely to receive a transplant [39]. In a retrospective cohort of patients with liver disease evaluated at a large transplant center, 48% of those evaluated were users of cannabis, with 7% being recent users and 16% daily users [40]. There was high prevalence of historical tobacco use (55%), alcohol use (89%), illicit drug use (47%), and prescription opiate or benzodiazepine use (31%) in this cohort. In another report of liver transplant recipients, patients reporting cannabis use were more likely to be former tobacco smokers (43% vs 28%) or to be diagnosed with either alcoholic cirrhosis (37% vs 20%) or viral hepatitis (49% vs 29%) [41].

In a study of 2067 kidney transplant candidates referred for addiction psychiatry evaluation, 3% met diagnostic criteria for cannabis abuse or dependence [77]. Fifty-eight percent consumed cannabis daily and 31% had a comorbid non-cannabis substance dependence diagnosis. The authors concluded that their study population could be more accurately conceptualized as polysubstance abusers. The likelihood of comorbid substance abuse serves to highlight several risk factors potentially jeopardizing the success of the transplant, such as negative health effects of cannabis and tobacco smoking, potential relapse/resumption of other substances of abuse, and impact on treatment adherence posttransplant when under effects of intoxicants. A retrospective study of outcomes in a large cohort of kidney recipients found an association between posttransplant cannabis abuse and dependence within the first year after transplant and alcohol and other drug abuse [17]. In a retrospective review of 1225 kidney recipients, cannabis users were more likely to report ever using alcohol, current or prior tobacco use, to smoke >10 cigarettes/day, to be considered moderate or high-risk transplant candidates on social work assessments, and to have a history of treated substance addiction [42].

Medical cannabis patients also have a high rate of coexisting addictive disorders. A study of 348 medical cannabis patients indicated that 96% had used cannabis before starting medical cannabis, with 61% using it daily. Sixty-eight percent used prescription opioids differently than they were prescribed within the last month, 40% had a history of non-medical use of opioids, 38% used hallucinogens, and 35% had used cocaine [78].

Interactions with Immunosuppressants

A recent case report of a 67-year-old man with lymphoma whose tacrolimus levels became toxic as a result of consuming edible cannabis gummies highlights the potential for calcineurin inhibitor toxicity with heavy cannabis use [79]. In vitro studies have shown that the tetrahydrocannabinoids found in cannabis can decrease the metabolism of calcineurin inhibitors by inhibiting the cytochrome P450 3A system [79, 80]. In addition, studies have also indicated that cannabinoids inhibit the P-glycoprotein transporter that is required for absorption of tacrolimus by the gut and dispersal to other tissues [81, 82]. Therefore, at least two mechanisms may contribute to erratic and unpredictable calcineurin inhibitor levels in cannabis users. Other agents used in transplant recipients, such as azole antifungals, may raise THC levels by inhibiting the CYP2C9

enzyme required for its metabolism, further complicating toxicity and pharmacokinetic issues [83].

The lack of accurate standardization and labeling of commercial cannabis products make assessment of the impact of cannabis use more difficult with both under-labeling and over-labeling of tetrahydrocannabinol and cannabidiol concentrations [81, 84]. An analysis of 84 cannabidiol extracts revealed a wide range of cannabidiol concentrations with accurate labeling in only 31%, with 26% over-labeled and 42% under-labeled [85]. Furthermore, other cannabinoid contaminants were found, most commonly Δ-9 tetrahydrocannabinol (THC) in 21% of the extracts, with other cannabinoids in lower concentrations. As a result, unpredictable calcineurin inhibitor levels and the potential for toxicity or underdosing may occur, particularly with intermittent use and from different sources.

Potential Benefits of Cannabis Use

Clinical benefits have been reported in the treatment of nausea, anorexia, chronic pain, seizures, glaucoma, and neurological conditions, including multiple sclerosis and epilepsy [29, 86–93]. Medical cannabis has moderate to high-quality evidence for treating chronic pain, neuropathic pain, spasticity in multiple sclerosis, and chemotherapy-associated nausea and vomiting [88–91]. Cannabis is also increasingly recognized as a promising therapeutic target in various digestive disorders [92]. In addition, anxiety, depression, and insomnia are common psychiatric symptoms that have been treated with cannabis [93].

In particular, among patients with end-stage renal disease who are on dialysis, anorexia, pain, sleep disturbance, anxiety, nausea, and depression have been reported in one-quarter to one-half of respondents [94] and as many as 60–100% of dialysis patients experience symptoms of uremic neuropathy [95]. A recent case report documents successful use of prescription cannabis to decrease the use of opiate analgesics following liver transplantation [96].

Case History

Mrs. X is a single, 36-year-old mother of two (children ages, 12 and 14 years) with a history of primary sclerosing cholangitis, which eventually led to liver failure and required treatment with a liver transplant 6 years ago. Prior to transplant, she smoked cannabis daily to treat chronic pain and was not required to abstain from the use of this substance prior to listing by the transplant center at the time. She had abstained from using alcohol for 5 years prior to her liver transplant and had never misused it, without episodes of alcohol intoxication or blackouts. She has never used tobacco products and denies any history of illicit/recreational drug use.

Mrs. X does not have a history of psychiatric treatment and denies a history of psychiatric illness or substance use disorders in her biological relatives. Her psychosocial evaluation prior to liver transplant surgery did not identify a psychiatric disorder and her use of cannabis was not qualified as pathological. Cognitive testing prior to transplant revealed mild deficits in attention, concentration, and memory, which were attributed to hepatic encephalopathy and medication side effects at the time. She was eventually cleared for transplant, listed, and advised to stop smoking cannabis after her surgery. She successfully abstained from cannabis for 2 months after her transplant but then resumed smoking up to approximately 3 g per day.

In the 6 years since her liver transplant, her adherence to medications and follow-up appointments has become more erratic. Her parents and older brother have provided support and encouragement since her liver transplant 6 years ago and they are understandably disappointed that she may need a second transplant at this time.

Mrs. X presents to her hepatologist's office with acute on chronic graft rejection and is accompanied by her parents, who appear supportive and caring. She is discouraged upon hearing the news that she may have lost functioning of her allograft. Even though she is disappointed and feels guilty about not having complied with the team's recommendations after her surgery, she is hopeful that she will be given another chance and appears determined to follow treatment recommendations from now on. The transplant team consults the psychiatrist, concerned that her cannabis use has contributed to her becoming less motivated and more forgetful, as well as to her non-adherence to posttransplantation treatment recommendations.

Mrs. X was cleared for her first liver transplant despite active ongoing cannabis use. It is unclear to what extent her posttransplant use of cannabis contributed to graft rejection. Without a clear consensus among US transplant programs on how long she should abstain from cannabis, if at all, the consulting psychiatrist is faced with several important questions.

Clinical Questions

1. Does Mrs. X have a cannabis use disorder?
2. Should her posttransplant non-adherence (for medications and follow-up appointments) be considered separately from her cannabis use, or is it a contributory (and treatable) factor in non-adherence?
3. Should the consulting psychiatrist recommend formal treatment of cannabis use prior to listing for a possible second liver transplant?
4. If so, how long a period of abstinence from cannabis should be recommended prior to listing Mrs. X?

Discussion

The case above illustrates some of the challenges inherent in evaluating individuals who use cannabis as potential transplant recipients. Mrs. X finds herself in the unfortunate situation of needing a second transplant. She was not required to stop using cannabis prior to transplant. Rather, the transplant team recommended that she abstain from using cannabis only after surgery. It is not surprising that she was unable to maintain abstinence as she was not expected to abstain from cannabis prior to surgery.

The most important question is does she have a cannabis use disorder? It is also important to explore other substance use since her transplant 6 years ago. If her use of cannabis rises to the level of a substance use disorder then treatment for it should be implemented right away, as not doing so would jeopardize her chance at a successful second liver transplant. A thorough review of alcohol, over-the-counter and prescription medications, and recreational and/or illicit drugs needs to be completed. As she had abstained from alcohol for years and did not have a history of non-cannabis illicit drug use, our main concern would be about the amount and frequency of analgesics and cannabis used since her surgery, especially as she has a history of chronic pain.

Additionally, the etiology of her chronic pain should be thoroughly evaluated and appropriate treatment strategies, different than cannabis, explored. As she used cannabis on a regular basis after transplant and she uses up to 3 g daily without medical oversight, despite having been told by the transplant team not to, it is conceivable that she has cannabis use disorder. On the other hand, she was treating chronic pain with cannabis before her transplant, and it could be argued that using this substance may be more favorable than using opioid analgesics on a chronic basis. If the patient is citing chronic pain as the reason she is using cannabis, then she should be managed through a chronic pain clinic with medicinal cannabis, if decided as the optimal treatment, being a prescribed therapy. In addition, medicinal cannabis should be in the form of edibles not smoked or vaped.

It is unlikely that her non-adherence is completely independent of her cannabis use. Using cannabis constitutes a type of non-adherence for Mrs. X, since the transplant team recommended that she abstain after surgery. An important consideration would be to learn from the transplant team what efforts they had made towards re-educating her about the need to be off cannabis following transplant and whether the transplant team performed biochemical monitoring to establish that she was free from cannabis. Her non-adherence should therefore be considered as a crucial component that needs to be addressed if she is to be listed for a second transplant. Psychosocial factors, such as inadequate social support or posttransplant depression or anxiety symptoms, can contribute to suboptimal compliance with treatment recommendations so it would be important to determine if such factors may need to be corrected or improved. Above all, it is important to understand why Mrs. X resumed using cannabis after her transplant. It would be important to characterize whether posttransplant cannabis use was medicinal, recreational, or pathological and treatment would have to be tailored to her specific situation and biopsychosocial formulation. In addition, cognitive testing could be performed before and after abstinence from cannabis has been achieved to identify the contribution of cannabis to any cognitive impairment. Her supportive parents would then be educated regarding how much assistance they, and other family members or close friends, would have to provide with reminders about medications and appointments, depending on the extent of any deficits.

If she has developed cannabis use disorder, treatment would need to be implemented as soon as possible. Psychiatric symptoms that could be contributing to cannabis use, such as the aforementioned anxiety and/or depression, would need to be treated aggressively, as well. A multidisciplinary treatment approach (consisting of psychiatrist, therapist, addiction specialist, social worker) using a variety of modalities (medications, individual and group psychotherapy, peer-led substance abuse support groups) would give Mrs. X the best chance to overcome her addiction and any comorbid mood and/or anxiety disorders.

While there is no consensus among transplant centers on the duration of abstinence from cannabis prior to listing, and as recommendations may vary if cannabis use is medicinal versus recreational, a minimum of 6 months would be suitable in the event that she were suffering from cannabis use disorder, which is quite likely given the amount of daily cannabis being used, especially if there is no other concerning substance use, she has appropriate social support, and any psychiatric symptoms are fairly well controlled. If, on the other hand, she does not have cannabis use disorder and uses cannabis to treat chronic pain, she should be referred to a pain specialist willing to work closely with the transplant team. Serial toxicology screens would have to confirm that she is abstaining from cannabis and other substances associated with poor posttransplant outcomes.

Conclusion

The literature that we reviewed and the case that we illustrated both establish that the evaluation of individuals who use cannabis and are being considered for transplant surgery is challenging and that there is limited evidence to guide their pretransplant psychiatric assessment. Legal and medicinal cannabis use is perceived more favorably by transplant

centers than recreational and illegal cannabis use and there is (some) literature to support this approach, as cannabis abuse and dependence are associated with non-adherence, decreased graft and patient survival, and other substance abuse in transplant patients. In addition, cannabis use has been associated with significant negative psychiatric outcomes (psychosis, conversion to schizophrenia, treatment-refractory psychosis, and depression) in non-transplant patients. These psychiatric sequelae would likely result in multifactorial negative outcomes in transplant patients, especially as they are at greater risk of complications due to their immunocompromised status and the increased potential for drug–drug interactions or additive medication side effects. The amount and frequency of use of cannabis need to be taken into account as there appears to be a dose-related phenomenon for several of the complications discussed in this chapter. A period of abstinence from cannabis with negative serial toxicology screens (to also confirm abstinence from the other substances which frequently accompany its use in medical populations) is essential, especially in individuals whose pattern of use is more problematic. Prompt referral to addiction specialists and enrollment in a formal treatment program would be crucial for those whose use rises to the level of a substance use disorder.

Medical cannabis is gaining more acceptance and there is a body of evidence suggesting that it could be of benefit in treating symptoms such as pain, nausea, insomnia, and depression, which are not uncommon in transplant populations. As the case we discussed proves, it is best to consider all the relevant psychosocial variables in order to put together a management plan and evidence-based set of recommendations that will give each individual transplant candidate the best chance at success in the postoperative phase.

Take Home Points

1. The mental health assessor should be familiar with their transplant programs policies, their state legislation as well as the potential risks and benefits of cannabis use in patients who are being considered for solid organ transplant surgery.
2. Assessment of cannabis users should include information on recreational vs medicinal use, quantity, frequency, route of use, whether the individual meets criteria for a cannabis use disorder and other substance use.
   (a) If a cannabis use disorder exists, is addiction counseling required?
   (b) If discontinuation of cannabis is required, toxicology screening can establish abstinence.
   (c) If the use is for medicinal purposes, what is the nature of the medicinal purpose and what other treatment strategies were tried? Are there better alternatives to medicinal cannabis?
3. Cannabis use is not inconsequential in transplant patients and can cause morbidity and mortality.
4. Until we know more about the microbial risks posed by medical cannabis, it seems prudent to advise immunocompromised patients against the use of vaporized or inhaled cannabis.

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Tobacco Use and Transplantation

22

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Introduction

Tobacco consumption is a major public health concern both for people in the United States and those undergoing transplant [1, 2]. In 2015, most Americans who use tobacco, use combustible tobacco products (68.6%), most commonly cigarettes (89.0%) [3]. The addictive potential of tobacco due to nicotine has been well defined for the past 50 years [2]. Nicotine addiction is facilitated by drug-taking behavior, the pharmacokinetics, and pharmacodynamics of nicotine, which leads among other effects, to the onset of withdrawal symptoms [2].

Tobacco use disorder is characterized by at least a 12-month history of tobacco use and at least 2 of the following symptoms: (1) using larger amounts or use over a longer period than was intended, (2) persistent desire/unsuccessful efforts to cut down/control use, (3) needing to spend a great deal of time in activities to obtain or use, (4) cravings, (5) recurrent use resulting in a failure to fulfill major role obligations, (6) continued use despite persistent/recurrent social problems due to use, (7) giving up activities as a result of use, (8) recurrent use in physically hazardous situations, (9) continued use despite knowing use exacerbates physical/psychological problems, (10) tolerance, and (11) withdrawal [4]. It can be further specified by severity: mild tobacco use disorder requires 2–3 symptoms, moderate tobacco use disorder requires 4–5 symptoms, and severe tobacco use disorder requires more than 6 symptoms. Remission status is specified as in early remission (3–12 months without use) and sustained remission (greater than 12 months without use) [4].

Nicotine, 3-(1-methyl-2-pyrrolidinyl) pyridine, is absorbed via the epithelium of the lung, the oral mucosa, the nose, and through the skin [2]. Within 7–15 s of inhalation, nicotine enters the brain where it has its effects [5]. Because serum nicotine levels decline rapidly after consumption, cravings can begin shortly after use [5]. Nicotine is metabolized by the liver via the CYP2A6 and CYP2B63 isozymes and has a 1–2 h half-life. The two major metabolites of nicotine are cotinine and trans-3′-hydroxycotinine [3]. Cotinine can last in the system for 7–10 days, and measurement of urinary cotinine and can aid in identification of continued nicotine consumption [6, 7].

Nicotine affects the release of several neurotransmitters including glutamate, dopamine, γ-aminobutyric acid (GABA), and norepinephrine. Nicotine precipitates the release of glutamate within the midbrain by stimulating nicotinic acetylcholine receptors (nAChR) on glutamatergic terminals [8–13]. These glutamatergic terminals stimulate dopaminergic neurons in the ventral tegmental area which project to the nucleus accumbens and prefrontal cortex [14]. The increase of dopamine in the nucleus accumbens reinforces the nicotine use via the mesolimbic reward circuit. nAChRs on GABA releasing terminals lead to GABA release and neuronal inhibition which has a downstream effect increasing dopamine [12, 15]. In addition to its effects in the brain, *chronic* nicotine use sensitizes the hypothalamic-pituitary-adrenal (HPA) pathway and amygdala [16].

Nicotine withdrawal syndrome is characterized by negative mood symptoms, cravings, insomnia, irritability, moodiness/anxiety, restlessness, decreased heart rate, and difficulty concentrating [5]. The hypothalamic-pituitary-adrenal sensitization from chronic nicotine use may lead to over activity in withdrawal, causing anxiety and drug-seeking behavior [16].

Tobacco use has been causally linked to several medical problems including solid organ cancers (oropharyngeal, laryngeal, esophageal, lung, stomach, liver, pancreatic, renal, genitourinary, colorectal), coronary artery disease, peripheral vascular disease, chronic obstructive pulmonary disease, and diabetes [2]. Many of these medical conditions may lead to the need for solid organ transplant.

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Despite societal advances in reducing smoking and increased popular knowledge about health effects of nicotine, smoking remains common in transplant candidates and recipients. In a recent study published in 2020, Ohiomoba et al. found that 56.8% of heart transplant recipients had a history of cigarette smoking [17]. Another cohort study reported that over 65% of heart transplant recipients smoked tobacco prior to transplant and more than 10% of recipients resumed smoking tobacco after transplantation [18]. Among lung recipients, about 60% had a history of smoking prior to transplantation and 11% resumed smoking after transplant [19]. More than half (56.6%) of liver transplant recipients had a history of cigarette smoking [20]. This is consistent with findings of previous studies showing 42–60% of liver transplant candidates had a history of smoking and 10–23% were actively smoking [21–24]. In systematic review of the literature, Hoffman et al. found that tobacco resumption ranges between 6 and 35% in heart transplant recipients and 0–15% in lung recipients [25–29].

The sequelae of tobacco use after transplant includes increased cancer risk, higher rates of infections, vascular thrombosis, and atherosclerosis. Regardless of organ types, post-transplant smokers have higher rates of newly developed cardiovascular disease, malignancies, and mortality as well as shorter survival time [7, 30–32]. Smoking post-transplant has been shown to increase graft loss and mortality in solid organ recipients [33]. There is an increased risk of diabetes, transplant failure, and cardiovascular disease in patients who smoked post-kidney transplant [34]. Smoking in post-heart transplant patients has been linked with increased coronary artery disease; and death due to graft vasculopathy, and malignancy [35].

These risks highlight the importance of evaluating and providing resources for post-transplant tobacco use. Despite treatment options for tobacco use disorder, rates of smoking after transplant remain high, at 10–40% [6, 7]. Post-transplant tobacco use was higher among transplant recipients with substance use [36, 37], correlated with the duration of pre-transplant tobacco abstinence [6, 7, 38]. Post-transplant anxiety is also associated with smoking resumption [39]. Being aware of some of the risks for post-transplant tobacco use can be helpful, such as pre-transplant tobacco use, male gender, alcohol intake, and tobacco use among close relatives [40]. Resumption of tobacco use post-lung transplant is highest among those with COPD (chronic obstructive pulmonary disease) and short duration of smoking cessation prior to transplant (<12 month) [38, 41]. Educating patients on the effects of tobacco use and how stopping early could be beneficial. For example, quitting tobacco use 2 years before liver transplant has been shown to decrease the risk of vascular complications (hepatic artery thrombosis) by 58.6% [20].

Pre-transplant psychiatric evaluations aim to evaluate for and treat psychiatric disorders in order to prevent post-transplant complications. Evaluations of transplant candidates should include a thorough tobacco use history. Although inhaled tobacco is the most common type of tobacco use, pre-transplant evaluations should include a detailed information on the duration of use, substance types (including cigarette/cigar, e-cigarette/vaping, chewed tobacco, and nicotine replacement), duration of abstinence periods, attempts to quit/relapses, and historical treatment (such as medication-assisted treatment). Patient insight into tobacco use (including knowledge of triggers) and motivation to quit or maintain abstinence should be evaluated. During the evaluation, special attention should be paid to the patient's social support network for other smokers/tobacco user. Although patients who undergo solid organ transplant are expected to adhere to specific policies regarding tobacco use, smoking policies are varied by transplant program and smoking cessation is not required at all institutions for non-cardiothoracic solid organ transplants [6, 42]. However, cardiothoracic transplant programs consider continued smoking an absolute contraindication to transplantation.

We present two cases of nicotine use, one prior to transplant and the other following transplant to illustrate situations mental health providers may be called upon to evaluate and treat tobacco use disorders.

Case Histories

Case 1: Pre-transplant Evaluation of a Patient with Tobacco Use

A 64-year-old unmarried female with a 10-year history of chronic obstructive pulmonary disease (COPD) and no past psychiatric history presented to psychiatry for a pre-lung transplant evaluation. Two years prior to presentation, her pulmonologist brought up possible lung transplantation, but at that time, she did not want to pursue transplant because she was the main caregiver for her mother. After her mother passed away, she became open to the idea and began inquiring about it. Six months prior to presentation, she met with the transplant team and began the evaluation process. During the psychiatric evaluation, she reports understanding of the transplant process, adherence to medical treatment, and motivation for transplant. She reports stable mood and denies symptoms concerning for a current mood, anxiety, and psychotic disorders. There were no concerns for suicide or homicide risk.

The patient started smoking tobacco daily in her 20s. She has a total of 80 pack-years of smoking history. She has never used chewed tobacco or e-cigarettes. She tried to stop "at least a dozen times" by "quitting cold turkey" and ultimately stopped smoking 7 years ago with nicotine replacement therapy (specifically patches). The patient started oxygen 3 years ago and relapsed twice the same year in the setting of a difficult family situation. Her symptoms at the

time were consistent with adjustment disorder with anxiety. She denies any tobacco use since. She denies current cravings. She reports high motivation to maintain abstinence; however, she admits to limited knowledge of her triggers for use and coping mechanisms for anxiety and stress. Patient demonstrates stability in her ability to abstain from tobacco use after her relapse 3 years ago. She reports that she would contact the transplant team where she was able to relapse but believed that she would not smoke following transplant. The patient recognizes the danger of concurrent combustible tobacco use with oxygen and the negative effects that tobacco would have on her lung disease. She acknowledges that tobacco use would affect healing of a transplanted organ. She has no children and currently lives alone. The patient has a college education, a history of maintaining employment for 20 years, and is currently retired. After transplantation, she plans to move in with her non-smoking sister; however, she does admit that her sister has been a source of stress in the past.

Case 2: Evaluation Post-transplant for Relapse on Tobacco

The transplant team was consulted to see a 52-year-old man with a 50 pack-year history of tobacco use disorder in remission and heart transplant. The patient had quit tobacco use about 6 months prior to transplant without nicotine replacement therapy (NRT) or medications after being told by the transplant team to quit. After heart transplant, the patient did well; however, 1-year post-transplant, he presented for a follow-up transplant appointment and had a tobacco odor. The patient told the transplant team that he was around a family member who was smoking. Several weeks later, the patient was hospitalized with concerns for rejection. At this point, urinary cotinine was tested, which was positive for active nicotine use. The patient admitted to active tobacco use, and psychiatry was consulted for tobacco use counseling. On psychiatric evaluation, the patient reported that he relapsed about 2 months prior to admission due to worsening anxiety in the setting of relationship issues with his wife. Patient stated that he had been smoking about 1–2 cigarettes per day and that he lied to the transplant team due to feelings of guilt. He was interested in treatment interventions to help him achieve and maintain abstinence from nicotine.

Clinical Questions

1. How would you assess this patient's risk for tobacco relapse?
2. How can tobacco use be monitored pre and post transplantation?
3. What treatment options exist for transplant candidates and recipients regarding tobacco cessation?

Discussion

How Would You Assess This Patient's Risk for Tobacco Relapse?

Our first patient above demonstrated a good understanding of transplant, was adherent to medication, attended medical appointments, and had strong social support. She had no significant psychopathology and normal cognition; however, she had a history of severe tobacco use disorder, in remission. She used tobacco to cope with stressful situations in the past and made multiple attempts to quit with multiple relapses. The patient has low-to-moderate risk for tobacco relapse. She has maintained approximately 7 years of sobriety with the help of nicotine replacement therapy (NRT) with two relapses about 3 years ago. She notes that her family support system does not smoke tobacco; however, her sister was a source of stress leading to relapse in the past. The patient was not able to name many triggers for use. She was agreeable to attending a smoking cessation and abstinence group, evidence that she was motivated to maintain sobriety.

For our first patient, we constructed a treatment plan to assist her in maintaining abstinence from tobacco. First, she was offered psychoeducation. Given her good insight, good premorbid cognitive status, and limited understanding of her triggers for relapse and coping mechanisms, we suggested that she could benefit from a smoking cessation group. We provided psychoeducation related to the impact of transplantation on anxiety, which can increase her risk of relapse. At the time of evaluation, she was not using tobacco; however, if she was to relapse prior to transplant, we would recommend medication management with NRT since she had used this successfully in the past. Additionally, we coordinated with the transplant team to continue monitoring tobacco use through active inquiry and urine cotinine.

How Can Tobacco Use Be Monitored After Transplantation?

Given the high prevalence of post-transplant smoking, we should actively screen patients during the pre- and post-transplant period. Screening should begin with asking patients at every clinic appointment about any tobacco or nicotine use or cravings. In addition to self-reporting utilizing standardized questionnaires, urine cotinine levels have been shown to be reliable in assessing tobacco use [38]. Recommendations for monthly urine cotinine levels in the pre-transplant period and yearly in the post-transplant period have been suggested [38]. After transplant, measurement of urinary cotinine can aid in identification of continued nicotine use [6, 7]. Anabasine, a metabolite specific to tobacco use, is excreted in the urine and can be used to

evaluate continued tobacco use in people using NRT [43]. As nicotine and tobacco abstinence requirements in transplant patients vary, location- and organ-specific policies should be considered when determining abstinence monitoring.

What Treatment Options Exist for Patients Regarding Tobacco Cessation?

Addressing tobacco use with patients begins with education about the addictive and relapsing nature of tobacco use and continues with psychosocial interventions and medication-assisted therapy.

Psychoeducation: Since this patient has a history of tobacco use and relapse in the setting of stressors, it would be important to discuss risks of relapse, as well as the importance of informing her transplant team of any pre- or post-transplant stressors and cravings for tobacco use. About 44% of all cigarettes consumed in the U.S. are by those with psychiatric disorders [44]. Nearly 20% of kidney, 30% liver, and 60% of heart transplant recipients develop mood and anxiety disorders within the first 5 years which puts patients at higher risk of using tobacco [45]. Lung recipients are at significantly higher risk for panic disorder [45].

Brief Psychosocial Intervention: When patients are identified as smokers, providers can improve outcomes by first advising them to quit smoking and using motivational interviewing [46–48]. For patients ready to attempt quitting, evidence-based pharmacological and referral to psychosocial treatment (i.e., cognitive behavioral therapy, mindfulness skills) interventions or community-based resources can help with developing problem-solving strategies for coping with cravings and triggers [5]. In addition, there are national resources through the Centers for Disease Control and Prevention as well as the American Lung Association which are easily available online.

Nicotine replacement therapy (NRT): generally, NRT is used to treat nicotine withdrawal symptoms and promote smoking cessation [49]. There are five vehicles for treatment including a patch, gum, lozenge, inhaler, and spray. In a comparison of NRT vehicles, they are generally equal in efficacy [50]. Of the five vehicles, the patch is the only long-acting vehicle. In general, there are no significant adverse effects, hypertension, or cardiovascular disease associated with NRT [51, 52]. Compared to cigarettes, NRT has low-abuse liability [5]. Dosing guidelines, frequency of use, duration, and side effects of each of the vehicles are listed in Table 22.1. NRT is safe in advanced liver and lung disease, but severe renal disease reduces nicotine clearance [45]. NRT is relatively contraindicated in patients with serious heart disease due to the potential for worsening angina, increasing heart rate, and possibly exacerbating arrhythmias

Table 22.1 Vehicles for nicotine replacement therapy

Vehicle	Dose	Frequency	Side effects
Patch (OTC)	7, 14, and 21 mg	1 patch per day	Skin reactions, myalgias, vivid dreams, insomnia
Gum (OTC)	2 and 4 mg	One dose every 1–2 h	Mouth/throat irritation, mouth ulcers, hiccups, and chewing-related jaw ache
Lozenge (OTC)	2 and 4 mg	One dose every hour	Mouth and throat irritation, indigestion, hiccups, and gastrointestinal symptoms
Inhaler (prescription)	1 inhaler	6–16 cartridges per day	Irritation of the mouth and throat, cough, headache, nausea, runny nose, and gastrointestinal symptoms
Spray (prescription)	10-mL spray bottle	1–2 sprays per hour	Nose and throat irritation, coughing, runny nose, and watery eyes

[45]. The impact of e-cigarettes (vaping) on tobacco cessation is still under debate. A systematic review from 2020 indicated that there was limited evidence supporting e-cigarettes as treatments for tobacco use disorder [53]. In 2021, a systematic review of the literature found that there were no significant differences in smoking cessation, harm, and smoking reduction between e-cigarettes (vaping) and NRT [54].

Varenicline: Varenicline is a partial nicotinic receptor agonist. Like NRT, it is renally excreted. There are no significant drug–drug interactions with other medications. Varenicline is started 7 days prior to planned smoking cessation: The starting dose is 0.5 mg per day for 3 days, followed by 0.5 mg twice per day for 4 days, starting on the planned quit date, start 1 mg twice per day. This treatment will last 11–23 weeks; however, long-term use (up to 12 months) appears to maintain tobacco abstinence [55]. Major side effects of varenicline are nausea, gastrointestinal symptoms (constipation, flatulence, and vomiting), and sleep disturbances (insomnia, abnormal dreams). It carries with it a black-box warning for neuropsychiatric symptoms and severe cardiac symptoms. These side effects and the cardiac warning may be problematic in transplant patients [45].

Sustained-Release (SR) Bupropion: Bupropion is a norepinephrine and dopamine reuptake inhibitor [56]. Bupropion in its sustained release form has been shown to be effective for treating tobacco use disorder [28–58]. Bupropion SR is started 7–10 days prior to the planned tobacco cessation. The starting dose is 1 week of 150 mg every morning followed by 150 mg every 12 h for 8–12 weeks. The major side effects include difficulty sleeping and decreased seizure threshold. Given immunosuppressant can also reduce the seizure threshold, bupropion is typically not recommended in post-transplant patients [25, 45]. There is limited information on the drug–drug interactions between NRT and bupropion in transplant candidates

or recipients; however, NRT and bupropion are used safely in the general population.

Our patient is in the hospital at the time of our evaluation, which is an ideal time to offer counseling with ongoing supportive contacts for smoking cessation after discharge from the hospital [49]. In addition to counseling, nicotine replacement should be offered, especially if patients are experiencing acute nicotine withdrawal [49]. NRTs are generally safe in advanced liver and lung disease; however, severe renal disease may affect nicotine clearance. NRTs are contraindicated in patients with serious heart disease due to their potential for worsening angina, tachycardia, and exacerbating arrhythmias [45]. Bupropion could also be helpful in aiding smoking cessation; however, the risk of lowering seizure threshold must be taken into consideration. Varenicline is renally cleared and its side effects of nausea and vomiting may be problematic in transplant patients [45].

Take Home Points

1. Tobacco use is one of the most common and impactful substances of abuse for transplant patients.
2. Pre-transplant evaluation for tobacco use and assistance with cessation is a critical mental health role.
3. Monitoring for tobacco use after transplant should be done by clinical interview at all clinical appointments and with screening through biomarkers.
4. Psychiatrists should understand the treatments available for tobacco cessation, how to monitor tobacco use in transplant patients, and understand the risk factors for relapse.

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Gambling Disorders in Organ Transplant Recipients

23

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Introduction

Gambling disorder (GD) is defined as a problematic behavior in which people use something of value to obtain something of greater value that leads to negative consequences [1]. The negative consequences of GD have been well documented and include significant decreases in quality of life, increases in nicotine abuse, greater depression/anxiety, increased incidence of violence, criminal behavior, and negative effects on family [2, 3]. Patients with GD frequently have a history of childhood trauma [4]. GD was previously known as pathological gambling which is the term that was used in the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) [5]. The term pathological gambling was changed to GD in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) [6]. GD was also switched to the group of substance-related and addictive disorders instead of impulse control disorders since it has been shown that the activation of the reward system and behavioral symptoms in GD are comparable to those found in substance use disorders [6]. For its diagnosis, the DSM-V recommends that a person meets four of nine possible criteria in 12 months [6]. The criteria are (a) increasing amount of money gambled to get same effect; (b) irritability when trying to stop; (c) trying to stop or decrease gambling without success; (d) having persistent thoughts of gambling; (e) gambling to relieve distress like anxiety or depression; (f) going back to gamble to recover what was lost; (g) gambling has caused problems with relationships, work or education; (h) lies to significant others about the amount of gambling; and (i) uses others to help with financial problems related to gambling. In addition, gambling in GD cannot be associated with a manic episode [6].

Of note, GD can occur as a medication side effect of dopaminergic treatment in Parkinson's disease. In these cases, it belongs to a spectrum of behavioral disorders called the dopamine dysregulation syndrome (DDS) which also includes mood symptoms and impulsivity [7].

Some authors are arguing that DSM-V criteria does not capture the full array of gambling-related problems and have proposed a different classification: recreational gamblers (60% of a sample of 582 subjects gambling 5 times or more a year), problem gamblers (29.2% in the same group), and pathological gamblers (10.5%) [8].

Multiple studies have explored the neurobiological substrate of GD and have shown that patients with GD have altered impulse control related to frontal lobe dysfunction similar to those in addictive disorders [9–11].

The prevalence of GD is estimated to be between 0.5 and 6% in the United States and worldwide [12–19]. The prevalence of GD has been increasing in the past 20 years and is expected to continue to increase in relation to the increase in number of casinos and availability of online gambling [20, 21]. The prevalence of GD also appears to be higher in certain populations like veterans, adolescents, and young adults [22–24]. In addition, its prevalence may be as high as 33% in people with substance use disorders [25–27].

Patients with early (adolescent) onset GD have been found to have more medical problems later in life compared with general population [28]. GD is associated with increased risk of tachycardia and liver disease even after controlling for the presence of alcohol use disorder, mood, or anxiety disorders and body mass index [29].

Case History

BD was a 62-year-old man with long history of coronary artery disease, admitted for worsening congestive heart failure. The cardiology team asked for a psychiatric assessment as standard procedure for the evaluation for heart transplan-

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tation. The primary team had no specific concerns about his psychiatric state or behavior. A preliminary chart review indicated that patient was prescribed Escitalopram 10 mg daily by his primary care provider.

The patient was eager to speak to the psychiatry team. He clarified that the Escitalopram had been started approximately 7 years prior when he became depressed due to his medical problems and that the medication has helped his mood. He described his depression as being of moderate intensity years ago, never affected his self-care or safety and that he had not had any additional episodes of depression in years. He denied any history of psychosis, mania, anxiety disorders, substance misuse, or eating disorders. He denied any family history of psychiatric problems. His mental status examination was unremarkable.

At the time of this evaluation, patient was divorced, lived alone and mentioned his son who lived out of state and with whom he rarely spoke to. A niece who lived two towns away routinely checked on him after he was discharged home following a hospitalization. For the last several years, he had been able to live independently, except for 1–2 weeks after hospitalizations when he needed visiting nurse services and occasionally acute physical rehabilitation. He was receiving disability benefits. He described that he used to own a limousine company in a nearby state but in his early 40s, he developed severe coronary artery disease and he had to stop working. His described a monotonous life, with very limited social interactions and he could not describe any hobbies or enjoyable activities that he engaged into regularly.

The medical record showed that patient had been consistent with his regular outpatient medical care for many years. Over the years, patient had worked diligently with the nutritionist and other ancillary services as recommended. There was no concern about his adherence with medications, appointments, or lifestyle recommendations. Regarding the transplantation, he indicated that he "knew this was coming" for many years, he had had multiple discussions with his cardiologist about when and if he would pursue transplantation. He had good knowledge about the process, about post-transplant care, and he was very motivated to proceed as he wanted to maintain his quality of life.

At this point in the evaluation the interviewer detected a discord between patient's high level of motivation to pursue a complex medical intervention and his previous presentation of a monotonous and joyless life. Wishing to clarify further the factors that motivate the patient to pursue heart transplantation, the psychiatrist asked the patient what his expectations were for life after transplant surgery. Patient revealed he would like to continue to go to the casino and gamble, as he had been doing for years.

Should Screening for Pathological Gambling Be a Part of Routine Pre-transplant Mental Health Evaluation?

GD is a rare disorder in the general population. Full diagnostic interview for GD is time consuming and likely not practical in the transplant setting, as decisions often need to be made rapidly and patients do not have the physical ability to withstand a long interview process.

Several screening tools for GD have been developed (Table 23.1); however, their validity in medically ill patients has not been studied.

We are advocating that screening for GD should be considered as a part of standard psychiatric evaluation in groups with higher risk, such as adolescent and young adults, patients with comorbid addictive disorders and patients with a history of trauma. Hospitals who serve geographical areas with a high density of casinos or where online gambling is widespread should also consider screening for GD. At our center, we ask about gambling activities after completing the substance use history: "Do you gamble regularly?" If yes—"In what setting do you gamble- do you go to the casino/online/other?" "What is the most money you lost gambling in one day?" (an answer over $100/day would prompt a more detailed evaluation), "Has anyone close to you ever considered your gambling as being a problem?"

The diagnosis is based on the DSM-V criteria as described above and remains the gold standard [6]. For patients diagnosed

Table 23.1 Screening instruments for gambling disorder

Reference	Instrument	No of items	Comments
Lesieur et al., 1987 [30]	South Oak Gambling Screen (SOGS)	20	The most common scale used to assess GD Criticized for high rate of false-positive findings in various population groups
Hodgin et al., 2004 [31]	NORC DSM Screen for Gambling Problems (NODS)	17	Sensitive for severe gambling problems but low sensitivity for less serious problems, not suitable for settings that prioritize brief interventions
Back et al., 2015 [32, 33]	Problem and Pathological Gambling Measure (PPGM)	14	Better sensitivity and positive predictive power than NODS or SOGS
Miller et al., 2013 [34]	Problem Gambling Severity Index (PGSI)	9	Weak in assessing low-to-moderate problem severity, a notable limitation of most brief gambling screens

with GD, serum brain-derived neurotropic factor (BDNF) has been investigated as a potential predictor for treatment: a high BDNF level was associated with more severe gambling regardless of age or level of depressive symptoms. A significant decrease in BDNF level was associated with response to treatment as monitored by the Iowa Gambling Task[1] [35].

Case History (Continued)

Patient described that unless he was physically ill, he went to the casino 4 times a week, 3 weekdays, and one weekend day, between 6 pm and 10 pm. He never gambled more than $ 1500 or 4 h in 1 day, no matter which one occurred first. He proudly said that over the past 10 years, every year he had won more than he had lost and had made around 10 K per year in income this way. He used that to supplement his disability payments. He described skills he used to maximize his winnings, appeared to be very good at probabilities. He made sure to tell us he did not count cards but had a good memory.

He started gambling as a kid growing up on the streets of a big city. At age 17, he started lying about his age in order to get access to the casino. By the age of 23, he made enough money from gambling to start his own car business, which grew over the years. In his 20s, he did drink alcohol to intoxication repeatedly and tried various substances such as cocaine or cannabis but was able to stop for extended periods of times without any form of assistance. He married at age 29 and 2 years later his son was born. Following the birth of his son, his gambling and alcohol use increased to the point that impacted his marriage. After 6 years, his wife left him and took his son away. Following the divorce, the time and money he was spending gambling continued to increase. Soon after turning 40, his heart disease, which he had ignored for several years, worsened. Between hospitalization for ischemic events and continued gambling, he had to sell his business. He left the city and moved to the state where he is living now in a modest apartment. He joined Gambler anonymous (GA), a self-help group similar to Alcoholic anonymous. These changes empowered him to stop gambling and cease the use of alcohol, but soon he developed symptoms of depression. Escitalopram prescribed by his primary care physician helped his mood. After 5 years of financial stability on disability benefits, at the brinks of poverty, he resumed gambling. He utilized all the skills he had acquired add that GA meetings in order to keep his gambling under control. He remained abstinent from alcohol.

His niece confirmed that the patient had not used alcohol or any other psychotropic substances in years that he has been able to maintain functional and financial independence with the exception of the above-mentioned brief post hospitalization episodes when he needed more help from her and from visiting nurses. She knew that he plays poker regularly, but she did not know details about it. The social work evaluation concluded that patient had stable finances and the insurance coverage was sufficient to support post-transplant access to medical care. The family support was considered adequate to proceed with transplantation. The psychiatrist diagnosed GD in remission and Alcohol use disorder, moderate, in sustained remission.

How Can GD Influence the Care of Transplant Recipients?

There is no systematic evidence that GD directly impacts the medical or psychiatric outcomes after organ transplantation. GD is, however, frequently associated with conditions or psychosocial factors that may influence the transplantation outcomes: addictive disorders, including nicotine dependence, depression, and financial problems. Severe financial problems may impact patients' ability to afford post-transplant medical care. Patients with GD seem to have a higher risk of suicide [36], a high ED utilization rate, and medical co-morbidities [29] and a higher risks of somatic complaints [37] which can complicate the management in the pre and post-transplant setting. Interestingly, obsessive compulsive personality disorder (OCPD) appears to be a protective factor against progression from recreational gambling to pathological gambling [38].

Case History (Continued)

At the time of his initial psychiatric evaluation, our patient did not meet criteria for GD for the previous 12 months. Contrary to substance use disorders, GD diagnosis does not have any specifiers. If GD was treated as an addictive disorder, it would have been considered in "partial remission" (he was still gambling) and his use of behavioral skills to keep his gambling under control a form of harm reduction treatment.

Patient underwent heart transplantation 6 weeks after the initial psychiatric evaluation. His postoperative course was marked by extended delirium, physical deconditioning and 30 days of physical rehabilitation after discharge from the hospital. He recovered and was eventually sent home. For several months after transplantation, his attendance to clinic appointments and his adherence with medications were excellent.

Nine months after transplantation, he was hospitalized for shortness of breath and found to have a massive pulmonary embolism. He was in need of acute anticoagulation treatment

[1]Iowa Gambling Task (IGT)—a computerized assessment that evaluates decision making. Bechara, A., Damasio A.R., Damasio H., Anderson S.W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition, 50*, 7–15.

in the hospital, but he did not require intensive care. On the second day of hospitalization, an urgent psychiatric consultation was requested because patient wanted to leave against medical advice. His International Normalized Ration (INR) that morning was 4 and the team wanted to closely monitor him while adjusting his heparin and transition to warfarin. When seen by the psychiatric team, patient was alert, cooperative, and coherent with no evidence of delirium. He was able to recite all the risks of leaving the hospital at this point in treatment, and he readily acknowledged that it is a day when he typically went to the casino to meet with his gambling buddies. He pointed out that he had been very open with the transplant team about his activities, and he must be allowed to leave the hospital because he was entitled to make a life choice. He agreed to allow the psychiatric team to speak with his niece who revealed that patient's gambling had been accelerating in the last month, to the point that he was spending full nights at the casino. The niece had been increasingly concerned because when she visited him the fridge was empty, he had fired his visiting nurse and was not taking all his medications. She did not know details, but she suspected the patient had an argument with his son and that sent him in a self-destructive spiral. When confronted with this information, patient acknowledged that he became angry after a dispute with his son and decided "to live my life to the fullest." He realized that the effort to keep his gambling under control was exhausting and it was only gambling that made him "feel alive." As he was making this statement to the psychiatric team, the transplant social worker interrupted the evaluation to inform the patient and the team that patient's insurance had lapsed and if discharged home, he could not receive his anti-rejection medications for 2–3 weeks. Patient acknowledged this and continued to ask for discharge, stating that "I will take my chances, I do not think my body will reject my heart."

The psychiatric team concluded that the patient lacked capacity to sign out AMA as his GD was now active and interfering with his judgment. Despite angry about this assessment, patient remained in behavioral control and cooperated with his medical treatment. He was discharged 4 days later with a therapeutic INR and with his insurance benefits reinstated and outpatient services in place. With encouragement from the psychiatry team, he reconnected with GA and agreed to resume attending the meetings. He also agreed to make his niece a temporary payee, at least until his gambling is better controlled, in order to reduce the financial impact of his GD. Individual psychotherapy was recommended in order to help him improve his relationship with his son. He never returned for psychiatric follow-up, but records indicated that 1 year later he was following up with his transplant team, his medication levels were therapeutic and his niece continued to be his financial representative and primary support.

What Interventions Are Available for Pathological Gambling and Can They Be Implemented Before or After Transplantation?

When a clinician makes a GD diagnosis, it is important to perform a full mental health assessment to identify potential psychiatric co-morbidities such as anxiety disorders, mood disorders, or addictive disorders. Medications need to be reviewed to ensure gambling is not a side effect of a dopaminergic agent. In the transplant setting, it is important to review adherence with treatment (which may be impacted by the gambling itself like being too absorbed in gambling to remember about medications or appointments). Assessing the patient's social support and finances may reveal sequalae of prior severe GD, when patients become estranged from their families and/or sustain severe financial losses that make housing and health care unaffordable.

At present, there is no Food and Drug Administration (FDA) medication-approved medication for GD. A meta-analysis on opioid receptor antagonist, mood stabilizers, and antidepressant found that these agents were all equally more effective than placebo in randomized controlled trials [39]. Subsequently open studies found memantine [40], ecopipam[2] [41], naltrexone [42, 43], nalmefene [44], and paroxetine [45] to show positive effects in treatment of GD. To our knowledge, there are no studies comparing pharmacotherapy with psychosocial treatments and no reports of these treatments in transplant patients. Pharmacotherapy for GD appears to be helpful when treating comorbid disorders such as bipolar disorder, depression, substance use disorder, attention-deficit hyperactivity disorder, or obsessive compulsive disorder that are often present in patients with GD [46].

The main psychosocial interventions for GD are Gamblers Anonymous (GA), cognitive therapies, cognitive behavioral therapy, and motivational interventions. Several psychosocial interventions have been assessed in controlled studies to manage GD [47] and a meta-analysis of psychosocial interventions for GD showed promising results, but more studies were felt to be needed [48]. In addition, few people follow up on referrals for psychosocial treatments [49]. A helpful resource for gamblers and their family members is the website for The National Council on Problem Gambling (www.ncpgambling.org) where one can find information on Gamblers Anonymous, Gam-Anon, and counseling services. On-line interventions for GD are showing promising results [50].

Social interventions are aimed at mitigating the financial impact of gambling through referral to assistance programs or help with appointing a financial representative which can reduce some of the impulsive spending.

[2]A Dopamine 1 receptor agonist used in treatment of Tourette's syndrome. In the US, FDA approved it as an investigational drug in 2020.

Ideally, treatment should be available and completed before patient proceeds with transplantation, in order to reduce the risks of GD escalating after transplantation. On our initial evaluation pre-transplantation, our patient had already had psychopharmacological (an SSRI) and psychological treatment (through GA) and was using the behavioral skills with good effect. We did not think that any additional treatment would have been contributory. Many transplant candidates are too ill at the time of the evaluation and listing to participate in psychotherapy. Our patient had to wait for 6 weeks in the ICU for his heart transplant. Social interventions, such as involving family in education about GD and appointing a payee to reduce the financial impact of gambling, can be theoretically accomplished in the acute medical setting, either pre or immediately post-transplantation.

There is no literature to guide the long-term follow-up for GD once the disorder is in remission. Clinically, asking the patient if there has been a change in his/her gambling activity may reveal a recurrence of GD. If the patient solicits help from the transplant team (typically social worker) with financial difficulties, such as not affording medications, and the patient lives in an area where gambling is common, this may be an opportunity to inquire about gambling behaviors and its impact on the patient's life.

Take Home Points

1. Screening transplant candidates for GD should be considered in geographical areas where gambling is common and in high-risk clinical populations, such as young adults, patients with addictive disorders or patients with a history of trauma.
2. GD can impact the post-transplant course through treatment interfering behaviors (such as leaving against medical advice or non-adherence with medications) and through the financial impact which can lead to deterioration of patients' social stability and indirectly impact their ability to participate in post-transplant medical care.
3. Psychological treatments and psychotropic medications can help reduce symptoms of GD and address psychiatric co-morbidities.

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Part IV

Psychiatric Disease and Systems of Care in Organ Transplantation

Challenges in the Patient–Clinician Relationship

24

Devendra S. Thakur, Melissa M. Ley-Thomson, and Brittany Wade

Introduction

The care of transplant patients with significant psychiatric illness is fraught with challenges. Such patients face significant stressors in the form of the initial organ failure (which itself is often a life-or-death matter), the waiting period (which is generally characterized by anxiety and uncertainty, and during which organ function may further decline), and the transplantation process, which involves a complex surgery, the risk of complications, dependence upon others for support and care, and a lifelong need for post-transplant care [1, 2]. During the post-transplant period, a serious concern is the effect of psychiatric symptoms and maladaptive behaviors on adherence with post-transplant care plans [3, 4].

Personality disorders pose a particular challenge. The demands of the organ transplantation process require significant adaptations in physical, psychological, and social functioning, including the ability to cooperate with the transplant team. Personality disorders, which are characterized by rigid and persistent maladaptive patterns of behavior, lead to impaired interpersonal relationships and social functioning [5]. Perhaps not surprisingly, personality disorders have been associated with reduced quality of life and poorer outcomes after transplant [6].

According to one survey, some US transplant programs consider personality disorder to be an absolute contraindication to transplant (14.1% of heart transplant programs, 8.7% of liver transplant programs, and 5.2% of kidney transplant programs) [7]. Another study showed that borderline personality disorder specifically was associated with weaker social support, a tenuous working relationship with the transplant team, and non-adherence to post-transplant care plan [8]. Certain personality disorders can exacerbate other known risk factors for poor outcome after transplant. For example, a study, revealed that 50% of patients with antisocial personality disorder and comorbid substance use disorder-resumed alcohol or other substance use after liver transplant, compared to 20% of patients with substance use disorder alone [9]. Steroid medications needed after transplantation can exacerbate the affective volatility often displayed by patients with Borderline personality disorder [10].

In this chapter, the authors describe a complex case that illustrates how personality disorders can create challenging patient–clinician relationships, and how these relationships can be adjusted to still provide quality care despite these difficulties. These relationships are considered broadly: between the patient and her doctors, her nurses, her rehabilitation therapists, her inpatient psychotherapist, and the hospital system.

Case History

Ms. S is a 32-year-old woman with a past medical history significant for systemic lupus erythematosus (SLE), end-stage renal disease (ESRD) secondary to lupus nephritis, cadaveric donor renal transplant in her 20s, chronic pain (on chronic opioid therapy), TBI caused by an all-terrain vehicle accident, anxiety, and BPD. She was in regular contact with a therapist in the community, but not consistently taking psychotropic medications. Her therapist diagnosed Ms. S with borderline personality disorder and recommended dialectical behavioral therapy (DBT). While Ms. S strongly agreed with this diagnosis, she found it logistically challenging to participate in a DBT program. Ms. S was initially diagnosed with SLE in her mid-teens; in her late teens, she developed lupus pericarditis with tamponade, lupus cerebritis, and class IV proliferative glomerulonephritis. By her early 20s, she was hemodialysis dependent, eventually resulting in high-risk deceased donor renal transplant. Her post-transplant course was notable for fluid overload, Legionella pneumonia, multiple urinary tract infections (UTIs), and rising creatinine,

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necessitating at least nine acute hospitalizations over the subsequent 5 years.

During an admission several years later, renal biopsy showed evidence of antibody-mediated rejection and recurrent lupus nephritis. Ms. S received pulse steroids, thymoglobulin, apheresis, and rituximab, with initial benefit, but kidney function again began to decline. The primary team and nursing staff expressed increasing frustration with her hospital stay was marked by affective lability, behavioral dysregulation including self-injury or threats to self-injury, and provocative statements and actions—all of which progressively intensified in the setting of declining renal function.

For instance, early in the hospital stay, psychiatry was consulted when Ms. S was hitting herself in the head with the hospital phone and making statements about her desire to be euthanized, to slit her wrists, or to "go on a shooting rampage." At other times, she engaged in yelling profanities at staff, physical aggression toward staff, intentionally urinating on the floor, intermittently refusing treatment, using material from the cot in her room to superficially cut her wrists, and attempting to make a noose in the bathroom. When questioned about these behaviors, Ms. S was adamant that they reflected her high level of emotional distress and not a true desire to end her life.

Outside these episodes of dysregulation, patient was able to calmly discuss the profound impact that the combination of lupus, TBI, and BPD, had had on her life. Ms. S demonstrated good insight into her BPD and reflected on the ways in which she identified with that diagnosis. She acknowledged her tendency toward black-and-white thinking, unstable relationships, identity disturbance, impulsivity, and difficulty modulating her anger. She discussed her tendency to want to inflict the difficult emotions she felt onto others, to lash out in moments of anger, and later to regret those words and actions.

Despite her insight, her anger outbursts escalated in the context of the news that her renal graft was failing, the addition of high-dose steroids to treat acute inflammation, and the extended hospitalization this required.

Throughout the hospitalization, psychiatry was called for numerous episodes of dysregulated and provocative behavior. The psychiatric consultants sought to modify these behaviors by aligning with Ms. S on her goals to save her kidney and safely discharge from the hospital and by exploring behavioral strategies for achieving these goals with her. She was receptive to reframing her narrative in terms of agency rather than helplessness, identifying behaviors that moved her toward her goals and engaging in skill building to replace goal-interfering behaviors. Ms. S was able to discuss specific steps she could take, including consenting to timely treatment and focusing her energies on healing rather than directing them toward conflict with staff. Psychiatry recommended and modeled verbal de-escalation and provided recommendations regarding the use of medications for agitation and physical restraints only if absolutely necessary. While security presence and medication administration were sometimes helpful in the short-term to re-establish safety, they were perceived as punitive and authoritarian by Ms. S and carried the risk of escalating conflict in the longer term.

During her repeated hospital stays, Mr. S's made frequent threats or attempts to leave against medical advice (AMA), which prompted repeated evaluations of patient's capacity to make such decision. On one occasion, after being told that her pain would be treated with PO hydromorphone rather than with the IV formulation she requested, she declined the PO medication, yelled profanity-ridden insults at staff, ran around the unit threatening to pull out her port, and insisted on leaving AMA. When psychiatry arrived to assess her capacity to leave AMA, she was crying and said "if I had a piece of glass, I would cut my throat right now" and "you will see me in the obituary on Monday morning." She was unable to show an understanding of the risks of leaving the hospital at that moment and found to lack capacity to sign out AMA. In general, when in a heightened emotional state, she was unable to demonstrate appropriate understanding and appreciation of her clinical situation or to engage in rational manipulation of information, and she lacked capacity to choose to leave AMA. Verbal de-escalation was typically unsuccessful in such instances, so haloperidol would be offered, which provided temporary benefit. When calm, patient displayed good knowledge about her medical condition and high level of insight into her psychiatric problems. These fluctuations in capacity to make decisions about her medical care were distressing to the medical staff, especially as her renal function deteriorated, and refusal of care could lead to increasingly serious consequences, including death. Medical staff also expressed confusion and disagreement about management strategies (such as use of security presence, involuntary medications, restraints, and a behavioral plan with clear consequences). Psychiatry helped to set realistic expectations with caregivers that meaningful behavior change would require long-term treatment outside of the acute care hospital setting, and emphasis was placed on interventions focused on goal alignment, achievable behavior modification, and patient empowerment. Although this contributed to increased cooperation with care and fewer behavioral outbursts, dangerous treatment-interfering behaviors persisted. In order to manage them, psychiatry utilized a combination of verbal de-escalation, one-to-one sitters, security presence, psychotherapy, and medication management, to ensure patient and staff safety.

Clinical Questions

1. How can a psychiatric consultation team help primary teams with the care of transplant patients with complex medical and psychiatric comorbidities, particularly when patients struggle immensely with interpersonal management?

2. What strategies can help transplant patients with personality disorders who at times engage in treatment-interfering behaviors?
3. How can teams caring for transplant patients manage acute behavioral crises to maintain safety while also promoting the patient's relationship with providers (and thereby increasing positive engagement with post-transplant care) over the longer term?

Discussion

Ms. S exhibited extreme emotional dysregulation and impulsivity during her recurrent hospitalizations as she struggled to cope with post-transplant complications and lengthy hospital stays. Her high level of psychological distress interfered with delivery of care, posed challenges to her safety as well as the safety of staff and other patients, and elicited feelings of helplessness among providers. Interpersonal hypersensitivity—dramatic shifts caused by fluctuating interpersonal contexts—was pronounced as nurses and medical staff rotated on and off the medical team [11]. Ms. S cycled between idealizing and devaluing providers, struggled to negotiate social boundaries, and felt distrustful of the intentions of her care team.

To address these challenges, the psychiatric consultation team employed a multilayered approach, including (1) initiation of psychotherapy to support Ms. S in coping with illness and hospitalization and working to improve interpersonal management, (2) direct psychiatric consultation to the primary team, (3) liaison with the interdisciplinary healthcare team on psychiatric and behavioral management, and (4) formal training for nursing staff on management of BPD in the acute care setting.

Initiation of Psychotherapy

Dialectical Behavior Therapy DBT is an evidence-based form of psychotherapy that teaches emotional regulation, interpersonal effectiveness, distress tolerance, and self-management skills. It is based on the dialectical perspective that absolute and indisputable facts do not exist and aims to teach how to balance opposing points of view—particularly acceptance and change [12]. Numerous studies demonstrate the efficacy of DBT for the treatment of BPD [13–16], and it is suggested that DBT skills can be adapted to the treatment of challenging patients in the general hospital [17].

To support Ms. S in coping with post-transplant complications and extended hospitalization, a consulting psychotherapist met with her multiple times per week over the course of her multiple inpatient stays. The therapist employed DBT-informed interventions, such as supporting emotion regulation by practicing recognizing emotions in the moment without giving in to emotional urges and increasing interpersonal effectiveness by expressing needs with appropriate language. These interventions focused on bolstering Ms. S's ability to tolerate distressing medical events, navigate relationships with her interdisciplinary healthcare team, and employ skills to regulate her emotions. The therapist also assisted Ms. S in identifying goals for her health, determining questions for her care team, and building awareness of physical manifestations of psychological suffering to aid in symptom management. Ms. S built a strong rapport with the therapist, who was able to effectively diffuse crisis situations, prompt the use of skills in the moment, and provide positive reinforcement. Ms. S benefitted from a warm, supportive, and empathetic therapeutic approach balanced with consistency, boundary setting, and direct feedback. It was recommended that she engaged in outpatient DBT after discharge to best prepare her to cope with ongoing post-transplant care and the possibility of organ failure. For units where inpatient intense psychotherapy is not available, the mental health consultant and the primary teams can utilize DBT-informed techniques such as distress/affect validation, limit setting, enhancing continuity of care by having same providers whenever possible, and reinforce positive coping skills (such as encouraging use of mindfulness techniques).

DBT theory suggests that engaging family members of patients with BPD can help them to build a greater understanding of their loved one and involve them in reinforcing skilled over unskilled behavior [12]. The consulting therapist worked with Ms. S's family, who worried she was not receiving optimal care as a result of her mental illness and struggled to cope with watching her suffer, at times resulting in conflict with the medical team. Gathering family collateral was invaluable in helping the psychiatric consultation team develop a more holistic understanding of Ms. S's personality, character, strengths, and challenges. By engaging her mother, who had served as her main support person since her initial lupus pericarditis diagnosis, the consulting psychotherapist gleaned insight into Ms. S's triggers, and learned what the family had found effective for de-escalation. The therapist provided psychoeducation on BPD and how the general hospital setting is exacerbatory, validated their experience, and communicated the interventions being employed by the psychiatric consultation team to equip Ms. S's caregivers to provide psychiatrically informed care and build a consistent customized care plan. Joint sessions were held with Ms. S and her family to build a collective understanding of both the medical and therapeutic plan. In addition to facilitating conflict resolution between the patient and her family, involving family in this way helped to reduce the splitting occurring between the patient's family and hospital staff. The therapist provided psychoeducation to the family on DBT skills being taught in individual therapy so they could assist with skills coaching between sessions. The therapist also met independently with Ms. S's mother to facilitate emotional processing

as she grappled with the role of being a caregiver to a child with chronic illness and BPD. This approach increased the family's confidence Ms. S was receiving quality care, fostered a greater sense of trust in her caregivers and shifted the family–provider dynamic from that of conflict to collaboration.

Direct Psychiatric Consultation to the Primary Team

In working with a seriously medically ill patient with BPD, a primary goal of the psychiatric consultation team should be early intervention with hospital staff to foster understanding of the patient's behaviors and strengthen their ability to provide empathic and non-punitive care to the patient [18]. The psychiatric consultation team sought to accomplish this by providing regular direct consultation to the providers caring for Ms. S, as well as participating in interdisciplinary meetings.

One issue the team struggled with was determining whether Ms. S had the capacity to leave AMA. They initially expected the psychiatric consultation team to provide a definitive answer as to whether or not she had capacity in general, so that this could be clearly documented and then either she could be discharged, or decision making would be deferred to an alternate decision maker. However, Ms. S only expressed a desire to leave AMA during acute periods of dysregulation, during which she was unable to participate in a discussion of risks and benefits, or values and future plans [19]. Although she clearly did not have capacity to make the decision to leave AMA during these times, a determination that she lacked capacity in general would not have been consistent with how she usually presented when not acutely dysregulated. At these other times, she was cooperative with care and focused on getting all necessary medical treatment, and she was able to describe her previous treatment refusals and expressions of wanting to leave AMA as reflective of her emotional state rather than of her actual values and goals. With this understanding, the psychiatric consultation reframed the question of capacity for the primary team, helping them to consider Ms. S's fluctuating decision making as a feature of her BPD that would best respond to strategies specific to that disorder (see below), rather than as a shift in cognitive ability or in values that would require the usual legal and ethical approach involved in assessment of decision capacity.

Ms. S's self-harm behaviors, suicidal behaviors, and statements, and violent behaviors and statements also posed a significant challenge for the medical team. Similar to her impairments in decision-making capacity, her inability to remain safe was not persistent but rather episodic and presented during periods of acute emotional dysregulation. Ms. S had difficulty with her providers' responses to her provocative statements and dangerous behaviors; when she was calm and appropriate, she expressed frustration and confusion at precautions (e.g., 1:1 sitter, security searching her room, a "safety tray" for meals with no silverware) which were instituted after behaviors that occurred hours or days prior. The psychiatry consultation team validated the primary team and nurses' desire to keep Ms. S, other patients, and staff safe, while highlighting the role that the hospital system plays in exacerbating the situation (especially through inconsistent responses by different providers). The psychiatry consultation team helped develop an approach to safety that was neutral to positive and consistent, by developing a behavioral plan that used language focused on highlighting Ms. S's agency, allowed for flexibility when appropriate, and clearly delineated consistent responses to unsafe behaviors.

One such response was the utilization of one-to-one sitters to prevent recurrent self-harm. The psychiatric consultation team recommended direct observation by a sitter following any self-harm behavior and maintenance of observation until Ms. S had gone more than 24 h without any further unsafe behavior. Although there is a lack of evidence supporting the efficacy of sitters in reducing self-harm, alternative approaches, namely pharmacotherapy and physical restraints, are associated with an increased risk of severe complications, thereby making constant observation a key component of a multi-modal approach to maintaining patient and staff safety [20, 21]. Ms. S's tendency to idealize and devalue providers, to engage in denial of unacceptable aspects of reality, and to struggle with change, were especially apparent in her response to the one-to-one sitters. She effusively praised certain sitters, commending their empathy and crediting them for her success in refraining from self-harm, while she was distrustful and rageful toward others. When expressing bafflement and annoyance at having a sitter, the psychiatric consultation team explained that the one-to-one observation was necessary due to Ms. S's self-report of difficulty managing her behaviors when dysregulated, reiterating that it was not in place for acute suicidality but rather due to impulsive self-harm. Psychiatry worked with nursing and the primary team to ensure that all members of the care team understood and consistently communicated this reasoning.

During periods of such extreme emotional dysregulation that Ms. S demonstrated an imminent risk to harm herself or others, the psychiatric consultation team recommended utilization of emergency medications, specifically haloperidol or olanzapine. Haloperidol's minimal drug interactions make it a frequent choice for treating acute agitation and self-directed violence in medically compromised patients [21, 22]. Given that haloperidol can cause QTc prolongation with associated risks, the psychiatric consultation team recommended to obtain a baseline EKG prior to initiating haloperidol as well

as daily EKGs when haloperidol was being utilized. The primary team was encouraged to offer Ms. S. the oral formulation of the medication in an effort to increase her sense of control. Similarly, when Ms. S later expressed a preference against haloperidol, psychiatry counseled her about other options and honored her request to transition to olanzapine when verbal de-escalation alone was not sufficient to maintain safety.

Consultation to the Interdisciplinary Care Team

In addition to the direct psychiatric consultation provided in order to aid the primary team in managing agitation and resolving issues of decisional capacity, a series of interdisciplinary "complex care meetings" were held to discuss challenges that various team members faced in caring for Ms. S and to determine goals to guide interventions. These meetings involved primary and consulting physicians, the therapist from the psychiatry consultation team, nursing leadership, rehabilitation therapists, nurses, care management, risk management, and hospital security. These meetings aimed to answer the following questions: (1) How can we support the patient with emotional regulation such that she can meet her goal of receiving essential post-transplant care? (2) How can we prevent burnout and support staff while they support the patient? and (3) How can we focus the treatment team's energy to minimize harm and disruptive behavior while delivering efficient and quality post-transplant care?

A crucial role of psychiatric liaison is to educate and support medical caregivers of patients with borderline psychopathology [18]. The psychiatric consultants provided education on BPD in order to help Ms. S's care team to contextualize her behaviors as symptoms of an illness, thereby allowing them to more objectively interpret the behaviors and curb their own emotional responses. The psychiatric consultation team also set expectations for the larger interdisciplinary team, based on this shared understanding—namely that the destabilizing acute care setting is not conducive to promoting long-term behavior change in patients with BPD. Thus, the team was encouraged to invest energy into tailoring care to minimize triggering emotional dysregulation in the patient. These meetings also served as a forum for the interdisciplinary team to openly express feelings and share authentic dialog about the strong reactions elicited by caring for Ms. S. The psychiatric consultation team validated the challenging role of caring for a patient with complex medical and psychiatric comorbidities and normalized the tumultuous emotional landscape of working with patients with BPD.

From the discussions held during these meetings, a formal behavioral care plan was developed. This plan described (1) reasons for a care plan, (2) post-transplant diagnostic procedures and treatments to be accomplished, (3) a medication protocol, (4) a consistent nursing plan, (5) environmental safety modifications, (6) supportive services, and (7) psychiatric management. Specific strategies that were highlighted included scheduled interdisciplinary team rounding, clustered nursing care, consistency in nursing assignment, scheduled medication, and a clear protocol for responding to safety concerns. The various functions of the psychiatric team, including psychotherapy, capacity evaluation, safety assessment, and medication management, were clearly outlined for ease of utilization. A copy of this plan was scanned into the patient's medical chart for ease of access by team members across admissions. Additionally, referrals were placed to inpatient supportive services, including therapeutic massage, reiki, visual and writing arts, chaplaincy, and pet therapy, to support Ms. S during her admission.

Nursing Education

Studies demonstrate a need and desire for greater nursing education on management of BPD and self-harm, to empower nurses to confidently care for this complex population [23–25]. Over the course of Ms. S's recurrent admissions, numerous nurses who cared for her articulated feeling helpless and regularly sought out recommendations from the consulting psychotherapist on how to best navigate the interpersonal relationship. It was determined, in collaboration with nursing leadership that the therapist should deliver a formal training for nurses on management of borderline personality disorder in the acute care setting.

The training first provides an overview of the diagnostic criteria for BPD and explains the biosocial theory of BPD. This theory, developed by Marsha Linehan, suggests that BPD develops from a combination of biological sensitivity to emotional vulnerability and impulsivity, coupled with an invalidating and ineffective social environment in childhood [12]. It explores the invalidating aspects of the hospital setting to help nurses identify potential triggers for emotional dysregulation and recommends that nurses validate emotional reactions to unavoidable triggers to prevent further perceived invalidation. The content includes common core conflicts that arise in caring for patients with BPD, including difficulty with optimal interpersonal distance; tendency to perceive rejection, criticism, or abandonment; impaired impulse control; a worldview of others as either all good or all bad; preoccupation with blame; learned helplessness; perception of feelings as facts; and poor adaptation to change.

The next portion of the training focuses on strategies for managing these core conflicts in the acute care medical setting. A major focus is on balancing boundaries and flexibility in acknowledgement of the fast-paced, ever-changing, and at

times chaotic nature of the hospital environment. Emphasis is placed on avoiding reinforcement of black-and-white thinking, by not promising consistency in an environment that is fundamentally inconsistent, and instead preparing patients with BPD for this reality and supporting them in coping with it. Other strategies include explaining reasoning with pragmatism, giving the patient a choice when possible, compromising with a shared goal in mind, being consistent in enforcing non-negotiable boundaries and policies, proactive expectation setting, avoiding unnecessary power struggles, modeling accountability, and using neutral-to-positive language. The common experience of "staff splitting" is discussed and reframed as an unskillful attempt to meet a need, which has worked in previous dysfunctional environments, to discourage nurses from personalizing what is often perceived as manipulation. Self-harm and suicidal behaviors are explained within the context of BPD to assist nurses in recognizing safety concerns and to help them understand the function that these behaviors play in borderline psychopathology. Techniques for crisis de-escalation are taught, including verbal de-escalation, environmental modification, and prompting the use of previously taught DBT crisis survival skills.

The final part of the training covers recommendations for preventing nurse burnout in caring for patients with BPD. Limiting patient interactions as clinically appropriate, managing boundaries, reframing interpersonal challenges within a BPD framework, utilizing the support of colleagues and supervisors, and engaging in self-care inside and outside of work, are all recommended. To complement the educational series, the consulting therapist met separately with nursing leadership to discuss ways they can support their staff.

Feedback from nurses who attended the formal training sessions was overwhelmingly positive, and nurses reported feeling more equipped to provide quality care to patients with BPD. In addition, attendees reported feeling more supported by the psychiatric consultation team and nursing leadership in caring for patients such as Ms. S.

The individual, team-based, and systems-level interventions employed in caring for Ms. S demonstrate how multilayered psychiatric intervention has the potential to bolster the capacity of acute care hospitals to deliver quality care to transplant patients with BPD, and meaningfully improve post-transplant outcomes for this complex population.

Take Home Points

1. The care of complex patients with multiple medical and psychiatric comorbidities, especially transplant patients, can be meaningfully improved by expanding beyond the traditional consult-to-provider model, toward interventions such as team-based psychoeducation and formal staff training.
2. Providing evidence-based forms of psychotherapy, such as DBT, to transplant patients with personality disorders during an acute care hospitalization, can reduce care-interfering behaviors, improve patient–clinician relationships, and promote development of skills that bolster compliance with ongoing post-transplant care.
3. In cases of intermittent agitation and dangerous behaviors arising within the context of severe emotional dysregulation, measures that may be perceived as authoritarian or punitive (such as placement of a one-to-one sitter, administration of as-needed medications, involvement of hospital security, and especially use of physical restraints) should be avoided except when absolutely necessary. Furthermore, incorporating these measures into a formal behavioral plan, as part of a "last resort" response to acute unsafe behaviors, helps providers to maintain consistency, increases transparency, and promotes patients' agency.

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The Multiple Roles of the Transplant Psychiatrist

25

Michelle Nichols and Paula C. Zimbrean

Introduction

The need for psychiatric assessment and care in transplant patients became obvious early on, with the first reported cases of "graft psychosis" in the 1960s [1] and the observed psychiatric side effects of immunosuppressants [2]. Over the following two decades, many reports suggested that untreated psychiatric conditions could negatively impact patient outcomes, as many chapters of this volume illustrate. Psychiatric symptoms have been associated with non-adherence with medical treatment [3, 4] and a lower quality of life independent of the medical status of transplant recipients [5]. As the organ shortage became an issue of increased public health concern, mental health providers were increasingly asked to help with selecting the candidates with better chances of survival and less likelihood of post-surgical complications [6, 7]. Transplant mental health clinicians play a significant role in the pre-transplant evaluation and risk stratification pre-surgery [8, 9].

Knowledge from short- and long-term follow-up of transplant candidates and recipients has supported the significant need for ongoing mental health services in transplant patients. This stems from several factors: high prevalence of psychiatric illness in patients with end-stage organ disease [10, 11], worsening of psychiatric symptoms related to the stress of physical illness, uncertainty of transplantation, psychiatric sequelae of the surgery [12], and psychiatric side effects of immunosuppressants [13, 14]. In addition, recent literature has supported the position that patients with severe psychiatric diseases, such as psychotic disorder, can be successful transplant candidates provided that they receive adequate psychosocial support [15, 16]. Attempts have been made at implementing mental health programs within transplantation centers focused on behaviors or psychiatric symptoms directly related to transplant eligibility [17] and adjustment post-transplantation [18].

In this chapter, we will discuss a case illustrating the pre-transplant evaluation and long-term post-transplant follow-up of a kidney transplant recipient with bipolar disorder. This case illustrates the various roles of the transplant psychiatrist at specific points in the patient's journey which began before dialysis was needed and continued years after patient underwent transplantation surgery.

Case History

At the time of initial presentation to the transplant center, DC was a 61-year-old woman with history of bipolar disorder type I who was referred for potential kidney transplantation. Five years prior she had developed chronic kidney disease thought to be related to lithium treatment. She arrived for her pre-transplant psychiatric evaluation with a letter written by her treating psychiatrist stating that patient had a diagnosis of bipolar disorder in remission and that she was an "excellent candidate for kidney transplantation."

D.C. had been diagnosed with bipolar disorder in her early 20s, 6 weeks before her wedding. She was hospitalized in her native European country and stabilized on lithium in less than 2 weeks. Shortly after discharge from the hospital, she married and moved to the United States. In going through the US naturalization process, immigration authorities mandated that she continue to see a psychiatrist for treatment of her bipolar disorder. She subsequently had no episodes of mania or depression for decades and oftentimes wondered if she still needed to take the medication. However, she was fearful her visa might be revoked if she discontinued her medication, so she continued lithium and her monthly psychiatric visits. She did not recall having blood work done during this time. Over the years, she maintained part-time

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work as a secretary, raised her son, became very active in her grandchildren's upbringing, and maintained her hobby of painting, even participated in several local exhibitions. When her first psychiatrist retired, her primary care provider (PCP) continued to prescribe lithium. During one of her regular checkups, it was noted that her blood urea nitrogen (BUN) and creatinine (Cr) values were abnormal, and she was referred to nephrology.

She was diagnosed with lithium-induced kidney disease and recommended that she stopped taking lithium. Eight weeks after lithium was discontinued, she started to develop hypomania. She was then referred to an outpatient psychiatrist (Dr F.) for additional management.

A difficult year followed. Her mood fluctuated between depression and mania for which he was hospitalized once. Records described her being in a quasi-catatonic state requiring close to 10 weeks of hospitalization. The catatonic features responded to lorazepam 1 mg three times a day; however, her mania persisted, with lack of therapeutic response to risperidone up to 6 mg daily for 2 weeks and no benefit from lamotrigine up to 300 mg daily. She could not tolerate divalproex due to severe tremor nor quetiapine due to dizziness and orthostasis. Eventually, she was stabilized on the following regimen: olanzapine 10 mg in the morning and 20 mg at bedtime, carbamazepine 600 mg twice a day, clonazepam 0.5 mg at bedtime, and perphenazine 16 mg in the morning and 32 mg at bedtime. Although she had been off lithium for almost 1 year, her creatinine continued to deteriorate to the point of dialysis was recommended.

About 2 months after this extended psychiatric hospitalization, she was referred for transplant evaluation. She was a pleasant woman who denied any current symptoms of mania or hypomania but reported significant anxiety primarily related to her medical problems. Her sleep was interrupted by anxious ruminations about life on dialysis. She had no motor side effects with the above medications. Her family was very supportive and knowledgeable about patient's psychiatric disease. She had no history of suicidality, self-harm, or substance use. Psychotic symptoms in the form of grandiose delusions and disorganized thought process had only been present during manic episodes and were absent at the initial interview. She had no significant cognitive impairment (Montreal Cognitive Assessment MOCA 7.1 score was 26). She was motivated to get better, and there were no concerns about treatment adherence. During the initial interview, she indicated that she was aware of the average wait times for a kidney graft. However, she was convinced that the transplant center will find her a living donor soon, "because I am such a great artist and I have to continue my artistic work." She eagerly described, with mildly pressured speech, that she is working on 5 paintings, out of which one was "big as my living room wall, I need that much space because it will illustrate the ultimate triumph of life."

At the time of the initial evaluation, the transplant psychiatrist connected with the outpatient psychiatrist to obtain a full history and coordinate care.

Another point of the discussion with the outpatient psychiatrist was patient's understanding of transplantation. The transplant psychiatrist provided Dr. F. with a brief overview of the pre-transplant evaluation, waiting times in the region, and the process of finding a living donor. Following this exchange of information, Dr. F. reinterpreted patient's comments about finding living donor as grandiosity with more treatment time needed to ensure patient reached full remission.

The recipient review committee discussed her case in detail due to concerns about refractory bipolar disorder. It was noted that patient had significant strengths: she had maintained adherence with medical treatment even when her psychiatric symptoms were severe, her family served as a strong support system including a very knowledgeable husband. Additionally, due to the regional organ shortage, the transplant team felt that there was adequate time from listing to cadaveric transplantation (5–6 years of waiting expected) to allow monitoring, intervention, and reevaluation of transplant candidacy if severe psychiatric decompensation occurred. Patient was added on the waitlist for a kidney transplant.

Six months later she had to start dialysis. This was extremely distressing for her, and in this context, she became depressed but did not require hospitalization. Her outpatient psychiatrist added escitalopram for depression, but patient developed hypomania and severe anxiety. Escitalopram was stopped, and clonazepam was increased up to 4 mg a day with good effect on anxiety. She was re-evaluated by the transplant psychiatrist, and her mood symptoms were again in remission, but she started developing cognitive problems (MOCA of 18) and frequent falls. She became so fearful about falling that she reduced her physical activity level significantly and essentially became home bound. Family and Dr. F considered the cognitive difficulties and frequent falls as an inevitable consequence of dialysis. A discussion with the dialysis nephrologist and transplant nephrologist revealed that patient's dialysis parameters were considered very stable and did not explain the falls or the forgetfulness. All providers agreed that it was worth starting decreasing the clonazepam which was likely contributing to her current cognitive problems and falls. A slow taper over the next 3 months (to a maintenance dose of 0.5 mg twice a day) led to improved gait and cognition without rebound mania or anxiety symptoms. Throughout this period, the patient continued to be engaged in her care and was adherent with dialysis and all medications.

About a year after listing, patient's niece was found suitable to be a living kidney donor. The transplant team asked

the transplant psychiatrist to reevaluate the patient and comment about optimal time to schedule the surgery. Her outpatient psychiatrist was concerned that the patient would need close psychiatric follow-up not available in the typical outpatient setting. The decision was made to proceed with surgery with the following caveats: perioperatively, while in the hospital and for the first post-operative months, she would be followed by the transplant psychiatrist in the general hospital and in the transplant clinic. Due to concern about medication resistance and slow response, it was agreed that it would be helpful to obtain genetic testing for P 450 chromosome. The insurance company had refused to cover it when requested in the past; however, they agreed with the testing now, as a part of preparations for kidney transplantation.

The surgery was uneventful, patient was discharged home after 5 days. However, the first 6 months after transplantation were marked by multiple medical readmissions due to development of recurrent thromboses. During this time, the transplant psychiatrist continued to see her in both inpatient and outpatient settings. Due to concerns for drug–drug interactions with warfarin and difficulties maintaining a therapeutic INR, her carbamazepine was discontinued. She developed delirium twice in the context of infections, and her clonazepam was reduced to 0.5 mg twice daily and then tapered off in the outpatient setting due to persistent cognitive impairment. Nine months after surgery patient was stable in acute rehabilitation and resumed her visits with her outpatient psychiatrist. Her medication regimen included olanzapine 30 mg daily and perphenazine 16 mg in the morning and 32 mg at bedtime.

She continued care with Dr. F. Eighteen months post-transplant, DC presented again for consultation with the transplant psychiatrist at the request of Dr. F. Patient had started displaying hypomanic symptoms and the family told Dr. F they were due to the "new transplant medication" that had been started 4 weeks prior. At this time, patient's immunosuppressant regimen included prednisone 2.5 mg daily, mycophenolate mofetil 500 mg twice a day, and tacrolimus extended release 7.5 mg daily. The change the patient mentioned was from the regular form of tacrolimus to the extended release formulation, and the tacrolimus level had remained stable at 8 mg/mL. It was concluded that there was a low possibility the hypomania was due to the change in tacrolimus formulation and that patient was most likely exhibiting symptoms of her underlying bipolar disorder. Valproic acid was added for mood stabilization with good result upon hypomanic symptoms.

Three years later, after the loss of her brother, she became manic again with a presentation very similar to her previous hospitalization described above. Based on previous genetic testing, her medications were cross titrated rapidly with risperidone replacing olanzapine and perphenazine. The patient's symptoms subsided rapidly, and she was discharged after only 10 days. She remained asymptomatic for the next 5 years.

Clinical Questions

1. What is the role of the transplant psychiatrist in the pre-transplantation phase when the patient already has a mental health care provider in the community?
2. How can the transplant psychiatrist facilitate the long-term psychiatric care for patients?

Discussion

The Pre-transplant Psychiatric Evaluation

The work of the transplant psychiatrist typically begins with performing a general psychiatric evaluation, usually in the pre-transplant setting, with the goal to identify psychiatric and psychological factors that increase the risks of complications after transplantation. For this evaluation, the psychiatrist is usually in a consultant role and utilizes information obtained from the clinical interview, interview of the patient's family or other relevant social support, review of medical and psychiatric records, and review of information pertaining to the patient's ability to participate in medical care. Structured psychiatric instruments (such as scales aimed to screen for depression or other psychiatric conditions) may be administered [19]. For patients who are receiving mental health treatment in the community, the information obtained from the treating mental health providers is invaluable. Treating psychiatrists, psychotherapists, and case managers often have a better awareness of patient's strengths compared to the transplant team who only sees the patient in a time of crisis or high emotional burden. However, most outpatient mental health providers have a limited understanding of the transplantation journey and associated challenges. Transplant psychiatry is only a marginal topic in general psychiatry training [20], most general psychiatrists are not familiar with the process of transplantation, and therefore, their ability to assess patients capacity to provide informed consent may be limited. This was also illustrated by our case, as patient had unrealistic expectations about how a living donor would be found. After that process was clarified to the outpatient psychiatrist, it became obvious that the patient still had residual manic symptoms which could have easily been overlooked if the evaluator was not familiar with the process of organ procurement and transplantation. The transplant psychiatrist is usually in a unique position that allows him/her to perform a comprehensive psychiatric evaluation which often benefits from access to relevant medical information that may not be available to the outpatient mental health provider.

The Pre-transplant Risk Assessment

Once the transplant psychiatrist has a good understanding of the psychiatric diagnosis and psychological profile of the patient, he/she can identify the psychiatric and psychological factors that may increase the risk of complications after transplantation. Psychiatrists or mental health clinicians embedded within transplant centers work closely with the transplant teams, are familiar with the specific challenges raised by transplantation upon the psychological wellbeing of the patients, and are also experts at recognizing psychiatric complications that occur in the perioperative setting. They can fully appreciate the ability of the patient to provide informed consent for transplantation and adhere with the medical care required. The transplant psychiatrist is also familiar with the psychiatric manifestations of end-stage organ disease and can help distinguish between those and the underlying psychiatric disorders. This happened with our patient as her expectations about transplantation pointed toward persistent grandiosity and residual manic symptoms.

The results of this evaluation may take the form of a risk assessment (low, moderate, high) or a yes/no verdict (when a psychiatric condition may be a contraindication to transplantation listing). Structured instruments aimed specifically at quantifying the psychosocial risk of transplant candidates may also be utilized [21–24].

The question is raised at times if the treating/outpatient mental health clinician should be the one determining the pre-transplant psychiatric risk for a patient and render an opinion if the patient should be placed or not on the waitlist. This practice may raise significant challenges. A clinician treating the patient may be concerned that the impact of a "negative" assessment of transplant candidacy upon the therapeutic alliance. In addition, not all psychiatrists have a full understanding of the challenges of the transplantation journey and may have difficulty assessing the psychiatric risks.

Although the resources for psychiatric expertise vary between transplant centers, it is increasingly common practice that the pre-transplant risk assessment is done by mental health clinicians affiliated with the transplantation centers, typically separates from the community providers. It is important that both transplant psychiatrist, the patient and his/her family, as well as the medical team have a clear understanding if the transplant psychiatrist remains in a consultant role or is entering a therapeutic relationship with the patient. It is also paramount to inform the patient about the limits of the confidentiality in this setting (as the transplant psychiatrist will communicate with the rest of the transplant team as clinically necessary).

In many instances, the transplant psychiatrist is a consultant, an expert examiner in third-party assessments, and is not entering a treatment relationship. Ethical frameworks of the expert psychiatrist and treating psychiatrist are overlapping to a degree (e.g., in the obtaining of informed consent) but fundamentally occupy distinct ethical domains. In forensic psychiatry and pre-surgical bariatric assessments, there is a movement toward separation of the psychiatrist's role as treating doctor versus expert consultant/administrative advisor [25–27]. In our case, this separation was clear pre-transplant. The evaluator moved into the treating clinician role during the immediate post-operative phase and then again transitioned to the role of consultant when patient returned to see her outpatient psychiatrist. These transitions were possible as patient and her family had clear boundaries, secure attachments, and the transplant surgery could be planned in advance being that a liver donor was available. In other patients, especially those with difficult interpersonal boundaries, the distinction between consultant and treating clinician may need to be clarified repeatedly.

Contributions to the Longitudinal Mental Health Care of Transplant Patients

Prior to actual transplantation, the transplant psychiatrist is in a unique position to formulate a comprehensive treatment plan to address the risk factors identified during the evaluation.

He/she can help the patient, family, and outpatient mental health provider with relevant medical information regarding the course of treatment and explain some of the major challenges, such as concerns for drug–drug interactions or risk of psychiatric decompensation during the stress related to the waiting for a graft or surgery. For instance, a common challenge for transplant candidates is distinguishing between various phases of transplantation and misrepresenting the imminence of the transplant. In other instances, the need for transplant may be the only reason that patient agrees with an intervention they resisted for years, despite a good relationship with their treating provider. In our case, patient was very reluctant to taper off benzodiazepines and agreed to do so only when it was emphasized to her that her cognitive problems had the potential to negatively impact her post-transplant outcomes. In spite of not the case for our patient, another change frequently motivated by the need for transplantation is becoming abstinent from addictive substances. A skilled mental health professional familiar with the transplantation requirements may incorporate those into motivational enhancement technique aimed at promoting health related behaviors.

On a practical level, like it was in this case, a "transplant status" can help with insurance coverage for interventions that are tested or not routinely available to patients with psychiatric illness.

During the transplantation journey, the transplant psychiatrist may step into the care provider role at various times. It is important that these transitions of care are made clear to the patient, the family, the community mental health provider, and the medical team. The most common such situation involves the immediate postoperative care where a transplant recipient may be followed by the transplant psychiatrist or by a separate inpatient psychiatry consult service.

Postoperatively, when patients return to their outpatient providers, the transplant psychiatrist may facilitate the transition by providing information about any medication changes and the reasons for them, plans for medical care moving forward, while addressing recovery expectations with patient, family, and outpatient providers. The liaison with outpatient mental health providers continues if a transplant recipient needs psychiatric care. As seen with our patient, the transplant psychiatrist may consult again at later stages of transplantation for specific questions such as psychiatric side effects of immunosuppressants or drug to drug interactions.

Team Education About Psychiatric Symptoms, Diagnosis, and Prognosis

The transplant psychiatrist is also in a unique position that allows direct patient's advocacy by helping the medical team to understand the patient's behavior, psychiatric symptoms when applicable, and the prognosis of the psychiatric disorder. In our case, the transplant team had significant concerns about patient having bipolar disorder and the risk of worsening her condition with steroids after transplantation. It helped that the transplant psychiatrist was able to clarify that patient was likely to respond to psychotropic medication, and that she had good insight and good support to facilitate early diagnosis of manic decompensation and prompt intervention. Presenting a clear and concrete treatment plan that addressed her risk of recurrences assured the transplant team that psychiatric complications would be addressed promptly and would not impact the patient's medical condition and the graft survival. The transplant psychiatrist or psychologist can help the team identify strong countertransference reactions which medical providers may experience, more commonly toward patients with personality disorder.

In summary, the transplant psychiatrist can serve multiple roles in the evaluation and long-term care of transplant candidates and recipients aimed at optimizing patients' success with transplantation. The roles themselves must be clarified with the patient, the patient's support team, outpatient mental health providers, and medical service, especially when the needs of the patient require assuming or transferring caregiving responsibilities.

Take Home Points

1. The transplant psychiatrist may fulfill multiple roles during a patient's journey through transplantation.
2. By evaluating and identifying psychiatric and psychological risk factors for transplantation, the transplant mental health clinicians may help formulate comprehensive treatment plans that would reduce the risk of psychosocial complications post-surgery.
3. The transplant psychiatrist may transition in and out a care provider role as the patient progresses through the transplantation; these transitions must be made clear to patient and medical providers.

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Interprofessional Teamwork in Organ Transplantation

26

Gerald Scott Winder, Anne C. Fernandez, Erin G. Clifton, and Jessica L. Mellinger

Introduction

Organ transplantation is a quintessential example of a patient care setting requiring long-term interprofessional care [1]. Not only do transplant patients possess remarkable medical and surgical complexity inherent in end-stage medical disease but their intricate psychosocial profiles and risks are intertwined with key transplant outcomes [2]. This means that the ways in which transplant teams recruit, embed, and interact with psychosocial specialists is of the utmost importance for patient care.

Interprofessional teamwork (IPT) is a decades-old principle which has been studied in fields and industries outside of medicine [3, 4]. Within medicine, IPT has been prioritized by prominent societies and organizations as part of the foundation of quality medical care [5, 6]. IPT affects patient safety and clinical care across the health system: ambulatory clinics [7, 8], rehabilitation units [9, 10], operating rooms [11–13], intensive care units [14, 15], and emergency departments [16, 17]. Healthcare IPT can be defined as "a group of individuals with diverse training and backgrounds who work together as an identified unit or system [18]." An interprofessional team "consistently collaborates to solve patient problems that are too complex to be solved by one discipline" and "creates formal and informal structures that encourage collaborative problem solving [18]." As important as IPT in medicine is, too often it is deprioritized and left to chance.

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In this chapter, we will use a fictional case example to show the importance and impact of IPT in organ transplantation. While a liver team and their interactions are depicted, the circumstances and principles illustrated can be extrapolated to other organ teams and patient psychosocial matters. Furthermore, we deliberately demonstrate interprofessional challenges among psychosocial specialists as well as in their interactions with medical and surgical colleagues to show the breadth and depth of transplant IPT.

Case History

A liver transplant team employed a single full-time social worker who was responsible for evaluating all prospective candidates and providing following up on post-liver transplantation (LT) patients regarding their psychosocial needs and general welfare. During multiple annual performance evaluations in recent years, this social worker reported increasing work-related stress primarily from the volume and complexity of LT patients she was asked to see. Leadership had been satisfied with her work performance but until now had quietly disregarded her repeated reports of increasing stress and requests for additional help managing the sizable psychosocial workload. The advent of highly effective antiviral medications meant that hepatitis C-related cirrhosis was waning, making alcohol-related liver disease (ALD) the most common indication for LT [19] which was reflected in this center's patient population.

Eventually, the liver transplant (LT) team leadership, all surgeons, and hepatologists, themselves grew increasingly concerned about the changing psychosocial profiles of the candidates that they were evaluating and the recipients they are following. This was heightened further when the team experienced a particularly difficult outcome where, unbeknownst to them, a post-LT patient heavily relapsed to alcohol weeks after his transplant surgery and incurred significant graft damage requiring rehospitalization. As the social worker followed up with the patient in clinic and on the

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phone, she discovered that the patient had several psychiatric risk factors including major depressive disorder and a previous suicide attempt that had gone undetected pre-LT due to her high case volume and complexity along with more limited time with each patient. She learned that the patient's depression had recurred post-transplant and was implicated in the serious alcohol relapse. The social worker believed that a larger multidisciplinary psychosocial team would have been more likely to detect this history and make needed adjustments pre- and post-transplant with medications, psychotherapy, alcohol relapse prevention, abstinence monitoring, and/or case management.

After discussing the psychosocial details of the case in a morbidity and mortality conference, which heretofore typically had focused primarily on medical and surgical matters, the team decided to reevaluate their general psychosocial evaluation and follow-up workflows. Out of ensuing team meetings, the high patient psychosocial complexity and volume along with limited personnel convinced the transplant medical/surgical team that additional social work and mental health clinicians were needed. Discussions with the health system's existing health psychologists identified a clinician who would be able to allocate a portion of his clinical time to the LT team and, months later, a new addiction psychiatrist was hired whose job description included time dedicated to LT. Soon afterward, another social worker with transplant experience was hired. Now, the sizable psychosocial workload was shared among a growing team and the LT candidates and recipients had access to a wider array of psychosocial specialists.

In the year following the expansion of psychosocial personnel, several new challenges arose. First, more expertise meant that psychosocial recommendations to medicine and surgery were more comprehensive and assertive. Heretofore, medicine and surgery had been selective about which psychosocial recommendations they followed. This new assertiveness led to several difficult, prolonged, and contentious discussions around whether candidates should proceed toward transplant or closed. Chief among the controversial topics were acute ALD patients, particularly those with acute alcohol-associated hepatitis, many of whom were young people without much medical comorbidity meaning they tended to be excellent medical and surgical candidates and the team wanted to move forward with them. Their psychiatric and substance use disorder (SUD) comorbidities, however, were often severe and the hepatologists and surgeons grew frustrated when the psychosocial clinicians did not recommend LT for these otherwise favorable candidates. Several times, medicine and surgery reverted to overriding psychosocial colleagues' recommendations and proceeded with LT without providing any additional clinical data or literature to support for their decisions, much to the consternation of transplant social work, psychology, and psychiatry who were then tasked with follow-up.

Second, the addiction psychiatrist regularly recommended ongoing monthly toxicology for many of her patients which often fell onto the transplant hepatology nurses for management. These nurses were unfamiliar with these labs and their interpretation. Furthermore, patients were often disgruntled about the stigma and logistical challenges of having to comply with serial drug, alcohol, and tobacco screens, and the nurses were on their own managing these patient encounters.

Finally, the social workers, psychologist, and psychiatrist developed numerous challenges working together. These four clinicians had never previously worked together prior to their LT roles and had less experience working closely with other psychosocial disciplines with significant overlap in expertise and job descriptions where direct and frequent collaboration was essential. They quickly realized that, while conflict was rare, they did not particularly get along well personally or professionally due to differences in personality, experience, and professional training. They disagreed with each other about clinical care matters and transplant-related decisions. The social workers knew the importance of definitive recommendations to the team while the psychiatrist and psychologist were vaguer and more noncommittal. The psychiatrist began referring to herself as the psychosocial team leader by virtue of her medical training though this was never formally agreed upon. The psychologist was opposed to psychiatric and SUD medication use even when they were clearly indicated.

These circumstances eventually led to deterioration in teamwork and social work, psychology, and psychiatry worked mostly separately, minimizing direct personal contact, and communicating mainly through periodic email and electronic medical record messages. As a result, this meant that LT psychosocial clinicians were often discussing complex psychosocial matters in person among themselves for the first time during selection conferences while the rest of the team looked on. This further impacted the meeting's already unfavorable length and efficiency.

Clinical Questions

1. What are key IPT principles relevant to transplant psychosocial clinicians?
2. What strategies can psychosocial clinicians use to optimize interprofessional communication with medical and surgical colleagues?
3. How can psychosocial clinicians best collaborate when new psychosocial team initiatives require additional training and create additional work for medical and surgical colleagues?
4. Describe key interprofessional strategies that can maximize IPT among psychosocial specialists.
5. What potential barriers exist to improving transplant psychosocial IPT?

Discussion

What Are Key IPT Principles Relevant to Transplant Psychosocial Clinicians?

It is a fallacy to assume that simply assembling multidisciplinary professionals together with a common goal will ensure the formation of a collaborative team. It is similarly a mistake to assume that an existing team's interprofessional collaboration will durably improve after an email, workshop, and/or a couple of days of teambuilding. While there is no single definition of IPT or well-defined protocol for promoting it, there are several general principles, practices, and insights [18] that can be helpful in durably optimizing interprofessional psychosocial work in transplant. Such an ongoing effort entails cultivating a culture that accepts differences, promoting trusting relationships and frequent communication, developing systems for working through conflict, and maintaining leadership support.

Collaborative interprofessional teams build and maintain a culture which accepts and capitalizes on differences among individuals and disciplines. The establishment of such a culture is not a single event and rarely occurs spontaneously. Rather, it is a deliberate and dynamic process that takes place in stages over time [18] which entails acknowledging and valuing the various roles and skillsets that comprise a functioning team, agreeing upon team goals and mission, committing to ongoing interprofessional didactic education, and setting up a mechanism by which teamwork efficacy is prospectively promoted and tracked. Where there is overlap in expertise and job descriptions, which will be common on a large transplant team, job descriptions should be well defined by consensus to reduce redundancy and confusion.

IPT relies on robust patterns and processes of interdisciplinary communication. Addressing highly complex problems like those found in organ transplantation will and should generate significant discussion and conflict. As a team culture promotes trusting relationships among its clinicians and invites open personal and professional communication, dissent and conflict can be invaluable sources of productive and innovative clinical work as well as team growth. When intransigent problems develop in teamwork or patient care, there should be well-defined procedures which individuals can use to file grievances, find solutions, and improve team operations. Without such cultural and communication structures to support it, conflict is likely to be destructive to team unity and patient care.

The culture and practice of IPT are less likely to flourish without the buy-in and ongoing support of team leadership. Team leaders must endorse and embody IPT principles in the way they interact with colleagues and conduct patient care. They should use their influence to ensure that hiring practices seek candidates with IPT aptitudes and that teamwork is part of job expectations and performance evaluations.

What Strategies Can Psychosocial Clinicians Use to Optimize Interprofessional Communication with Medical and Surgical Colleagues?

Many psychosocial specialists naturally adopt holistic perspectives and understanding of their patients (personhood, emotions, relationships, life events, desires, etc.) while internists, pharmacists, nurses, and surgeons may be accustomed to focusing more reductionistically on anatomical, physiological, and pharmacological parameters when providing clinical care. The philosophical divide between holism and reductionism can engender real-world disconnects in team communication and deficits in understanding among transplant clinicians of different disciplines. Ideally, a team establishes and maintains an interprofessional education program which develops a broad and shared understanding about the wide array of medical, surgical, and psychosocial phenomena regularly encountered in transplant. Psychosocial specialists earn their colleagues' trust when their team sees that they have invested in their own understanding of transplant medicine and surgery; this also clearly communicates how much esteem psychosocial clinicians have for their teammates.

There is an art to "packaging psychosocial data for medical and surgical consumption." Said another way, there is an art to clearly and concisely communicating the high complexity and uncertainty inherent in psychosocial phenomena to medical and surgical colleagues in a way that rapidly helps them to understand their patients better and assists the team in making appropriate and timely clinical decisions. There are several parts to this effort: excluding extraneous detail; having a single clinician present the case; avoiding psychiatric jargon; citing relevant medical, psychological, and sociological literature including discrete statistics when available; presenting narrative and data in a predictable format; transparently sharing uncertainty, gaps in understanding, and disagreement when present; and speaking with appropriate levels of confidence about one's understanding of patients and clinical recommendations about what should be done. It behooves psychosocial clinicians to have vetted and debated cases among themselves before formal presentation to the broader team in selection conferences to ensure that case presentations and recommendations are as polished as possible; this work could be accomplished in a separate and regularly occurring psychosocial clinician case conference meeting.

Medical and surgical providers have the prerogative of synthesizing the psychosocial information they receive and gradu-

ally becoming more familiar with supporting bodies of literature. Some may have to resist the tendency to view psychosocial data as less real or impactful than medical and surgical data. With firm professional relationships and trust, psychosocial specialists can catalyze their colleagues understanding and appreciation for various psychological and social phenomena. These shared knowledge bases and skillsets allow a team to then continue to refine how they collectively synthesize data in their complex decision-making processes [20].

How Can Psychosocial Clinicians Best Collaborate When New Psychosocial Team Initiatives Require Additional Training and Create Additional Work for Medical and Surgical Colleagues?

Improved IPT in transplant will often result in need for additional training and added workload as new team operations and clinical initiatives are implemented. As discussed above, it is the prerogative of psychosocial clinicians to ensure that they build and maintain their own knowledge base of medical and surgical concepts to ensure that they are prepared to collaborate on new initiatives from other disciplines. Hypothetical examples of new psychosocial initiatives which a psychiatrist may initiate include increased toxicological screening, adoption of a new biomarker (i.e., phosphatidylethanol), use of psychopharmacology requiring medical and pharmacy surveillance, adjustment of team policies around psychosocial matters (i.e., allowing certain patients to use medical cannabis, requiring social support persons to be present in clinic, etc.), regularly querying prescription drug monitoring programs [21], and advocating for opioid use disorder patients to continue on agonist therapy through their surgical course [22]. A psychologist may see rationale for regular use of a broader array of psychometric instruments for screening and follow-up, implementation of a psychosocial clinician-rating scale (i.e., Stanford Integrated Psychosocial Assessment for Transplant [SIPAT]) [23], more frequent referrals for patients to undergo neuropsychological testing, among many other possibilities. Each of these initiatives would require understanding, buy-in, and collaboration of medical and surgical colleagues.

These proposals are best prepared in written format accompanied by a face-to-face discussion with team leadership. (The section above discusses communication strategies which may be useful to psychosocial clinicians making such presentations.) Proposals and presentations should be clear about benefits for patients and families as well as return-on-investment for team members and the health system. Requested additional resources and budget implications should be clearly discussed. Prior to implementation, focus groups and educational sessions are helpful ways to disseminate information about the new initiative as well as gather early feedback and critique from colleagues. For example, an interprofessional transplant-sponsored ALD clinic to better study, detect, and treat ALD in patients with end-stage liver disease conferred numerous clinical, research, and educational/training benefits to all stakeholders across medical, surgical, and mental health disciplines and was successfully implemented and maintained according to this general plan [24, 25].

After an initiative's launch, inviting additional input and guidance prospectively from colleagues ensures that additional training can be provided as needed. Ongoing interprofessional education sessions are effective venues to continue to build a team's shared understanding about the empirical foundations and rationale of a new psychosocial initiative. Psychosocial matters in general may evoke strong emotions in medical and surgical colleagues; periodic open-door staff discussions where processing and mutual support take place are helpful ways to assist any colleagues in need.

Describe Key Interprofessional Strategies That Can Maximize IPT Among Psychosocial Specialists

The scopes of practice of psychiatrists, psychologists, and social workers within organ transplantation resemble the overlapping circles of a Venn diagram. Just as conflict between people who share a close connection (i.e., family, marriage) can be particularly acrimonious, disagreements among clinicians whose expertise overlaps can also be distinctly contentious. There are several practical IPT strategies which can assist psychosocial clinicians with different training backgrounds work closely together amidst the challenges in organ transplantation. These recommendations have been discussed in more detail elsewhere [26].

Given the unfavorable effects of clinician stress on IPT (discussed below), clinician wellness should be a priority. Psychosocial specialists should seek out formal and informal social opportunities inside and outside of the workplace to build the personal and professional relationships and trust that IPT requires; co-located workspaces in proximity may facilitate this. Job descriptions for team members should be clearly laid out, agreed upon, and adhered to. During psychosocial team meetings, time should be set aside for candid discussions about team operations and any interpersonal issues needing to be addressed. Collaborative psychosocial colleagues can compensate for each other's weaknesses, fill in individual blind spots, and politely correct biases making the team greater than the sum of its parts; healthy relationships and trust are requirements for this to occur.

What Potential Barriers Exist to Improving Transplant Psychosocial IPT?

Psychosocial work in transplant has several unique challenges. First, burnout is endemic among healthcare professionals [27]

and clinician stress unfavorably affects IPT [28]. Organ transplantation imposes several unique stressors on its clinicians in addition to the baseline challenges of evaluating and treating psychiatric problems and SUD. Transplant involves end-stage diseases which raise the stakes, intensify the work, accelerate timetables, and imbue clinical decisions with life-and-death implications. Identified teamwork attributes known to promote team building in industry [3] are often not present in organ transplantation and elsewhere in healthcare.

As discussed above, medical and surgical colleagues deal with well-described diseases and circumscribed technical parameters (i.e., Model for End-Stage Liver Disease [MELD] scores, ejection fractions, glomerular filtration rates, etc.) that they alone are qualified to interpret as opposed to psychosocial data (mood, anxiety, adherence, social support, etc.) which are often subjective, diffuse, and open to interpretation by anyone. This can lead to unrealistic and stressful expectations from medicine and surgery about what can truly be known about current and future patient psychology, behavior, and social relationships and what can be done, if anything, about them.

Second, transplant clinician emotions often run high. This is due to the general passion in the field; strong bonds formed among clinicians, patients, and families; stewardship for rare and precious donor organs; and the unique nature of transplant work. In addition to the innumerable benefits of such a powerful emotional climate, drawbacks of intense feelings include their propensity to flatten nuance, compromise objectivity, obscure complex data, and introduce bias.

Finally, human beings' tribal nature creates problems in medicine [29] and transplant work involves numerous specialties and disciplines: pharmacy, medicine, psychiatry, surgery, social work, nursing, psychology, dietetics, coordinators, administrators, and financial specialists among others. Such diverse training backgrounds and professional cultures are likely to be incongruent at various levels in certain situations. As a function of differences in training and professional culture, team members will likely have widely different aptitudes for developing and maintaining strong relationships with their colleagues. The degree of interprofessional disconnect will likely impact the construction of strong relationships and trust required for optimal IPT. Complicating group differences further, healthcare is often perceived to have various traditional professional hierarchies where real or perceived power rankings can impact how a team collaborates.

Conclusion

Despite their challenges working together, social work, psychology, and psychiatry could agree that their medical and surgical colleagues needed some additional education and support around the increasing psychosocial issues that were arising in their LT patients. This obvious need represented a unique opportunity for these four clinicians to meet face to face and discuss a plan. Being in the same room on that occasion yielded several spontaneous and unexpected lighthearted interactions as they made unified plans to design an educational series for their colleagues on ALD and its psychiatric comorbidities and provide training to the team about the use of toxicology in transplant. These plans required fresh collaboration among them and led to a series of regular meetings that they decided to continue even when they had met their goals.

With a growing sense of team unity, their subsequent meetings evolved into discussions about difficult patient cases that they were struggling with. During these conversations, they began to appreciate the unique skillsets that each member possessed and value the diverging perspectives on what should be done. Gradually, a genuine fondness and warmth developed which kept them in the room together socializing for a few minutes after meeting's end. This new connection allowed them to openly discuss, for the first time, feelings of frustration they had experienced in response to past slights and missteps by their colleagues. Hearing how they had offended or discouraged their colleagues, each person made needed adjustments. Until now, these emotions had been suppressed and had contributed to the ill will which had, heretofore, affected their collaboration. In time, these four clinicians began to meet periodically for dinner after work with their significant others.

As their professional efforts gradually transformed the way that psychosocial work was done in the transplant center, they began to see several opportunities for research and scholarship. They jointly authored a grant proposal for some internal funding and submitted a manuscript; each included all team members as co-authors and collaborators. The ensuing success of these projects, and others, helped everyone in their career advancement. During annual meetings with transplant leadership, the feedback these psychosocial clinicians received contained ever more appreciation and gratitude for the invaluable services they were providing transplant patients and families as well as the foundational education and support their colleagues now enjoyed.

Take Home Points

1. Organ transplantation represents a clinical effort that is far beyond the expertise and skillset of any individual clinician or single discipline which means IPT practices should be implemented by all transplant centers.
2. IPT is a broad and well-established concept, often overlooked despite its valuable insights and strategies, which is useful to psychosocial transplant cli-

nicians who seek to improve collaboration among themselves and with their medical and surgical colleagues.
3. Personal and professional relationships, shared understanding, agreed upon goals, and respect and appreciation for all roles and disciplines are prerequisites for successful IPT implementation.
4. Improving IPT across a transplant team is a deliberate, intensive, and prospective process rather than a single event which requires the establishment of a new kind of team culture of interprofessional communication and education; it is unlikely to occur spontaneously.
5. Given the expertise of individual psychosocial clinicians from different training backgrounds significantly overlaps and their duties are often interchangeable, they are vulnerable to frustrating redundancies in workload, confusion related to job descriptions, and resentments about clinical decisions and outcomes; all these factors can lead to breakdowns in teamwork and a need for IPT practices.

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Evaluation of the Incarcerated Transplant Candidate

27

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Background

The sophisticated transplant psychiatrist should have a cursory understanding of the legal framework governing transplant care for incarcerated persons. The legal considerations outlined by various state and federal courts ensure that these difficult decisions will not be unduly influenced by an individual physician's own value judgments. The legal precedent may help a transplant psychiatrist to recognize their own potential biases relating to crimes that an incarcerated patient has been convicted of committing. Knowing that the courts have weighed the many complicated factors involved in transplant surgery for people in prison, frees the psychiatrist to focus on helping make the medical determination. Numerous issues exist around organ transplants for incarcerated persons, from both a medical and legal perspective. Those considerations are discussed more fully below.

Psychiatric Comorbidities in Correctional Settings

The incarcerated population exploded from the early 1980s until the early 2000s, and since then, there has been a slow gradual decline every year since 2009, as of the most recent published data [1]. Nevertheless, the US had over 1.48 million people incarcerated in prisons as of the end of 2017 [1]. It has been estimated that between 200,000 and 400,000 inmates in the prison system have a severe mental illness [2]. The prevalence of people with mental illness in prison is disproportionally higher than in community dwellers. Among the entire state prison population, 23% of inmates reported symptoms of major depression, 15% met criteria for a psychotic disorder, and 30% met criteria for mania [3]. Prisoners also commonly report symptoms of a psychiatric disorder without having received a prior diagnosis. Inmates with mental illness have an astonishingly high rate of comorbidity with substance use disorders, with 74% of state prisoners and 64% of federal prisoners having a history of a substance use disorder [3]. The high rates of mentally ill people in prisons is likely a product of deinstitutionalization (though there has been some controversy regarding this), as well as the proliferation of tough on crime policies enacted in the 1980s–1990s [2, 4].

The delivery of mental health treatment to prisoners has been problematic. The features of severe mental disorders, including delusions, perceptual disturbances and disorganized thinking, make it difficult for inmates to follow the highly regimented strictures of the prison environment, which can lead to further disciplinary actions [5]. The use of segregation or restrictive housing is known to aggravate psychosis and often leads to worsening of depression and suicidal behavior [5]. Few exceptions are made for prisoners with mental illness, as security personnel fear that this could encourage malingering from non-mentally ill inmates in order to receive special treatment [5]. Clashes between the clinical and security staff can occur, and clinical staff can over time become inured to the complaints of such patients, increasingly labeling disruptive behavior as malingering [5].

Prisoners and Aging

Another area of concern regarding the prison population is aging. Old age in prison is defined as starting 10 years below

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of what is typically defined in the general population (55 years of age) due to the fact that incarcerated individuals often have inadequate healthcare and risky lifestyles, which effectively advances the progression of chronic diseases and the aging process [6]. The trend of the aging prison population is attributable to an increasing incarceration of state prisoners over 55 years of age and older, and higher amount of older prisoners serving longer sentences (mostly for violent offenses) [7]. Inmates 55 or older made up only 1% of the total population in 1993, but 4% in 2013 [7]. As prisoners age, they also accumulate medical comorbidities. The most common conditions among the state prison population were arthritis (32.6%), hypertension (30%), heart problems (13.3%), history of tuberculosis at any time (15%), hepatitis (11.7%), and diabetes (11.3%). Germane to the issue of transplant, kidney and liver problems were seen in 5.7% and 2.9%, respectively [8]. One study found that the prevalence of liver failure was three times higher in prisoners compared to general population [9]. Due to high prevalence of end-stage kidney disease in some prison populations, specific transplant programs targeting this patient group have been described [10].

Legal Precedents in the Provision of Medical Care for Prisoners

Incarcerated persons in the United States are entitled to organ transplantation under the Eighth Amendment of the US Constitution, which prohibits cruel and unusual punishment of prisoners [11]. Nevertheless, there has been substantial debate in the public sphere regarding the ethics of providing organs which are already in limited supply, to incarcerated patients. The number of prisoners who meet medical indications for organ transplantation will only increase as the prison population ages. It is expected that transplant psychiatrists will increasingly be involved in evaluations of prisoners due to the confluence of an older, sicker, and more psychiatrically complex population.

Several cases have garnered media interest and raised concerns regarding tax payer money for transplants, whether people would be disinclined to identify as organ donors, and whether donors could exclude incarcerated persons as recipients [11]. In 2003, a woman serving a sentence for murder was evaluated for a liver transplant by the state of Nebraska, but not listed for transplant [12]. In the same year, a man on death row in Oregon was considered for, then denied a kidney transplant [13]. An incarcerated person in California received a heart transplant at tax payer expense in 2002, but died later due to lack of adherence with the post-transplant medication regimen [14]. In 2012, a 27 year old received a liver transplant, paid for by Rhode Island and Medicare [15]. Controversy arose in 2011 when a man serving a sentence for rape was evaluated to receive a heart transplant at Strong Memorial Hospital in New York [16]. Ultimately, he declined the transplant, reportedly due to public outrage [17].

The Supreme Court case *Estelle v. Gamble*, decided in 1976, clarified the obligation of prisons to provide medical care for incarcerated persons under the Eighth Amendment [18]. Although the Supreme Court found against the incarcerated individual seeking care, the court emphasized that authorities must provide medical care for those incarcerated, as denial of medical care would result in unnecessary suffering. The *Estelle* case established the fundamental legal test to assess whether an Eighth Amendment violation has occurred in an injury or illness setting: a prisoner must show that either prison doctors or guards acted with *deliberate indifference* to a serious illness or injury. The court further stated that "this conclusion does not mean, however, that every claim by a prisoner that he has not received adequate medical treatment states a violation of the eighth amendment." The deliberate indifference towards an illness must cause "an unnecessary and wanton infliction of pain" or be "repugnant to the conscience of mankind" [18].

The *deliberate indifference* standard has subsequently been applied and clarified by lower courts. In addition, it has been discussed in several legal journal articles. Frank's review in the George Mason University Civil Rights Law Journal parses the deliberate indifference standard into a subjective component (is a culpable state of mind present?) and an objective component (is the deprivation sufficiently serious?) [18]. The subjective component was defined by three subsequent court cases, *Farmer v. Brennan*, *Wilson v. Seiter*, and *Whitley v. Albers*. *Farmer* elucidated the subjective test by reifying that deliberate indifference is met when prison officials (e.g., guards, doctors) fail to mitigate a risk for which they were aware of and they failed to act in a way that is more than negligence [19].

The issue of cost of medical treatments, and who should be responsible for payment, did not arise in the *Estelle* decision. There are, however, two subsequent cases which have addressed payment. In the case of *Reynolds v. Wagner*, the court held that while prisons are mandated to provide basic medical care for prisoners, there is generally no constitutional right to free health care [20]. The court also noted that prisoners are not free from the considerations that non-prisoners face when accessing health care such as cost [20].

Two cases have dealt directly with the issue of organ transplantation of prisoners, *Barron v. Keohane* and *Fernandez v. US*. Fernandez was convicted of racketeering and drug charges, and received two 12-year concurrent sentences [21]. He suffered from significant coronary artery disease and had several angioplasties as well as coronary artery bypass graft surgery. A doctor within the federal Bureau of Prisons determined that a heart transplant would be the only way to prolong his survival. Fernandez peti-

tioned the Bureau of Prisons to either provide a transplant, give him a medical furlough to seek treatment, or reduce his sentence. He was denied and filed suit against the agency, arguing that his Eighth Amendment rights were violated by denying him a lifesaving heart transplant. The court disagreed, finding that the medical treatment he had received did not meet the deliberate indifference standard, did not fall below a "minimal civilized standard," and that prison officials did not act with a culpable state of mind [21]. In fact, Fernandez had received sophisticated treatment at the Mayo Clinic, had been treated with specialized cardiovascular procedures, and was maintained on cardiac medications. Additionally, he had been relieved of prison work duties to ameliorate his symptoms. The court also noted that per Bureau of Prisons policy, inmates are required to show an ability to pay for an organ transplant, something Fernandez had not done.

In the *Barron* case, plaintiff was suffering from membranoproliferative glomerulonephritis and contended that his Eighth Amendment rights were violated because he was being maintained on kidney dialysis instead of being listed for transplant. The courts decided against Barron, finding that his treatment with dialysis instead of transplant did not violate the deliberate indifference standard, as dialysis is an acceptable treatment for end-stage kidney disease and was not contraindicated [22].

The issue of whether organ transplants must be provided to indigent prisoners at tax payer expense is hotly debated [23]. Some legal scholars have commented that based on interpretations of the law, a high cost can never be used to justify denying medical care [11]. At the same time, others convincingly argue that while cost cannot "excuse an unconstitutional level of healthcare, case precedent and logic provide that cost is necessarily a consideration in defining an unconstitutional level of healthcare" [18]. It has been argued that the fact that prisons would impose the same cost limitations that non-prisoners seeking organ transplants face would not offend the decency of mankind, especially given the current focus on rising healthcare costs in the US [18, 24]. Interestingly, in *Barron v. Keohane*, Barron did not challenge the BOP policy regarding requirements that prisoners must demonstrate ability to pay for organ transplantation, but the court noted that "denial of a transplant to an inmate who needs – but cannot pay for – a transplant may raise constitutional concerns" [22].

In addition to addressing what legal imperative may exist for providing organ transplants to convicted criminals, a transplant psychiatrist may ask whether there is an ethical imperative. For every patient who receives a lifesaving organ transplant, another one will die for lack of a transplant. Given the scarcity of organs available, it might be tempting to consider measures of societal worth in determining candidacy for transplant. Prior to the federal funding of kidney dialysis in 1972, selection committees would designate who could receive such treatment [25]. In Seattle, one such committee member was quoted as saying he had voted against allocating treatment to a former prostitute and a young man he considered a "playboy" [26]. Such value judgments in the pursuit of rationing of healthcare were poorly received once revealed to the public, and this helped catalyze the federal government's decision to fund dialysis. The United Network for Organ Sharing consensus is that decisions about organ transplant candidacy are based on equity. Convicted criminals should not be precluded from consideration for transplant, though UNOS also notes that their position does not inform how governments should allocate limited funds for medical procedures [27].

Case History

A 57-year-old man with no past medical history is transferred to the cardiac intensive care unit from an outside hospital for management of cardiogenic shock and evaluation for advanced heart failure therapies. He is currently incarcerated in a medium security state prison due to an armed robbery and sexual assault conviction. For the past several months, the patient had noted increasing dyspnea on exertion but had not brought it to medical attention. He was admitted to the hospital after he began complaining of abdominal pain and severe shortness of breath. He was found to have new class IV heart failure, congestive hepatopathy, and a high lactate. He received inotropic support with milrinone infusion due to cardiogenic shock (low cardiac evidence and systemic signs of hypoperfusion) and was at one point intubated for acute respiratory failure from pulmonary edema [28]. A workup for his heart failure included left heart catheterization, which did not reveal obstructive coronary artery disease, and a cardiac Magnetic Resonance Imaging which showed non-ischemic cardiomyopathy with an ejection fraction of 15%. There was no evidence of myocarditis. The consult psychiatry team was asked to assess the patient's psychosocial candidacy for left ventricular assist device as a bridge to heart transplantation.

On interview, the patient described a long history of alcohol use disorder starting in teenage years and escalating into adulthood. He reported that most of his crimes were committed while he was intoxicated with alcohol. In addition to criminal activity, he also had multiple disciplinary actions due to showing up to work under the influence of alcohol. He did manage to sustain a prior 5-year period of sobriety which he attributed to regular church attendance; however, he never participated in formal substance abuse treatment. He relapsed after a musculoskeletal injury for which he was prescribed oxycodone, which led him to selling his pain medications in order to buy alcohol. Besides alcohol, he reports use of heroin once in his life as well as periodic use of cocaine and marijuana.

Patient reported that he had been sober for the entirety of his 7 years in prison, and he planned to maintain sobriety with church. He was not interested in considering additional substance use treatment. Interview and review of available records indicated that patient had no mental health diagnosis or treatment history and was never in mental health treatment.

Social history review revealed that patient was not married and had five children. Prior to prison, he had worked in a factory. Of note, he provided conflicting details about the use of alcohol on the job. He had several siblings and was close to his sister who he planned to move in with after his release from prison in a few months.

In terms of his understanding of the left ventricular assist device and heart transplantation, the patient showed a good understanding into the nature of the therapies being proposed to him and describes a strong motivation to adhere to the necessary medical care. In the hospital, he participated in his care well without any treatment interfering behaviors.

Clinical Questions

1. Does the patient have any psychiatric conditions that can impact his ability to maintain a health status and follow necessary medical care after transplantation?
2. Should the patient's status as a state prisoner convicted of multiple felonies play a part in any decision making regarding candidacy for transplant?
3. Who would pay for a transplant if the prisoner was indigent?
4. While incarcerated and after release, does the patient have access to the necessary medical care and/or psychiatric care, if applicable?

Discussion

By legal precedent and UNOS position statement guidelines, the patient discussed in the case should receive full consideration for heart transplant despite being convicted of a felony and currently serving prison time. He is being punished for his crime with incarceration and as he is expected to return to society following his prison sentence, he should not be disqualified from a transplant solely on the basis of his criminal history. He is expected to be rehabilitated to function in the community. The patient denies a psychiatric history of major mood or psychotic disorders and does not appear to meet criteria based on review of psychiatric symptoms. The transplant psychiatry team contacted a point person in the Connecticut Department of Corrections and corroborated that he in fact had no mental health diagnoses in their records and had not visited his prison's mental health clinic. There was no documentation of any substance use with contraband during his incarceration. He had no chronic disease history so assessing his ability to adhere to medical regimens is difficult. Nevertheless, he presented as a bright and motivated patient who had a good understanding of the ramifications of transplantation.

There was a strong suspicion for antisocial personality disorder (APD) given his recurrent criminality dating back to childhood, and indifference to the victims of his crimes. There are some data that nonadherence rates are higher post-transplant in patients with personality disorders, and this may place our patient at risk of graft failure [29]. Given the concern for personal profit and frequent comorbid narcissism, one might hypothesize that a patient with APD or psychopathy could be *more* likely to adhere to a transplant regimen in a desire for self-preservation. The patient's extensive history of substance use is the most concerning aspect of his history with regard to candidacy for transplant. He claims to have maintained sobriety throughout his prison sentence, and a review of prison records can help corroborate this. Despite this, the institutionalized and restricted prison environment confounds the assessment of his sobriety.

The social work and case management team coordinate with the prison to determine which facility could manage the medical needs post-transplant, and whether a transfer would need to be arranged. In Connecticut, the Department of Corrections (DOC) can provide a range of services from outpatient care to inpatient level acute medical care, and inmates are given a health rating on entry into the system which determines to what facility they will be sent [30]. In this patient's case, social work/case management coordinated with the DOC, and they arranged for the patient to be transferred to the state correctional institute which can house highly medically complicated patients including those with LVAD. In this patient's case, the patient proceeded to LVAD implantation as a bridge to transplant with the hope that heart transplant could be pursued, should he be released after his upcoming parole hearing.

In the federal BOP, the clinical director of an institution makes a determination that an inmate has a medical necessity requiring transplant evaluation, and will be referred to an organ transplant specialist [31]. If the specialist determines the inmate may be a transplant candidate, he will be referred to a transplant center in the vicinity of the correctional facility [31]. Once the transplant center decides that the inmate is a suitable candidate, the prison compiles relevant medical and psychiatric history and forwards it to the Medical Director, who will make a determination that there is a medical indication [31]. If this determination is made, the transplant is approved "In accordance with Bureau policy, transplant center regulations, and state and federal laws" [31].

Given the aging prison population and the high medical and psychiatric comorbidity among the country's custodial population, evaluation of prisoners will become an increasingly common occurrence. The transplant psychiatrist must be aware that per constitutional law and UNOS position statements, prisoners cannot be denied consideration for transplant based on their incarcerated status. However, denial of a transplant to a prisoner based on a medical judgment would not rise to the level of a constitutional violation. Whether or not the state must pay for the cost of the transplant in the event, the patient is unable to pay is somewhat more unsettled. Some states have paid for transplants. The federal BOP program statement for patient care indicates that the government will pay costs associated with organ donors but leaves out mention of recipients. Assessing patient's ability to remain adherent to a complex medical regimen, if they have been living in an institutional setting for years, may be difficult. A multidisciplinary team involving social work and case management is important for coordinating care between the transplant center and the department of corrections, to ensure that post-hospital care can be delivered appropriately.

Take Home Points

1. Patients cannot be denied evaluation for transplantation based on their incarceration status.
2. There is a high prevalence of psychiatric disorders in the prison population, due to preexisting mental health problems and the effects of incarceration. The pre-transplant psychiatric evaluation must take into consideration the treatment needs and patient's access to that treatment.
3. Evaluating patient's ability to adhere to medical treatment in the community is more difficult for patients who are incarcerated, as often they lack a recent history of managing their medical disease independently.
4. Care management is essential in ensuring patient has access to the necessary post-transplant medical and psychiatric care.

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Part V

Effects of Chronic Illness and /or Transplantation

Impact of the Transplantation Process on the Caregiver

28

Mary Amanda Dew, Andrea F. DiMartini, and Donna M. Posluszny

Introduction

Lay caregivers play vital roles in providing daily care and assistance for organ transplant candidates and recipients. However, these caregivers—usually close family members such as the spouse or adult child of the patient—may experience prolonged strain associated with their role. Thus, unfortunate and often unrecognized costs of the transplantation process can be the psychological distress, negative impact on physical health, and undesirable changes in social circumstances (e.g., difficulty balancing work and home responsibilities) that these caregivers experience. Declines in caregiver well-being can, in turn, have detrimental effects on patient well-being and longevity both before and after transplantation. We present a case that illustrates that it is insufficient merely to establish that potential transplant candidates have readily available emotional and practical support from one or more caregivers. Instead, transplant professionals must not only evaluate the nature of available support during the initial psychosocial evaluation for transplantation, but continue to monitor the nature and extent of patients' support systems—and principally their relationship with their primary family caregiver—in order to ensure optimal outcomes for families as they navigate the transplant experience.

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Why Do Patients Need Family Caregivers?

Across all types of organ transplantation, potential transplant candidates are either required or strongly recommended to have a family caregiver, a position supported by extensive empirical evidence showing that both candidates and transplant recipients have better psychosocial and clinical outcomes if they have better social support. Thus, no matter whether social support is defined in terms of quantity or quality of support provided, large literatures show that better support before or early after organ transplantation—particularly from the primary family caregiver—is associated with reduced patient risk for post-transplant medication nonadherence, relapse to substance use, psychological distress, poor health-related quality of life, and poor life satisfaction [1–13].

Better support is also associated with better clinical outcomes, including lower risks for graft loss, morbidity, and mortality [6, 14–16]. Patients themselves find social support to be helpful: a systematic review of qualitative studies focused on heart recipients found that recipients reported psychological benefits from having strong social support, including less distress, greater optimism, a greater sense of control, and feelings of greater independence [17]. Finally, quantitative studies show that social support can mitigate, or buffer against, the potentially deleterious effects of other psychosocial risk factors for poor outcomes in organ transplantation, including cognitive impairment, intellectual disability, mental health problems, and exposure to stressors [2, 3, 18].

It is noteworthy that, in contrast to other systematic reviews and meta-analyses, one recent systematic review [15] concluded that social support was not related to medication adherence after organ transplantation. However, the authors of this review noted that their analyses collapsed across different sources of support (e.g., from family vs. friends). Thus, their conclusions did not adequately take into account the considerable available evidence that family support (particularly from the primary family caregiver) is rela-

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tively more important than other types of support for reducing medication nonadherence risk [11].

Although less literature is available on patients who are awaiting transplantation, social support also appears to be an important correlate and predictor of these individuals' psychological outcomes, medical adherence, and clinical outcomes. However, beyond a systematic review of end-stage renal disease patients on dialysis (some of whom were transplant candidates) [19], there have not yet been comprehensive summaries of this literature. Nevertheless, individual studies in candidates for heart, lung, and liver transplantation suggest the value of social support for these patients [20–25]. Similar benefits accrue for transplant candidates receiving other organ replacement strategies such as mechanical circulatory support for end-stage heart disease: patients with better support show better health-related quality of life, and reduced risk for hospital readmissions and for mortality [2, 3].

What Are the Costs and Benefits of Caregiving for the Caregiver?

Negative consequences of caregiving have been documented both during families' wait for transplant and after transplantation. During the waiting period, key stressors include the deterioration and uncertainties regarding the patient's medical condition; role and lifestyle changes within the family (e.g., the patient may no longer be able to perform usual social roles); and financial stressors associated with the patient's formal and informal care needs [26–28]. Up to 50% of family caregivers experience depression and anxiety symptoms [29–34], and a majority of caregivers report that they have undertaken more caregiving tasks and feel more burdened by caregiving as their loved one's health has declined [32, 33, 35–37]. Caregivers' psychological and overall well-being appears to be closely associated with that of the transplant candidate [36–40]. However, caregivers may be more susceptible to distress as the wait for a transplant grows longer: one study found that compared to transplant candidates' distress levels—which appeared to remain relatively stable during the waiting period—caregivers' distress rose as the waiting period continued [31]. Further, distress and burden levels experienced by caregivers to transplant candidates exceed those of other caregivers to patients with chronic disease [33, 38]. Aside from the duration of the waiting period for transplant, other important correlates of caregiver distress and perceptions of caregiving burden are the caregiver's use of avoidant or passive coping strategies [30, 37, 41, 42], the patient's use of such strategies [30, 37, 39, 41], and longer duration of the patient's disease [32].

After transplantation, family members continue to provide significant care and assistance to patients. Post-transplant medical regimens are complex and can require substantial involvement of the caregiver. Patients may develop new morbidities, including those arising from the long-term use of immunosuppressant medications. They may experience acute graft rejection and/or develop chronic rejection. These types of stressors may account for the findings of high rates of diagnosable psychiatric disorders—mostly depressive and anxiety disorders in family caregivers—with rates resembling those observed among family caregivers of patients with other types of chronic disease [34, 42]. The level of distress observed in transplant family caregivers can be as high as that observed in transplant recipients themselves [43–46].

Family caregivers' elevated distress levels may be due not only to their continuing concerns about the well-being of the transplant recipient, but also to the specific burdens associated with post-transplant caregiving. Caregivers often have ongoing responsibility for household and nursing tasks, and they also may perceive that caregiving is constraining their time and ability to engage in other activities such as employment; fulfill other family roles and responsibilities; and address their own healthcare needs [45–49]. Caregivers may report strains on their relationship with the recipient, which in turn increases risk for poor caregiver mental health [45]. Moreover, caregivers' physical and mental health go hand in hand [43, 47], and caregivers who themselves experience poorer health-related quality of life in both physical and mental health arenas may place their transplant recipients at higher risk for mortality post-transplant [46, 48]. Such adverse effects for patients may arise because those caregivers are less able to provide the levels of support that patients need [46, 48]. Finally, transplant recipients' health may decline with time post-transplant, and they themselves worry about the burden that their healthcare needs may place on family members including primary caregivers [50].

In organ transplantation, as in other chronic disease populations, the literature examining impact on caregivers has focused more heavily on costs than benefits for the caregiver. However, some studies provide both qualitative and quantitative evidence that caregivers can attain a variety of personal benefits [32, 33, 51, 52]. A recent synthesis of the literature, which included both transplant-related and nontransplant populations, indicates that caregivers report several types of benefits: feelings of satisfaction as a result of their role; the discovery of inner strengths; development of an emotionally closer relationship with the care recipient; finding personal meaning in the caregiving role (e.g., because it was consistent with values important to them or consistent with the tenets of their religious faith); and attaining personal growth [53].

Case History

Psychosocial Evaluation. Mark was referred by his local cardiologist to the transplant center for a medical and psychosocial evaluation for a heart transplant and/or support with a ventricular assist device (VAD). He was 60 years old and was a retired construction worker with a tenth grade education. His wife of 43 years accompanied him and was present for the psychosocial evaluation.

During the psychosocial evaluation, Mark reported that his health had been getting worse over time and that heart problems "ran in the family." Nevertheless, he was shocked when he was told that he might need a transplant or possibly a VAD. He became tearful and said he did not think that these treatment options would help him. He felt that his mood was poor and he was not interested in anything anymore. He was unwilling to consider medications for this emotional decline because he already had "too many pills." His wife reported that this frustrated her because she felt that he did not want to do anything to help himself to feel better.

He felt that his memory was not as good as it used to be, but a recent screen for cognitive impairment in his medical record was unremarkable. Regarding substance use, he used to drink at least one 6-pack of beer a day, but he stopped drinking on his own a few years ago and his wife confirmed this. He currently smoked about one half-pack of cigarettes a day. He was willing to try to stop smoking but, after 45 years of smoking, he thought he would need a lot of help. His wife also smoked but said she would try to smoke only when she was not with him.

Mark reported no difficulties in remembering to take medications or keep medical appointments. His diabetes was under control but he was morbidly obese. He was aware that he needed to lose weight and that there would be many lifestyle changes after a transplant or with a VAD. He thought he could make any changes needed, and he and his wife understood that they would be educated on what changes were expected.

His wife worked at a convenience store but said that she would be able to take time off during his recovery period after he received a VAD or a transplant. Their adult daughter, who lived near them, was also willing to help with caregiving needs. His wife's extended family lived nearby as well. Mark and his wife had not done any financial planning for the transplant or for a VAD and they knew that it would be difficult for them financially.

Subsequent Events. Mark received a VAD as destination therapy, but with the possibility that his status could be changed to bridge to transplantation if he demonstrated abstinence from tobacco use and lost weight. He achieved these requirements, although his mood did not improve. He had significant financial difficulties paying medical and other bills. Electricity to his home was turned off several times due to outstanding bills. Each time, his wife called the transplant program, who quickly intervened to request power restoration due to medical urgency. His wife lost her job, ostensibly due to downsizing. However, she felt it was because she missed too much work due to his care needs, and Mark reported that she became depressed, irritable, and less willing to help him with daily care needs. He said that she had never been told that she was going to have to spend so much of her time assisting him with so many things. His daughter and some of his wife's family stepped in to provide more help with transportation and other caregiving needs.

Eighteen months after VAD implantation, he received a heart transplant. He did well for the first year post-transplant. Thereafter, he began to miss follow-up appointments and fail to get medication prescription refills because he said he did not have transportation or forgot. He was rehospitalized for an episode of graft rejection and developed several infections. At 1-year post-transplant, he reported that he and his wife had legally separated because she did not want to be a "permanent nurse" to him and she said she had sacrificed her relationships with everyone else in her family just to care for him. His daughter had moved out of state and he could identify no other family caregiver. When asked whether he and his wife considered marriage counseling, he said "I can't even pay the bills I have. How could we possibly pay for something like that?" He and his wife continued to live together for several more months, however, and she occasionally was willing to bring him to clinic appointments. At 18 months post-transplant, following a major argument over medical bills, he moved into an apartment by himself. One week after moving in, his wife stopped by to deliver some of his belongings. She found him deceased. Distraught and crying, she ran out of the apartment for help. A neighbor called emergency medical services and the police. It was concluded that he had fallen and hit his head on the edge of a counter. There was dried blood on the counter edge and on the floor, but no other sign of foul play. The cause of death was listed by the transplant program as accidental trauma.

Clinical Questions

1. Based on the psychosocial evaluation, what areas of intervention might have been considered to ensure that the patient had adequate social support before decisions were made about VAD implantation or listing for transplant?
2. What steps should transplant teams take to foster caregiver understanding and "readiness" for taking on new patient care responsibilities, as well as educate caregivers about potential stressors during the waiting period for transplant (which may include VAD support), as well as after transplantation?

3. To what extent and how might the transplant team have intervened with the caregiver to address her distress over her job loss and feelings of caregiver strain? Should more priority have been placed on offering the patient interventions for his ongoing depressed mood (including non-pharmacologic strategies) not only to alleviate his distress but also to potentially lessen some of his wife's distress and caregiving burden?
4. Post-transplant, how could the team have explored and intervened to address psychosocial factors and circumstances that were adversely affecting the patient's ability to adhere to the medical regimen? Should the team have actively assisted the patient to identify new sources of social support? What is the team's level of responsibility here?

Discussion

Caregiving to transplant candidates and recipients can be associated with significant burden and strain for the caregiver. These negative aspects of caregiving cannot be overlooked by the transplant team, given the critical role the caregiver plays in ensuring good clinical outcomes for the patient. Moreover, costs to the caregiver in terms of burden and adverse psychological and psychosocial outcomes must be considered as components contributing to the total costs associated with organ transplantation. The importance of considering caregiving burden during the transplantation process is receiving increasing attention in the transplant community. Not only has research in this area expanded, but there is growing recognition that caregivers need educational resources specific to the transplant process—resources that may be beyond the capacity of any single transplant program to develop on their own. As a result, the Psychosocial and Ethics Community of Practice within the American Society of Transplantation (AST) convened a consensus conference of research, clinical, and caregiver stakeholders in October, 2019 with two chief goals: (a) to delineate research priorities for better understanding the impact of transplant caregiving and (b) to develop a "toolkit" of resources and educational materials to offer individuals who either may become caregivers or are already performing caregiving activities for transplant candidates and recipients [54]. The caregiver toolkit will be an online resource that is freely available to transplant programs and the general public via the AST website.

In parallel with these national activities, transplant programs should maintain and further develop their own protocols for evaluating each patient's social support network (including key sources of both emotional and practical support), interviewing and educating the individual likely to serve as the patient's primary caregiver, and in general, supporting the caregiver throughout the transplantation process. Consideration of the adequacy of potential caregiving and social support resources available to the patient begins with the pre-transplant psychosocial evaluation. This evaluation provides a prime opportunity to examine not only the patient's psychosocial strengths and liabilities in many areas, but the primary family caregiver's readiness to take on caregiving responsibilities, their expectations about their role, and their understanding of patient care needs, potential caregiving burdens, and strains associated with addressing those needs. This may guide the tailoring of patient and caregiver education efforts offered by the transplant program.

Further, although the psychosocial evaluation may indicate that the patient's available social support network is adequate, it is critical to bear in mind that the nature of such support and caregiving—in terms of quality, quantity, and who provides it—may change during the waiting period for transplantation or after transplantation. Therefore, continued assessment of the patient's psychosocial circumstances is needed, with prompt identification of changes that bode poorly for the patient. Although the primary family caregiver is not a "patient" receiving care from the transplant team, thus limiting the team's ability to directly intervene to address some caregiver problems (e.g., mental health issues), the team should provide timely psychoeducation and referrals, and facilitate care for the caregiver. Moreover, ensuring that patients receive interventions to improve their physical and emotional well-being may have salutary effects on caregivers and their perceptions of caregiving burden.

If family caregivers exit the caregiving role either before or after transplantation, it is ultimately the patient's responsibility to identify other sources of support and assistance. Even so, the transplant team should attempt to actively assist the patient in identifying and developing new supports. Indeed, the team must be alert to the loss of caregiving support because of its potential to lead to adverse clinical outcomes for the patient. If no additional caregivers can be identified (other family members, close friends), the team may be able to refer the patient to appropriate community-based services that could address basic needs such as transportation to medical appointments or in-home assistance with daily activities so that the patient's well-being is not compromised. Financial factors may limit the range of services feasible for a given patient, and thus working with the patient to draw on his/her connection with communities that may be able to provide services in a voluntary manner (e.g., faith-based communities) may be essential. In fact, searching for support via these avenues of activity may be helpful well before caregivers contemplate exiting the caregiving role: to the extent that caregiver burden can be reduced, caregivers may feel that they can continue to support the patient.

Take Home Points

Caregivers are essential for transplant candidates and recipients. Yet, while caregiving benefits the patient and may also offer some benefits to the caregiver, it is often associated with significant burden and strain for the caregiver. These personal costs to the caregiver must be carefully considered when evaluating the complete risk–benefit profile associated with organ transplantation for a given patient. As a result, the transplant team must not only assess whether the patient has a caregiver and an adequate support system at the time of the pre-transplant psychosocial evaluation but must (a) monitor the caregiver's response to the caregiving role as time passes during the wait for transplant and during the post-transplant years and (b) take steps to intervene to address or avert high caregiver burden and other adverse effects on the family caregiver. Ultimately, these actions will not only benefit the caregiver but will increase the likelihood that patients will achieve maximum benefit from the medical treatments they receive while awaiting transplantation and achieve optimal clinical outcomes post-transplant.

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Challenges with Adherence with Medical Care

29

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Introduction: Adherence in Organ Transplantation

One of the greatest challenges in discussing treatment adherence in organ transplantation is defining this seemingly simple term. Adherence has been called "a continuum, shaped through a complex interplay of influential factors at the individual and personal level" [1]. As defined by the World Health Organization (WHO), adherence is "the extent to which a person's behavior, taking medications, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider" [2]. Definitions of non-adherence tend to focus on medication adherence despite the importance of other aspects of self-care, such as attending medical appointments, diet, and monitoring of vital signs. Thus, non-adherence can be loosely defined as any "deviation from the prescribed medication regimen sufficient to influence adversely the regimen's intended effect" [3, 4]. Quantifying this "deviation," however, can be challenging and varies greatly in the research community: missing, forgetting, or altering the dose of medication at least once per month; taking medications 2.5 h late at least once per month; and missing at least 10 or 20% of doses [3, 4].

Treatment adherence can be incredibly burdensome to patients. When asked about their own barriers to medication adherence, patients have reported a wide variety of concerns, including medication dosing and side effects, frequent clinic visits or coordination with healthcare team members, regular changes to medication regimens, over-sleeping, effects on their ability to work, placing restrictions on their lifestyle, anxiety, and even perceived carelessness or forgetfulness [3, 5, 6]. Research suggests that patients with higher healthcare-related quality of life (HRQoL) are more likely to be adherent to immunosuppressant medications [7]. Likewise, patient perceptions of distress negatively affect HRQoL, adherence to medications, and subsequent graft survival [8–12].

There are high rates of non-adherence reported across all forms of transplants, from 22 to 68% [13]. Non-adherence has consistently been shown to predict morbidity and mortality in transplant patients [14]. Non-adherence with medications, specifically, is considered one of the most significant contributors to negative health outcomes and has been directly correlated with late acute graft rejection and graft loss [3, 15]. Measuring rates of non-adherence can be difficult, making validation of research around adherence particularly challenging and limited. Formal approaches to monitor adherence have varied. They include use of electronic pill bottles, radiofrequency identification (RFID)-tagged medications, review of refill records, measurement of serum drug levels, and completion of self-report surveys) [3]. Self-assessment studies have reflected higher rates of non-adherence [5], although it is unclear if this is due to truly higher rates of non-adherence or if the patients' perceptions of their own adherence differ from reality.

It is important, therefore, to view adherence as a behavior that is dynamic, rather than static, and that depends on the recommended regimens, geographical area, and cultural factors between the patient and the healthcare community [5, 14]. The WHO provides a framework for conceptualizing the factors affecting adherence for any chronic disease [2]. This has been adapted several times over the years since its publication in 2003 to specifically address the organ transplant community [1, 3, 4, 14, 16, 17]. These are summarized in Table 29.1.

Healthcare system factors represent the organizational structure in which the care is provided and how patients

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Table 29.1 WHO risk factors for non-adherence in patients who have received a solid organ transplant [1–4, 14, 16, 17]

Risk factors for non-adherence	Subtypes (if applicable)	Specific factors
Healthcare system factors		Longer distance from the transplant center Rural location Access to care Public insurance status Communication between treatment team and patient
Clinical factors	Condition-related factors	Longer time since transplant Pre-morbid medical history Prior treatment non-adherence Type of transplant (organ type, donor type) Physical limitations Previous treatment failure, including prior transplants
	Therapy-related factors	Complexity and frequency of medications Side effects of medications Influence of the treatments on quality of life
Patient personal factors	Sociodemographic factors	Male gender Young age Non-Caucasian ethnicity Low socioeconomic status Education level Employment status
	Psychosocial factors	Feelings of distress, depression, anxiety Low self-efficacy Lack of supports (family, caregivers, social) Cognitive impairments and forgetfulness Negative treatment beliefs and satisfaction Substance use Poor health literacy Daily routine changes

access this care. **Clinical factors** are those related to the patient's health diagnoses and status (i.e., condition-related factors) and those related to the treatments for those conditions (i.e., therapy-related factors). **Condition-related** factors may include the patient's level of disability from the illness, the severity of symptoms, and the rate of progression of the illness. Some view this as pre-transplant factors to clearly differentiate it from **therapy-related factors** which are, by definition, post-transplant. **Therapy-related** factors refer to the aspects of treatment itself affecting adherence, such as medications. These can include the complexity of the medication regimen, side effects of the regimen, time to perceived benefit from the medications, and frequency with which these regimens may change. **Patient personal factors** are divided among those which are **sociodemographic**—such as sex, age, and income—and **psychosocial factors** which encompass the health beliefs, attitudes, and perceptions which influence the patient's motivation for treatment and resilience to stressors associated with care [1–4, 14, 16, 17].

These various factors can also be viewed as modifiable versus non-modifiable. Non-modifiable factors which have been associated with non-adherence include younger age, non-Caucasian race, increased time since transplant, and male gender. Modifiable factors which have been associated with non-adherence include poor social support, poor access to transportation or rural location, negative perceptions of health or medications, public insurance (i.e., Medicare or Medicaid), poor health literacy, greater pill burden, and frequency of medication dosing [3]. This can be helpful when considering areas for interventions to improve adherence and when devising targeted interventions.

Screening and discussion with the patient about modifiable barriers to adherence should always be the first step in generating tailored recommendations for each patient. Lapses in adherence should be discussed openly and non-judgmentally with the patient. Rather than discouraging non-adherence, emphasis should be placed on the need for maximal adherence with treatment recommendations. Hu et al. emphasizes that published interventions focused on patient-level factors even though adherence is a multidimensional issue [18]. Further, validated interventions to improve adherence are rare. Therefore, a combination of interventions is recommended [1, 3] and no "one size fits all" approach should be used. The COMMIT (Consensus on Managing Modifiable Risk in Transplantation) Group suggests treating adherence as the "fifth vital sign," which should be consistently evaluated at all clinical encounters [16]. Prior adherence is one of the best predictors of future adherence, especially regarding immunosuppressive medications. While there is significant variation across types of organizations and reviewing bodies on the specific details, it is consistently recommended that transplant clinicians evaluating adherence use a combination of methods to identify

these risk factors and, once identified, implement targeted interventions for modifiable ones.

There are four categories of interventions to improve adherence: (1) education around transplant-related information (e.g., medication instruction pamphlets, videos on life post-transplant, including medication taking), (2) behavioral interventions to promote medication adherence (e.g., pill reminders by text, cell phone apps, alarms, medication organization packaging or tools, establishing medication routines, simplifying medication regimens, or modifying them to minimize side effects), (3) psychosocial and emotional support (e.g., involving family members and friends, encouraging rapport building by treatment team members, involvement of mental health, substance use, or case management services), and (4) financial support (e.g., enrolling in medication assistance programs, enrollment in, and discussion of insurance coverage) [1, 3, 19].

Assessment of a patient's adherence should be considered prior to and following the transplant. Medication refill and health records (including routine medical appointments, emergency room visits, and dialysis sessions if appropriate) can be helpful for identifying adherence as well as lapses in regular care. Therapeutic drug-level monitoring and monitoring for development of new donor-specific antibodies (DSAs) should be considered. Various self-reporting scales exist to assess adherence. These can be used on initial screening and/or for longitudinal assessment. The Immunosuppressant Therapy Adherence Scale (ITAS) and the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS) both assess medication adherence, while the Immunosuppressant Therapy Barrier Scale (ITBS) and Medication Adherence Barriers Questionnaire (IMAB-Q) assess barriers to medication adherence [16]. Clinician administered pre-transplant tools specific to assessing psychosocial factors which may affect adherence also include the Stanford Integrated Psychosocial Assessment Tool (SIPAT) [20], Transplant Evaluation Rating Scale (TERS) [7, 21], and the Psychosocial Assessment of Candidates for Transplant (PACT) [22].

Case History

Shawn is a 28-year-old, single, domiciled, unemployed African American woman with history of systemic lupus erythematosus (SLE) complicated by lupus nephritis and a psychiatric history of steroid-induced psychosis and adjustment disorder with depression. Shawn is in your office for psychiatric evaluation for a renal transplantation.

Shawn was diagnosed with SLE at age 24 after developing a butterfly-shaped rash on her face. She was reluctant to accept the diagnosis at first and was not adherent with medications until 6 months after her diagnosis. She was hospitalized at age 27 after going to the emergency room for lower extremity edema. She was found to be in renal failure, later confirmed by biopsy to be lupus nephritis. During this time, she was given high dose steroids. Shawn became psychotic and agitated during this hospitalization, though she did not require psychiatric hospitalization. She was discharged from the hospital with a short course of olanzapine 2.5 mg nightly and recommended to follow up with a psychiatrist in the community.

Shawn's renal function did not improve, and she was placed on dialysis about 6 months ago. Shawn was recommended for and is now interested in a kidney transplant. Shawn has not had any significant psychotic symptoms since hospital discharge but has started to experience moderate depression characterized by feelings of anhedonia, hypersomnia, weight gain, and at times hopelessness although she is future oriented overall. She has no prior history of suicide attempts or self-harm. She did not see a psychiatrist after her hospital discharge, nor did she continue taking any psychotropic medications. She is skeptical of taking new medications for her lupus and depression due to concerns about side effects, including becoming psychotic again. She admits that she recently started smoking cannabis nightly, due to feeling anxious and fearful that she will not get a transplant.

She now spends most of her days either taking care of her mother, with whom she resides, or attending to her own healthcare care needs. Most of her family and supports are out of state and, in Shawn's words, "living their own lives." She attends dialysis reliably three times a week. After careful review of her refill records, you see that she fills 30-day prescriptions for her immunosuppressant medications every 1.5–2 months. She has visited the emergency room twice since her initial presentation, once for anxiety and once for a refill of her immunosuppressant medications. She attributes her non-adherence to often being out managing either her own or her mother's medical care, causing her to forget to take medications.

She takes buses and the subway to her medical appointments. The collective household income for her and her mother is well below the federal poverty line, and both are Medicaid and Supplemental Nutrition Assistance (SNAP) recipients. Shawn lives in an apartment with her ill mother in a low-income area of a major metropolitan center in the northeastern United States. Shawn completed high school and worked in retail until her diagnosis with SLE. She drinks alcohol socially (1–2 times per month) and smokes cannabis, as discussed above. She otherwise denies any significant illicit drug or tobacco use.

Clinical Questions

Within the WHO structure for risk factors for non-adherence, for each category (healthcare system, clinical, and patient personal risk factors):

1. What are at least two risk factors for non-adherence that should be considered in this case?
2. What are possible areas for monitoring or intervention to enhance adherence?

Discussion

Healthcare System

While income itself is an independent sociodemographic factor, it is undeniable that it helps "create the socioeconomic milieu of non-adherence" [3]. Access to services is often tied to the financial resources or supports one has. In a 2010 study of US kidney transplant programs, 70% reported that their patients have extremely or very serious problems affording medications, and 43% reported patients were not taking medications as prescribed because of the difficulty affording them [13]. Insurance status and ability to afford care also influences patients' ability to even be listed for transplantation. Individuals with low incomes or non-commercial insurance (Medicare or Medicaid) report hindrances in completing a transplant evaluation and getting placed on the transplant waitlist. As of February 2020, Medicare covers approved immunosuppressive drugs under Medicare Part B. However, this coverage ends after 36 months for those younger than 65 who do not otherwise qualify for the program. This leaves many without financial means to afford expensive immunosuppressive medications after this window ends [23, 24]. Shawn is Medicaid recipient and lives below the federal poverty line, which may continue to be a barrier for her receiving pre-transplant evaluation and care. Linking Shawn as early as possible to case management and social work services will be critical for both improving and maintaining adherence.

In addition, transportation and distance to services have long been established as barriers to care for chronic health conditions, especially in populations with lower incomes or no insurance coverage [25]. In this case, Shawn lives in an urban region with good access to public transportation. While cost of transportation may be a barrier, she may qualify for transportation assistance through the city or state, should it exist in her region. Telemedicine, which has expanded during the COVID-19 outbreak years, may help patients overcome some of these system barriers.

Clinical Factors

In the case of this patient, her prior adherence to treatment recommendations is a considerable concern. One meta-analysis in renal transplant patients found that 36% of graft losses were associated with prior non-adherence [26]. Prior treatment adherence had historically been shown to strongly predict future treatment adherence [16], especially regarding adherence with prior recommended medication regimens and future immunosuppressant compliance [3, 27, 28] with some evidence that this does predict clinical outcomes, such as late acute rejection [3], likelihood of DSA formation [5] although recent findings have questioned that assumption [29].

Shawn has already had a significant new side effect from a medication (steroid-induced psychosis) and has expressed fears about medications causing serious side effects again. These are not entirely unfounded. Psychiatric adverse events are a common, if not anticipated, side effect of high dose systemic corticosteroids with mild to moderate reactions affecting about 1 in 4 patients and severe psychiatric disturbances in 1 in 20 [30]. Expanding to the general transplant population, patients often identify medication side effects as well as concerns about the long-term consequences of these medications as barriers to medication adherence. Immunosuppressant medications can cause a variety of drug-related symptoms [9] (e.g., hair growth or loss, trembling hands, tiredness, bruising, difficulty with concentration) and increase the risk for multiple medical comorbidities (e.g., hypertension, hyperlipidemia, diabetes, skin cancer, and lymphoproliferative disorders, osteoporosis, anemia, and gout) [31]. More complex medication regimens have also been shown to negatively impact adherence [5, 17, 27]. This has prompted clinicians to explore if moving tacrolimus dosing from twice daily to once daily may improve adherence and subsequent outcomes post-transplant [1, 3, 15, 16].

In addition, overall rates of non-adherence are highest in kidney transplant patients when compared to other solid organ transplants, 36 cases in 100 patients per year (PPY) versus 7–15 cases in 100 PPY in other types of solid organ transplants [14]. In a large meta-analysis, non-adherence rates specifically for kidney transplant recipients were 36% annually for taking immunosuppressant medication, 22–31% annually for lifestyle modifications (such as diet and exercise), and 5–15% annually for medical care requirements (such as appointment attendance and laboratory attendance) [14]. It is believed that these high rates of non-adherence in the kidney transplant population may be related to patient's prior experience with dialysis and/or appreciation that organ failure may not be fatal. Research suggests that pre-transplant non-adherence, dialysis prior to transplantation, recurrence of underlying renal diseases, higher medical comorbidity, and lower self-rated health are all risk factors for non-adherence after kidney transplantation [4].

In this case, it is interesting that Shawn has been adherent with dialysis but not with recommendations for medications or psychiatry follow-up. It is important that this be explored with her to help her accept psychiatric interventions in the

future, should the need arise. Education with the patient as well as her medical providers about the risk of steroid-induced psychosis and the management of it may also be of value since it is likely she will require steroids in the future. Consultation with a pharmacist may also be helpful to provide education on the side effects of her medications—both current and future—and to develop behavioral interventions, such as alarms or pill boxes, to promote more regular adherence. Helping Shawn to understand the importance of medication adherence and tangible and relatable outcomes would be of value. Use of ITBS or IMAB-Q may be of value in the patient to make more targeted interventions.

Patient Personal Factors

Shawn, unfortunately, carries significant risk factors for non-adherence due to patient personal factors. Formal assessment of these using one of the various psychosocial screens (e. g., SIPAT, TERS, etc.) may be of value in addition to clinical exam or chart review.

In general, specific sociodemographic are associated with medication non-adherence; these include younger age, male gender, non-white or Black race, low socioeconomic status, unemployment, education level, and poor perceived health and social support [3, 4, 14, 26, 32]. Shawn is young, has limited social supports, non-white, and with low socioeconomic status. Her female gender and education level (completed high school) are likely protective factors.

Assessment of health literacy formally could be considered, since this could be a factor contributing to why Shawn is adherent with some aspects of care but not others. There are a number of validated assessment tools in the literature: The Test of Functional health Literacy in Adults (TOFHLA) [33], the Newest Vital Sign (NVS) [34], and the Rapid Estimate of Adult Literacy in Medicine-Transplant (REALM-T) [35]. The Health Literacy Model in Transplantation (Heal-T) developed by Chisholm-Burns et al. presents an excellent structure for assessment of health literacy and making targeted interventions to improve it with transplant patients [36]. Health literacy is an important consideration, but an in-depth discussion of this concept is beyond the scope of this chapter.

Additional research is needed to clarify if there are direct, mediated, or more complex causal relationships between these sociodemographic factors and adherence. For example, evidence on the impact of minority race/ethnicity is mixed, with some studies demonstrating increased medication non-adherence in these patient groups [5] and others not [37–39]. One consideration is that the perceived effect may be more significantly influenced by other healthcare system and psychosocial factors, such as insurance status, income, and access to care, which all more directly correlate with non-adherence [5]. Similar issues can be seen when considering the effect of a patient's education and employment status [3, 4] as well as psychological factors, such as stress and depression [37].

Prior substance use had been shown to strongly predict both post-transplant substance use and medication adherence [14, 40]. In one meta-analysis by Dew et al. [14] prior substance use treatment strongly ($r = 0.62$) predicted post-transplant substance use. However, the rate of illicit drug, tobacco, and alcohol use remained very low (0.9–3.6%) when compared to other areas of non-adherence, such as taking immunosuppressant medication and exercising. Subgroup analysis of kidney transplant patients reflected similar findings. Literature on marijuana use, however, is limited. A single-center survey of kidney recipients found that 3% of patients used marijuana based on self-report or urine toxicology screens [41]. Another retrospective cohort study found 3% of kidney transplant candidates met criteria for cannabis abuse and dependence, with the severity of the cannabis use inversely associated with transplant listing [42]. Limited research does suggest that marijuana may affect tacrolimus levels through a drug–drug interaction with CYP3A4 enzymes [43], and inhaled cannabis has been implicated in increased risks of lung infection in solid organ recipients, including kidney [44].

Shawn's psychosocial risk factors are significant, though many are modifiable. She has a history of depression, anxiety, and psychosis, as well as poor adherence with prior recommendations for mental health care. Continuing to have Shawn be engaged with mental healthcare service will be critical. Support groups may be considered in addition to individual psychotherapy, both to help normalize her experiences and to find healthy coping strategies for dealing with depression and anxiety. Interval meeting with a psychiatrist should continue to assess if the use of psychotropic medications may be indicated. If she meets criteria for a substance (cannabis) use disorder, referral to addiction treatment programs should also be considered. The role of treatment of substance use disorders, including whether regular drug screening would be recommended, is discussed elsewhere.

Take Home Points

1. While most often associated with medications, adherence can include all aspects of the recommended treatment plan, including dietary restrictions, regular exercise or activity, regular medical appointments and drug monitoring, and abstinence from illicit substances.

2. Non-adherence is a result of multiple dimensions impacting patients' health behaviors, including healthcare system, condition, treatment, sociodemographic, and psychosocial factors. These can be modifiable or non-modifiable.
3. Screening for and discussion of adherence should be a regular practice for patients undergoing transplant evaluation as well as following transplantation. Modifiable risk factors should identified and used to develop targeted interventions.

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Post-transplant Employment and Return to Work

30

Elizabeth Hovis, Mary Amanda Dew, and Andrea F. DiMartini

Introduction

Beyond identifying and lessening the impact of mental health disorders on transplant outcomes, mental health professionals can contribute to transplant care by working with patients, families, and interdisciplinary teams to optimize quality of life and functional status following transplant. Post-transplant employment is an important component of quality of life and functional status. For many, employment is an essential part of their psychological wellbeing with associated benefits of having a purpose, identity within a career, social connectedness, and financial solvency. In addition, employment following transplantation is a strong indicator of general health and recovery [1]. Many patients anticipate improved survival and quality of life following transplant, with the ability to resume prior roles within their family, community, and workplace. Although improvements are indeed achieved for perhaps most recipients, there is substantial evidence that many transplant recipients do not achieve the quality of life of healthy controls [2, 3].

Numerous barriers to return to work can develop along the transplant continuum. Specifically, physical limitations resulting from deconditioning, fatigue, and pain can impede an individual's likelihood of returning to work. Transplant recipients can develop cognitive issues either as a sequela of protracted illness, from events occurring perioperatively, or as side effects of powerful immunosuppressive medications. Recurrent or de novo psychiatric illness may create barriers to post-transplant employment. Finally, while finances may seem to be a motivating factor for return to work, for some the possibility of losing healthcare benefits tied to disability income when comparable health benefits may not be available with a job can be a substantial disincentive to return to work [4, 5]. In this chapter, we review return to work issues and, through a case presentation, illustrate how these issues may come to light for a mental health clinician. We also review strategies for addressing barriers to return to work.

What Proportion of Transplant Recipients Return to Work and What Factors Contribute?

Overall, employment rates for individuals post-transplant are significantly lower compared to the general population. The available literature depicts wide variability of return to work rates within and between organ types [6]. According to a recent systematic review, the percentage of patients who return to work at 1-year post-kidney transplant varied from 26 to 71% with a weighted mean percentage of 39% [1]. The return to work percentages ranged from 22 to 63%, 26 to 69%, and 0 to 44% for liver, heart, and lung, respectively [7, 8]. However, not all reviews take into account work status or life stage (e.g., retirees, students) prior to transplant, and thus, the percentages reported may underestimate the true return to work potential. In comparison, a single study investigating Japanese kidney recipients who were able to remain employed in paid jobs up to the point of transplant found high rates of partial/full return to work at 2, 4, 6, and 12 months of 22.3%, 59.0%, 77.1%, and 85.0%, respectively [9].

Many potential factors appear to contribute to an individual's likelihood of returning to work after transplantation.

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Physical limitations and pain often persist following transplant and may limit an individual's ability to return to work. In a group of 22 lung transplant recipients, reduced levels of physical activity persisted beyond 1-year post-transplantation [10]. Despite the potential for initial, short-term gains in quality of life, there can be gradual and consistent increases in physical limitation and decrements in general health and ability to work over years following transplant [11]. Furthermore, in a cross-sectional study of heart transplant recipients, individuals who reported even mild pain were more likely to endorse lower health-related quality of life and were less likely to be employed postoperatively [12]. Some factors affecting the likelihood of return to work may be related to underlying illness: for instance, a systematic review by D'Egidio et al. found that a shorter duration of dialysis prior to kidney transplant and receiving a living donor organ were each positively associated with return to work [1]. However, other factors appear to transcend the specific type of organ transplantation. Specifically, pre-transplant employment, younger age, higher education level, self-perceived health, and good social support are positive predictors of post-transplant return to work regardless of transplant type [1, 6].

The strong correlation between pre- and post-transplant employment is multifactorial. Unemployed individuals have been shown to be at a disadvantage in terms of being listed for and/or receiving a renal transplant [13]. Furthermore, in the case of prolonged medical absence, advancements in technology and procedural changes may force individuals to acquire new skills in order to return to work and length of time away from work likely impacts whether an individual's position will be available postoperatively [6]. The influence of age on return to work may be secondary to the increased availability of jobs for younger individuals as well as increased cognitive reserve of younger patients. Likewise, individuals with higher levels of education have access to jobs that are less physically demanding and more conducive to physical limitations experienced in post-transplant recovery.

How Might Mental Health Contribute to Return to Work?

Psychiatric illnesses, including mood and anxiety disorders, are common among critically ill populations and transplant recipients. Up to 63% of heart, 30% of liver and lung, and 20% of kidney transplant recipients experience symptoms of depression in the first several postoperative years [14, 15]. While there is conflicting evidence regarding the effect of depression on post-transplant return to work, some studies have shown a significant correlation between post-transplant depression and post-liver transplant unemployment [16, 17]. In considering the well-recognized psychological benefits of employment, including time structure and regular activity, social interaction and identity, as well as a sense of collective purpose [18], it is unclear whether unemployment contributes to post-transplant depression or vice versa. To the extent that depression reduces the likelihood of post-transplant employment, the mechanism for this association may be that many of the core symptoms of depression—apathy, amotivation, anergia, and cognitive dysfunction—can hinder an individual's motivation to return to work as well as their performance in the workplace. While psychosocial evaluations prior to transplant assess for the existence of pre-existing or chronic psychiatric illness, it is not yet standard of care to screen for depression in the early postoperative period.

How Might Cognitive Issues Impact Post-transplant Return to Work?

The high prevalence of cognitive dysfunction in individuals with end-organ failure is well recognized, with rates of cognitive impairment in 50–87% of patients on dialysis [19], 51–70% of individuals with cirrhosis [20], 40–58% of heart candidates [21, 22], and 45% of lung transplant candidates [23]. Whether pre-transplant cognitive impairment fully resolves following transplant is difficult to predict in part due to the significant methodological heterogeneity in the literature within and across organ type and the potential for additional cognitive insults to occur along the transplant course. Notwithstanding these issues, for some recipients, regaining organ function does not return cognitive status to normal following transplantation [21, 24, 25]. For instance, a cross-sectional study by Gupta et al. found 58% of kidney transplant recipients met criteria for cognitive impairment. Similarly, rates of cognitive impairment in the years after heart transplant and lung transplant remained high at 39% [21] and 57–67% [23, 25], respectively. Overall, transplant recipients' cognition may be expected to improve following transplant; however, cognitive functioning is unlikely to fully recover or match healthy individuals [24]. Such lasting cognitive deficits can negatively contribute to quality of life and functional independence, including return to work.

What Are Some of the Financial Considerations for Return to Work?

In the US many transplant candidates are on Social Security Disability (SSD) as they wait for a transplant. Following transplantation, most patients continue to medically qualify for SSD benefits for at least 12 months after surgery, while lung transplant recipients qualify for a full 3 years after

transplant [26]. It is not uncommon for transplant patients to be hesitant about returning to work due to concerns over losing healthcare benefits that are tied to their disability status [27]. This may be especially true if the patient has SSD benefits, as sometimes earnings can adversely impact eligibility for medical coverage. However, federal programs, such as the Ticket to Work Program [28] and other work incentives from the Social Security Administration, can allow patients to prepare for and return to work while protecting their benefits. Ticket to Work connects participants with free employment services, including career counseling, vocational rehabilitation, job placement, and training [28]. Participants receive free assistance from a service provider to prepare for, find, and keep a job, while working toward financial independence. Rehabilitation services may also be provided directly by the state where patients reside through their department of vocational rehabilitation. Services provided by departments of vocational rehabilitation vary by state and can include assessing job skills, abilities, and aptitudes as well as medical, psychological, and vocational testing. Agencies work with participants to develop individualized, written rehabilitation plans to enhance skills and abilities to reach employment goals [29].

Other countries have similar systems. For example, Brazil has a National Health Service and the National Institute of Social Security which both provide universal coverage. A return to work study found that most Brazilian renal recipients remained on social security benefits following transplantation with a small proportion, only 26%, returning to work [30]. They found that the total duration of disability benefits, before and after transplant, was associated with return to work, with benefit durations longer than 3 years most likely to result in permanent disability or retirement on disability. In the Brazilian welfare system, disability benefits and medication coverage can be lifelong, which contrasts with the US system limits and may partly account for the low rates of return to work [30].

The following case illustrates a number of these return to work issues.

Case History

Mr. B, aged 48, received a kidney transplant 18 months ago. He had been a landscaper before starting dialysis 5 years ago. Following his transplant, although he had normal kidney function, he did not feel back to his prior state of health and did not feel capable of resuming his job, which required heavy lifting. In addition, he developed chronic pain around his incisional site and requested pain medications. The transplant clinicians were not willing to prescribe narcotic pain medication for his complaints of pain. The patient believed he had an incisional hernia and wanted the surgeon to repair it so he could be pain free. At his most recent appointment with the transplant team, he was tearful and angry, and stated that he did not want to go on living like this. Psychiatry was requested to assess his mood.

During the evaluation, the mental health clinician discovered that, in addition to his concerns about his debility and pain (both of which limit his functioning and would prevent return to his prior work), he was notified that his SSD benefits would end at the end of the month. He did not feel ready to return to work and his prior job is no longer available. He will lose his health insurance and did not know how he will pay for his transplant immunosuppressive medications or other bills.

He enjoyed his job as a landscaper—he was proud of his skills and felt good at his job. He had not thought of any other line of work. While he planned to return to landscaping, he felt unable to work at that capacity. He questioned why he underwent transplantation when it did not restore his physical functioning and quality of life to his original state of normal health. Although he denied feeling depressed, he was irritable, angry, demoralized, and complained of being in pain.

The mental health evaluator referred Mr. B to counseling. After 2 months, Mr. B's mood improved and he felt his problem solving skills had been strengthened. The counseling helped him to adjust to the realities of his post-transplant limitations. As a psychotherapeutic intervention, the post-transplant recovery period was reframed as a transitional time with new opportunities for positive changes. After the surgeons determined he did not have an incisional hernia, the mental health clinician referred him for assessment at a pain clinic which identified other non-narcotic pharmacologic treatments to manage his pain. His mood and demeanor changed, he became less hopeless and more open to suggestions for considering return to work. He enrolled in a return to work program which protected his benefits while he retrained for a new job. Despite his apprehension about changing fields of work, he underwent aptitude testing and began to consider other lines of work.

Clinical Questions

1. What proactive measures could have been taken to assist the patient with return to work issues before a problem developed?
2. How might mental health clinicians assist the team in educating patients prior to transplant about return to work and other lifestyle changes that they might need to make?
3. How might a patient's ability to adapt to return to work changes be assessed prior to transplant?
4. How might a mental health clinician evaluate psychological and cognitive issues post-transplant in considering return to work? Under what circumstances might formal testing be considered?

5. How might a mental health clinician consider the priority of physical/cognitive rehabilitation including return to work in the early recovery period?

What Interventions Exist for Mental Health Professionals to Assist Recipients in Return to Work?

Although employment counseling may not be commonly considered within a mental health clinician's expertise, a thorough assessment of the patient's mental health, motivation, desire, and ability to return to work is a key part of guiding them to the proper treatments and resources. Mental health providers may uncover these issues when interviewing patients as they typically spend more time asking about stresses and other elements affecting mood and behaviors. Mental health clinicians may also be asked to determine whether an individual meets disability criteria due to a mental illness or cognitive impairments and to complete disability paperwork. A mental health clinician may need to refer the patient for employment counseling or assessment in a federal return to work program or vocational rehabilitation. If the patient has cognitive issues following transplantation, formal neuropsychological testing may be indicated. Some vocational rehabilitation programs can perform cognitive and skills assessments to determine an individual's skills and types of work for which an individual is suited. Cognitive rehabilitation programs for individuals with brain injury can also perform assessments and assist in cognitive retraining and adaptive skills for re-integration back to a prior job or to functioning at a new job. Patients may benefit from physical rehabilitation to regain strength and balance and many patients qualify for physical therapy services due to deconditioning from illness and transplantation. While there is conflicting evidence regarding the utility of exercise training and rehabilitation programs, some studies have shown improved physical functioning, health-related quality of life, and employment rates in lung and kidney transplant recipients who undergo structured exercise training and/or physical rehabilitation [31, 32]. Additionally, assessment of pain and appropriate referral for pain management may improve a patient's functioning. While there is limited evidence regarding alternative management strategies for chronic pain following solid organ transplantation, a multidisciplinary approach with involvement of pain management specialists may offer increased ability to monitor and control chronic pain in the post-transplant period [33, 34].

One observational study involving a multipronged intervention for quality of life after kidney transplant, of which employment/vocational counseling was one component, found 86% of those employed prior to transplant returned to work by 6 months after transplantation. Among those unemployed prior to transplant, who averaged 57 months of disability time before transplant, 42% and 86% had returned to work at 6 and 12 months post-transplant, respectively [35]. Another study which evaluated pre-transplant educational and social support sessions emphasizing return to work after transplant, reported high rates of non-disability (69%) at 3 years post-kidney transplant [36].

While proactive return to work interventions are not widely available, it is important for the transplant team members to adequately inform transplant recipients that SSD is temporary unless they are deemed permanently disabled. Plans for return to work whether at their original job or some other type of work is important to consider before the SSD deadline terminates their coverage. This is especially important as immunosuppression medication can be very expensive and a strategy to cover these expenses before SSD terminates is critical. For those returning to a prior job, emotional support may help in the transition. Many patients worry they will not be able to resume the same pace or keep up with the workload after being off for an extended time. They may have to pace themselves or ask for light or part-time duty to reenter the workplace. They may have to deal with questions from co-workers about their illness or time off. Transplant team social workers often assist in a variety of these situations, but proactive planning by all transplant team members with appropriate referrals to clinicians or programs with the required expertise is essential.

Discussion

In the context of improved survival following solid organ transplantation, quality of life measures, including post-transplant employment, are increasingly important outcomes. There are many factors that influence an individual's likelihood of return to work following transplant. In this chapter we have covered potential areas that, if optimized, can improve post-transplant outcomes, including return to work. The most consistently observed positive predictor of post-transplant employment is pre-transplant employment. With this in mind, steps should be taken to encourage ongoing employment throughout the transplant evaluation process and the waiting period for transplant, and to assist patients and employers in finding ways to accommodate for critical illness. In one review, only half of transplant patients received sufficient vocational rehabilitation information [1], suggesting this is an important area for further intervention. Psychological factors, including self-perceived health, cognitive function, and depression contribute to return to work as well. Although cognitive impairment is common following solid organ transplantation, post-transplant physical and occupational rehabilitation may decrease the likelihood or severity of lasting cognitive impairment [25]. Furthermore,

preparing patients, families, and workplaces for potential neurocognitive dysfunction following transplantation may result in the development of compensatory and accommodating strategies to mitigate the effects of impairment. Recognizing symptoms of depression in the early postoperative period through validated psychiatric assessments with referral to mental health services when appropriate can optimize an individual's mental health and prevent the potential negative effects on post-transplant outcomes. In summary, a multitude of factors contribute to post-transplant outcomes, including return to work. Improving survival and quality of life depends upon an interdisciplinary team that can optimize not only the biomedical aspects of an individual's post-transplant treatment regimen but, when possible, also address the social and psychological outcomes as well.

Take Home Points

1. Return to work is less likely the more time that elapses following transplant. Early return to work within 6–12 months post-transplant should be encouraged. Continuing work as much as possible up until transplantation should be recommended, if feasible.
2. Preparation for return to work issues should be considered and addressed prior to transplant.
3. Quality of life and physical functioning benefits can decline with time following transplant. The first postoperative year represents a critical time for intervention with greater emphasis placed on restoration of basic physical functioning and physical and emotional rehabilitation.
4. When possible, effective rehabilitation programs depend upon a multidisciplinary team and an individualized approach to each patient.
5. As psychiatric illness is treatable, identifying and treating psychiatric disorders can optimize post-transplant outcomes and potentially the ability to return to work.
6. Cognitive and aptitude testing can provide information on areas that may require modification in order to facilitate return to work.

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Existential Issues in Transplantation

31

Yelizaveta Sher

Introduction

Transplant mental health clinicians routinely evaluate, diagnose, and treat mood, anxiety, and substance use disorders in patients pre- and post-transplantation. However, these psychological problems do not fully encompass the totality of the experience of someone facing a serious medical illness, and transplant patients frequently bring in concerns beyond the diagnosable mental health disorders neatly categorized by the DSM5. Being evaluated for and/or surviving and living after transplantation means that the person has faced their own mortality and they continue to live with a chronic medical condition, facing an uncertain future. For many people, the themes of death and dying, meaning of life, individual freedom versus dependence on others, loss of dignity, change in relationships and roles, and life legacy become integral components of their journey, especially during the waiting period for transplantation, challenging post-transplant recovery, and/or when facing new complications and post-transplant deterioration. These are all existential concerns, stemming from our contemplation of our existence and its limitations, marked by our mortality. Existential distress brought on by these concerns has been studied in oncology patients and palliative care settings [1–3]. However, a search for articles combining the themes of "existential distress" and "transplantation" produces almost no articles on solid organ transplant candidates or recipients [4]. Yet, existential distress is common in patients facing significant medical challenges. In fact, 30 to 50% of cancer survivors report existential concerns due to the uncertainty, a sense of uncontrollability and difficulty incorporating the cancer experience into their identity [2]. In a study of 164 adults with cystic fibrosis (CF), a genetic life-shortening disease, which frequently leads to the need for lung transplantation (and at times, liver transplantation), authors identified significant unmet existential needs, with most frequent ones being fears about CF worsening (50%) and uncertainty about the future (39%) [5]. A descriptive study of Irish patients with kidney failure receiving outpatient hemodialysis either awaiting a kidney transplant or an evaluation for a transplant also described existential concerns brought on by the experience of living with a deteriorating medical condition while being on dialysis and considering transplantation [4]. These concerns included uncertainty and anxiety waiting for a transplant, living in a limbo and inability to plan for the future, and overcoming distressing existential moods [4].

Similarly, in the collective clinical experience of transplant mental health clinicians, transplant candidates and survivors both struggle with feelings of loss and grief in the context of medical illness cutting short their expected life experiences, difficulty incorporating their transplant experiences into their identities, relationship and life role changes, searching for meaning behind their challenging experiences, feeling as if they are living on borrowed time, or yet again directly facing mortality when they develop new complications and organ/graft failure. This chapter further explores these themes by describing a case of a lung transplant recipient facing chronic rejection and existential themes brought on by his deterioration.

Case History

Mr. A was a 48-year-old man with interstitial lung disease who underwent lung transplantation 5 years ago. Unfortunately, his course was now complicated by bronchiolitis obliterans syndrome (BOS), a form of chronic rejection, and he experienced declining lung function with associated shortness of breath, reduced endurance, and increased fatigue, requiring increasing amounts of supplemental oxygen. Mr. A was found not to be a candidate for re-transplantation due to significant scarring in his chest cavity. He was now referred to a transplant psychiatrist, with whom he had worked with early on after transplantation, for

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what the transplant team thought were worsening symptoms of depression.

Mr. A described feeling sad about his yet again experiencing declining health. After his transplantation 5 years ago, he had been hopeful about longevity, but was also painfully aware that the median survival for lung transplant recipients was indeed 5 years. Now with worsening chronic rejection, his symptoms were similar to his initial symptoms of end-stage lung disease and the patient shared his associated grief and fear. Mr. A. understood his condition and although his immediate prognosis was not clear, he knew that he was irreversibly declining. Mr. A was particularly sad about leaving his wife of 20 years and their three children behind. His older daughters were 25 and 22 years of age and thus more established, but he felt sad about his younger daughter, who was only 13 years. He was concerned about the financial well-being of his family after his is gone. He wanted to be remembered by his family, but he did not want his wife to spend her life mourning him. He felt sad and disappointed that he would not be there with her into her old age, and he did not want her to be alone. He also felt disappointed that his winemaking business did not take off as he had envisioned it. In addition, he expressed guilt of putting more burden onto his wife and older daughters to take care of him and the household.

In addition to feeling these losses, Mr. A was scared about the actual experience of further deterioration and dying. He had a complicated recovery after his lung transplantation, having spent many days in an intensive care unit on the ventilator and he did not want to be intubated again if it would not lead to his recovery. He was also anxious about what dying would be like and of course did not want to suffer. At the same time, he was unsure about the afterlife.

Mr. A and the psychiatrist spent time processing all of these important and valid concerns. It was important for Mr. A to have an open and supportive space to speak about his feelings and thoughts and feel validated. He was able to work through his grief and accept the life that he had lived so far. He was able to re-frame his feelings of being a burden on his family into gratitude for their presence and support. He was able to appreciate that his legacy would continue with his daughters, especially since one of them was learning winemaking after being inspired by him. He also was able to appreciate that his family will be financially secure with his wife's income and provisions he would leave behind for them. He told his wife to re-marry after his death and decided to write a series of letters for his younger daughter for important occasions in her life.

The psychiatrist and Mr. A also discussed what dying might look and feel like; this enabled patient to further discuss his end-of-life goals and code status with his transplant team. Patient was referred to the palliative care team to address any physical symptoms at this point of his condition and to provide additional structural support to him and his family. Additionally, Mr. A was able to reintegrate his faith into his overall experience. He was still unsure about the afterlife, but expressed that he "was curious and excited to find out what happens after." While he felt sad about his early death, he was able to express that he had lived his life the best he could and to focus on the small joys left to him: spending time with his family, eating a few meals, and sitting outside in his garden. Eventually, he was enrolled in an outpatient hospice program who managed his worsening dyspnea due to progressive respiratory failure. The psychiatrist discussed dignity therapy with the patient and Mr. A was very enthusiastic about doing it. Unfortunately, patient was not able to return to his outpatient psychiatry appointments due to his now quickly deteriorating state. He died peacefully at home surrounded and supported by his family.

Clinical Questions

1. What existential themes are brought up in context of transplantation?
2. What psychological interventions are available to psychiatrists working with transplant patients struggling with existential distress?
3. What practical interventions are available to psychiatrists working with transplant patients struggling with existential distress?

Discussion

While research on existential themes and existential distress specifically in transplantation is lacking, the available literature in the fields of psycho-oncology and palliative medicine provides an excellent blueprint to be applied to similar issues in transplantation medicine.

When discussing working with patients facing their mortality, Kissane expands on Yalom's work and lists major sources and categories of existential distress: (1) death anxiety, (2) loss and change, (3) freedom and autonomy, (4) dignity of the self, (5) fundamental aloneness, (6) altered quality of relationships, (7) meaning, and (8) mystery [6]. Many of these themes come up for transplant candidates and recipients. Patients are appreciative and reassured when mental health (and medical) providers are able to connect to this experience, normalize it, and help patients process these difficult, yet very human and common, experiences, and emotions. Breitbart summarizes the existential literature and elaborates further: he explains how as humans aware of our existence, we feel compelled to respond to this existence with creating our own unique meaning and living out our lives to the best of our potential [7]. But since we all invariably fall short of these expectations at some point in our lives, we are bound to experience *existential guilt*, the sense of "I should have done more" [7]. Breitbart states, "In the

clinical setting, existential guilt is manifest when the arc of the trajectory of a patient's life has been knocked off course by an obstacle, a limitation, cancer, the loss of roles, the proximity of death. The larger the delta between the idealized trajectory and the one that has unfolded is proportionate to the existential guilt experienced." [7] Transplant candidates or recipients, who might be living with a chronic deteriorating medical condition or acutely decompensate, younger or older, are eventually aware of their impending mortality, associated losses, and grief. Patients might grieve the loss of their career or never having children or not having the retirement and dignified old age the way they imagined and hoped for. Mr. A was grieving the loss of his hopes to live out his life with his wife into their elderly years and to be there for his daughters. He fell short of his expectations to raise his younger daughter and to further establish his wine-making business. An important intervention was to allow Mr. A the opportunity to express his sadness, grieve these losses, accept them, acknowledge that he did the best he could, and then allow him to plan how to care of his loved ones even after he was gone. Mr. A did this by voicing to his wife that he wants her to eventually re-marry, leaving letters for his younger daughter, and appreciating that his family will be financially stable after he is gone.

Appreciating the sources of existential distress and creating space for patients to acknowledge it can be very powerful. In addition, several existential therapies exist to particularly speak to this experience and help patients transform it and find solace and meaning. While none of these have been specifically studied in transplant candidates or recipients, evidence from other chronically ill communities may be extended to this patient population. Existential psychotherapy, built on the ideas of Victor Frankl and Irv Yalom, aims to address questions about existence and to understand and ease patients' anxiety when facing questions about mortality. It is imperative for patients to have a witness and a partner in their medical journey not only as a patient but also as a human, and as a "fellow traveler," the mental health clinician can support the transplant patient confronting anxiety in the setting of death, isolation, and emptiness inherent in one's suffering [8]. They can help the patient focus patient on making choices and decisions based on their responsibilities and deriving meaning from their experiences [8].

Other, more structural existential psychotherapies, traditionally developed for end-of-life patients, offer important themes that likely can be integrated throughout the chronic disease continuum and experience of transplantation, while particularly poignant at end of life. Meaning-centered psychotherapy, developed by Dr. William Breitbart at Memorial Sloan Kettering Cancer Center for advanced cancer patients struggling with despair, hopelessness, and desire for hastened death, was initially introduced as a group therapy (8 sessions) for demoralized patients with limited prognosis and later adapted for individual sessions (7 sessions) [8, 9]. The therapy aims to bring meaning to patients' lives via helping them to consider attitudes toward life and death, connecting with life through love, art, humor, nature, and relationships; engaging with life through creative pursuits; and developing a deeper understanding of their identity and legacy [9].

Another form of structured existential therapy is dignity therapy, developed by Dr. Harvey Chochinov for patients nearing death, focusing on the production of a "generativity document" and aiming to maximize the dignity conserving practices and perspectives of the patient [10, 11]. It has been studied in terminally ill patients, cancer patients, and patients with Huntington's disease, but not in transplant patients. We recently published a case report of modified dignity therapy (prolonged over several months) in a patient with CF who declined lung transplantation [12]. This therapy is most appropriate for patients nearing terminal situations, but is at least 2 weeks away from their predicted death. However, as in the case report above, themes and strategies can be extrapolated beyond the traditionally recommended several sessions towards the very end of life [12].

Mr. A was introduced to the idea of Dignity Therapy which resonated with him and he was interested to participate in creating a Generativity Document for his family, but unfortunately, his health deteriorated so that he was not able to return to the clinic to finish it. Usually, this therapy can be done in hospital or inpatient hospice settings, but fortunately for the patient, he was able to spend his last days at home surrounded by his family. Nonetheless, Mr. A's willingness to consider and participate in this therapeutic modality suggests that this intervention may hold promise for transplant patients in similar situations.

Practically, transplant psychiatrists can also offer a lot to their patients facing existential distress. Offering and encouraging such practical interventions as taking care of finances, deciding on surrogate decision makers if not already done, code status, burial arrangements, and so on helps patients not only feel in more control of their lives but also take care of others, knowing that their loved ones will be empowered with patients having already made some important decisions. In addition, having addressed and faced "the unthinkable" to the best of their ability allows the patient to re-focus on the here and now, and enjoys present life as much as possible. For some patients it is important to decide who will inherit their favorite collections, while others decide who will take their daughter for prom dress shopping if they are no longer there. As difficult as these decisions are, this allows patients to stay in control and take care of their loved ones. Patients can be encouraged to further express their feelings at this time through any methods that best speak to them: further discussion with mental health professionals, talking with family, friends and online communities, creating or appreciating art and music, journaling, being in nature, prayer, and meditation [13].

In addition, transplant psychiatrists can encourage patients to verbalize and ask important questions of their

transplant teams, that might not have been addressed but be important (e.g., how long do I have left, how will my death might look like, how will doctors ease my pain and suffering). Not infrequently transplant psychiatrists act as a translator between the medical world and the human existential experience for transplant candidates and recipients. In the same capacity, it might be the transplant psychiatrist who recognizes the need for and suggests the involvement of the palliative care team. Historically, transplant teams have tended to be very protective of their patients and averse to involvement of the palliative care transplant patients, either before or after transplantation, are still infrequently referred to palliative care [14]. Some of the barriers to these referrals and collaboration include (1) unrealistic expectations for survival on behalf of patients, (2) unwillingness on the part of patients and their families to plan end-of-life care, (3) seemingly contradictory goals of transplant and palliative care, (4) medical teams equating palliative care with end of life, (5) patient fear of abandonment by the transplant team, and (6) lack of access to palliative care services [14]. It may fall on the transplant psychiatrist to educate both the patient and the transplant team on the importance of palliative care interventions and involvement.

Working with transplant patients' existential distress and concerns is challenging and yet it might be the most rewarding aspect of being a transplant mental health clinician where our combination of medical and mental health expertise as well as human experience can bring the necessary space and wisdom to our transplant patients to transcend their suffering into meaning.

Take Home Points

1. Transplant patients, either pre- or post-transplantation, will bring a variety of existential concerns to their mental health providers, focusing on grief of lost experiences and expectations, meaning of life, fear and thoughts of death and dying, changes in relationships and roles, individual freedom versus dependency on others, and sense of dignity. It is important for transplant clinicians to be able to create the safe space for patients to bring up and discuss these experiences and feelings, normalize, bear witness, and validate.
2. Existential interventions, which have been studied in other chronically ill populations, can be applied to transplant patients. These include existential, meaning-centered, and dignity therapies. Studies on these interventions for transplant recipients are lacking, but would be most welcome.
3. Practical interventions that transplant mental health clinicians can employ with patients with existential distress are guiding patients to yield control over decisions they can make, while also taking care of others in their life: bringing finances into order, making a will, burial arrangements, as well as leaving letters/videos/memories for loved ones, making amends, saying goodbyes, and so on, depending on an individual case. In addition, transplant mental health clinicians can provide further education about and connect the patient with the palliative care team, if not already done.

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Psychological Adaptation Post-Transplantation

32

Susan Rubman

Introduction

The United Network for Organ Sharing (UNOS) reported that there were nearly 40,000 organ transplants performed in 2019 in the United States [1]. Clearly, the first and most immediate goal of solid organ transplantation is to prolong the life of the recipient. As survival rates for all types of organ transplantation improve and transplant recipients live longer, evaluation of post-transplant life becomes the focus of attention. Ultimately, the goal of transplantation is to restore not only the individual's physical health status but also the mental health, lifestyle, and the quality of life (QOL) of the individual.

Recipients' immediate post-operative course is, necessarily, dominated by medical stabilization and management, adjustment of immunosuppressant regimens, and attendant surgical sequelae. Early complications while patients are still hospitalized, such as bleeding, infection, return for additional surgery or graft dysfunction, can provoke significant anxiety, depression and, in some cases, post-traumatic stress disorder specific to transplant (PTSD-T). Post-operative complications, high-dose steroids, other immunosuppressant medications, and extended Intensive Care Unit (ICU) stays contribute to the onset of delirium with symptoms of hallucinations, delusions, disorientation, agitation, and confusion. These early events can challenge patients' hopes for a smooth recovery and create anxiety about the future.

Following transplant surgery, recipients typically express relief and gratitude at being "reborn" or "given a second chance at life." As they physically recover, their expectations shift toward the hope and expectation of a life not dictated by their illness and a return to premorbid activities. Patients' experiences following transplantation, however, are often considerably more complicated than this, with resultant effects on psychological functioning.

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Mental health issues after transplantation take one of three forms: new onset, return of prior conditions, or exacerbations of pre-existing disorders. Poor or impaired psychological function prior to transplant is associated with poorer adjustment and mental health concerns post-transplant [2, 3]. Table 32.1 outlines the factors that influence the development of impaired psychological adjustment post-transplantation.

Mood disorders following organ transplantation have received significant attention in the literature. Rates of depression and anxiety following transplant are higher than in the general public and also higher than populations of patients with other medical conditions [4]. In the first year following lung transplant, rates of depression were found to be 26%–30% [3]. Heart transplant recipients experienced similar rates of depression in the first 3 years post-transplant [5], although some estimates are considerably higher [6, 7]. Approximately 25% of kidney transplant recipients experience depression [8] and prevalence rates are similar for liver transplant recipients, although some studies do reveal higher estimates [9–12]. Significantly, depression has been found to increase risk for post-transplant morbidity and mortality [12]. In a meta-analysis evaluating risk factors for morbidity and mortality, depression increased the relative risk of post-transplant mortality by 65% [4].

Anxiety disorders also occur with a high degree of frequency post-transplant. Between 10% and 25% kidney transplant patients experience significant anxiety with rates ranging as high as 50% [9, 13]. Prevalence rates for lung transplant recipients are similar to kidney outcomes [14]. Prevalence data for cardiac transplant are also similar, with 26% of recipients experiencing some form of anxiety [7]. Liver transplant patients experience anxiety at a slightly higher rate, with estimates up to 35% for recipients experiencing symptoms [2]. Anxiety and depression are also considered risk factors for disrupted body image post-liver transplant [15].

Transplant recipients, by definition, are exposed to extraordinary stressors, e.g., life-threatening illness, surgery,

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Table 32.1 Factors affecting psychological adjustment post-transplant

Pre-transplant psychological conditions
• Anxiety
• Depression
• Post-traumatic stress disorder
• Alcohol/substance use
• Ineffective coping strategies
• Inaccurate expectations of transplant
• Psychotic disorders
Medical or physical changes
• Medication side effects
• Sleep problems
• Cognitive changes/delirium/encephalopathy
• Sexual dysfunction
• Pain or discomfort
• Physical limitations or decreased physical endurance
• Sequelae of alcohol or substance use
Contributing stressors
• Complicated medical regimens/medication non-adherence
• Financial impact of transplant (medical costs, loss of income)
• Altered body image
• Alteration in social functioning
• Alteration or loss of vocational functioning
• Alteration or loss of recreational functioning
• Need to accept assistance from others
• Inadequate social or instrumental support

and ICU stays, which predisposes them to stress responses. In a recent systematic review, Davydow [16] and colleagues addressed the prevalence of Post-traumatic Stress Disorder post solid organ transplantation PTSD-T and found that from 1% to 16% of patients experience full PTSD-T and that up to 46% of patients experience significant PTSD-T symptoms. PTSD-T is noted to occur in all categories of solid organ transplants.

Substance use post-transplantation is a significant concern for all patients, but in particular, relapse is a concern for those individuals whose original illness was related to alcohol or other substances. The majority of studies in this area focus on alcohol use in patients who underwent transplant for alcohol-related liver disease, although relapse is noted in other populations as well. One meta-analysis of risk of alcohol relapse indicated that approximately 6% of patients per year will relapse to alcohol use and that new relapse events can occur as long as 10 years post-transplant [17]. Viewed from a different perspective, a separate systematic review investigating alcohol relapse in patients transplanted because of alcohol-related liver disease reported relapse rate of 22% over approximately 4 years [18]. This clearly presents a serious health risk.

Although most transplant patients experience significant and dramatic improvements in their health, post-transplant life does not always mean an immediate or complete return to their premorbid health or lifestyle. Data consistently indicate that quality of life (QOL) after transplant is superior to pre-transplant QOL, particularly in the areas of physical and social functioning, and mental health [19, 20]. Many patients, however, continue to experience reduced physical capacity compared to their pre-illness status, and for all transplant patients, physical QOL is worse than that of healthy populations [19]. Improvements in QOL appear to be relatively consistent across liver, kidney, heart, and lung transplantation [16]. Patients' social support and activity levels are found to be mitigating factors in QOL post-transplant [3, 20, 21].

Transplant surgery is not the "finish line" of an individual's illness, but rather, it marks a transition to a new status, one which requires ongoing adaptation. The case below highlights some of the challenges that patients face.

Case History

History of Presenting Complaint

Mr. C. was a 57-year-old male diagnosed serendipitously with non-alcoholic steatohepatitis (NASH) cirrhosis while undergoing workup for an unrelated condition. Initially, his disease course was uneventful and remained stable for several years. Eventually, however, he began to develop complications of his cirrhosis including several significant episodes of gastrointestinal bleeding, requiring banding of esophageal varices. He further developed portal hypertension, hepatic encephalopathy, and ascites.

In the early phase of his illness, Mr. C. was employed full time in a sales position. He was able to work, socialize, and maintain his regular activities and lifestyle. At the time of his diagnosis, he was married with adult children. His wife and family were supportive throughout the course of his illness.

Mr. C. had been passionate about sports all his life and was a highly competitive mixed doubles tennis player. In addition to his regular work, Mr. C. and his long-time tennis partner had opened a tennis school and were involved in private coaching. Mr. C, his wife, and their children considered his tennis partner a member of the family, even though they were not actually related. As his liver disease progressed and his episodes of decompensation rose, he had to withdraw from the majority of his activities. Over a five-year period, he retired from his job, quit playing tennis, reduced, and eventually stopped coaching tennis, but nominally retained his business relationship with his tennis partner.

Mr. C's brother was found to be a suitable candidate to be a living liver donor for him and transplant surgery was subsequently scheduled. One week prior to the procedure, in a pre-surgical abdominal MRI, Mr. C. was noted to have a non-occlusive portal vein thrombus, and a lesion suspicious for hepatocellular carcinoma. Surgery was deferred while he underwent additional evaluation and anticoagulant therapy for

the thrombus. Mr. C. was disappointed but understood the reason for the postponement of the surgery. He was able to maintain a grossly appropriate mood and adjustment to this event.

After 5 months, he progressed to transplant and received a right lobe from his brother and underwent portal vein thrombectomy. The procedure was unremarkable, and he was discharged home after 7 days. Early phase recovery at home was noteworthy for one episode of hallucinations in the setting of significant use of narcotic pain medication. He also noted increased pain from prior tennis injuries and significant muscle weakness and deconditioning, limiting his participation in activities of daily living. He had physical therapy and made good physical gains, largely regaining his independence.

Five months post-operatively, Mr. C. presented to a hepatology follow-up appointment and reported that for the past month he had been experiencing significant mood changes, tearfulness, and anxiety. He was subsequently referred to Transplant Psychology for evaluation.

Mental Status and Behavioral Observations

Mr. C. presented as awake, alert, oriented, with functional attention and concentration, capacity for goal directed behavior, planning, and abstract thought. Grooming, attire, and social behavior were appropriate. Presentation was dramatic, with large gestures. He stated that he believed he might be experiencing PTSD associated with his pre-transplant health experiences.

Affect was labile and patient became tearful abruptly and frequently over the course of the evaluation. This alternated with appropriate affect. Mood was reported as variable ranging from dysphoric, anxious, and irritable to euthymic. Sleep was disrupted by middle of the night awakenings, which were prolonged by worry. In addition, because of sleep disruption, he developed inconsistent morning rise times, which affected the timing of his immunosuppressant medications. He occasionally missed doses, which was atypical for him. He denied nightmares or intrusive recollections of his procedure or illness. Appetite was stable. He acknowledged fleeting, passive thoughts of death, without suicidal ideation, plan, or intent. There was no evidence of manic or hypomanic symptomatology. There were no obsessions or compulsions, and no evidence of panic disorder.

Despite his sad mood, irritability, and anxiety, Mr. C. was extremely grateful for his transplant; he felt better physically than he had in years. He was appreciative of the sacrifice his brother had made for him and of the care that his wife had provided for him. He was eager to return to work and had even tried returning to playing a little bit of tennis. But he described substantive deterioration and conflict in his relationships with his wife, his business partner, and with his brother, as well as new and frequent disagreements between his wife and tennis partner. He felt that his increased irritability and anxiety had somehow caused this discord and he felt both helpless and responsible for the changes in these relationships.

It is of note that steroids had been discontinued several weeks prior to assessment. He was not taking any psychotropic medications.

Psychiatric and Substance Use History

Mr. C. had a history of one episode of depression 20 years earlier and was prescribed a Selective serotonin reuptake inhibitor (SSRI) for approximately 1 year. He discontinued the medication because he felt that it blunted his emotions. There was no family history of bipolar disorder.

Alcohol use was historically limited to 2–3 glasses of wine per week, discontinued upon recommendation of his physician several years prior to transplant. There was no other substance use history.

Diagnosis and Treatment

Patient was diagnosed with Major Depressive Disorder. Treatment plan included Cognitive Behavior Therapy (CBT) for depression, active problem-solving skills training, and Transplant Psychiatry referral for medication evaluation.

Quite early in the course of psychotherapy, Mr. C. revealed that several weeks prior to his referral to Psychology, he felt that he was ready to step back into his old life and began to resume his prior social and vocational functioning, picking up right where he had left off. He noted that conflicts with his wife and business partner tended to occur around his participation in work-related activities, chores, or other tasks at home. He did not recognize that, out of necessity, others had adapted to his absence and moved forward for the past 5 years, assuming responsibility for tasks that had previously been his, while he had been attending to his health. His tennis and business partner had hired new staff and changed procedures. Similar shifts occurred at home. His attempts to return to his old pursuits were unsuccessful and he was frustrated and disappointed.

Mr. C. was typically conflict averse. His social style in general was very expressive and easily misinterpreted. He was aware that he was being perceived as "demanding, suffocating and critical of others," and his anxiety and depression increased as conflict increased.

CBT was targeted toward increasing his understanding of how his thoughts and behavior affected his mood, as well as how his behavior affected those around him. Therapy was also directed toward improving his ability to communicate appropriately and effectively with others. At the same time,

he was instructed in listening techniques to improve his understanding of other peoples' communication with him. He was very receptive to these strategies and implemented them effectively, reducing conflict significantly.

He was prescribed a low dose SSRI which eliminated his lability but did not blunt his emotions.

Therapy continued to address his accelerated expectations of his return to a non-illness-based lifestyle. Over the course of several sessions, he was able to recognize that during his illness "time had not stopped" for those around him; things had changed, and his reintegration needed to take this into account. At home, he deliberately revised his interactions with his wife, and rather than ruminating silently or being critical of her handling of chores, driving or other tasks, he was intentional and genuine in showing his affection and his appreciation of her care of him. They began to work collaboratively to accomplish activities and restore their relationship.

At work, he adopted more flexibility in his goals and became appreciative of his partner's new business activities, with the recognition that she had to make decisions in his absence. She, in turn, felt more respected and less criticized, and they were able to renew their working partnership and friendship. He began to coach again.

Although he experienced some health challenges in his transplant recovery, including neutropenia, and some renal concerns, as his relationships and functional capacity improved, mood improved to normal, and sleep issues and anxiety resolved. He was fully adherent with his medication regimen.

Over the next several months, Mr. C. began to reflect on his life-long involvement with the sports and tennis industry and began to withdraw his participation somewhat. He had not returned to his pre-illness level of tennis ability and he also began to recognize that his priorities were shifting. In the months following transplant, it had been imperative to him that he returned to his old life, and he attempted to do it with little regard for anything but his own definition success, a checklist made up of activities from his premorbid routine. But as he progressed, he became aware that his transplant experience had refocused his values and goals. He independently noted less reliance on external rewards (such as attention for athletics), as well as improvement in self-esteem and more satisfying relationships. He began to feel that his life had a new purpose. He continued to coach but increased spending time with his wife, family, and friends. He elected to continue psychotherapy on an as-needed basis, with occasional check-ins but felt ready to move forward comfortably with his life.

Clinical Questions

1. What was the role of social support in Mr. C's psychological adjustment?
2. How is this case consistent with the known literature regarding psychological adjustment post-transplant? How is it inconsistent?
3. Mr. C readily acknowledged his mood changes and reported them independently to his transplant physician, which enabled him to obtain early intervention. What is the possible trajectory of these mood changes without intervention?
4. What steps can be implemented to reduce the frequency, severity, and impact of mood and adjustment changes post-transplant?

Discussion

Mr. C's mood changes, although consistent with the literature regarding depression following transplant, were something of a surprise to his treatment team. He had shown great resilience to stressors prior to surgery, and his recovery from surgery had been remarkably smooth. He had no recent history of mental health issues and he had good social support prior to transplant. The reasons for his decline in mood were not immediately obvious.

For many individuals post-transplantation, mood changes are attributable to obvious triggers of anxiety and depression; pain, prolonged recovery from surgery, medical setbacks, cognitive changes, or an inability to participate in recreational or reinforcing activities. For others, however, the precipitants of mood issues are less obvious. Mr. C was grateful for his restored health and was able to return to several aspects of his prior life, but his expectations and goals were not entirely realistic. This led to significant frustration, and his coping and problem-solving style led to conflict and decreased social support. In this context, his depressive symptoms are entirely predictable and understandable. Treatment was directed toward resolving the problematic underlying beliefs, as well as managing his social behavior and disruptive emotional lability. Mr. C's intact cognition and motivation to participate in therapy were assets which allowed him to benefit significantly from treatment. Given the potential effects of mood on health behaviors and mortality, it is critical to be able bring a variety of evidence-based interventions to the problem and be able to intervene effectively.

The process of recovery from transplant surgery is not linear. Early in the course of recovery, daily life actively revolves around health maintenance regimens and assessment of physical health. As physical recovery and adaptation occur over the longer term, QOL variables become more salient. This case highlights the importance of treating the whole individual and recognizing the value of ongoing assessment of mood and adjustment.

Take Home Points

1. Post-transplant psychological adaptation means navigating the contrast of gratitude for the opportunity for a longer, healthier, more meaningful life, against the sometimes unexpected challenges of medical and psychological sequelae associated with transplantation.
2. Mood changes do not always occur in the immediate post-transplant period, and ongoing assessment at medical follow-ups is critical.
3. Optimizing psychological function post-transplant not only directly affects QOL but may also impact risk for other negative health events.

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The Choice of Not Pursuing the Transplantation

33

Yelizaveta Sher

Introduction

Transplant clinicians routinely make pre-transplant determinations about patients' psychosocial candidacy guided by existing evidence [1–4] and ample clinical discussion. However, there is less discussion and research about patients who choose to decline transplantation, potentially even before their official referral and evaluation. While patients have an absolute right to this decision, which is hopefully congruent with their values and goals, their physicians might worry that this decision is premature, not based on full knowledge and appreciation of prognosis and risks of declining versus pursuing transplantation, guided by anxiety or depression, and/or simply not in the best interests of the patient (of course as defined by the physician). This might be especially morally distressing to the clinical team when the patient has a relatively excellent prognosis after transplantation.

Transplant psychiatrists and psychologists, thus, might be consulted by the transplant teams to specifically address the question of patient's ambivalence toward or strictly declining transplantation in an otherwise "good or excellent candidate." Psychiatrists might also be integrated into or consult to the medical referring teams (e.g., heart failure team, nephrology clinic, cystic fibrosis (CF) program) and thus called upon for their expertise, when patients decline referral to the corresponding transplant program even for an initial evaluation.

While there is a greater need for studies on patients' decision-making and refusal of transplantation, several papers have started to shed light on patients' perspectives. A study of 164 adult chronic dialysis patients in Slovenia demonstrated that 35.0% of patients declined transplantation and 20.0% were undecided [5]. Of note, patients declining transplantation were significantly older as compared to those who wanted to be transplanted (67 ± 16 vs. 57 ± 16 years; $P < 0.001$). The main reasons to decline transplantation were feared side effects of immunosuppressant medications (31.6%), worry about unpredictability of transplant outcomes (29.8%), and poor outcomes in fellow patients (28.1%) [5]. A qualitative paper of attitudes in patients with CF declining lung transplantation (at least initially) described the following reasons: (1) prior encounters (e.g., patient's experience with fellow patients' negative transplant outcomes); (2) psychological (e.g., acceptance of a shortened lifespan due to religious belief); and (3) medical [6]. The medical reasons included perceived discrepancy between patient's and physician's understanding of patient's prognosis, patients' fear of acquiring new medical conditions and complications, trading one disease they know (CF) for another they do not (transplant), and feared side effects of the immunosuppressants [6].

In addition, a blogger on the CF Foundation website shared his reasons behind choosing not to select lung transplantation for his progressing CF, including the costs of the procedure and the debt he might leave his family with, his personal medical risk versus benefit analysis, and the actual stress of the transplant evaluation, all coupled with the sense of peace and appreciation of life he has already had [7].

To add to this increasing and important conversation, this chapter describes a case of a young patient with CF declining referral to lung transplantation and explores the role of a psychiatrist in evaluation of her decision-making as well as provision of support to the patient, her family, and the referring medical team.

Case History

Miss A was a 25-year-old woman with CF, complicated by pancreatic insufficiency, diabetes, malabsorption, CF-related liver disease, and end-stage lung disease. Miss A's CF team had discussed lung transplantation with the young woman on several occasions and finally recommended referral when

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her forced expiratory volume in 1 s (FEV1) dropped to 27%, in line with the guidelines from the CF Foundation [8]. They were surprised, however, when Miss A turned down this referral. Despite teaching and multiple discussions with the CF team, the young patient declined to even meet with the lung transplant clinicians for further education and initial evaluation. Thus, the CF team consulted an embedded CF psychiatrist (also a transplant psychiatrist) to further evaluate patient's decision-making and any potential psychiatric contributors to her decision, such as depression and/or anxiety.

Miss A welcomed an opportunity to meet with the psychiatrist to explore her own reasoning and to find further support. In an interview with the psychiatrist, she discussed her upbringing in a family with supportive parents and a younger sister without CF. She shared that her Christian faith provided her with a lot of meaning. Miss A was single without children and lived with her parents. Miss A was proud of finishing college as her grandparent had been an educator and she felt proud to honor her loved one with this accomplishment. She enjoyed working for her parents' private business when she physically could.

During an evaluation, Miss A expressed that she had thought a lot about lung transplantation and made her decision to NOT pursue lung transplant after much deliberation. She declared that she clearly understood her underlying condition of CF, its progressive nature, and her deteriorating course with early mortality. She shared that she was able to appreciate the risks and benefits of transplantation from her own education, some education from the CF team, and knowledge from her friends who had pursued it, as well as the consequences of not going through transplantation. In fact, she had several friends with CF who underwent lung transplantation but had only lived for 2–3 years afterward with significant complications and she did not want to repeat their experience. She understood that people with CF typically have a longer life expectancy after lung transplantation compared to her friends who unfortunately had negative outcomes, as well as compared to individuals going through lung transplantation for other than CF reasons. However, she felt that transplantation was not consistent with her personal and spiritual values.

Miss A felt that she had been through a lot of physical suffering in her life, such as multiple prior treatments and hospitalizations, challenges with her prior gastrostomy tube, and a particular hospital admission during which she required Bilevel Positive Airway Pressure (BiPAP) in the intensive care unit (ICU). However, by this time in her life, she was against invasive interventions, such as intubation, insertion of chest tubes, or transplantation of someone else's lungs into her body. She did not want to go through the pain and the distress associated with these procedures, be connected to tubes and machines, or stay in the intensive care unit (ICU). In addition, she strongly felt that that she wanted to live her best life and then die with her native organs inside of her body. Miss A did not have regrets about her life and felt accomplished looking back. She wanted to live and have a good quality of life, but she did not want invasive interventions to prolong her life.

The patient shared that she had struggled with anxiety and depression, but had no psychiatric hospitalizations, history of suicidal ideations, or suicide attempts. At this time, she felt sad about her situation and prognosis, felt guilty about the pain she might cause her parents and sister with her further deterioration and then her passing, and was worried about them. She had increased anxiety with progression of her respiratory condition. She worried that her parents might not understand her choice. She had good sleep, but decreased appetite and energy in context of her physical illness. She was bothered by dyspnea, nausea, and pain.

The patient was diagnosed with anxiety secondary to her medical condition and adjustment disorder with depressed mood. She was found to have capacity to make a decision regarding transplantation, given that she clearly articulated her choice and understood her diagnosis, prognosis, proposed intervention and alternatives with risks versus benefits, and appreciated the gravity of her decision.

With patient's permission, the multidisciplinary meeting was facilitated with all the members of the CF multidisciplinary team, patient, and her family, co-facilitated by the CF pulmonologist and the psychiatrist. Her current situation, prognosis, and options were again discussed, and patient again clearly expressed her choice. She was able to address her parents with the support of her team and her parents were supportive of her decision, even though they understandably had wished that patient would choose a life-prolonging intervention.

Patient was referred to the palliative care team for management of her physical symptoms. She continued to work with the CF psychiatrist addressing her psychological symptoms with medications (e.g., mirtazapine and bupropion) and psychotherapy (e.g., modified dignity therapy) [9]. Patient's quality of life was optimized (e.g., her dyspnea, cough, fatigue, and nausea were managed) and she was able to experience several events important to her (e.g., taking few short trips with her friends and family, enjoying her time with her loved ones). She died 18 months later on hospice surrounded by her family.

Clinical Questions

1. How do we ensure that a patient who declines evaluation for transplantation makes a decision based on reasonable information?
2. How do we appreciate a possible contribution of psychiatric conditions, such as depression or anxiety, to patient's decision not to pursue transplantation?

3. What support should patients who decline transplantation receive from their medical teams?

Discussion

During a transplant evaluation, patients receive important education from the evaluating transplant team, including additional information about their disease, the natural prognosis of their condition, and expectations with and without transplantation, including associated risks and benefits. Throughout this process, patients' understanding of the transplantation process is assessed and the informed consent is obtained. Patients are assumed to have capacity unless there are obvious concerns, such as a cognitive or psychiatric condition, that clearly impair their decision-making.

On the other hand, it is harder to assess patient's decision-making as the one based on full appreciation of their medical situation and treatment options, when a patient does not receive this official education from the transplant team. It then falls upon the referring team to provide their patient with this education, while being tactful and mindful of patient's wishes and reservations (e.g., expressed anxiety to even receive such information). Patients decline referral for multiple reasons, and it is important for clinicians to understand and appreciate these reasons. Patients might fear facing their mortality and thus reject interfacing with the transplant team and the medical decision that clearly places this reality in front of them. Patients might have other anxieties about this significant intervention that they avoid confronting (e.g., pain, intubation, complications). They might have had friends or fellow patients who have had negative transplant experiences (as our patient did and as echoed in the existing literature [5, 6]). At the same time, while the patient might decline any conversations about transplantation with their referring treatment team, the medical providers are also cognizant of the fact that transplant evaluations are frequently time sensitive, and postponement of such evaluation might jeopardize a patient's chance to do well. Thus, the team has a responsibility to tactfully provide important information to ensure that the patient indeed has the necessary facts to make an informed decision.

There are several strategies that the referring team can employ to aid such discussion and facilitate the best non-pressured environment to provide patients with the best information. One intervention is ongoing work with the patient to fully understand the patient's goals, values, and reasons behind their resistance to or refusal of referral. Elements of motivational interviewing can be used to highlight patient's decisions congruent and discordant with these goals. The mental health professional can be very important and helpful with this approach. The team can also choose the medical provider who patient has the best rapport with to provide important information around the transplantation. In addition, the team can provide education to the patient in written forms (e.g., educational pamphlets, books [10]), offer links to important sites (e.g., CF Foundation for patients with CF [11], The International Society of Heart and Lung Transplantation (ISHLT) for cardiothoracic candidates [12]) and available decision-making tools (e.g., Kidney Transplant Decision Aid for kidney transplantation [13]), and connect patients with other peers. It might be important to see this patient more frequently in clinic and check back during the next clinic visit (or in a follow-up phone call) in regard to information digestion and any follow-up questions that patients might have. Again, psychiatrists and psychologists might play a very important role during this phase. These mental health clinicians may incorporate elements of motivational interviewing, such as enhancing ambivalence, encouraging change talk, and others, as well as their expertise in transplantation medicine to guide the team in conducting these important conversations with the patient. At the end, this is a patient's decision, but the referring team has an obligation to provide necessary information for patient to base their decision on the best facts.

In the case of Miss A, the team had provided her with relevant information over the years and she had also sought out additional information on her own. The psychiatrist was able to have a discussion with the patient around her decision where she was able to share her knowledge and explain the reasons behind her decision. The multidisciplinary meeting involving patient's family further cemented her and the team's understanding. For Miss A, it was a clear that a combination of her knowledge of transplant, unfortunately tainted by the negative experiences of fellow CF patients, but also coupled with her strong faith, belief that she was meant to die with her native organs, and appreciation of her limitations of what she was willing to physically undergo and tolerate provided a clear basis for her decision.

In addition, it is important to evaluate patients for the presence of any mental health conditions that might negatively contribute to the patient's decision to decline referral for evaluation or transplantation itself. Patients with chronic medical conditions are indeed at higher risk for mental health conditions and, in particular, patients with CF have 2–3 times higher rates of depression and anxiety compared to the community samples [14]. There are instances when patient's anxiety can severely impede their ability to confront their mortality via evaluation for transplantation or depression might contribute to the desire to hasten death and thus be a driving factor behind forgoing any interventions to prolong life. It is of course important to properly diagnose and treat these conditions via psychoeducation, psychotherapy, medications, and/or interventional treatments in an attempt to overcome these barriers. Untreated mental health conditions can indeed interfere

with the patient's ability to fully take care of themselves and their new organ and/or contribute toward the ambivalence about transplantation and thus make the patient a minimally acceptable or poor psychosocial candidate for transplantation. These conditions would need to be resolved before the patient could be fully recommended for transplantation for their own well-being as well as the stewardship of the precious donor resources. However, anxiety and depression can co-exist with the decision to forgo transplantation and not impair the decision-making or necessarily influence the decision (see Chap. 5). In any case, it is the responsibility of the referring team (in this case, the CF team) to provide necessary mental health resources to such patient, in order to either to address mental health concerns to clear the way for referral and transplantation and to ensure the best post-transplant outcomes, and/or to decrease patient's suffering and optimize quality of life regardless of the decision about transplantation. In the case of Miss A, clinical assessment demonstrated that while she had comorbid symptoms of anxiety and depression secondary to her medical condition, they were not the main influencers in her decision to decline transplant. In fact, it was reassuring that the patient felt proud and accomplished looking back at her life versus desponded and regretful. She wanted to continue living as long as she had fair quality of life and denied the wish to die or hasten her death. Miss A was provided with mental health services within the CF clinic, where her symptoms were treated with psychotropic medications as well as psychotherapy best suited for her existential concerns. Both interventions allowed her quality of life to be optimized. Of further note, treatment of her anxiety and depression did not change her decision to decline transplantation.

In addition, it might be helpful and important to inquire about patient's spiritual or religious beliefs. This can help the team to understand if such beliefs influence or guide patient's decision-making about transplantation and whether these beliefs (and potentially associated community) provide the patient with the additional support system. One approach is by starting with simple open-ended questions embedded in the rest of the interview, such as "Are religion or spirituality important parts of your life? or Do you rely on your faith during challenging times?" [15]. If patient answers yes to these questions, you can further ask about particular beliefs and offer to connect them with appropriate further resources, if needed, such as a chaplain. For Miss A, both religion and spirituality were important and helped her to make decisions while providing enormous sources of support. Honoring and showing appreciation of her background allowed the team to also show further support to her.

While Miss A's referring CF team was disappointed that she turned down the referral to transplantation and thus the chance to prolong her life, the team was understanding of her decision. The patient and her team had many important discussions regarding her goals of care and values. It was important for the patient to optimize her quality of life, but not undergo any invasive procedures. She was also referred to the palliative care team. Thus, the patient was able to be followed closely by the medical and mental health providers from the CF team as well as the palliative care team to provide her and her family with necessary medical, mental health, existential, spiritual, and structural support. The patient was able to continue to enjoy her life and even have a few small trips with her family. When her physical condition deteriorated to significant dyspnea and anorexia, she was admitted to the hospice and died in comfort and peace several weeks later.

When patients decline transplantation, their medical teams will continue to provide patients with medical care congruent with patient's goals and values. It is important for the team to fully discuss patient's wishes, including advanced care planning and decisions regarding intubation and resuscitation as appropriate. In addition, ideally, medical teams would connect their patients who decline transplantation to appropriate services, such as palliative care and mental health providers, if not done already. It is important to accurately introduce palliative care team to the patient, as the multidisciplinary team able to provide a variety of supportive services aimed to optimize patients' quality of life across the disease continuum, including, but not exclusively toward the end of life. However, many patients also feel reassured knowing that there are clinicians who specialize in comfort toward end of life, ensuring that they will not suffer and can die with most dignity. It is also important to remember that it is not only patient, but their family who is going through this experience. By taking care of the patient holistically, the team also is taking care of their family, anticipating their grief. The family who knows that their loved one has made their best decision for themselves and was taken care of throughout their disease continuum including end-of-life and dying, is aided in their grieving process.

Physicians are hard wired and trained to work toward prolongation of their patients' lives. There are times when patients have different values and goals, such as in cases of individuals declining transplantation. Transplant and consult liaison psychiatrists might be called in such cases to help evaluate and support such patients. While particularly challenging, these cases might be especially illuminating and meaningful for medical and mental health professionals.

Take Home Points

1. Consult liaison mental health clinicians may be particularly skilled in evaluating patients who decline referral for transplantation, focusing on understanding their values and goals, connecting patients with resources to receive necessary information for their decision-making, and guiding medical teams to best support their patients.
2. It is important to evaluate patients for depression and anxiety, which might influence patient's decision-making to decline transplantation, and then appropriately address these symptoms. However, it is important to note that symptoms of depression and anxiety can coexist with the decision to decline transplantation, but not be responsible for it.
3. Medical and mental health providers of patients who decline transplantation have an obligation to support their patients incorporating their values and goals in context of not pursuing transplantation. These patients most likely would also benefit from referral to palliative care team for a more thorough support of their and their families' physical, spiritual, existential, and practical needs.

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Psychiatric Impact of Glucocorticoids in Organ Transplantation

34

Jordan H. Rosen

Introduction

Despite advances in immunosuppression, the use of glucocorticoids in different phases of transplantation remains common. Pulses of high doses of steroids are regularly employed in the peri-operative period and for treatment of acute rejection. Lower dose regimens are routinely used for maintenance therapy. Organ-specific regimens may differ in their usage of these agents [1]. While glucocorticoids' efficacy has been demonstrated in randomized controlled trials [2], there are numerous associated adverse effects, both acute and chronic.

While the somatic effects of glucocorticoids are well understood, the mechanisms of neuropsychiatric complications are less well characterized [3, 4]. Numerous symptoms have been reported, including, but not limited to agitation, anxiety, distractibility, dysphoria, fear, hallucinations, hypomania, indifference, insomnia, irritability, lethargy, labile mood, paranoia, pressured speech, restlessness, and tearfulness [5]. In clinical practice, subsyndromal anxiety, insomnia, and irritability are very common.

The prevalence of neuropsychiatric side effects ranges in the literature from 2 to 62% with 3–6% suffering from severe symptoms [6–8]. A majority of patients develop neuropsychiatric symptoms early in treatment. Hall et al. found 86% of symptoms occurred within 2 weeks of initiation of treatment, with up to two-thirds of patients developing symptoms within the first 5 days [9]. Lewis and Smith's review found a median time to onset of symptoms of 11.5 days with 62% developing symptoms in the first 2 weeks and 89% developing symptoms within 6 weeks of initiation of steroids [7].

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Multiple authors have come to the conclusion that affective symptoms appear to be the most common psychiatric adverse effects of corticosteroids [7], [10–12]. In the early stages of steroid treatment and those on higher doses, patients are more likely to experience manic or hypomanic symptoms. Long-term therapy, similar to Cushing's Disease, is more likely associated with depressive symptoms [4, 8, 13]. Steroid-induced affective disorders appear to be accompanied by psychotic symptoms more frequently than primary mood disorders [7, 11]. Suicide risk is also increased; in a national database UK study, the hazard ratio for suicide or suicide attempt in patients exposed to steroids as compared to controls was 6.89 [14]. Cognitive deficits (especially impairment in verbal and declarative memory, and particularly recall deficits in the elderly) are also common with glucocorticoid treatments [9, 15, 16].

Duration of affective or psychotic symptoms has been reported with significant variability likely relating to variation in discontinuation and intervention [3]. Patients with delirium may recover more quickly, with one study reporting a mean duration of 5.4 days vs. 19.3 days in those with depression, mania, or psychosis [17]. Varney and colleagues noted that cognitive deficits resolved within 3 to 11 months after discontinuation of glucocorticoids, though Hall and colleagues noted 7% had persisting deficits [9, 17].

There appears to be a clear dose relationship between glucocorticoids and neuropsychiatric symptoms [18]. The Boston Collaborative Drug Surveillance Program studied 718 consecutive patients receiving steroid therapy and found that 1.3% of patients receiving doses up to 40 mg per day, 4.6% of patients receiving doses between 41 and 80 mg per day, and 18.4% of patients receiving doses greater than 80 mg per day developed neuropsychiatric side effects [6]. Similarly, Lewis and Smith found that 77% of patients with neuropsychiatric symptoms had received 40 mg per day or more of prednisone [7]. Most patients undergoing organ transplantation who receive steroids receive high doses.

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In addition to the steroid dose, other speculated risk factors for development of neuropsychiatric side effects include hypoalbuminemia, disruption of the blood–brain barrier, prior steroid-induced neuropsychiatric symptoms, cytochrome p 450 inhibition, longer acting corticosteroid preparations, female sex, and increasing age [4, 14]. Many of these factors are common in patients requiring transplant: many patients with liver failure have hypoalbuminemia; the blood–brain barrier can be compromised during large surgeries; and other medications involved may affect the cytochrome p 450 system.

Withdrawal of glucocorticoid agents can also lead to neuropsychiatric symptoms. This can be due to suppression by exogenous steroids or endogenous production leading to a derangement in the hypothalamic–pituitary–adrenal (HPA) axis, but also may represent a stand-alone withdrawal syndrome with preserved HPA function [5]. This syndrome has been characterized by sleep and appetite disturbance, depression, anhedonia, fatigue, irritability, depersonalization, poor concentration, anorexia, agitation, psychosis, and suicide [3]. Secondary mania, psychosis, and delirium are also possible [19, 20]. While symptoms improve and often resolve within 2–8 weeks [21], symptoms can persist and may require a second, more gradual taper [19].

Several agents have been trialed as prophylaxis for neurocognitive side effects during glucocorticoid administration. Trials of mood stabilizers, such as lithium carbonate and lamotrigine, have been published which show efficacy, although the trials have limitations including small sample sizes, low doses of prednisone, or lack of quantification of symptoms [3, 22, 23]. There is limited case literature showing possible efficacy for valproate as a prophylactic agent [24]. Phenytoin, levetiracetam, and amantadine did not show significant differences for affective symptoms when compared to placebo in small studies [3, 25–27].

When symptoms do arise, a number of different steps can be taken to manage the symptoms. Discontinuing or decreasing steroids to less than 40 mg per day equivalent dose of prednisone is suggested generally, though this may not be possible in many transplant cases. Mood stabilizers have not only shown efficacy in prophylaxis but also in treatment [3]. Their use is often limited in transplant populations by need for other nephrotoxic agents, significant fluid balance shifts in the peri-operative window, and drug–drug interactions.

Antipsychotics have also been shown to be effective in treatment of both mood and psychotic symptoms. Davis and colleagues found symptom resolution with low-dose antipsychotic treatment in 83% of patients with psychosis, including 33% in 3 days and 60% in 1 week [28]. Similarly, Brown and colleagues found olanzapine effective in 11 of 12 patients with manic or mixed symptoms with mean daily dose of 9.2 mg per day [29]. Since many antipsychotics are usually well tolerated in the short term, not dependent on fluid balance, and have relatively fewer drug interactions, they often represent first-line treatment for both manic and psychotic symptoms associated with steroids in transplant patients.

Case History

A 31-year-old woman with a history of liver failure secondary to primary sclerosing cholangitis was admitted to the hospital for liver transplantation. Her medical history was significant for hepatic microabscesses on chronic antibiotics (most recently ciprofloxacin and metronidazole) and Crohn's disease being treated with vedolizumab. She has a psychiatric history of bipolar affective disorder, type 2, in remission prior to surgery and previously on lamotrigine but off medications for 10 years, with no previous history of substance abuse. Prior to transplantation, laboratory tests were notable for hemoglobin and hematocrit of 10.9 and 34.9, respectively, total bilirubin of 3.9, alkaline phosphatase of 531, alanine aminotransferase of 383, and aspartate aminotransferase of 585. She underwent an orthotopic liver transplant during which multiple hepatic microabscesses were appreciated and thought to be consistent with known lesions. No major operative complications were noted and blood loss was estimated to be 800 cc. She was extubated and off pressor supported on post-operative day 0. She was given 160 mg of methylprednisolone on the day of her transplant, followed by a 4-day taper down to 40 mg before transitioning to a 6-day prednisone taper from 20 mg daily to 10 mg daily. She was also started on tacrolimus. She did well during the initial post-operative period with no signs of affective, psychotic, or cognitive disturbance though developed a mild tremor. Opioids were discontinued by post-operative day 5, with no more than one dose daily of as needed tramadol administered thereafter.

On post-operative day 8, she was diagnosed with an acute rejection with signs of hepatic damage. A dose of methylprednisolone 500 mg was administered and prednisone was increased to 20 mg daily 3 days later. On post-operative day 13, she became intermittently disoriented and had trouble sleeping. Vital signs and laboratory investigations, including comprehensive metabolic panel, complete blood count, and liver enzymes, were stable or improved from previous days. During the following 2 days she developed auditory and visual hallucinations, paranoid ideation, insomnia, rapid and illogical speech, inattention, distractibility and significant anxiety, and intermittent mild agitation. Her mood ranged from dysphoric to irritable and her tremor worsened. Brain magnetic resonance imaging (MRI) did not show any abnormality. Tacrolimus levels were noted to be in the lower range of therapeutic.

Psychiatry was consulted on post-operative day 16. Quetiapine was initiated and titrated over the next 3 days to 200 mg nightly with 50 mg as needed doses with limited

effect on sleep and continued psychotic and manic features. On post-operative day 20, the decision was made to discontinue quetiapine and olanzapine was started and titrated to 10 mg over the next 2 days with good effect on sleep and improvement in attention, orientation, as well as manic and psychotic symptoms. Blood glucose initially became elevated with the second methylprednisolone pulse, with daily ranges from 140 to 220, and this was exacerbated when olanzapine was titrated with resulting ranges between 150 and 250. Full resolution of symptoms was achieved on day 24 and olanzapine was tapered over the next 4 days due to increasing day time sedation with no relapse in symptoms. Blood glucose normalized within 1 week after discontinuation of olanzapine and continued steroid taper.

Clinical Questions

1. What factors in the patient's history raise her risk for developing a glucocorticoid-induced affective disturbance?
2. After the patient's mental status changed on post-operative day 13, what would your differential diagnosis include, and what investigations might you pursue to clarify it?
3. Why was it important to obtain brain magnetic resonance imaging in regard to the worsening tremor and altered mental status?
4. In this patient, what considerations would you consider in choosing whether to initiate a pharmacologic agent and which one to start?
5. Would you consider prophylactically prescribing a medication to the patient in the future if she required another pulse of steroids, and if so, which medication?

Discussion

This case presents a number of the difficulties that can be associated with diagnosing and treating glucocorticoid-induced neuropsychiatric symptoms in the setting of transplantation. When the patient developed new cognitive and mood symptoms on post-operative day 13, the differential was broad and included hepatic encephalopathy in the setting of acute rejection, delirium due to new infection or other post-operative complication, side effects from co-administered immunosuppressants (in this case, concern for tacrolimus-induced neurotoxicity), side effects from high-dose steroids, or an exacerbation of a previously diagnosed bipolar disorder.

When the patient went into acute rejection, her liver enzymes became elevated and her international normalized ratio (INR) began to increase, suggesting hepatic damage and malfunction. Interestingly, her mental status did not worsen until 5 days after acute rejection was first noted and treated with a second pulse and taper of steroids. When symptoms did develop, her liver function was improving. This made hepatic encephalopathy less likely as a cause for the changes in her mood and cognition.

With the onset of disorientation and alteration in sleep, delirium was suspected and a medical work-up was started which demonstrated stable or improved complete blood count, comprehensive metabolic panel, and liver enzymes. Her mental status deteriorated and was accompanied by worsening tremor, raising concern for a tacrolimus-induced neurotoxicity and posterior reversible encephalopathy syndrome (PRES). With regard to tacrolimus-induced neurotoxicity, it was reassuring that her tacrolimus levels were not elevated, though this does not rule out a tacrolimus-related neurotoxicity. In addition, her blood pressures were not elevated and the MRI ruled out PRES. However, given the evolution of her symptoms following the second steroid pulse and her relative tolerance of tacrolimus up until this point, her new neuropsychiatric symptoms were thought to be more likely related to glucocorticoids.

The patient had multiple factors that raised her risk for adverse effects with high-dose steroids. She had been previously diagnosed with bipolar disorder, which has not been consistently shown to be a risk factor, but was not currently treated. Her sex also raises her risk. Due to her pre-existing liver disease, she also had hypoalbuminemia prior to transplant and this had not yet recovered post-transplant before the second steroid pulse was given. Since methylprednisolone is bound to albumin, low albumin levels can lead to increased free methylprednisolone levels in the blood and has been associated with an increased frequency of steroid-related side effects [30]. She was also given two pulses of high-dose steroids within a relatively short period of time, and the second pulse and taper were followed 5 days later by changes in mood and cognition. As discussed earlier, most patients develop symptoms within the first week of starting steroids, and two-thirds within 5 days.

On exam, the patient showed a mixed picture of manic, psychotic, and inattentive features. While visual hallucinations are rare in primary psychiatric conditions, they are common in the case literature surrounding glucocorticoid-induced psychoses. Her neuropsychiatric symptoms were worsening with more prominent psychotic features, persisting insomnia, and concern that she would soon be unable to participate in care. In addition, steroid discontinuation was deemed to be too high risk by the primary team, and thus, another pharmacologic intervention was necessary. An antipsychotic was favored over a mood stabilizer due to the presence of psychotic symptoms, the need for improved sleep, evidence of hepatic damage, and continued concern for fluid shifts. Quetiapine was initially trialed for both its sedating effects and relatively lower anticholinergic activity as compared to other more sedating antipsychotics.

When symptom improvement was not attained with escalating doses of quetiapine, the medication was changed to olanzapine to allow for a faster titration to therapeutic doses. Olanzapine was titrated with good effect and eventual full symptom resolution. The patient did not experience anticholinergic side effects. Olanzapine was tapered off slowly while the patient was monitored for relapse of symptoms in the hospital. Blood glucose did show elevation with steroid taper with mild exacerbation while olanzapine was administered, but returned to normal after discontinuation of the latter. No further symptoms were noted.

In the peri-transplant period, some of the common side effects of atypical antipsychotics can become more impactful. Anticholinergic side effects can also lead to increased urinary retention in the post-operative period which could increase the risk of urinary tract infection in a population already at higher risk. Many atypical antipsychotics can also have metabolic effects, including impairing insulin sensitivity leading to increases in blood glucose, compounding with the effects of steroids. QT prolongation can also be exacerbated by other transplant medications (e.g., tacrolimus, antibiotics), as well as post-operative electrolyte shifts. Antipsychotics' ability to lower seizure threshold is also worth considering since some of the immunosuppressants can also lower this threshold.

The patient previously had wanted to remain off medications for her bipolar illness as she had been symptom free for the last 12 years and without medications for the past 10 years. The consultation service discussed with the patient the options of re-initiating a maintenance mood stabilizing medication or starting treatment in the future if she were to need another course of steroids. It is unclear whether her risk of another mood episode due to her primary psychiatric condition is increased by this glucocorticoid-induced episode; though given the hardship this episode caused and her desire to avoid a similar event in the future, she ultimately agreed to pursue prophylaxis in the event of another course of high-dose steroids.

In recommending a prophylactic medication to this patient if future need did arise, multiple factors were considered. She had previously done well with mood stabilization on lamotrigine, but this medication takes a long time to titrate to therapeutic doses and if the need for a higher steroid dose is urgent or emergent, we may not be able to titrate quickly enough to attain prophylaxis. Valproic acid, while rapidly titratable, also has risk for hepatotoxicity. In addition, antipsychotics are easy to titrate and often reliable in these cases. If she did require another dose of steroids, it would likely relate to hepatic transplant rejection which would make a medication with risk for hepatotoxicity less desirable. Atypical antipsychotics were discussed with the patient, and she chose olanzapine for possible future use given her experience with its efficacy and tolerability.

Take Home Points

1. High-dose glucocorticoids are commonly used in transplant patients.
2. While steroid-induced anxiety and insomnia are quite prevalent, affective disorders are the most common major disturbance.
3. There are several risk factors for glucocorticoid neuropsychiatric effects that are common in patients requiring transplant. The most validated risk factor is the higher dose of glucocorticoids, with other contributing factors, including hypoalbuminemia, disruption to the blood brain barrier, and co-prescribed medications that may affect the cytochrome p450 system.
4. Given the comorbidities involved in organ transplantation, management options require careful consideration of their potential risks and benefits.

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Neuropsychiatric Adverse Effects of Immunosuppressant Agents

35

Stephanie H. Cho and Catherine Crone

Introduction

Immunosuppressant (IS) medications, critical to survival in SOT, can cause severe neurotoxic complications that pose major threats to quality of life and organ graft viability. Prompt recognition and intervention can be difficult due to the wide variety of clinical manifestations which can include psychiatric and behavioral symptoms. Psychiatrists play a critical role in the recognition and management of these complications, which require close interdisciplinary collaboration and careful consideration of risks and benefits.

Improved immunosuppressive therapies have improved survival in solid organ transplantation (SOT), with 5-year survival rates now ranging from 55% for lung and up to 80% for kidney [1–3]. However, post-transplant complications are common, impair quality of life, and are associated with increased morbidity and poorer outcomes [4, 5]. ISs are one of the leading causes of neurological complications among all organ transplants, accounting for one-third of cases [6, 7]. Symptoms of IS-induced neurotoxicity are wide ranging and may be acute or chronic, peripheral or central, and often occurring in the early post-transplant period [1, 5, 6, 8]. Of the agents used in transplant immunosuppression, the calcineurin inhibitors (CNIs) and corticosteroids are the most associated with neurologic adverse effects [1, 7].

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Calcineurin Inhibitors

Cyclosporine and tacrolimus inhibit T-cell activation via calcineurin inhibition [9–11]. The CNIs have become the standard of care for immunosuppression in solid organ recipients [12, 13]. They are so highly efficacious that over 90% of SOT recipients are managed with a CNI for early and maintenance prevention of rejection, despite their narrow therapeutic indices [5, 14] and adverse effects which include nephrotoxicity in addition to neurotoxicity [13, 15]. CNIs are the leading cause of drug-related neurotoxicity in transplant recipients [1]. Neurologic complications occur in up to 30% of patients treated with CNIs [10, 16–19], though the incidence appears to be decreasing with improved dosing strategies [20]. Tacrolimus is widely favored due to superiority in preventing acute rejection [1, 13, 21]. While tacrolimus has a higher incidence of neurological syndromes, the overall profile of neuropsychiatric effects is similar to that of cyclosporine [5, 22].

Mild symptoms are most common, occur in 40% of patients [7, 10, 13, 17], and include headache, neuralgia, neuropathy, insomnia, anxiety, and other sleep and mood disturbances [5, 10, 16–18]. Fine tremor, usually in the upper extremities, is a common and characteristic symptom [7, 13]. Seizures occur in 5–10% of patients, usually early in the post-transplant course [1, 18], and are typically generalized [10, 23]. Patients often do well, without need for ongoing anti-epileptic medication [5, 12].

Severe complications are rare, affecting around 5% of transplant recipients [13, 24]. Perhaps the most well known is posterior reversible (leuko)encephalopathy syndrome (PRES). Thought to be mediated by vasogenic edema, PRES can manifest with a wide range of symptoms, including headaches, nausea and vomiting, confusion and altered mentation, visual disturbances, intracranial hemorrhages, seizures, and focal neurologic deficits [1, 5, 25]. Diagnosis is based on characteristic magnetic resonance imaging (MRI)

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findings of bilateral symmetric edema, usually with diffuse white matter hyperintensities, that are classically, but necessarily, in the "posterior" parieto-occipital areas [5, 25]. While PRES is often reversible, progressive cerebral ischemia and infarction can cause lasting morbidity and an increased risk of mortality [1, 5, 13]. Other neurotoxic complications have been reported, including optic neuropathy, cortical blindness, speech disorders, multi-focal demyelinating sensorimotor polyneuropathy, neuromuscular complications, central or extrapontine myelinolysis, encephalopathy, and coma, as well as psychiatric and behavioral symptoms [5, 13, 16, 26, 27].

Severe psychiatric manifestations of CNI neurotoxicity include mania, psychosis, catatonia, and akinetic mutism [1, 5, 10, 13, 28, 29]. While the type and frequency of classically neurological manifestations of CNI toxicity are well described in the literature [28, 30], psychiatric and behavioral manifestations have not been as well described, often being incorporated into the broad umbrella of "neurotoxicity" or "neuropsychiatric" symptoms. Although case reports of CNI-induced psychiatric symptoms have increased in recent years [18, 24, 28, 31–47], the incidence and range of psychiatric and behavioral manifestations remains poorly understood, and it is unclear what proportion of these symptoms occurs as a direct consequence of other neurological complications, such as seizures, stroke, or acute encephalopathy/delirium.

Calcineurin is highly expressed in the CNS, comprising more than 1% of the total protein content in the brain, which may account for the significant CNS neurotoxicity with CNIs [10, 48, 49]. The pathophysiology of CNI-induced neurotoxicity is unclear, though several possible mechanisms have been identified. Though lipophilic, the ability of cyclosporine and tacrolimus to cross the blood–brain barrier (BBB) is limited by their large molecular size [10, 11]. However, SOT recipients often have comorbid infection, inflammation, or metabolic derangements that compromise the BBB and enable increased CNS drug concentrations [1, 5, 10, 48]. CNIs also directly increase BBB permeability by inducing apoptosis in endothelial cells [50], which can facilitate passage of both drugs and fluids, potentially contributing to increased CNS drug concentrations and cerebral edema. CNIs are both substrates and inhibitors of the efflux transporter p-glycoprotein, thus inhibiting their own efflux when they do cross the BBB [51]. CNS drug metabolism is not fully understood [52] and it is possible that CNS drug levels may decrease at different rates and take a longer time to clear compared to serum drug levels, contributing to persistence of severe neurotoxicity symptoms even after the offending IS has been withdrawn and serum levels have decreased [12, 16, 28, 53–55].

Once in the CNS, CNIs may mediate neurotoxic complications in a variety of ways. Endothelial compromise, systemic hypertension, and increased CNS nitric oxide, all CNI induced, may contribute to vasogenic edema [5, 10, 13, 48]. CNIs may increase oxidative stress by altering mitochondrial function, thereby inducing cellular damage [48], while modulated neuronal excitability and depolarization via Na/K ATPase could result in a variety of central and peripheral manifestations, including peripheral neuropathy [10]. CNI-associated depletion of neuronal serotonin may underlie tremor and mood disturbance [13]. CNIs may cause neuralgia via potentiation of N-methyl-D-aspartate (NMDA) receptor activity in the spinal cord [13], while NMDA receptor sensitivity modulation and decreased gamma-aminobutyric acid (GABA) signaling may play a role in the development of seizure, catatonia, and akinetic mutism [10, 13, 56, 57].

The mechanisms by which CNIs induce symptoms of psychosis and mania are currently unknown. However, increasing evidence supports calcineurin insufficiency as a risk factor for psychosis [17, 49]. Variations of the PPP3CC gene, which encodes the catalytic subunit of calcineurin, are significantly associated with both schizophrenia and bipolar disorder [58]. NMDA hypofunction, which appears to play important roles in both psychotic and mood disorders [59], has been associated with calcineurin hypofunction [49, 60]. Additionally, D2 receptor antagonist antipsychotic drugs have been shown to modulate calcineurin expression and activity [61], and it has been postulated that calcineurin exerts a buffering action against excessive dopamine signaling [58]. Thus, it is possible that CNIs induce symptoms of mania and psychosis through modulation of NMDA and dopamine pathways.

Corticosteroids

Corticosteroids are often used to facilitate immunosuppression in SOT, with prednisone and methylprednisolone being common agents. They can be used alone at high doses or in combination with other agents for induction and maintenance of chronic treatment, or for treatment of acute rejection [13, 62–64]. Immunosuppression is mainly mediated through receptor binding that regulates gene expression, inducing anti-inflammatory genes and inhibiting pro-inflammatory factors [13, 48].

The adverse neuropsychiatric potential of corticosteroids is well recognized [65] and can include a range of symptoms from insomnia, anxiety, irritability, depression, mania, psychosis, suicidality, delirium, and other cognitive changes [5, 53, 66]. The incidence of neuropsychiatric symptoms with steroid use varies widely with reports ranging from 2% to 60% [53, 65]. As with CNIs, accurate assessment of psychiatric symptom incidence has been limited. Most studies have not specifically addressed psychiatric side effects, and there

is significant heterogeneity among the methods and results of those that have [53, 65]. Though a common term, "steroid psychosis" has no clear definitions or criteria and various conditions and symptom presentations, including those without psychotic symptoms, have been reported under this broad umbrella [53].

As with CNIs, most patients experience only mild symptoms [12]. Insomnia is common, reported as 72% in one study [65]. The weighted average incidence of severe depression, mania, and psychosis was found to be 6% in one meta-analysis [53], and the incidence of severe psychiatric adverse effects in transplant recipients has been reported as 3–4% [5]. The most common severe neuropsychiatric effects are depression (35%), mania (31%), psychosis (14%), delirium (13%), and mixed states (6%) [66]. Depressive symptoms are more common with long-term therapy, while manic symptoms have been more associated with short-term or pulse treatment [53], approaches that are more common in treatment of acute rejection. Mood symptoms may be more likely to be accompanied by psychotic symptoms when steroid induced, found in 73% of manic and 56% of depressive presentations [66, 67].

Cognitive deficits can be seen in both short- and long-term use, with the most common deficit being impairment of verbal or declarative memory [53]. Peripheral symptoms, most commonly proximal myopathy, can occur with long-term use [5]. Other rare symptoms include steroid-induced dementia syndrome and radiculopathy due to epidural lipomatosis [5]. Most symptoms develop within a few days or weeks of starting treatment and most will resolve with steroid discontinuation [53, 67]. Although symptoms duration is variable, recovery is likely on the order of days for delirium and weeks for depression, mania, or psychosis (mean 19.3 days), while cognitive impairment may persist for months [53].

Broadly, neuropsychiatric symptoms are thought to result from synthetic steroids preferentially binding to glucocorticoid receptors over mineralocorticoid receptors, leading to cognitive impairment and emotional disturbance [68]. Alteration in gene transcription of neurotransmitters, including serotonin and dopamine, may contribute to mood and psychotic symptoms in corticosteroid-treated patients [53]. Patients treated with high-dose steroids have shown reversible atrophy in the hypothalamus and amygdala, which has a dense collection of glucocorticoid receptors, which regulate emotional learning and stress response [53, 69]. Cognitive impairment is thought to be due to effects on the hippocampus which is also dense in glucocorticoid receptors and is involved in creation and maintenance of memory [53]. For a more detailed discussion of psychiatric effects of steroids treatment in organ transplantation please see the preceding chapter in this volume Chapter 34.

Antimetabolites

Antimetabolites, or cell cycle inhibitors, block cell division and proliferation in lymphocytes [5, 7]. Common agents are mycophenolate mofetil and azathioprine. Antimetabolites have been used in steroid and CNI-sparing strategies in maintenance immunosuppression [5, 62]. Neuropsychiatric effects are rare and mild, manifest as depression and headaches, and may result from effects on biochemical pathways of homocysteine and adenosine [5, 48].

mTOR Inhibitors

Sirolimus (or rapamycin) and everolimus inhibit the mammalian Target of Rapamycin Complex 1 (mTORC1), impeding mRNA translation, thereby reducing IL-2 mediated T-cell proliferation and cytokine production [5, 13, 48]. Both sirolimus and everolimus can cross the BBB; however, their potential for neurotoxic vs. neuroprotective effects is unclear [5, 48]. Because the mTOR pathways have been associated with neurological, cognitive, and psychiatric pathogeneses, mTOR inhibition may be helpful, and some studies have shown mTOR inhibition to be neuroprotective [5]. However, blockade of the mTOR signaling pathways has also been shown to mediate depressive symptoms [13]. The mTOR inhibitors can alter cell metabolism in astrocytes, which may result in tremor, confusion, agitation, and headache [13]. Dizziness, sensory abnormalities, somnolence, bilateral optic neuropathy, and even PRES have been reported, though rarely [5, 13]. Overall, mTOR inhibitors are considered low risk for neurotoxicity [8, 48], and studies are increasingly establishing a role for mTOR inhibitors in CNI-sparing protocols in specific recipient groups [62].

Biologic Agents (Monoclonal and Polyclonal Antibodies)

Monoclonal and polyclonal antibodies are most often used for induction immunosuppression and treatment of rejection in SOT [7, 62]. Mechanisms of action are variable, though generally monoclonal antibodies block activation of T-lymphocytes, whereas polyclonal antibodies induce lysis of lymphocytes [5, 7, 13]. As a group, the biological therapy agents show very low incidence of neurological adverse effects [5, 7].

Impact of Psychiatric Manifestations of IS-Induced Neurotoxicity

Severe psychiatric manifestations of IS neurotoxicity can have a devastating impact when they occur. The impaired cognition, judgment, behavioral control, and reality testing

that characterize severe psychiatric symptoms imperil the health of the patient and grafted organ. One study of renal transplant recipients found that presence of psychosis, mostly attributed to drug toxicity and delirium, increased the risk of both death and graft loss (Adjusted Hazard Ratios of 2.09 and 1.79, respectively) [70]. Psychiatrists working with SOT recipients must be able to recognize the wide range of psychiatric and behavioral manifestations and proactively assist transplant teams in providing effective and safe care.

In the following case, we describe a transplant recipient who developed severe tacrolimus-induced neurotoxicity that manifested as a manic episode of new onset. Using this example, we will highlight important considerations and offer suggestions to support clinicians in the approach and management of these challenging cases.

Case History

Mr. C is a 65-year-old man who had undergone orthotopic liver transplant for decompensated alcoholic cirrhosis complicated by hepatic encephalopathy, which resolved after transplant. His postoperative course was unremarkable, and he was discharged home on mycophenolate mofetil 500 mg twice daily, tacrolimus 4 mg twice daily, sulfamethoxazole–trimethoprim 400 mg–80 mg twice per week, and valganciclovir 450 mg every 3 days. Tacrolimus trough level was 8.5 ng/mL (normal range 5.0–15.0) on discharge. On follow-up, mycophenolate mofetil was discontinued due to persistent diarrhea. To maintain adequate immunosuppression, tacrolimus was increased to 5 mg every morning and 4 mg every evening with goal trough level of 8.0 ng/mL. Tacrolimus level at that time was 5.6 ng/mL.

One month later, Mr. C was brought to the emergency room. His family reported that over the past month, Mr. C had become increasingly irritable and verbally abusive, with erratic and impulsive behaviors. He had become distrustful and paranoid toward his wife and revoked permission for her to be involved in his medical care. As his daughter was driving him, he seized her hair yelling "You're not my daughter!" The next day, he barricaded himself in a bedroom, then left the house by the bedroom window. He was admitted to the hospital after law enforcement found him wandering. Mr. C's family reported that while he had continued to take his medicines, he was increasingly suspicious and required more encouragement to continue taking them. Mr. C and his family reported no use of opioids, anticholinergics, alcohol or other substances, and no other notable events. Family also reported that the recent behavioral changes were distinctly different from episodes of hepatic encephalopathy prior to transplant which had been characterized by confusion and fluctuating alertness.

Vital signs were within normal limits. Physical exam was notable for a new onset fine tremor of the bilateral upper extremities. Complete blood count and metabolic panel were unremarkable. Urine toxicology was negative, as were blood alcohol, aspirin, and acetaminophen levels. Chest X-ray showed no acute abnormalities or signs of infection. Computed tomography (CT) of the head demonstrated chronic microvascular ischemic changes, unchanged from prior to transplant. Cerebrospinal fluid (CSF) analysis was unremarkable. Magnetic resonance imaging (MRI) of the brain was negative for acute changes, including PRES, and electroencephalogram (EEG) showed no epileptiform discharges. A comprehensive infectious work-up later returned negative. However, tacrolimus trough level on admission was 25.5 ng/mL (5.0–15.0). The elevated serum level raised suspicion that the acute behavioral changes may be manifestations of tacrolimus-induced neurotoxicity. Tacrolimus was discontinued and the immunosuppressive regimen was switched to cyclosporine.

Mr. C became increasingly irritable and agitated, at times becoming combative with staff. He was restless both day and night and attempted to leave the hospital. Psychiatry was consulted to assist with management of agitation. During the initial psychiatric evaluation, Mr. C was restless, hostile, and irritable. His affect was labile. He demonstrated flight of ideas and pressured speech with poor insight and judgment. He was convinced that his wife, nursing staff, and later the psychiatric team attempted to "control" him. He perseverated on paranoid beliefs that the medical staff "wants to kill me," though simultaneously expressing that "this is the best day of my life!" He denied suicidal ideation, homicidal ideation, and hallucinations at the time of evaluation. His substance history was limited to alcohol use disorder, now in sustained remission. He had no history of previous psychiatric symptoms or treatment, and no family psychiatric history. Mr. C declined to engage in formal cognitive testing; however, he was oriented to self, place, and time, with intact sensorium, and no gross impairments or other focal deficits noted. There was no evidence of fluctuating mentation, impaired alertness/arousal, or periods of disorientation, consistent with observations from the nursing, neurology, and transplant teams since admission.

Psychiatry diagnosed tacrolimus-induced bipolar and related disorder. Olanzapine was chosen for initial management as he exhibited mania with delusions and decreased sleep. This choice was further supported after literature review identified published case reports describing successful management of IS-induced manic symptoms with olanzapine. Olanzapine 2.5 mg twice daily was started and gradually titrated to target mania and agitation. Irritability and agitation showed mild improvement. After 3 days of olanzapine, Mr. C began to demonstrate insight into his condition, stating "there is another person in my head and I want him to leave, but he is still here." Paranoia significantly improved, though irritability and increased energy largely persisted. Additional

tacrolimus serum levels results returned as undetectable. After in-depth discussions with transplant and pharmacy teams regarding risk versus benefit, valproic acid 250 mg twice per day was added to further target mood lability.

After seven days of olanzapine treatment, Mr. C demonstrated an acute change in mentation. He reported visual hallucinations, feelings of confusion, was oriented to self only, and demonstrated poor attention despite good effort, concerning for delirium. Work-up for acute encephalopathy, including infection, metabolic derangements, and vascular event, was unremarkable. Due to concern for anticholinergic delirium, olanzapine was discontinued and haloperidol 2.5 mg daily was started. The next day, Mr. C appeared sedated but with improved orientation. Delirium completely resolved within 7 days. Manic symptoms also improved significantly with combined haloperidol and valproic acid treatment. He was referred to outpatient psychiatry and discharged to family on cyclosporine 150 mg twice daily, haloperidol 5 mg every afternoon, and valproic acid 125 mg every morning and 375 mg every evening. Mania fully resolved by 6 months, after which haloperidol and valproic acid were successfully discontinued without recurrence of psychiatric symptoms.

Clinical Questions

1. What factors may increase an individual's risk of developing severe psychiatric or behavioral adverse effects from ISs?
2. What factors should be considered during the assessment of suspected IS-induced psychiatric symptoms in a post-transplant patient?
3. How should IS-induced psychiatric and behavioral symptoms be managed?
4. When should switching or discontinuation of IS agents be considered?

Discussion

Factors Associated with Development of Severe IS-Induced Neuropsychiatric Symptoms

Factors resulting in higher CNS drug levels are thought to increase the likelihood and severity of IS-induced neuropsychiatric symptoms [16]. Disruption of the BBB has been found to be an independent risk factor for IS-induced neurotoxicity for both CNIs and steroids [53, 71]. As discussed earlier in this chapter, increased BBB permeability is thought to increase the amount of IS that crosses the BBB [1, 5, 10, 11, 48]. Thus, an individual's risk for CNS neurotoxicity is increased by factors with potential to impair BBB integrity, such as past encephalopathy, cerebrovascular disease (including hypertension), infection, or treatments, such as chemotherapy [5, 13, 53]. Hypocholesterolemia may also increase IS uptake into the CNS [5, 72]. Similarly, factors that increase serum drug levels may also result in higher CNS drug levels [73]. These include drug–drug interactions and impaired hepatic metabolism [5, 7, 74]. Although genetic testing is not yet available for clinical use, genetic polymorphisms may limit elimination of ISs, such as the adenosine triphosphate binding cassette transporter BI (ABCB1) and cytochrome pigment (CYPE) genes [5, 75–77].

Metabolic derangements such as hyper- or hyponatremia, hypomagnesemia, and hyperglycemia may increase an individual's risk for neurologic symptoms [5, 13]. Prolonged surgical period [78], advanced age of the organ donor [79], and history of alcohol use [80] have also been identified as risk factors. Unfortunately, often medical conditions related to organ failure may predispose an individual to severe complications [1]. Many of these risk factors are commonly associated with liver failure, including alcohol use, hepatic impairment, and encephalopathy, which may explain the higher rates of neurotoxic complications seen in liver recipients [1, 80, 81].

There is no clear evidence that either a personal or family history of psychiatric disorders increase the risk for steroid-induced neuropsychiatric symptoms [53, 66]. This has not been directly studied in CNI use; however, severe psychiatric symptoms have been reported in patients both with and without previous psychiatric history [24]. There have been reports of recurrent symptoms with repeated steroid treatment; however, it is unclear if a history of steroid-induced neuropsychiatric disorders predisposes to future episodes [53]. Recurrent CNI-induced neuropsychiatric symptoms have been reported, particularly in the case of re-challenge with tacrolimus [44].

Dose is the most significant risk factor for developing steroid-induced neuropsychiatric symptoms, and a dose-dependent relationship has been demonstrated with a nearly 20% risk in patients taking 80 mg or more of prednisone per day [53, 82]. As such, SOT recipients treated with high-dose corticosteroids may be at greater risk of developing severe symptoms, including those who are critically ill, immediately post-transplant, or in acute rejection.

In contrast, despite improvement with dose reduction or discontinuation, CNI neurotoxicity does not reliably correlate with dose or absolute serum trough levels [30, 80, 83]. This may be particularly true of severe adverse effects, such as psychosis, catatonia, seizures, and PRES, which have been reported at therapeutic trough levels [1, 5, 24, 30, 36, 45, 47, 84–87]. However, animal studies have found a correlation between neurotoxicity and increased CNS concentrations [88], consistent with higher risk associated with BBB impairment. CNI neurotoxicity is also associated with rapid rise in

drug levels prior to symptom onset [1]. Unsurprisingly, symptoms are more common with IV administration, and improve with oral administration and dose reduction [16, 30]. As such, patients are particularly vulnerable to severe neurotoxicity early in the postoperative course during which time drugs are often used in combination, administered intravenously, and aggressively titrated and dosed to prevent graft rejection.

Mr. C had an elevated serum tacrolimus trough level, with additional risk factors, including history of liver transplant, past alcohol use, cirrhosis, pre-transplant episodes of hepatic encephalopathy, as well as chronic microvascular changes which suggest increased BBB permeability.

Approach to the Assessment of Suspected IS-Induced Psychiatric Symptoms

From a psychiatric perspective, severe psychiatric or behavioral symptoms due to IS drugs are most appropriately classified as medication-induced disorders. The Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-5) criteria for medication-induced psychiatric disorders have a common framework (Table 35.1) that can be used to guide the diagnostic approach [89]. The common features of these disorders are the presence of prominent psychiatric/behavioral symptoms (Criterion A) that are concluded to result from the physiologic effects of a medication (Criterion B). This conclusion is drawn from evidence that supports a temporal relationship between symptom onset and exposure (Criterion B1) to a medication capable of producing the symptoms (Criterion B2). Criterion B2 reinforces how important it is for the transplant psychiatrist to be aware of the range of neuropsychiatric symptoms that can result from IS treatment. Criterion B1 underlines the need to obtain detailed history and objective findings that support a clear temporal relationship. Use of a standardized scale can be useful in considering probability of adverse drug reactions [90, 91]. Two common methods are the Naranjo Adverse Drug Reaction probability scale [92] and the World Health Organization-Uppsala Monitoring Center (WHO-UMC) system for standardized case causality assessment [93, 94].

Table 35.1 General diagnostic framework for medication-induced psychiatric disorders. Adapted from the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition [89]

A. Prominent psychiatric/behavioral symptom(s) (i.e. mania, psychosis)
B. Presence of evidence that supports **both**: 1. Temporal relationship between symptom onset and medication exposure 2. Suspected medication is capable of causing the observed symptoms
C. Not better explained by another psychiatric condition
D. Does not occur exclusively in the course of delirium
E. Causes clinically significant distress or impairment

Medication-induced psychiatric disorder is a diagnosis of exclusion [94] and the need to consider other possible causes, including other medications, is highlighted in both the Naranjo and WHO-UMC scales. The psychiatric or behavioral symptoms should not be better explained by another psychiatric disorder (Criterion C), as new onset psychotic or manic symptoms can arise from a wide range of etiologies. Even in patients with known psychiatric history, psychiatric symptoms may be medication induced, particularly if new psychiatric symptoms occur [44]. The post-transplant patient has elevated risk for a wide spectrum of potentially causative conditions, including infection, metabolic derangement, vascular events, or graft rejection. Additionally, SOT recipients often have complicated medication regimens such that polypharmacy and effects of other medications or substances must also be considered. It is imperative to maintain a wide differential diagnosis and proceed with a comprehensive and detailed evaluation, including history, collateral, physical exam, as well as neurological, cognitive, diagnostic, and laboratory testing.

The symptoms of a medication-induced psychiatric disorder should not occur exclusively during course of delirium (Criterion D), an acute encephalopathic state characterized by deficits in arousal, attention, awareness, and cognition, that commonly fluctuate throughout the day [95, 96]. Acute encephalopathy is common in SOT recipients, with rates as high as 30–40% [1]. Delirium must be quickly and accurately diagnosed to avoid inappropriate or delayed treatment of the underlying, and often multifactorial, etiologies [1, 95, 97]. In the case of transplant recipients, a misdiagnosis of IS-induced neuropsychiatric symptoms may not only delay appropriate treatment but may also lead to unnecessary decrease or discontinuation of immunosuppression, endangering graft survival. Despite symptom overlap, the global nature of brain dysfunction seen in delirium can help differentiate the two entities [97]. Whereas delirium presents with changes in each core symptomatic domain of the DSM-5 diagnostic criteria (Table 35.2), an IS-induced psychiatric disorder would likely demonstrate dysfunctions in only a subset of these domains [97].

In Mr. C's case, the new onset manic symptoms were temporally related to the increase in tacrolimus dose and supratherapeutic level and an extensive work-up failed to clearly identify other etiologies. Although the onset was over a relatively short period of time, his clinical presentation was not consistent with delirium until late in his hospitalization when he demonstrated an acute change in mentation with disturbance in attention, awareness, orientation, and perception (hallucinations) that fluctuated throughout the day.

Table 35.2 Clinical manifestations and assessment considerations for core symptomatic domains of delirium. Adapted from [97]

Major Symptomatic Domain	Clinical Manifestations	Assessment Considerations
A1: Disturbance in attention	Inability to appropriately focus, sustain, or shift attention	Can the patient engage meaningfully in conversation or successfully perform a task?
A2: Disturbance in awareness	Impaired awareness of one's situation or environment	Does the patient understand what is going on around them?
B: Develops over short period of time, tends to fluctuate during course of day	Acute change; classically waxing and waning	Are the symptoms new? Does it get improve or worsen over a course of hours?
C: Additional cognitive disturbance	Impairment in memory, orientation, language, visuospatial, or perception	Deficits noted in interview, history, or bedside cognitive testing.

Management of Severe Psychiatric or Behavioral Symptoms Due to IS Toxicity

The approach to management of severe psychiatric adverse effects of ISs is similar to management of other medication-induced psychiatric symptoms (see Table 35.3) [94]. Correction of supratherapeutic levels or dose reduction reliably improves symptoms for most patients [53, 66, 98]. Where possible, corticosteroids should be tapered to the equivalent of less than 40 mg per day of prednisone [53, 55, 65]. Care should be taken to identify and minimize factors with potential to increase IS levels, such as drug–drug interactions. The specific manner in which the patient takes the medication should also be clarified, as factors such as food can significantly alter absorption [99], and frequent missed or late doses will also impact serum peaks and troughs.

Non-pharmacologic interventions to manage psychiatric and behavioral symptoms should be maximized. If the dose cannot be reduced or severe symptoms persist, symptomatic management with an appropriate psychotropic medication should be judiciously pursued [16, 30, 65, 100, 101]. Patients who do not improve with decreased corticosteroid dose typically respond to psychotropic treatment [53, 66, 101]. In the case of CNI, colleagues have reported successful symptomatic management of severe psychiatric symptoms with continued CNI treatment [18, 39]. In such cases, psychotropic treatment may afford an opportunity for symptoms to spontaneously resolve over time as clinical stability allows the CNI dose to be gradually reduced. However, it should be noted that it is not known if psychotropic use produces or simply hastens symptoms resolution [55]. Management plans may be developed with the expectation that psychotropic treatment will be short term, as even serious neurotoxicity symptoms typically resolve with reduction or discontinuation of the offending IS.

Unfortunately, there is an overall lack of research regarding psychopharmacological treatment in transplantation [14]. The evidence currently available to guide psychotropic selection in IS-induced psychiatric symptoms is mainly limited to case reports and expert consensus, with a far greater body of evidence for corticosteroids than for CNIs or other agents. Broadly speaking, general psychopharmacological principles can be followed with specific attention to factors individual to the post-transplant patient.

Low doses of antipsychotics, including haloperidol, risperidone, and quetiapine, have been effective in treating psychotic and manic symptoms induced by steroids [53, 55] and may be used for agitation, delusions, and hallucinations in SOT recipients [12]. Haloperidol is available by intravenous route and is considered low risk for extrapyramidal symptoms and neuroleptic malignant syndrome [102], though excessive sedation may occur in elderly patients and those with severe hepatic or renal failure [29]. In a small series, olanzapine was effective in 92% of patients with steroid-induced mania or mixed symptoms [55, 103]. Case reports have also shown haloperidol, risperidone, and olanzapine to be effective in managing CNI-induced mania and psychosis [18, 34, 37–39, 104, 105]. As atypical antipsychotics may provide effective treatment of acute manic and psychotic symptoms, they may be useful in mixed or unclear clinical presentations. However, the potential adverse effects of individual medications, such as the deliriogenic potential of olanzapine, should be considered.

Use of a single agent minimizes polypharmacy and potentially decreases risk of additional iatrogenic complications. However, insufficient symptom control or medication intolerance may necessitate adjunctive use of a mood stabilizer [38, 45, 104]. The mood stabilizers valproic acid, lamotrigine, and carbamazepine have been found to be safe and effective for manic symptoms in steroid-treated individuals,

Table 35.3 General approach to management of IS-induced adverse psychiatric effects. Adapted from [94]

Preventative & Corrective Measures	Direct Symptomatic Management
• Correct therapeutic drug levels • Minimize polypharmacy • Minimize drug-drug interactions • Monitor and reduce modifiable risk factors contributing to adverse effects	• Maximize non-pharmacologic interventions for psychiatric & behavioral symptoms • Judiciously utilize psychotropic agents for symptomatic management, monitoring closely for adverse effects
• Collaborate closely with primary transplant providers and other treatment teams • Communicate management plan clearly and effectively • Educate patient and family regarding etiology and management of symptoms	
Consider discontinuing immunosuppressant **only after** aggressive symptomatic management has proven inadequate and careful consideration of risks and benefits	

though carbamazepine can result in reduction of IS levels due to CYP3A4 induction [53]. While there is evidence supporting the effectiveness of lithium to prevent mania in patients taking corticosteroids [106], the potential for toxicity due to fluid shifts presents a potential risk [12]. Valproic acid has been successfully used as adjunctive treatments for patients with CNI-induced symptoms [38, 45, 104, 107] and has otherwise been recommended for use in transplant patients with bipolar disorder [29]. However, providers should be aware of the potential to decrease serum CNI levels via CYP450 3A4 induction and small risk of hepatotoxicity [12, 14, 16, 29].

For CNI-induced catatonia, benzodiazepines can be used [36, 42], with memantine as a possible alternative for refractory cases [24]. Case reports have demonstrated success with Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin and Norepinephrine Reuptake Inhibitors (SNRI) agents in the treatment of steroid-induced depressive symptoms [53, 55]. Escitalopram, sertraline, and citalopram (unless there is concern for QTc) are likely the best SSRI choices for transplant recipients [12]. Tricyclic antidepressants are not recommended due to risk of exacerbating delirium via anticholinergic effects and the risk of worsening symptoms in mixed states [53, 66, 67]. For severe psychiatric symptoms that pose an imminent threat to safety, such as suicidal or homicidal ideation, safety must be secured, with psychiatric hospitalization if necessary.

Mr. C's course of treatment illustrated complications that can occur during management. Olanzapine was initially chosen as he exhibited mania with delusions and decreased sleep; however, its considerable anticholinergic effects likely precipitated delirium in concert with other risk factors of older age, chronic microvascular disease, and disrupted sleep. Though switch to haloperidol improved overall cognition, Mr. C experienced notable sedation and symptoms of mania persisted. After multiple discussions with the primary transplant providers regarding risk and benefit, valproic acid was added, with good effect.

Decision to Alter IS Treatment Regimen Due to Neurotoxicity

Neurologic complications are associated with poor outcomes and quality of life [4, 5]. However, alterations to IS regimens have the potential to drastically impact graft health and survival and should not be taken lightly. Fortunately, high-dose corticosteroids are typically used in short-term courses, such as induction or treatment of acute rejection [12]. In these cases, it may be more feasible to provide symptomatic management until the course of steroids is completed or the dose is decreased.

Multiple concerns arise when altering CNI-based regimens, especially when neurotoxicity occurs within therapeutic drug levels, where dose reduction would likely result in inadequate immunosuppression. As tacrolimus is widely favored over cyclosporine due to superiority in preventing acute rejection [1, 13, 21], there is concern that switching CNIs may elevate the risk of graft rejection. Two large series studied outcomes in liver transplant recipients after switch to cyclosporine due to tacrolimus neurotoxicity [108, 109]. These studies found that neurotoxicity resolved in nearly all cases, and that there was no difference in rejection rates, supporting the feasibility of switching between CNI agents.

When switch to another CNI is undesirable or not tolerated, there remains concern that CNI dose reduction may lead to inadequate immunosuppression and increased risk of rejection [5]. In recognition of significant toxicity burdens, CNI-sparing and avoidance strategies are increasingly being studied and show promise as viable immunosuppressive options in individual cases [7, 9, 110, 111]. In 2013, Peddi et al. reviewed the safety and efficacy of mTOR inhibitor-based CNI dose reduction (rCNI) regimens in SOT, the findings of which have been further supported by recent studies [112]. Compared to standard doses, rCNI regimens have good overall efficacy and better preserve renal function [113–116] without significant changes in rates of rejection [63, 113–120] or graft loss [64, 114, 116, 118, 121]. Cytomegalovirus infections and malignancy rates are low [64, 118, 119, 121]; however, other adverse effects were

more common, including dyslipidemia, hypertension, proteinuria, new onset diabetes, and wound complications [64, 115, 116, 118, 119, 121, 122].

Studies in liver recipients have also demonstrated that mTOR inhibitor-based rCNI regimens result in decreased rates of neurotoxic adverse effects. In one study, the incidence of tremor decreased to 7.5%, as compared to 12.5% in standard CNI dosing [115]. In another, neurologic complications, including mood alterations, developed in 7.1% of patients on everolimus-based regimens, versus 16.9% in CNI treatment ($p < 0.039$), with similar graft and patient survival at 1, 3, and 5 years [81]. A multi-center, prospective, randomized trial of early everolimus introduction found the incidence of neuropsychiatric complications to be 13.9% versus 31.9% ($p < 0.05$) [113]. The neurotoxic complications studied included hallucinations, delirium, disorientation, agitation, confusion, depression, anxiety, and mood alteration. It should be noted that supportive findings have been mainly in heart, liver, and kidney transplant. Although there is some evidence in support of CNI-sparing strategies with everolimus treatment in lung transplant, its use is limited as mTOR inhibitors inhibit lung fibroblast proliferation, increasing the risk of anastomotic dehiscence if introduced too early in the post-transplant course [123].

The feasibility of complete CNI discontinuation with mTOR inhibitor use is less clear. Acquaro et al. found that complete switch to everolimus did not result in an increased risk of late acute rejection in heart transplant recipients with CNI-induced nephrotoxicity [120]. Other studies in heart, liver, and kidney recipients found increased rates of biopsy proven acute rejection with everolimus treatment combined with early, complete withdrawal of CNI, though the observed increases did not always reach statistical significance [63, 122, 124]. Interestingly, one study in heart recipients found that an increased rate of acute rejection in the first-year post-transplant did not result in graft impairment on long-term follow-up five to seven years later [124]. Already approved for rejection prophylaxis in kidney transplant, belatacept has been identified as a potential alternative for transplant recipients who fail treatment with CNIs. Small series have been conducted that show belatacept-based, CNI-free IS regimens may be possible in heart, lung, and kidney transplant occurring after liver transplant [125–128].

Ultimately, discontinuation may be necessary in severe and serious symptoms that interfere with medical treatment, persist despite serum level correction or adjustment to minimally acceptable doses, and are unable to be managed with aggressive symptomatic treatment. The decision to completely discontinue treatment with a CNI should be considered only after aggressive attempts at symptomatic management have proven inadequate and the risks and benefits have been carefully discussed. Multidisciplinary collaboration is vital to ensure appropriate attention to all facets of the patient's individual situation. Frequent interdisciplinary communication and discussion must be maintained to provide psychoeducation, appropriate psychiatric perspective, and to facilitate collaborative treatment plans to optimize the likelihood of good outcomes.

Take Home Points

1. Corticosteroids and the CNIs, which have become the backbone of immunosuppression in SOT, are well known to cause neuropsychiatric adverse effects. IS-induced neurotoxicity can have a wide range of manifestations and occur even at therapeutic doses and serum drug levels. Though rare, the transplant psychiatrist should be aware of the many presentations of severe IS-induced neurotoxicity which can include mania, psychosis, catatonia, or akinetic mutism. Factors that disrupt the BBB or otherwise increase CNS drug levels increase the likelihood and severity of IS-induced neuropsychiatric symptoms. Such factors are often seen in SOT recipients, thus increasing their vulnerability to IS-induced neurotoxicity.
2. When IS-induced psychiatric disorders are suspected, a thorough and extensive investigation must be completed to rule out the many possible etiologies in the post-transplantation patient. Correction of therapeutic drug levels, or dose reduction if feasible, is often sufficient for symptoms resolution. When needed, symptomatic management should maximize non-pharmacologic interventions. Psychotropic selection should be guided by the patient's specific needs, however second-generation antipsychotics, haloperidol, and valproic acid may be effective agents. The decision to switch CNIs or pursue CNI-sparing strategies may be reasonable options for selected patients, though these alternative immunosuppressive strategies remain second line [62, 110]. CNI discontinuation should be considered only after careful consideration of the attendant risks and benefits and aggressive attempts at symptomatic management have failed. In such difficult cases, collaboration with the transplant team and careful discussion of risk versus benefit are essential to provide optimal care. Transplant psychiatrists should proactively engage transplant providers in close collaboration throughout treatment to appropriately weigh the risks and benefits of individual interventions in the interest of providing high-quality, multidisciplinary care.

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Part VI

Special Populations

Pediatric Transplant Psychiatry

36

Diana Shellmer

Introduction

Pediatric solid organ transplantation has been well accepted as a treatment method for a variety of underlying medical conditions that would otherwise significantly limit the life expectancy and/or quality of life of children and adolescents. Solid organ transplantation, however, requires a lifetime commitment to care and a host of associated responsibilities. Adherence to the medical regimen, in particular to medications, is considered vital to avoid rejection of the transplanted organ and to ensure the health and well-being of the patient. In pediatric transplantation, the post-transplant immunosuppressive regimen has been the primary focus of medical adherence research and clinical activity. Medication adherence garners such focused attention because its lack has been associated with organ rejection, graft loss, patient death, increased need for medical interventions, and increased medical costs [1–8]. The perception that adherence is also a *potentially modifiable behavioral factor* has created consistent interest in "solving the nonadherence problem."

One of the first challenges in assessing and treating medical adherence is defining what constitutes "good adherence." Given that adherence is not a single behavior or a single aspect of care, but rather a pattern of behaviors throughout time, identifying when a patient transitions from being adherent to nonadherent can be difficult. The medical community tends to utilize the definition of adherence penned by the World Health Organization (WHO) that describes it as "the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a healthcare provider." However, when determining whether a patient has "been adherent," providers tend to focus more on whether the patient has "adhered enough" to avoid a negative outcome. In fact, a national consensus conference on adherence in transplantation [9] considered adherence to be "satisfactory" as long as "... the gaps between the recipient's dosing history and the prescribed dosing regimen have no effect on [the] therapeutic outcome" (p. 36). This is in part due to the challenges of actively measuring adherence on a dose by dose fashion. At this time, there is no true gold standard for identifying nonadherence. Self/parent report is not always reliable, blood serum levels can be affected by a variety of factors, pharmacy reports/pill counts are difficult to reconcile due to changes in prescription doses/changes in pharmacy and insurance, and third-party monitoring (e.g., electronic pillboxes, adherence apps) does not guarantee the medication was ingested [10, 11]. Due to these assessment challenges, most research examining adherence suggest utilizing multi-method approaches with the hope of capturing a composite picture of what adherence may be for a designated patient and determining whether an association exists between the constructed adherence profile and negative outcomes for that patient [12–14]. Unfortunately, to date, there is no clear metric that can be consistently applied to every patient to let them know how many doses they can miss before they develop rejection and place themselves and/or their transplanted organ in peril. As a result, the primary focus continues to be on identifying any nonadherence defined as "any identified instance when the patient deviated from the prescribed regimen" and subsequently limiting the frequency of such events.

To add further complexity, adherence in pediatrics cannot be truly viewed as a personal responsibility, but rather a series of shared tasks between the child and their family/support system that evolve over time and need to map on to the developmental level of the target patient [15, 16]. For many children with a solid organ transplant, the decision to transplant occurred at a time when not even *assent to the procedure was possible* (e.g., infancy, toddlerhood, early childhood). Hence, these patients "inherit the responsibility of adherence." Pediatric patients often undergo transplant when their understanding of post-transplant adherence

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demands may be completely absent and/or rather limited. In addition, in several instances, children with underlying medical conditions (e.g., short-gut syndrome, hypoplastic left heart syndrome, metabolic conditions, end-stage kidney disease) that lead to solid organ transplantation may also exhibit a variety of emotional, cognitive, social, academic, and physical delays. Although not all pediatric transplant patients evidence delays, a significant number of patients do. From a physical perspective, infants and toddlers evidence muscle weakness, limited physical ability, nutritional deficiencies (e.g., failure to thrive), and oral/feeding aversions, while older children may have delayed puberty and short stature [17–19]. Children and/or adolescents with end-stage kidney disease, end-stage liver disease, and congenital heart disease have been found to have compromised cognitive ability with patients falling in the low average range of cognitive ability and demonstrate attention problems, problems with visuospatial manipulation, and fine motor delays [17–19]. From an academic perspective, transplant patients have difficulty with school re-entry, overall school performance with math and reading falling below peers, and educational attainment [17–20]. In addition, pediatric transplant patients often exhibit delayed social development, including isolation from peers, communication and social engagement delays, and even lower rates of employment and marriage in the long term [20].

When we consider "adherence" within the rubric of a complex series of behaviors, initially agreed upon by a family system, and potentially mandated upon an older child/adolescent who may also be experiencing physical, cognitive and/or academic delays and psychological concerns, it is easy to deduce that challenges in adherence may be commonplace.

For researchers and clinicians alike, identifying patients who are "at risk" for nonadherence is based on associations between known challenges (e.g., oppositional behavior), measured adherence behaviors and/or barriers to adherence (e.g., difficulty swallowing medications), and potentially negative clinical outcomes (e.g., rejection, graft loss). Research in this area suggests that rates of nonadherence vary widely by age of the recipient (worse in adolescents and young adults than younger children), organ transplanted (e.g., more common in kidney transplant patients than lung transplant patients), and family factors (e.g., poorer adherence in chaotic families) [1–7, 18–20]. Other factors that have been found to be associated with nonadherence include a previous history of nonadherence, minority race/ethnicity, lack of or limited social supports, poor perceived health, parental and child psychological and behavioral functioning, and parental distress and burden. In this chapter, we will consider some of these factors in relation to the evaluation, treatment, and long-term outcomes for a solid organ transplant pediatric patient.

Case History

One of the main goals of the pre-transplant psychological evaluation is to assess known barriers to adherence, previous and current patterns of self-care, social supports, mental health history for the parents and the patient, financial resources, developmental level, and medical understanding/literacy as a way to identify potential risk factors for long-term success. When considering a specific case, clinicians benefit from having an overview of the patient, the caregivers, the overall family system, and the interactions between the patient/family and the medical environment.

In this chapter, we will present the case of a patient who received a heart transplant as a school-age child, and we followed for 10 years post-transplant thus far.

The 11-year-old patient presented to the emergency department (ED) after experiencing shortness of breath, fatigue, nausea, dizziness, and feeling generally unwell. Patient was found to be in late stages of heart failure and was urgently admitted to the cardiac intensive care unit. The patient was intubated and in need of mechanical support limiting the ability to effectively assess the patient's understanding of their prognosis and the steps taken to address medical needs. At the time that the patient was hospitalized and diagnosed, treatment options were limited to heart transplantation if the patient was to survive. Patient was found to have a familial form of cardiomyopathy that had been recently identified in one of the parents. The patient's parents were divorced but reported having an amicable relationship regarding the children. Parents reported having high levels of familial support which was supported by multiple extended family members present at bedside. Parents did report some concerns about practical and financial resources but denied that these factors would interfere with their ability to support the patient or the patient's ability to engage in post-transplant care.

At bedside, the family presented as involved and engaged, vested in learning more about the patient's medical condition, and willing to engage actively with the medical team. The transplant team was, however, concerned that the family did not seek suggested screening in their other children due to concern for familial cardiomyopathy. However, given the recency of the parental diagnosis, the issue was not pressed. Family reported no behavioral concerns regarding patient and denied any concerns regarding other family interactions and relationships. Based on this initial evaluation, clinical presentation of the child, age of the child, and presence of the family at bedside actively engaging with the medical team, the patient was cleared for listing for transplantation and received a heart shortly after initial presentation.

Following transplantation surgery, additional information regarding the patient and family revealed behaviors associated with nonadherence. It became evident that family had withheld information regarding the patient's behavioral pro-

file and family circumstances. Our team inferred this was possibly secondary to distrust of the medical establishment due to belonging to a minority group. Given the urgency of the presentation, the transplant mental health clinicians did not have the time to build a therapeutic relationship with the patient or the family which would have supported more candor about the family's circumstances. Following transplantation, parents disclosed that the patient exhibited high levels of oppositionality at home, could be physically aggressive toward siblings, and would at times disregard family rules and discount behavioral expectations. Parents characterized these behaviors as the patient "being himself." The family disclosed that in the past the way they addressed these concerns were to disengage from the patient, ignore, and/or send the patient away for a couple of weeks to the home of relatives. Family also disclosed a more chaotic environment at home than originally shared. Mother reported that older siblings, particularly the patient, provided a lot of babysitting for the youngest child and were frequently without clear parental supervision as mother was often away and working. Parents continued to report a generally cordial relationship, but paternal presence at bedside diminished significantly post-transplant. Over the course of time, it became evident that the patient had some gaps in the level of support they received at home. Once patient had recovered sufficiently, attempts at discussions with the patient were difficult as the patient did not openly nor easily engage with medical team providers/members (e.g., Child Life, physicians, nursing)) and was unwilling to report concerns.

As the above picture evolved, the embedded psychology service closely followed the family and provided support during the initial post-operative and post-discharge period. As the patient recovered and required fewer scheduled clinic visits, monitoring of adherence naturally decreased. Unfortunately, during this time, the family fell into a pattern of nonadherence unbeknownst to the medical team. Within a year of the original transplant, the patient presented back at the hospital with severe rejection associated with nonadherence. The patient had missed several laboratory blood draws, the immunosuppressant blood levels were below the target range, and a check of pharmacy records revealed that the family had not picked up medications consistently.

At this point in patient's post-transplantation care, the transplant psychologist intervened to help the medical team assess potential barriers to care, assess for psychosocial concerns, determine other mitigating factors contributing to nonadherence (e.g., misunderstandings regarding medical recommendations), and activate the family into behavioral change.

Meetings were scheduled with the family and members of the team (including the behavioral specialist) to assess the situation. A plan was devised which specifically stipulated the expectations for the family and the transplant team's commitment to supporting the family through more frequent visits, support for medication refills, and mental health treatment for the patient and family with weekly therapy sessions to help with modification of current behavioral patterns and implementation of a plan.

Through the course of behavioral treatment, it became evident that family members expected the patient to take medications independently without a specific plan for clear oversight from a parent or other designated adult caregiver. In view of this new information revealed, we worked with the family to provide additional education regarding post-transplant care requirements and expectations, information about developmentally appropriate expectations for the patient regarding medication adherence, and the consequences of nonadherence and poor engagement in medical care. Together with patient's family, we developed a plan to maximize the likelihood of success. Unfortunately, attempts at improving adherence were met with several practical barriers, including an ongoing lack of parental supervision, limited engagement from the patient, and a clear disconnect between the patient's perceived physical experience (e.g., patient denied symptoms of rejection) and clinical presentation (e.g., showing up to ED in cardiac distress). This last point was particularly troubling as the patient regularly reported no shortness of breath, fatigue, and/or dizziness even prior to fainting as a result of poor cardiac output associated with rejection. Attempts to facilitate behavioral activation to avoid these symptoms were not effective as the patient was not aware of these physiological changes. In addition, given the challenges the family continued to experience in truly adhering to care expectations, we were forced to refer the family to Child Protective Services (CPS). After a significant amount of work with the county, including educating officials about necessary treatment requirements following transplantation and needed engagement level from the family, improved adherence was achieved although not consistently maintained. Every time CPS engagement was scaled back, nonadherence would spike again. During this time, however, the patient did seem to develop a better understanding of their medical status and medical needs and appeared to at least be in the pre-contemplation stage of behavioral change.

Nonadherence continued through this patient's adolescence and as soon as the patient aged out of CPS' purview, the patient once again presented with severe rejection. Despite multiple attempts at helping the family develop a good adherence plan, their limited participation in treatment created a situation where mental health support was not sufficient to elicit change. However, our engagement did provide insight into some of the additional barriers that were present for this family and new in-roads have been made now that the patient is a young adult into assisting them in becoming more adherent to care. For example, the patient has now

been willing to discuss goals they would like to achieve and are now more aware of how adherence to care can help them remain healthy, out of the hospital, and moving forward in their lives. In addition, by providing ongoing support and being available to the patient, we likely mitigated the effects of a chaotic family life and potentially limited the number of rejection episodes that this patient could have experienced otherwise.

Clinical Questions

1. How do the circumstances under which pre-transplant evaluation information is obtained (e.g., urgency of patient presentation, chronic versus acute illness, stability of patient medical condition) affect the quality of information obtained and subsequently affect the likelihood of a thorough assessment allowing for a good gauge of post-transplantation adherence?
2. What behavioral components can provide clues regarding the potential challenges to adherence for this patient from a longitudinal perspective?
3. How relevant is self-efficacy, motivation, and engagement in self-monitoring to this case?

Discussion

If we look at our first question, we can appreciate that a compressed timeline prior to transplantation limited our ability to fully assess and thoroughly understand the existing factors. Sufficient time prior to transplantation allows providers to partner with families at a time when their interest in engaging in adherent behavior is at one of its highest points. Families often view the pre-transplant time as a time to put forth their best efforts and demonstrate their ability to care for the patient and adhere to medical care. Hence, this is a time when families are often highly committed and willing to make necessary changes as the benefits of change clearly outweigh any potential primary and/or secondary gain from existing patterns. In addition, if the patient had been in a position (not intubated and on support) to provide information and feedback regarding their understanding, we would have been able to better assess the barriers specific to the patient and develop a plan to initiate behavioral change. Additional time could have also afforded us the opportunity to more closely partner with the family at a point when non-adherence although problematic may not have had such dire consequences that it required CPS involvement. In addition, although there is no guarantee that such attempts at changing the outcome would have worked, it is fair to say that having more time to build rapport and gain trust the relationship between the patient and medical team could have positively affected adherence.

When examining our second question, the links between parental engagement, limited financial resources, typical discipline structures within the home, and known patient behaviors (i.e., oppositional and at times physically combative) would be of interest. For example, a clear understanding of common family expectations for the patient (e.g., helping with younger siblings, being self-reliant when managing medications) directly related to financial concerns (e.g., mother had to work) allowed the team to identify ways to support the family (e.g., pairing mental health and clinic visits to limit time taken from work). The fact that this was rather challenging to do post-transplant also highlights how family resources can significantly impact the provision of care even when the family believes they are coping well.

When considering our last question, it is evident that each construct played a role in this case. From a developmental perspective, each of these concepts takes time to mature. A school-age child has some autonomy and belief in their own skills. They also know that they can engage in certain self-care behaviors, such as showering, brushing their own teeth, and making a simple meal for themselves. However, developing self-efficacy is related to a host of factors, including prior experience, modeling by adults in their lives, expectations, reinforcement, and practice. Motivation and engagement in a behavior requires attributing either positive (e.g., this will help me by) or negative (e.g., this will help me avoid getting sick) values to those behaviors, with positive values serving as stronger drivers to engagement. Lastly, self-monitoring requires not only engagement and motivation but also executive functioning that allows for self-awareness. It is not surprising that when our patient was school aged and was operating in an environment with family challenges and limited parental oversight, they struggled to meet expectations. As the patient aged, they developed a better understanding of and insight into their behaviors. This has allowed for more productive therapy sessions, that although have not led to radical behavioral change, have led to recurrent efforts by the patient to improve adherence. Of interest, helping the patient reaches the point that they felt a need to also seek mental health support to improve their emotional health, opened the door to his and family's willingness to improve his adherence. Prior to reaching this juncture, the patient lacked the insight to see a connection between his emotional functioning and his willingness to engage in behavioral change to shift adherence patterns.

Conclusion

Managing the complex medical care regimen typically required following solid organ transplantation can be taxing and difficult. Families of children undergoing transplantation are often in a position that requires the

designation of care roles within a family structure with a variety of expectations. For example, the family must decide who will be responsible for administering medications, making sure medication does not run out, sets up medical appointments, and takes the patient for blood draws; each of these steps can easily become a place where adherence breaks down if communication between family members is unclear and/or roles are not defined. These families are also tasked with helping their child develop into an adult with skills and autonomy to engage in their own care. These families are often stretched thin and with potentially limited resources to make it through this process smoothly and effectively.

Nonadherence within the above context is predictably multifactorial in nature [1–5]. Treatment of nonadherence requires a tailored approach to care, taking into account the needs of the specific patient and their family [2]. Blanket approaches to treatment of nonadherence (e.g., educating the family about adherence without a clear understanding of what has led to the challenges, simply increasing frequency of visits without regard for resources needed) have not been effective and often leave the most nonadherent of patients untouched [21, 22]. By providing a thorough assessment of and developing rapport with the patient and their family and providing a safe space where families can openly discuss the barriers to adherence, a mental health professional can help lay the groundwork for a partnership to address nonadherence at a global level. Considering the individual patient within the context of their environment, mental health providers can help set the stage for a more holistic approach to the treatment of nonadherence.

Take Home Points

1. In the pediatric transplant patient, commitment to adherence is often implied without patient's assent, especially when transplantation occurs in early childhood.
2. Family participation is crucial in ensuring adherence needed to maintain health after transplantation.
3. Interventions to promote adherence must be flexible and target both the patient and the family, taking into consideration the developmental level of the child and specific needs of the family.

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LGBT Issues in Transplant Candidates

37

Caitlin McFarland and Ted Avi Gerstenblith

Introduction

The sexual orientation and gender identity minority (SGM) populations increasingly receive more attention from healthcare providers and researchers as organizations like the Institute of Medicine have highlighted the need for expertise in their healthcare needs. While it is a historically common belief to doubt the relevance of sexual orientation and gender identity (SOGI) to patient care, it has been observed that sex and gender minorities have an increased burden of physical and mental diseases relative to the general population [1–14]. This population also faces unique legal and psychosocial challenges in healthcare access and follow-up that have tangible impacts on health outcomes. In addition, there is much discomfort among clinicians regarding gathering a sexual history and discussing gender and sexual orientation with their patients [11–14]. Psychiatrists on transplant teams are well positioned to help transplant teams understand the significance of SGM identity to transplant candidacy and therefore directly improve health equity and long-term health outcomes in transplant recipients. In addition, transplant psychiatrists can address behaviors with increased prevalence in the SGM population that may have contributed to host organ failure.

It is important to consider that the terminology used to describe subgroups encompassed by the LGBT acronym continues to evolve. In particular, the LGBT acronym does not include groups identified by the longer LGBTQIA+ acronym [15]. The identities encompassed by these acronyms include "L" for lesbian, "G" for gay, "B" for bisexual, "T" for transgender, "Q" for both for queer and those who are questioning their gender or sexual orientation identity, "I" for intersex, and "A" for asexual. For convenience, the term SGM has increasingly been suggested for use since it is more representative of the intended populations. Sexual Orientation and Gender Identity (SOGI) usually refers to the collection of this information in an electronic medical record (EMR). Although gender minorities and sexual orientation minorities will be discussed as a group, it is important to note that gender minorities experience a greater burden of disparity in healthcare access, homelessness, and disease burden (somatic and psychiatric) than sexual orientation minorities and ideally would be considered demographically distinct groups [2, 3, 6, 9, 10]. The patient in this case example is transgender (and her sexual orientation is not made explicitly clear), and although there are parallels in the challenges that arise for these patients as compared to sexual orientation minorities and intersexed people, their care needs are not representative of all people encompassed by the LGBT or SGM acronyms.

Case History

Ada Johnson is a 57-year-old trans woman transferred from a community hospital to a tertiary hospital's intensive care unit for management of fulminant liver failure secondary to alcoholic cirrhosis and for emergent transplant evaluation. Psychiatric consultation was requested by the transplant team to assess her as part of a pre-transplant assessment. On initial evaluation in her hospital room, she was inattentive, oriented to self only, and diagnosed with hypoactive delirium. With the patient unable to identify a surrogate decision maker, the transplant team had been primarily communicating primarily with her adult son who lives out of state.

Ms. Johnson had been brought to the emergency department at the outside hospital after being found down in the rented motel room and was initially assumed homeless. She had been hospitalized for several days before her son was identified and was identified as her surrogate decision maker. It was determined that Ms. Johnson was married, employed as a social worker, and had been staying at the motel while in town for a professional conference. Her wife, who arrived from out of town not long before the psychiatric consult team

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arrived, was openly hostile toward the transplant and consulting teams, accusing providers of delaying transplant evaluation due to her wife's gender as well as inappropriately involving her stepson in medical decision making when she was next of kin. Ms. Johnson's spouse expressed skepticism that the transplant team would be unbiased toward trans patients and expressed concerns to the psychiatry consult team that the patient's gender identity would count against her transplant candidacy

1. In addition to performing a full psychiatric assessment, how might you guide the organ transplant team in partnering with this patient and their family?

   Based on the information presented, the complexity of the psychodynamic factors within patient's family begins to emerge. The patient is a trans woman with a child from a past relationship, and she is now remarried to a woman. Many LGBT individuals have contentious family relationships due to their sexual and gender identities [16, 17]. Unfortunately, SGM identity often leads to a more fractured support system and may contribute to undue bias against their candidacy for transplant due to this. In cases where there is a dearth of psychosocial support due to unsupportive family (or a delay in identifying relevant supports due to identity-related assumptions about the SGM patient's psychosocial situation), the transplant team may find themselves in the difficult position of balancing health equity in SGM patients against the practical realities of post-transplant care. The transplant psychiatrist can assist teams by spending more time exploring the nuances of the patient's complex family dynamics allowing for a more accurate assessment of a patient's risk before and after transplant.

   In addition to considering how SGM identity affects the quality of a patient's support system, added diligence identifying the patient's preferred decision maker is necessary. Not making assumptions about surrogate decision makers is particularly important for the LGBT community. Historically, long-term partners of SGMs were excluded from medical decision making because their partnerships were not legally recognized. This led to high rates of conflict between patients' long-term partners and their legally recognized family members. This difficulty has still not been fully resolved despite federal recognition of marriage equality starting in 2015. SGM patients may more often be estranged from their family members based on non-acceptance of their identity [18, 19]. In this case, it would be a good idea to make inquiries as to the ability of the patient's partner and son to collaborate in the patient's post-transplant care and consider any major differences in their perspectives on the patient's transplant candidacy.

   In this specific case presentation, the patient is legally married to her wife and unless there is a designated medical power of attorney who differs from her (i.e., the patient's son), she is the appropriate primary surrogate for medical decisions. Although not the case here, some SGM patients may deliberately conceal the nature of their partner relationships due to fears of discrimination by hospital staff. The transplant psychiatrist can foster greater rapport with patients by asking then about past healthcare experiences and whether there are any current concerns about receiving care [12, 20, 21]. The transplant psychiatrist can also assist the transplant team by helping them to consider their own implicit biases about SGMs as they consider this patient for the allocation of scarce resources.

   Another way to ease tension, particularly in light of prior misconceptions in this chapter's case description, is to use gender neutral terms when referring to family members. Use of inclusive words like "partner" when referring to the relationship between the patient and her wife unless otherwise directed will avoid unnecessary tensions. The transplant psychiatrist could directly inquire of the patient's wife, "By what name should I refer to your partner [the patient] and what pronouns would you like me to use?" Doing this shows respect for the patient's identity. Use of the patient's chosen name and consistently using correct pronouns during conversations about her healthcare facilitates better alliance and communication [13]. All these strategies will improve partnership between transplant teams and SGM families.

2. What unique challenges in clinical documentation might you anticipate for this case?

   In 2011, the Institute of Medicine released recommendations for care of LGBT individuals that included accurate documentation of sexual orientation and gender identity in the medical record [22]. Although there has been some improvement since 2011 in accurate documentation of SOGI in the EMR, accurate documentation of SOGI data remains a challenge on many EMR platforms. As patient's legal rights to medical record access expand, including to mental health documentation, the need for accuracy in patient pronouns and psychosocial history is increasingly non-trivial. Failure to recognize a patient's name and pronouns when they differ from their sex assigned at birth contributes to the patient's perception of stigma in the healthcare setting and provider avoidance. The impact of healthcare avoidance in the LGBT community on adverse outcomes cannot be overstated, and if the patient had an untreated viral or alcoholic cirrhosis that contributed to their current presentation, the avoidance behavior would certainly need intervention by the transplant team both before moving forward with transplantation as well as in the post-surgical care plan.

   In 2013, Deutsch et al., introduced a two-step method for charting sexual identity and sex at birth as well as col-

lecting information on preferred pronouns to display prominently when opening a medical record [23]. Depending on when a patient entered a particular hospital system, their chart may reflect their sex assigned at birth thereby leading to confusing interactions with hospital staff. The majority of gender diverse patients prefer their identity and pronouns in the chart [24]. Here, Ms. Johnson is unable to express a preference at this time but a conversation with her wife about documentation preferences would help create a welcoming, safe environment and minimize confusion among staff as to how to address Ms. Johnson and her family.

Transplant psychiatrists should take care to appropriately address patients in their clinical documentation. The historical relationship between SGMs and psychiatry is contentious. Homosexuality was included in the Diagnostic and Statistical Manual of Mental Disorders (DSM) as recently as 1972 and DSM-5 includes gender dysphoria as a psychiatric diagnosis currently, both contributing to poor perception of mental health providers as a result. While psychiatrists have unique skills that can facilitate trust and cooperation between patients with psychiatric comorbidities or psychosocial challenges and their transplant teams, this opportunity can be easily lost with unintentional insensitivity.

A final point on clinical documentation: the decision to take a gender history (including early childhood gendered play, onset of awareness of their gender identity, and timeline of social and medical transition) should be informed by its relevance to the patient's care at the time of the assessment. Taking a gender history from a gender diverse patient may be unintentionally stigmatizing if care specific to transition or gender is not being provided. Instead, it is important to ask questions related to how the patient's gender identity has influenced their care as will be illustrated next.

3. How would you inquire differently about this patient's psychiatric and substance use history? What details are important to address?

Taking a comprehensive psychiatric history from transgender and LGBT patients, when evaluating for or caring after transplantation, should be identical to gathering a history from any other patient, with some important additional considerations. The clinician should appreciate that SGM's have a higher prevalence of suicidal thoughts, suicide attempts, substance use (particularly alcohol and opiates), affective and anxiety disorders, and exposure to violence and other traumatic experiences [6, 7, 9, 10, 25, 26]. Simultaneously, SGMs have a lower utilization of health services due to multiple factors, including mistrust of healthcare providers and fear of stigma. Gender minorities are at especially high risk of suicide completion and suicide attempts; inquiring about current and past self-injurious thoughts and behaviors is critical, and the psychiatry consultant should be alert for any minimization of past self-harm or substance use while being sensitive to the patient's motivation for concealing this information from a mental health provider in particular.

For example, have they experienced discrimination or insensitive care in a healthcare setting? As recently as 2011, SGM patients continue to report discrimination in a visit with a healthcare provider [27]. Have they delayed medical or psychiatric care in the past due to fears of bias or discrimination? Medical school education specific to LGBT health is historically limited, often as little as five lecture hours in the pre-clinical curriculum leading to a shortage of physicians familiar with the care of this patient population [28, 29]. As a result, SGM patients report avoiding physician visits, resulting in poor preventive care and care for chronic health conditions [30–33]. The patient's wife in this case implies that the initial treating team delayed initiation of transplant evaluation due to assumptions about the patient's psychosocial circumstance. Of note, the factors that have contributed to poor past medical follow-up in this case may be mitigated by careful and sensitive post-transplant planning, however, will certainly affect risk stratification prior to transplant.

Discussion

Stigma against SGM patients plays out in healthcare not only in explicit but also in non-obvious ways as this case has attempted to address. Asking SGM patients about past healthcare experiences, particularly if there are significant gaps in their substance use or psychiatric treatment history, is crucial to developing a successful post-transplant care plan that includes services provided by mental health providers familiar with the LGBT population.

LGBT patients face cultural challenges with healthcare providers and decreased visibility in EMRs, healthcare access challenges, as well as financial and underinsurance problems. Despite these challenges, studies in cancer care have shown that barriers to providing inclusive care include physician doubts about knowing when SOGI is relevant to a patient's care as well as discomfort bringing it up [34, 35]. This case illustrates some of the avoidable problems that can arise in uninformed care of LGBT patients that derives from failure to acknowledge their identities.

The care of a transplanted organ requires high frequency and duration of contact with healthcare personnel [36–39]. Given the complex coordinated care required by organ recipients, awareness of trends in LGBT patients' attitudes about receiving healthcare and past avoidance of healthcare providers is a critical barrier to overcome for post-transplant care. Transplant psychiatry is uniquely positioned to address behaviors that may have contributed to host organ failure,

including avoidance of care for substance use, mental health, and other medical problems that have increased prevalence in LGBT population [40–42]. Psychiatrists on transplant teams also have the psychotherapeutic skills to address external and internal barriers to patient engagement with their transplant care team, and possibly rebuild the foundation of trust in future medical providers [8, 9, 43].

Take Home Points

1. When evaluating an SGM patient as part of a transplant candidacy evaluation, it is important to explore the patient's past relationships with healthcare providers.
2. SGM patients may have complex family relationships because of their identity.
3. Asking about pronouns and names at the beginning of an evaluation is important for establishing rapport with transgender patients and to ensure appropriate documentation in the EMR.
4. SGM patients are at higher risk of multiple psychiatric comorbidities and mistrust of healthcare providers and may require additional screening to elicit this information for risk stratification and post-transplant planning [44].

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Part VII

Organ Donors

Psychiatric Illness in Living Organ Donors

38

Stephen Potts

Introduction

Live donation has a history as long as transplantation itself. The world's first successful kidney transplant took place in Boston in 1954 [1], and the UK's first in Edinburgh in 1960 [2]. In both cases, the donors and recipients were monozygotic twins, whose genetics removed the immunological barriers and thereby the need for immunosuppression, which in those early days was at first non-existent and later heavily risk laden.

Since then, advances in surgical technique (e.g., laparoscopic nephrectomy) and enhanced donor work-up (e.g., high resolution radiological imaging of renal vasculature) have steadily reduced the risks to donors, while outcomes for recipients have steadily improved, through better immunosuppression and other advances in post-transplant care [3].

In recent years the ability to transplant across previously insurmountable barriers of blood group and/or HLA incompatibility barriers, either via pre-transplant treatment of potential recipients or through complex logistical arrangements for paired, pooled, and chain donations, has allowed more living donors with established relationships to recipients to proceed [4].

In parallel, the pool of potential living donors has also grown substantially, by expanding the range of permitted donor/recipient relationships: from those early genetically identical twins, to fraternal twins, to siblings, to more distant genetic relatives, to spouses and others with emotional but no genetic links to the recipient, and finally, in recent decades, to the so-called altruistic or non-directed donors, who have neither genetic nor emotional links to the recipient. A further recent sub-category has been established, termed directed altruistic donors (or "unrelated" or "unaffiliated" donors), when someone proposes to give, while alive, an organ (or a part of the organ) to an identified recipient not related or previously known to them, whose need for a transplant has been conveyed via social media, matching websites or similar means.

Despite these changes, the total number of live donor kidney transplants has remained broadly stable in the US at slightly over 5000 per year, and the proportion of all kidney transplants from living donors is also stable at 20–25% [5]. Comparable figures for the UK are 1000 live donor kidney transplants per year, making up almost 40% of all kidney transplants [6]. As part of an effort to increase the number of transplants, centers have shown a greater willingness to accept living donors previously thought of as marginal or unsuitable on the grounds of age, weight, or co-morbidity. For example, transplant centers in Edinburgh and London have undertaken transplant nephrectomies in altruistic donors in their mid-80s, and transplant centers regularly discuss accepting donors who would previously have been declined in grounds of high body mass index (BMI) or low glomerular filtration rate (GFR). In effect this means acceptable donor co-morbidity is now a matter of degree rather than category.

These trends—reducing physical risks, increasing distance in the relationship between donor and recipient, and increasing use of "marginal" donors—have prompted greater attention to the psychological, as well the physical health of potential donors. Some donors are at heightened risk of mental disorder arising from donation. This generates additional requirements for assessment, support, and treatment by mental health clinicians, both before and after surgery [7]. For a minority of potential donors, these additional risks are sufficient to exclude them from donation on the grounds that the risks posed to their mental health outweigh their suitability on a purely physical basis.

For the subset of altruistic potential donors, a recently published international consensus statement of transplant psychiatrists concluded that *all* of them should undergo mental health assessment. This should occur after initial screening, which may exclude potential donors on clear medical grounds and render mental health assessment unnecessary,

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but before donors are exposed to the medical risks arising from invasive investigations, such as angiography [8].

There is less consensus over whether the wider group of related donors should also all undergo mental health assessment, especially given evidence (albeit anecdotal) that donor decline rates on mental health grounds are considerably lower in related donors than in altruistic cases. In addition, many transplant centers lack the resources to undertake mental health assessments on all donors. It is therefore important to establish guidance on *which* potential-related donors should be referred. The Edinburgh Transplant Centre applies a simple pragmatic protocol, whereby any potential donors with a significant past psychiatric history, current prescription of psychotropics, or psychiatric symptoms evident at initial screening assessment will be referred. Doubts about the significance of past history or current symptoms are discussed directly with the Centre's transplant psychiatrist. Under this protocol, approximately 20–25% of donors are referred. Concerns about the dynamics of the relationship between the intended recipient and potential donor may also act as a trigger to psychiatric referral, although strictly speaking, in the UK, this is the province of the regulatory body, the Human Tissue Authority, via their Independent Assessors.

Mental health liaison services to transplant units have evolved in widely varying ways in the UK, US, and elsewhere. Most units have access to some form of mental health clinician, whether psychiatrist, psychologist, social worker, counsellor or nurse specialist, and many have access to more than one discipline. There is also variety in the degree to which such clinicians are embedded within the transplant team, as opposed to consulting from a different base. However the service might be configured, it is crucial that mental health specialists assessing transplant candidates should have a good understanding of transplant procedures, outcomes and risks. For transplant recipients, this should include the psychiatric side effects of transplant medications, and the physical side effects and potential interactions of psychotropic drugs. In the US, transplant programs include living donor advocates whose role is to assist with donor assessments with a focus on their well-being. This reflects the overriding concern that living donors should be exposed to no more risk to their physical and mental health than is necessary.

The fictional case presented below illustrates some of the issues that such donations can present to psychiatrists, psychologists, and the transplant teams they advise.

Case History

The donor is a 49-year-old woman who wishes to donate a kidney to her employer of seven years, whom she also considers a friend. Initial physical assessment and baseline investigations confirm that she is in good general health, with no significant past medical history, and no current physical contraindications. However, there is a long history of psychiatric symptoms, with several prior mental health diagnoses, and current long-term prescription of three psychotropic drugs.

At initial assessment with a transplant coordinator, she gave permission, somewhat reluctantly, to access her primary care and prior psychiatry records. Local protocols require all potential living organ donors with a significant past psychiatric history or current prescription of psychotropic drugs to be referred for psychiatric assessment before proceeding with an in-depth physical work-up.

Psychiatric evaluation established that she had no significant family history of medical or psychiatric illness, and no significant adversity in childhood or early adulthood. She had never smoked, drunk alcohol to excess, or taken illicit drugs. She married in her twenties but had no children before her husband left her for another woman when she was in her late thirties.

She was first seen by mental health community services in her adolescence, with subsequent intermittent contact. She was diagnosed at different times with recurrent depression, dysthymia, and bipolar disorder and treated with a variety of antidepressants of uncertain benefit.

She presented on several occasions in her twenties with low mood and suicidal thoughts, and was repeatedly admitted to her local psychiatric hospital, twice involuntarily, because of concern about suicide risk. There followed a period of relative stability until her marriage ended, when she presented with a suicide attempt via medication overdose. Psychiatric assessment recorded auditory hallucinations, low mood, and ambivalence about survival. A diagnosis of bipolar disorder was applied, a mood stabilizer and antipsychotic were added to her regimen, and she was admitted once more. After discharge, she was followed up for two years by a community mental health team, on a stable combination of an antidepressant, an antipsychotic and a mood stabilizer, which she is still taking. She was discharged to primary care follow-up and has remained stable for the last nine years.

She has worked in the same retail job for seven years and has a good relationship with her employer. She lives with her new partner of six years, and his teenage daughter by a previous relationship. Her partner did not attend her assessment appointments with her, though she reports him as passively supportive of her wish to donate her kidney. She said that her closest source of support is her younger brother who lives in a nearby city and is reportedly supportive of her wish to donate. She is registered as an organ donor, and she donates modest sums to animal charities, but she is not engaged beyond this in other altruistic activities.

Away from work, she is physically active. Her social life is restricted (by her preference) to weekly evenings out with her partner and step-daughter, occasional visits from her siblings, and invitations from her employer (the potential recipi-

ent of her kidney) to attend gatherings of his family on special occasions, which her partner does not normally accompany her to.

During interview, she was initially guarded in revealing her past personal history, but after discussion she cooperated fully. She presented as an articulate, intelligent woman, to a degree commensurate with her educational achievement. She had a good understanding of the mortality and morbidity associated with kidney donation, and there was nothing to call into question her decision-making capacity. She did not display any overt lowering of mood, undue anxiety, psychotic symptoms, or deficits in cognition. She agreed with the accounts of her previous psychiatric symptoms in her psychiatric records. She acknowledged that she was still prone to spells of lowered mood, but these were subclinical as they did not impair her function or lead to suicidal behavior. She usually dealt with them by increasing her physical activity. During these spells she occasionally experienced fleeting auditory hallucinations. The last such episode had occurred one year earlier, and resolved spontaneously.

The assessor concluded that the primary diagnosis was borderline personality disorder, with previous episodes of superimposed co-morbid depression, currently stable on her psychotropic regimen. Current traits of personality disorder were not evident at interview or by self-report, and her mental state examination was essentially normal. When this was put to her, she agreed in principle, but expressed concerns that such a diagnosis might lead the transplant team to exclude her from further donor assessment.

She was advised that she was at increased risk for recurrent depressive episodes in the post-operative period, especially with any significant complications of donation. In addition, becoming uninephric, with a necessarily reduced GFR, might require revision of her psychotropic regime, with the risk of a consequent loss of stability and limited treatment options. This was considered a relative but not absolute contraindication to donation. The donor stated that she would be willing to assume these additional risks. Her relationship with her recipient was also discussed. She made it clear that although, as an employee, she was in a position of (partial) economic dependence upon him, she regarded him more as a friend than her boss, and at no stage had she felt any pressure to donate.

The assessment's conclusions were discussed in detail at transplant multidisciplinary team meetings, where it was agreed she would go forward to the next, invasive stage of donor investigation.

Clinical Questions

1. To what extent does a history of mental illness in itself confer additional risks to the donor?
2. How is such risk to be assessed and, if possible quantified?
3. Can psychiatric contraindications to donation be divided into absolute and relative?
4. Does (or should) the degree of additional risk considered acceptable differ, depending on the nature of the relationship between donor and recipient? For example, is it possible that a degree of mental health risk considered unacceptable for an altruistic donor might be acceptable in donation to a spouse or child?

Discussion

To What Extent Does a History of Mental Illness in Itself Confer Additional Risks to the Donor?

The degree of additional donor risk conferred by a history of *physical* illness depends on its nature, time course, chronicity, prognosis, and consequences. For example, a potential donor with treatment-resistant hypertension and end organ damage will definitely be put at serious risk by donation. Transplant services are bound to exclude such donors in their best interests, however much they wish to proceed. A chronic treatment-resistant depressive illness, with recent serious suicide attempts, would constitute an analogous mental illness, one which confers additional risks high enough to make donation contraindicated. In the hypothetical case the depressive episodes have been recurrent, rather than chronic, and although severe (as measured by psychiatric admission under detention), only led to a suicide attempt on one occasion, and are now remote in time. The patient's mood has been stable for years on her current medication.

This case also highlights additional features which are *not* analogous between the mental and physical risks of donation. Firstly, there are no direct potential physical benefits to donation. There may be *indirect* benefits to donors who lose weight, increase activity, stop smoking, and drink less alcohol, in order to be accepted as donors, especially if these changes persist after donation, with engagement in post-donation follow-up, but there is no *direct* physical benefit of donation against which to offset the undoubted direct risks. However, there is evidence of improvement in mental health, including increased self-esteem, after donation, in both related and non-directed donors [9], though this is modest in degree, and does not always endure. Most transplant centers have encountered donors who achieved psychological benefit from donating an organ or part organ, but found the benefit short lived, and subsequently seek to make a further donation (for example, of a kidney after partial liver donation, or vice versa). In the hypothetical case described, the donor clearly saw an improvement in her mental health as a potential benefit of donation to her and gave this as part of her motivation in wishing to donate.

Secondly, actual or perceived rejection can trigger emotional distress, especially in people with borderline personality traits or vulnerability to depressive illness. Both factors

applied in this case, so a decision to exclude the donor could, in itself, *increase* the risk of adverse mental health outcomes (intensified distress, depressive relapse, self-harm, or completed suicide). Again, there is no direct equivalent in physical risk: declining a hypertensive donor does not worsen blood pressure control. Further research is clearly needed, covering mental health outcomes in donors who are declined on mental health grounds, to explore the degree to which this risk occurs in practice.

There is the related and largely unresolved question of what duties a transplant team owes to a donor they decline on mental health grounds, if this imposes a risk of relapse of mental disorder, and especially of suicide. In the absence of sufficient evidence, consensus is required, and it is not clear that it exists. Some, perhaps most, transplant units regard their responsibility has having been discharged once the assessment has been undertaken, and the decision to decline the donor made and conveyed to the donor: others might take the view that if a transplant team's decision increases risk, then the team has an obligation to mitigate that increase, whether by liaison with existing mental health services, primary care providers, or active direct follow-up and management of the declined donor, at least in the short term.

How Is Such Risk to be Assessed and, If Possible Quantified?

Clinicians undertaking assessments of potential live donors have to rely on their core clinical skills of history taking, mental state examination, and amassing and interpreting third party information. Some clinicians supplement these skills by administering clinical rating scales to quantify symptoms, such as depression and anxiety. While these may be helpful in grading the severity of any current symptoms, many were not originally developed for this purpose in the donor population, and their predictive validity is uncertain. Recent work in Europe [10] and the US [11] has developed a psychosocial assessment tool for living organ donors, but there is no rating scale yet available which can synthesize the multi-dimensional elements of a good clinical history and transform them into an evidence-based quantified stratification of risk. Clinicians must therefore rely on clinical judgement, in assigning donors to high, low, or intermediate levels of risk. The assessor in this case judged the risks of donation to the donor's mental health as intermediate, and not so high as to prevent donation. He made recommendations to mitigate the risk.

Can Psychiatric Contraindications to Donation be Divided into Absolute and Relative?

Transplant services regularly divide physical risks, such as those arising from hypertension, into these categories. The Edinburgh Transplant Centre uses a protocol for psychiatric assessment of potential liver transplant recipients in acute severe liver injury after paracetamol (acetaminophen) overdose, which explicitly lists absolute and relative psychiatric contraindications to listing for urgent transplant [12]. The former includes, for example, current active alcohol dependence and frequent recent acts of self-harm. This clearly establishes the principle that classifying psychiatric factors into absolute and relative contraindications is indeed possible and helpful for transplant *recipients*. The same may well be true of donors.

A further question applies to both physical and psychiatric risks: at what point do a group of relative contraindications *collectively* constitute an absolute contraindication? For example, a candidate donor (or recipient) may present several factors such as age, BMI, reduced GFR, controlled hypertension, and cardiac history, none of which is sufficient *in itself* to stand as a barrier to transplantation, while collectively they do. Without a secure evidence base or decision protocols, transplant teams wrestle with these decisions, which are open to inconsistency within and between transplant centers.

The case described above presents several relative psychiatric contraindications to donation, none of which stands as an absolute contraindication in its own right: recurrent depression, a single previous suicide attempt, multiple psychotropics required for stability, and underlying borderline personality traits. The assessor took the view that collectively they did *not* prevent going further with donor assessment: a different assessor may have taken a different view.

Does (or Should) the Degree of Additional Risk Considered Acceptable Differ, Depending on the Nature of the Relationship Between Donor and Recipient? For Example, Is It Possible That a Degree of Mental Health Risk Considered Unacceptable for an Altruistic Donor Might be Acceptable in Donation to a Spouse or Child?

In the earliest days of live donor transplantation, the donors and recipients were identical twins, with the presumption that the emotional closeness of their relationship stood in parallel with their genetic identity. It seems self-evident that to act as a psychiatric contraindication to proceeding with such a transplant, any psychiatric factor in the donor would have to be extreme: for example, a florid psychotic illness with delusions of immortality.

Extrapolating this apparent principle would imply that the looser and more distant the relationship between donor and recipient, the lower the threshold at which psychiatric factors act as contraindications, so that factors which would prevent an altruistic or non-directed donation would be regarded as relative contraindications in spousal or parent-to-child dona-

tion. More information is needed to better understand the impact between interpersonal factors (actual, imagined or desired pre- and post-donation relationship between donor and recipients) upon the psychological well-being of living organ donors. Currently, clinicians include the evaluation of envisioned relationship with the recipient in the overall evaluation of donor candidate's expectations about the outcomes of the procedures, under the overarching umbrella of ability to provide informed consent for the procedure. So long as these distinctions are drawn with regard to physical risk factors, it would seem unreasonable to prevent them being drawn in connection with psychiatric factors.

In this case the relationship is intermediate: the recipient is neither an unknown stranger nor a close family member, but a combination of employer and friend of several years standing. The assessor took the view that the relative contraindications listed would be enough to prevent an altruistic donation but were not sufficient to block the donation proposed.

Take Home Points

1. Until such time that a firm evidence base is established regarding mental health considerations for potential donors, transplant centers will need to rely on national and international consensus statements when faced with complicated donor evaluations.
2. Efforts have been made to standardize as far as possible the process of donor mental health assessments, to ensure consistency of approach within and between transplant centers [7, 10, 11].
3. While it is true that questions still remain, there is clear consensus on several matters. Firstly, all potential altruistic donors should undergo mental health assessment at an early stage. Secondly, while it might remain an aspiration that all related organ donors should also undergo mental health assessment, this is not currently practical. Nonetheless, a significant proportion of donors (specifically those with psychiatric histories, current psychotropic medication, or displaying psychological symptoms) clearly *do* require assessment. Thirdly, there is an initial consensus on the form such assessments should adopt.
4. For the minority of living organ candidates unsuitable, because of clear psychiatric contraindications, the challenge is how to handle the risks involved in declining them, and how to convey the decision in the most supportive way. As ever in medicine, most attention focuses on the marginal cases: those who *may* be unsuitable but are not self-evidently so, and in whom doubt persists even after extended assessment.

In addition to the familiar appeals for further research and consensus guidance to assist in such decisions, there is a continuing need for mental health professionals working with transplant teams to communicate with each other via national and international networks, in order to maximize shared learning by comparison between centers and across national boundaries, and thereby to ensure the best balance between the ethical principles of justice, beneficence, non-maleficence, and respect for autonomy in the specific context of living organ donations by people with psychiatric histories.

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Considerations on the Relationship Between Living Organ Donor and Recipient

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Introduction

As living organ donation becomes more common, relationships between organ donors and recipients can become increasingly complex. While the traditional scenario is that an organ donor will donate to a relative or someone else known to them, non-directed donation is becoming more common and accepted as a means of connecting potential donors to recipients. Transplant programs are also starting to see individuals in need of a transplant actively seeking out living donors. This is done via word-of-mouth or through various means of advertising, including via social media. This creates new dynamics in donor–recipient relationships. Organ donation is thought of as being a directed donation when the recipient is a relative or an individual previously known to the donor. At the other end of the spectrum is non-directed donation (sometimes called *altruistic donation*) in which individuals donate an organ to someone previously unknown to them. *Non-directed donation* is generally the term preferred over altruistic donation as the act of being a living organ donor is one of altruism, regardless of whether the donor has a designated recipient in mind or not. There are also situations in which a donor does not have a previously established relationship with the recipient. Often, donors perceive the act of donating as a spiritual calling which will provide a sense of fulfillment and improved self-esteem [1].

With all the possible variations in the relationship between donor and recipient, there arise several complexities in the relationship. These are areas that should be explored as part of the psychosocial evaluation prior to transplant for both the potential donor and recipient. While not commonly an area for such serious concern that it serves as the sole basis to prevent an individual from donating, exploring the dynamics between the potential donor and the intended recipient provides valuable insight into the motivation for donation and establishing realistic expectations.

While Organ Procurement and Transplantation Network (OTPN) guidelines for psychosocial evaluation for potential living donors state that any evidence of emotional coercion or financial inducement should exclude the donor from moving forward, there are no clear guidelines on how the relationship factors should influence the evaluation.

For example, there may be a situation in which a potential donor merely expresses interest in learning about the donation process after hearing about someone in need of a transplant. This may lead to a sense of pressure felt by the possible donor from the recipient, recipient's family, or healthcare providers [2]. This is even more likely in a circumstance in which the need for a living donor is considered urgent, such as in the case of a potential recipient with a low Model for End-Stage Liver Disease (MELD) score. A recipient or recipient's family could learn of an individual who has expressed interest and then act in a way that may encourage or even convince the potential donor to move forward with the process. At times, this is a subtle process whereby an individual may come forward in a preliminary fashion ("just to at least be tested to see if I'm a match."). The hope that the potential recipient and family experiences in this situation may cause the potential donor to feel pressure to donate. The potential donor may feel guilt regarding exercising the right to anonymously back out at any time, feeling that they now must move forward despite reservations due to concerns about causing further disappointment or hopelessness in a potential recipient or family who has "already been through so much."

Potential recipients are also affected by the impact that donation will have on the relationship with the donor. These concerns can be a barrier to living donor transplant, with potential recipients expressing hesitancy or aversion to even asking individuals to consider donation for fear of negatively impacting the relationship [3]. Living kidney and liver donation is correlated with better outcomes in recipients includ-

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ing lower rates of graft failure and improved survival compared to deceased donation [4, 5]. Even so, organ transplant patients sometimes choose to wait for a deceased donor transplant rather than ask for or accept a graft from a living donor. This decision is sometimes made due to concerns regarding how accepting the donation would impact the relationship with the donor, such as concern about whether there will be a lasting sense of obligation or indebtedness to the donor [2]. This may result in lost opportunities for living organ donation.

In situations in which there is already a relationship between the donor and recipient, the potential donor could view donation as a means of repairing a damaged relationship. There are no guarantees on how the organ donation surgery will change the relationship. Unrealistic expectations should be addressed during the pre-transplant process.

In non-directed donation, donors and recipients may disagree on whether to meet the other party. When a donor wishes to meet and the recipient does not, this could be a source of distress for the donor. Similarly, there are times when a recipient wishes to contact the donor to express gratitude, only to learn that the donor prefers to remain anonymous.

Case History

Consider the case of Ms. W, who is a 27-year-old single female with no past medical or psychiatric history who presented for evaluation for kidney donation. Her interest in donation was sparked after she read a post on social media in which a friend of a friend had a spouse, Mr. P, who needed a kidney transplantation due to End-Stage Renal Disease (ESRD). Ms. W had never met Mr. P, who was a 58-year-old male. Ms. W worked full time as an elementary school teacher and spent every summer since college volunteering in refugee camps abroad. During the academic year, she volunteers in an after-school reading program for at-risk students. Upon learning of Mr. P and his need for a kidney transplant, Ms. W reached out online to ask for additional information. The friends quickly placed Ms. W in contact with the recipient, who eagerly forwarded Ms. W information regarding how to set up the initial appointment to be evaluated for donation. While Mr. P and his family resided close to the transplant center, Ms. W lived over 100 miles away in a smaller town. They arranged a meeting and Ms. W quickly felt a connection with Mr. P which strengthened her desire to be evaluated to donate a kidney to him.

Ms. W's only close relative was her mother, who had raised her as a single parent. Her mother was concerned about Ms. W's desire to donate, expressing apprehension that Ms. W was exposing herself to unnecessary risks to her current and future health. Ms. W's mother discouraged her from going forward with donation. Due to her lack of support as well as her inability to take off work, Ms. W's mother was unable to be the designated post-donor surgery caregiver.

Ms. W awaited the end of the academic year when school would be out for the summer. She planned to travel for the pre-donation medical evaluation and Mr. P and his family insisted she stay with them while in town. Ms. W completed the pre-donor evaluation process uneventfully. She was a suitable match and there were no medical, surgical or psychosocial concerns that precluded her from moving forward. Ms. W, Mr. P, and his family were excited to schedule a surgery date.

Mr. P's wife was his designated caregiver. Because no one in Ms. W's family or circle of friends was able to serve as her caregiver, it was agreed upon that Mr. P's daughter would be Ms. W's post-donor surgery caregiver. Both surgeries proceeded uneventfully and with no complications. Although both Ms. W and Mr. P were discharged from the hospital within a few days, the decision was made for Ms. W and her caregiver (Mr. P's daughter) to stay at a local hotel rather than to return to stay with Mr. P in his home. After 3 days in the hotel recovering, Ms. W was surprised to learn that Mr. P's daughter had to leave to return to her out-of-town job, leaving Ms. W without a caregiver. Within a few days, Ms. W developed fever and nausea. There was a delay in her presenting to the hospital for these symptoms. Ms. W was diagnosed with a surgical site infection and an incisional hernia, which required admission for antibiotics and repeat surgical intervention several weeks later. In the months after the donor surgery, Ms. W went on to develop neuropathic pain at the surgical site. She developed a new diagnosis of hypertension despite continuing with healthy diet and regular exercise. While able to return to her job as a teacher, she frequently missed work due to severe bouts of abdominal pain. Ms. W got married 2 years post-donation surgery and became pregnant the following year. The pregnancy was complicated by pre-eclampsia, which required urgent delivery via cesarean section at 29 weeks gestation. By this time, Ms. W was not able to return to work and she began having financial difficulties, including difficulty paying for medical expenses. At this point, she had minimal contact with her recipient's family and the contact was limited to social media communications.

One day Ms. W read a post from Mr. P's daughter, which indicated that Mr. P was sick and in the hospital. Ms. W messaged Mr. P's daughter and learned that he was experiencing graft rejection after not taking his immunosuppressant medications because of side effects. Ms. W became despondent after learning of the graft rejection due to Mr. P's nonadherence. Ms. W began to feel persistently low mood and felt that her gift of organ donation was taken for granted. She felt that her sacrifice and multiple medical complications

were suffered in vain. Over several weeks, Ms. W developed a sense of hopelessness, feeling as though she would never return to her prior state of health free from medical complications. Ms. W began to have poor sleep with middle and terminal insomnia. She was no longer able to enjoy spending time with her spouse and child. She had a sense of regret for what her husband and child had experienced as a result of her own post-donation medical problems. She met criteria for Major Depressive Disorder and sought treatment. She was hesitant to take antidepressant medication, feeling as though her depressive symptoms were "situational" and preferring to avoid taking medication "unless it is absolutely necessary." She was referred for psychotherapy, which she found helpful. Due to financial constraints, she was only able to have a short course of psychotherapy, having lost her health insurance coverage.

Ms. W was left with an uneasy sense of ambivalence toward living organ donation. While stopping short of saying she regretted the donation, she admitted that she had not carefully considered all the possible negative outcomes surrounding living kidney donation surgery. She avoided communication with the recipient and his family and admitted she felt abandoned. She felt that she had been "used" for her kidney and believed that the connection she had with the recipient prior to donation had little meaning after the donation surgery. While Ms. W remains a supporter of living organ donation, she now also advocates for potential donors to more thoroughly consider possible negative outcomes and how the relationship with the recipient may change post-donation.

Clinical Questions

1. Does the threshold for suitability for organ donation increase if there is no direct relationship between donor and recipient?
2. What is the role of pre-surgical psychosocial evaluation in determining dynamics between the donor and recipient?
3. Should concerns regarding unhealthy or unrealistic expectations between donor and recipient ever be sufficient justification to recommend against proceeding with the organ donation and transplant?

Discussion

In the case of Ms. W, there were no psychiatric factors that would have suggested she was at an elevated risk of psychosocial complications post-donation. Her relationship with Mr. P was not that of a traditional directed donor, as she had no pre-existing relationship with him. At the same time, she does not fall into the category of anonymous or non-directed donation. Indeed, the donor–recipient dyad was the basis of Ms. W and Mr. P's relationship. Ms. W felt disappointed that Mr. P was emotionally distant after the surgery, and the connection she felt prior to donation seemed to fade. Some factors inherent in post-transplant treatment, such as fatigue, pain, and behavioral side effects to steroids and immunosuppressants, can impact the recipient's ability to demonstrate emotional connectedness to the donor [6]. Her desire to donate a kidney was congruent with her long history of altruism. She expected a lasting bond with Mr. P and his family. When that expectation was not met and she began to experience complications, Ms. W was left with a sense of vulnerability and abandonment that precipitated a major depressive episode.

Of some concern in Ms. W's case is the fact that a relative of the recipient was the designated post-donation surgery caregiver for Ms. W. While not frankly unethical or inappropriate, the fact that her own natural support person (specifically, her mother) was unable and unwilling to serve in the caregiver role may have been a clue that she was somewhat vulnerable to feeling exploited by the recipient's family. Also, without a direct and pre-existing connection to the donor, it is difficult to expect the recipient's relative to provide caregiver support beyond a routine, uncomplicated postoperative course.

Most living organ donors expect their relationships with recipients to improve after donation. In cases of living related kidney donors, this can be due to donors' hopes that the recipient will have improved function and thus be more able to engage in family activities and have less health-related impairment in functioning, thus indirectly improving the donor's quality of life [2]. Because Ms. W did not have an established relationship with Mr. P independent of her role as organ donor, she would not have stood to benefit in this way from his improvement in functioning. Donors and recipients have reported feeling a special bond brought on by the process of living organ donation [6]. Isolation from Mr. P likely failed the expectation Ms. W had for the relationship and special bond she was hoping to have with him as her recipient. Complexities in the donor–recipient relationship are challenging, as it is difficult to predict whether these factors will lead to adverse psychosocial consequence post-donation surgery. Indeed, often the relationships are strengthened post-donation. For example, most kidney donors report better relationships with the recipient post-donation [1, 7]. Donors generally report a favorable donation experience [8]. Outside of the frank exclusionary criteria from United Network for Organ Sharing (UNOS), it would be rare for other factors in the donor–recipient relationship to preclude proceeding with the donation process. In cases of directed donation, donor–recipient relationships that were positive prior to transplant are strengthened post-transplant. Similarly, dyads that have conflictual relationships prior to transplant tend to worsen after the surgery [9]. A reasonable role of the provider performing the psychosocial evaluation

would be to clarify the strength and resilience of the relationship prior to transplant and to identify potential areas of concern to ensure all factors have been considered. These may be posed as a series of questions, such as *What are your hopes or expectations of how this will affect your relationship with the donor/recipient?* The answer to these questions would reveal any possibly unrealistic expectations. An example of a concerning unrealistic expectation would have been if Ms. W had stated that she was hoping to gain Mr. P as a father figure after donating the kidney. If this were the case, it would need to be further explored and Ms. W would have to consider the possibility that the relationship does not progress to a father figure-type relationship post-donation. In non-directed donation, it is prudent to ask the potential donor if he or she expects to meet or develop a relationship with the recipient or the recipient's family. It is also helpful to ask the potential donor what his or her emotional response would be if the graft did not function, or if the recipient had rejection of the graft due to non-adherence. In scenarios in which there is already a relationship between the potential donor and intended recipient, it is helpful to ask the donor to describe the relationship, paying attention to any past discord and how the potential donor feels this will be impacted by the donation.

Donor emotional wellness can be influenced by recipient outcomes. The risk of developing depression or anxiety is higher in cases of graft failure or recipient death [1]. Similarly, better emotional donor outcomes are associated with cases of good transplant graft functioning [7]. Furthermore, if a recipient fails to adhere to required immunosuppressant treatment and experiences rejection of the transplanted organ, the donor may experience distress and a feeling that one's sacrifice and discomfort associated with the donation has been disrespected or devalued. Donors have reported emotional distress upon learning that the recipient has not properly cared for the graft, leading to feelings of anger toward the recipient [1].

When relatives of the recipient serve as the designated post-surgical caregiver for donors, the primary motivation for the donor's relative to care for the donor is so that their loved one will receive a transplant. As there is a wide variation in post-donor surgery recovery course, it is impossible to predict the extent of the caregiving needs. Because the relationship is based upon the need for the recipient to receive a transplant, the level of long-term dedication to the caregiver role may be less than in scenarios in which caregivers have a different connection to the donor.

It is also useful to consider how long-term complications may impact the donor–recipient relationship. If a donor goes on to develop medical or surgical complications, the donor may have an expectation that the recipient or recipient's family will provide support. Similarly, there can be financial hardships when a donor requires subsequent medical treatment due to complications. There could be delays in returning to work or even loss of employment related to complications from donor surgery. Often, donor's medical insurance is provided through their employer and in cases of medical complications, loss of heath care coverage can be financially catastrophic for the post-donation individual. If recipients do not respond to assist with the multitude of problems that can result from donor surgery in a way that meets the donor's expectations, it could lead to adverse psychological outcomes for the donor.

Take Home Points

1. The dynamics of the relationship between donor and recipient relationship are an important factor in the pre-transplant psychosocial evaluation.
2. Counseling potential donors and recipients on the implications donation can have on the relationship should be part of the pre-transplant process.

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Altruistic, Directed Anonymous and Non-directed Donation

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Background

Altruistic, directed anonymous and non-directed donors (NDDs) are becoming increasingly important in both living donor kidney transplantation (LDKT) and liver donor liver transplantation (LDLT). Often named "unspecified," "Good Samaritan," or "community" donors, they share the feature of having no prior relationship with the recipient. The United Network of Organ Sharing (UNOS) uses the term NDD [1]. NDDs donate to the waitlist which can help paired and chain donation, especially when there are incompatible donor–recipient pairs. NDDs are essential to start pooled chain donation which has helped increase LDKT. In the United States, 385 kidney NDDs donated in 2019 out of the 6863 LDKTs making up 5% of the total [2]. Prior recommendations for LDLT had been restricted to donors with a close emotional relationship with the recipient, but many centers have begun to accept NDDs. Correspondingly, in 2019, there were 53 liver NDDs out of 523 LDLTs making up 10% of that total. In 2019, another 2057 non-biological and unrelated *directed* kidney and liver donations occurred, some of whom could have been individuals with little relationship with the recipient prior to donation. Some of these individuals initially direct their donation efforts toward helping a specified patient found through their community, advertisement, social media, or platforms, such as matchingdonors.com, but are willing to donate to another patient if incompatible with the first.

We will retain the term NDD throughout this chapter as it has become the standard language for donors without a prior relationship with the recipient and we recognize that altruism lies on a continuum across all donor relationship types. The larger group of non-biologically related donors, including spouses and close friends, termed *living unrelated donors,* will not be the focus of this chapter.

The American Society of Transplantation (AST) has required all living donors to undergo an in-depth psychosocial assessment [3]. NDDs are even more carefully assessed for their motivations, understanding of donation and psychological risks [4, 5]. Donors who have no emotional connection to the recipient, may have unique and deeply personal reasons to donate. An evaluation of both manifest and latent content related to these reasons is essential to understand the nature of the motivation. What represents a good or acceptable motivation to donate an organ is not well defined. In the United States, organ donation for monetary compensation is illegal. The mental health professional has the opportunity to discover if a mental illness is driving the decision to donate. The psychosocial assessment plays a key role in both understanding the donor's decision-making process and managing their expectations. The current approach to the directed anonymous donor who initiated the evaluation due to an advertisement or social media appeal, and who does not have a primary relationship with the recipient, is to be evaluated similarly to an NDD.

The following psychosocial assessment of AD included a psychiatric interview to assess motivation, decision-making, and presence of any possible psychiatric diagnosis. The Live Donor Assessment Tool (LDAT) was utilized to review and score his candidacy. He also met with a social worker to focus on his social needs and a second evaluation of patient's decision to donate. In the case of AD, he started off as an anonymous donor to a potential recipient of the same religious faith, but then converted to being an NDD. He was interviewed again as a NDD and later to review expectations about meeting the potential recipient. Collateral information was sought from his friend and his brother. Through these interviews the psychosocial team reviewed AD's expectations, possible benefits, and possible negative impacts of being a live donor.

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Case History

AD is a 33-year-old single Orthodox Jewish male who initially presented 6 months ago as an anonymous living liver donor to a member of his religious faith. At the time, he wanted to serve as an "altruistic" directed donor to a hospitalized patient he had met while visiting a friend admitted for sepsis. During his visit he had been affected by all the suffering he saw around him in the hospital. During the same visit he also made a casual acquaintance with a young Jewish mother who had been hospitalized with severe ascites related to a genetic liver disease. At his initial presentation to the transplant center, many donor team members thought he was intense and driven. He called the donor coordinator regularly to confirm his evaluation status and the status of his intended recipient. The team was concerned that he was obsessing about donation in a pathological way. AD was in the process of his evaluation when this intended recipient received a deceased graft; he then represented as a NDD to a yet unknown potential recipient on the liver waitlist.

AD described a deep wish to help others, especially others in the Jewish community. He explained that his motivation was due to altruism; a wish to help other Jewish people. While he was willing to donate to anyone needing a liver, he believed that being a donor to another Jewish person is favorable in the eyes of God and will secure him access to heaven. On a scale from 0 to 100 he shared a 100% wish to move forward with no hesitation. He performed other good deeds or mitzvahs, such as driving a volunteer ambulance for his community, bringing food to Jewish people in the hospital, and helping in community schools. He had given bone marrow in the past and donated blood around every 60 days, as this was the recommended wait time between blood donations. As he tended to be in different towns due to his work, he had donated blood at various hospitals around the country. He kept records of his donations but denied experiencing any internal pressure or intrusive thoughts to donate. He explained that he felt satisfaction from helping, but no compulsion. AD explained that he knows this is the right thing to do and he is persistent, a trait that had worked for him over the years. As the youngest child, he would assert his will against his older siblings and his parents. He was the only one in the family to start his own business because he "didn't want to work for anyone."

He shared a good baseline knowledge about donation and demonstrated a strong capacity to learn. Initially, he believed that liver donation was less risky than kidney donation because the organ regenerates. After repeated discussion of various surgical options, he eventually appreciated that a left lateral liver donation to a child would be less risky and made it clear this would be his preferred option. He displayed a balanced sense of expectations but intellectualized negative outcomes. He shared some religious thinking about having a shluka mitzva or "powerful weapon" of protection if he is doing a good deed. He could appreciate that poor outcomes were possible for the recipient and himself regardless of his good intentions. He had a close friend who donated a kidney and struggled with recovery when the recipient died. He expected that if he had a setback he might be sidelined from his usual activity for a few months but believed that most things in life were temporary and would cope with possible setbacks in his postsurgical recovery.

He did not want his parents to know about his plan to be a donor out of for concern they would become worried. He wanted his roommate (also a close friend) to be his primary support and maintained that he would tell his parents about donation when a surgical date was set. Patient's medical history, surgical history, substance use history, and family history were unremarkable.

AD was born and raised in the suburbs to parents who were orthodox Jewish, the last of 9 children. He was a bright child, the youngest in the family, and regularly asserted his will against his parents and older siblings. He underwent religious schooling, but always "wanted to make money" and resisted his parents and older siblings imposing strict religious education. He completed a Bachelor of Science degree in computer engineering and found a job quickly working in cyber security. Subsequently, he started his own business in the same field. At the time of his evaluation, he was financially secure and single with no children. He prided himself as being able to make the correct decision in most matters outside of finding a partner. He found that his parents were religious but did not help others as much as he felt was needed. He volunteered regularly in the Jewish community and found most of his personal connection with others through his charity work. He maintained some contact with his parents and siblings, but he spent more time with his roommate and other friends.

Generally, he was not an anxious person and his mood was good. He put a lot of thought into decision-making and tried not to act impulsively. He was energetic and very active. He denied past obsessional behavior, episodes of depression, suicidality or suicide attempts. He had no formal psychiatric diagnosis and had never received psychiatric treatment.

At repeated interviews, AD was a healthy-appearing adult male. He was loquacious and seemed to want to connect and engage. He spoke with his hands and straightened his yarmulke often as he made his point. He was intense and driven. He has a broad affect. He denied any depressive symptomatology, there was no suicidal ideation, and mood was euthymic. He did not exhibit any delusional or obsessive thinking. He was focused on his decision-making being sound and was thoughtful about the risks. He wanted to go forward with being a donor because it was the morally correct thing to do. He was intelligent with no cognitive deficits. He understood that he could come across as overbearing and "a know it all" which had affected his finding a wife in the past 5 years. He

believed this was a perfect time to donate before he met his future wife and his responsibilities change.

His Liver Donor Assessment Tool score was 81/96. Points were deducted due to being a NDD with no relationship to the recipient, having no current partner, and exhibiting mild obsessive traits. The formal diagnosis was Psychological and behavioral factors associated with disorders or diseases classified elsewhere, F54.

His assessment concluded that patient had no formal psychiatric history, substance history, or functional problems. His motivation was "compelled altruism" or a strong wish to do the right thing for another Jewish person. His description of the role of mitzvah in Jewish faith was similar to other orthodox Jewish donors who had donated. He shared a balanced sense of risks. He had the capacity to fully recover and maintain focus on career and other endeavors.

Clinical Questions

1. How should motivation to donate an organ evaluated and what is an acceptable motivation to become a living organ donor?
2. Should mild psychopathology or personality traits be grounds for rejecting the NDD?
3. Should the NDD be required to discuss their donation plans with their family of origin?
4. Should there be different expectations for ability to provide informed consent for NDDs compared to related donors?
5. Should the so-called NDD be allowed to direct their donation to a specific group?
6. What is the optimal cooling off period for NDDs?
7. If the NDD wishes to meet the recipient prior to donation, should this be facilitated by the center?

Discussion

AD was the case of a single professional male of Jewish faith in his 30s who presented with altruistic motivation to be a liver donor to a yet unknown waitlisted individual of Jewish faith; he was considered appropriate to donate because he did not have any psychopathology that complicated his motivation to donate, he demonstrated a good understanding of the risks of surgery and was persistent in his intent to donate. Tools, such as the LDAT, list the critical psychosocial components of a living donor evaluation and may be a helpful survey for the psychosocial evaluator [6]. AD received a high score on this tool which was consistent with a low risk candidate. The case illustrates the situation of a nondirected donor (NDD) who initially presented as a potential directed liver donor to a woman he met in the hospital while visiting a friend. The case also demonstrates the NDD's not uncommon wish to direct their donation to a member of a specific group but to have the medical center decide on the specific recipient.

The acceptance of the NDD is based on the premise that the individual is motivated by altruism. One of the goals of the pre-organ donation psychiatric and psychological evaluation is to explore the sense of altruism as it relates to the potential donor's current psychology and past behaviors. The history of the present preoccupation with donation is explored through the medical, characterological, behavioral, and narrative perspective. The clinician should remain curious to discover the story of the donor's first interest in donation along with the responses by their family or friends and their trajectory of how they moved forward with their decision. Often the donor's past and present behavior reflect a consistent deep sense of purpose related to performing good deeds vis a vis others, and a pattern of "compelled altruism" emerges. These donors are emotionally moved by others' distress and respond with a strong desire to help. At times these good deeds can be complicated by intrapsychic and interpersonal conflicts. After AD met the young mother in the hospital and learned of the prospect of liver donation, he began to think about it every day like a "scratch that needed to be itched." The only comparable phenomena to his interest in donation was his tendency to obsess about marriage and explained "that this one part of (his) life hadn't developed." He had given himself a hiatus from dating which had been a focus in prior years when he had been consumed with the wish to find a bride, and his current thought patterns about donation seemed similar.

Despite these preoccupations he continued to meet expectations at his employment, tended to his own business, volunteered in Jewish organizations, and followed sports. His self-esteem remained intact despite these struggles in part due to his devotion to volunteering. Some potential donors share themes of a wish to improve their self-esteem or their standing within their own family or work through donation. Extreme care must be taken to understand these expectations and how they are connected to the wish to be a living donor. AD was asked to consider how his traits and life story could be related to his current motivation. AD did not appear to be donating due to psychopathology or for the correction of any psychological deficiency.

It has been noted that altruism is not necessarily negated if other motives are uncovered [7]. In one qualitative study of kidney donors, a variety of additional themes were found to drive donation such as personal benefit, spiritual confirmation, family expectation, inherent responsibility, and accepting risks [8]. Candidates may acknowledge personal benefits of donation, such as the positive feelings of satisfaction from helping others; however, some individuals may be looking for prestige, notoriety, or improved self-standing in their social circles. NDDs should also be discouraged to donate if it appears that there is a strong desire for recognition. Financial burden and risk for significant loss is reviewed in

the psychosocial evaluation. If there is an expectation or desire of financial reward, candidates require additional scrutiny. Additional motives for donation were explored with AD but he revealed no signs of primary or secondary gain.

Over half of NDDs spoke of religious or spiritual connection as their motivation to donate [9]. Moreover, in a comparison to donors who were not accepted for psychosocial reasons, NDDs were more likely to be guided by spirituality [10]. No religious group makes organ donation a duty or even an obligation but there was one case of a sect of "Jesus Christians" where the majority of members had donated a kidney [11]. This group had made national attention when a potential donor was declined by a center after his parents expressed concern that coercion was present. AD did not want his parents to know about his decision to donate until we had set a date for the surgery. He was concerned that his mother would worry too much. The donor team decided that if a NDD was financially or otherwise dependent on their parents, they should mandate that the NDD include them in the decision-making but that otherwise an independent adult should be able to choose their own support system. AD ultimately did tell his parents and siblings prior to donation, and they supported him in his recovery.

The donor's acceptance of risks is an important factor which leads to a better understanding of the donor's motivation. Some NDDs share a confidence in managing the risks and cite a prior surgical experience or past risk taking. Other donors have never been injured or experienced pain. Many NDDs are athletic or at least comfortable with their body and have a conviction that they can recuperate. AD did not have any prior surgeries or risk-taking behaviors. He felt confident after reading extensively about liver donation and speaking with other liver donors. He was able to detail the range of outcomes after donation and we discussed the potential impact on his work and quality of life. He was healthy, financially stable and did not have any dependents.

Most donors make up their mind to donate before they learn about the donation process or fully understand the risk of outcomes. Voluntary and immediate decisions are often made as soon as the need was learned [4]. When AD first met the young Jewish hospitalized mother waiting for a liver, he was taken by how weak she appeared and felt a deep sense of sadness for her. He shared heroic ideation and a promise to try to help her along with rationalizing that his act was one of the social responsibilities with the cost to him being much less than the benefit to her. In another case, a future NDD was enjoying a sunny day and while riding her bike across a bridge she was thinking about a prior conversation about organ donation and felt a deep commitment to act. She later learned much more about liver donation and felt like she could and should proceed. The clinician should re-visit this initial motivation and review it in light of the donor candidate's updated and evolving understanding of the process. The donor may not be attending to all concerns; despite learning through the evaluation, they may be selectively registering information that confirms their original feeling. In the case of AD, he could clearly describe the risks to himself, but he did under-appreciate the possible negative outcomes to the recipient. Ensuring the donors have realistic expectations about the risks of transplantation for the recipient is an essential part of providing informed consent. Poor recipient outcomes are linked with depression in organ donors [12].

NDDs often think about others' welfare above their own, and a theme of sacrifice can be present. The interviewer should explore the meaning of this sacrifice and how it could impact the donor after surgery. The clinician must not only be aware of the expected surgical, medical, and psychosocial outcomes to the donor but also be able to review possible recipient outcomes with the donor. The altruistic donor may feel that their own sacrifice is essential to the benefit of the recipient. Donors may find that the pain and the scar are important aspects of this sacrifice. Conversely, they may overstate positive outcomes to the recipient to help manage their own concern about risks. AD had reviewed the outcomes, shared a balanced understanding of risks to himself, and could describe a detailed recovery plan. Donor decision-making is the donor's ability to describe how their recovery and the risks can be managed considering the potential benefits to the recipient. Documenting this capacity for informed consent is critical in these healthy donors who have no relationship with the recipient.

The cooling off period serves as an additional time for considering the decision to donate. Often, the psychosocial evaluation is completed alongside the medical assessment and the donor's knowledge of the material may still be nascent. The initial meetings with the clinical staff help fill in donor knowledge gaps and ensure that the donor has the information needed to make their decision. Donors tend to interpret new information in a selective fashion in support of their initial choice [13]. Team members who are educating patients should actively observe the gaps in the donor's knowledge. Tools to query knowledge and decision aids have been created and could be used for this purpose [14]. Some centers use a standard time of 2 weeks for all donors, including NDDs [15]. Other centers have used longer waiting periods, using that time to find a suitable match while helping the donor with the decision process. During the cooling off period, AD was asked to review the outcome data for recipients who received living donor liver transplants.

AD wished to direct his donation to a member of his religious group, leaving the donor program to find a suitable match within that group. Ethical concerns have been raised about placing conditions on the group identity of the recipient [10, 11]. On the other hand, it has also been argued that a willing donor has the right to be partial and selective in their donation [16]. Religious or spiritual connection may drive more altruistic type of donation where none existed before. For example, in Israel, where deceased donation had been

discouraged, organ donation within a religious group is encouraged by community organizations which stress the spiritual importance of saving a life within one's community [17, 18]. Faith-based community organizations could start the search for possible recipients deferring the final assessment of medical need and matching to the transplant center. This practice has expanded the number of transplants and perhaps eased the burden on others waiting for a deceased organ. In the case of AD, the donor team looked for a match and found a child whose parents were of Jewish faith.

AD wanted to meet and become acquainted with the family prior to donation. He explained that meeting them would help him feel more confident about proceeding. The psychiatrist met AD again to discuss his motivation and to review the center policy of being unable to facilitate such a meeting. In this conversation, the psychiatrist again observed and interpreted that AD is looking for connections with people and donation may not result in meeting this need. He appreciated that the family could reach out to him if it was a mutual wish, but this would have to wait until after donation.

AD proceeded with left-lobe liver donation to a child from an Orthodox Jewish family and he recovered well without complication. He continued to express a wish to connect with the recipient family but the family chose not to meet with AD. He developed pain and discomfort and was initially thought to have developed a hernia at the six month follow up visit. It was deemed not to be a hernia but irritation at the incision site which responded well to a local anesthetic. The pain resolved and the rest of his recovery was smooth. He became engaged a little over a year after surgery and announced his joy to the donor team the following day. He wished to relay to the recipient family the news of his engagement and to let them know that he was doing well. He is now two years post-donation without surgical, medical, or psychiatric complication and satisfied with having been an organ donor.

Take Home Points

1. The NDD lacks a relationship with the recipient and their motives for donation should be consistent with their values and not psychopathology.
2. The value of altruism is an acceptable motivation for the NDD.
3. The NDD should be psychosocially stable, and they should have a realistic and balanced understanding of the risks.

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The Evaluation of the Transgender Organ Donor

41

Kelly J. Park and Stephanie H. Cho

Introduction

Psychiatrists often act as liaisons and intermediaries between the various stakeholders in a clinical situation. This is frequently the case in transplant medicine, a field in which multidisciplinary collaboration and coordination are essential to optimize patient outcomes. While the high number of stakeholders may complicate decision-making, multiple viewpoints and areas of expertise also generate greater insights and promote progress in transplant medicine. Transplant psychiatrists are uniquely positioned not only to recognize moments of misunderstanding but also to facilitate improved communication when these moments arise. They can, in addition, act as advocates for patients throughout this process.

In this case, we share and discuss our experiences in the living organ donor evaluation of a transgender man receiving gender-affirming hormone therapy. During this process, we encountered unexpected complications due to medical and psychiatric confounders in what had seemed to be an otherwise standard evaluation. While these challenges arose from a variety of factors, three fundamental themes emerged: (a) insufficient knowledge of transgender and gender non-conforming (TGNC) health among *individual* providers; (b) *systemic* limitations in addressing TGNC-specific health concerns; and (c) evolving understanding of TGNC identity in a broader *sociocultural* context. In the context of these themes, we identify and discuss potential medical and psychiatric complexities in the evaluation and management of TGNC living organ donors, ways in which transplant psychiatrists can act as advocates and educators, and recommendations to assist psychiatrist in supporting a TGNC-affirming approach to living organ donor candidates. Table 41.1 includes a non-comprehensive list of terms used throughout this chapter to describe sexual and gender identity. While we have attempted to provide definitions in keeping with the community to which these terms belong, these definitions are continually being revised and updated. To learn more, please visit https://www.hrc.org/resources/glossary-of-terms.

Background and Relevance

Despite recent strides in LGBTQIA+ (see Table 41.1 for definitions) advocacy in healthcare, TGNC individuals continue to experience significant disparities in medical care.

Table 41.1 Selected terms and definitions related to sexual and gender identity

Terms	Definitions
LGBTQIA+	Lesbian, gay, bisexual, transgender, queer or questioning, intersex, asexual; "+" acknowledges existence of other sexual and gender identities not defined by the other letters
Cisgender	An adjective that describes someone whose assigned sex at birth is the same as their emotionally and psychologically perceived gender
Transgender	An adjective that describes someone whose assigned sex at birth is different from their emotionally and psychologically perceived gender
Gender non-conforming	An adjective that describes someone whose gender and/or expression does not align with societal expectations of masculinity and femininity. This person may or may not identify as transgender. Other terms used by various communities to invoke gender non-conformity include "genderqueer," "gender-variant," "two-spirit," and "non-binary"
Transition	The process through which individual takes on a physical form that matches their gender identity, e.g., behavior, dress, hormones, and/or surgery

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TGNC people are less likely than their cisgender counterparts to have health insurance, see a physician regularly, or undergo preventive care [1]. Consequently, they also carry a higher burden of disability and multiple chronic conditions [2, 3]. If a TGNC individual utilizes medical interventions in gender transition, these disparities may cause them to pursue (or resort to) non-regulated services, increasing risk of health complications [4].

Many of these disparities stem from broader sociocultural patterns of discrimination and oppression. Many TGNC individuals endure estrangement from family, mistreatment by employers, landlords, and authorities, and systematic marginalization through economic, educational, and legal inequities. Furthermore, studies indicate that TGNC individuals are more likely to identify as minorities in other demographics (e.g., ethnicity and sexual orientation) and have less educational and economic privilege, increasing the burden of identity-based discrimination and its resulting chronic toxic stressors [2]. Many TGNC people fear for their physical safety due to high rates of sexual assault and violence specifically targeting their gender nonconformity. Participants in one study reported rates of intimate partner violence two to six times higher than cisgender women, with transgender women encountering the highest odds of physical intimate partner violence [5]. Other studies have found a higher prevalence of physical and sexual violence specifically related to perception of transgender identity compared with cisgender lesbian, gay, or bisexual people [6].

Unsurprisingly, this community experiences a disproportionate amount of mental illness. Whether gender dysphoria itself should remain a psychiatric diagnosis is an ongoing debate that is outside the scope of this chapter. However, studies have demonstrated a high prevalence of psychiatric pathology—predominantly depressive and anxiety disorders—in the TGNC population. TGNC people have reported high rates of suicidal ideation and attempts, substance use disorders, and autism spectrum disorders [7]. Children and adolescents are at particularly increased risk, with one study finding a 25-fold higher prevalence of suicidal ideation compared to cisgender peers [8]. Research elucidating the relationship between psychiatric symptoms and gender-affirming medical interventions is limited, though some data indicate that hormone therapy generally improves overall physical as well as mental well-being [9].

In the face of such significant need, transgender-affirming healthcare remains inadequate. Healthcare may be inaccessible, insufficient, or even discriminatory due to limited resources, education, and comfort with providing TGNC-affirming care [9]. Many TGNC patients delay visits to a provider out of fear of being misunderstood. Even when healthcare is accessed, non-inclusive healthcare experiences can worsen physical and mental health due to the stress of discrimination [10]. These concerns are not without evidence: as recently as 2017, 22% of physicians reported discomfort treating transgender patients [11]. Modern structures of healthcare, such as electronic medical records (EMRs), diagnostic imaging, and laboratory reference ranges, may also perpetuate confusion and unintended marginalization in TGNC care [12–15].

Transplant psychiatrists must be knowledgeable about these risk factors and health disparities to facilitate positive and effective evaluation and care, both pre- and post-transplant. However, the published research on TGNC-specific transplant medicine has been limited. The primary focus has been on the increased physiological and psychosocial risks and complications of TGNC organ recipients [16–18], with only very recent literature on the unique care needs of TGNC organ donors [19]. To date, no formal guidelines exist regarding TGNC-specific transplant medicine. Until further studies and evidence emerge, transplant psychiatrists must share and learn from each other's experiences to best serve these vulnerable individuals.

Case History

MK was a 40-year-old man undergoing evaluation to become a living kidney donor. During initial psychosocial assessment, he reported a history of depression, anxiety, and post-traumatic stress disorder (PTSD); however, he was not receiving psychiatric care. Due to concerns for untreated mental illness, he was referred for further psychiatric evaluation.

On psychiatric interview, he shared that he was assigned female at birth and had undergone gender transition 5 years prior to this evaluation. Prior to transition, he experienced panic attacks and depressed mood as a result of the stress of being misgendered and the pressures to conform to societal expectations of femininity. He disclosed a history of superficial cutting as a means of coping. In addition, he described thoughts of being better off dead about 15 years prior to the interview, though denied any suicidal attempts, plans, or intent. He also reported significant alcohol use in an attempt to cope but had attended Alcoholics Anonymous and had significantly decreased his alcohol intake after he was found driving under the influence.

He independently sought treatment with both medications and psychotherapy. He was told he had PTSD "because of all the trauma I went through being transgender." However, on further interview, he denied historical or current symptoms indicative of hyperarousal, persistent avoidance, or intrusive thoughts or re-experiencing. He had intermittently taken various antidepressants that were either ineffective or led to intolerable side effects. Lorazepam had been effective for panic symptoms; however, he experienced withdrawal symptoms when he abruptly discontinued use after being prescribed lorazepam daily by a primary care provider.

MK reported that he had been "emotionally stable" in the 5 years since gender transition, which included a double mastectomy and ongoing testosterone treatments that he received under the care of an endocrinologist. He reported no current or recent symptoms of depression, mania, or psychosis. He acknowledged that a few times a year he had episodes of intense anxiety, but that these were precipitated by specific and acute life or work stressors and were well managed with exercise and reaching out to close friends. He continued to take benzodiazepines on an as-needed basis for severe anxiety but attempted to minimize their use given his previous experience with withdrawal and had made the prescribing physician aware. He also had completely discontinued alcohol use for several months in anticipation of becoming an organ donor. Throughout the interview, he consistently communicated that past symptoms of severe anxiety, depression, and self-injurious behavior had attenuated or completely resolved since obtaining gender-affirming treatment.

The psychiatric impression was that MK did not meet criteria for a current episode of a depressive or anxiety disorder. Additionally, MK's reported historical diagnosis of PTSD was not felt to be an accurate representation of his psychiatric narrative: while he had indeed suffered immensely, he had not experienced specific symptoms of PTSD. Rather, his experience appeared more consistent with gender dysphoria. Although his history of alcohol use and benzodiazepine dependence (both physiological and psychological) raised some concern, past use appeared to be secondary to gender dysphoria and driven by attempts to cope. Furthermore, he demonstrated good insight and was taking appropriate steps to mitigate his risk by abstaining from alcohol and using benzodiazepines sparingly under supervision of a physician. Given his current psychiatric stability but in context of prior history of anxiety, panic attacks, and depression, it was recommended that MK re-establish care with mental health professionals in preparation for the stress of major surgery. MK agreed and expressed intention to re-establish care with a mental health provider.

While he was generally considered an acceptable organ donor, recommendations for risk mitigation differed between specialties. The psychiatric team recommended that MK continue ongoing gender-affirming treatments, including testosterone injections, to ensure continued stability of any symptoms related to gender dysphoria. In contrast, the transplant surgery team recommended testosterone discontinuation for several weeks prior to organ donation to minimize risk of venous thromboembolism (VTE). Risks and benefits from both psychiatric and surgical perspectives were discussed and appreciated by both teams. Multidisciplinary recommendation was to offer a thorough risk–benefit discussion with MK to assist him in making an informed decision regarding whether to continue testosterone during the living donor transplant process.

Donor evaluation was further complicated by discrepancies in health screening. MK was found to have borderline kidney function when calculated using "female" parameters for eGFR, but normal function when recalculated using "male" eGFR standards. The transplant nephrologist, therefore, recommended nuclear GFR testing for a more accurate evaluation of kidney function.

MK's organ donation evaluation stopped at this point for medical reasons unrelated to the complexities described above and the multidisciplinary transplant committee recommended that he re-apply at a later time.

Clinical Questions

1. How can implicit bias affect psychiatric diagnosis, risk stratification, and risk mitigation in TGNC organ donors?
2. How can TGNC status affect medical evaluation of organ donors?
3. How can psychiatrists support TGNC patients undergoing living organ donor evaluation?

Discussion

At time of evaluation, MK was psychiatrically stable with monthly injections of testosterone. However, donor acceptability was questioned due to concern for increased psychiatric risk due to untreated historically diagnosed PTSD and other psychiatric history, risk of VTE post-operatively due to "elective" exogenous testosterone treatment, and inadequate renal function based on "female" eGFR interpretation.

Psychiatric Diagnosis and Risk Stratification

Historical diagnosis of PTSD had raised concern. While data specific to risk stratification of living donors are limited, studies show that people with PTSD report more physical symptoms, higher pain severity, and worse health-related quality of life not only compared to people without PTSD but also compared to people with other anxiety disorders [20]. In MK's case, it was not only his reported PTSD that alarmed the transplant team but also an inappropriate treatment regimen (e.g., benzodiazepine monotherapy).

The psychiatric team was able to determine that his more severe psychopathology was inconsistent with PTSD, thereby alleviating concerns about baseline psychiatric stability and enabling prioritization of other concerns related to continuing gender-affirming care (see section on "Risk Mitigation" below). PTSD as described in the DSM-5 is characterized by exposure to life-threatening harm with development of unwanted intrusive memories or experiences of the event, avoidance of associated stimuli, mood and cognitive alterations, and high arousal and

reactivity [21]. In contrast, gender dysphoria involves a persistent desire to be rid of one's assigned sex and secondary sex characteristics and instead inhabit the physical, psychological, and social role of another gender [21]. Many TGNC individuals are indeed at higher risk of enduring trauma and therefore PTSD [22] due to the violence of discrimination, criminalization, and transphobic hate crimes. However, MK's history of substance use, self-injurious behavior, and prior emotional distress appeared more strongly associated with his gender-related concerns than with an index trauma. Additionally, these symptoms had resolved with gender transition, and he described having full support of his family and peers in his current gender identity. He therefore did not meet criteria for PTSD at the time of evaluation, and the psychiatric team suspected that his previous PTSD diagnosis resulted from unintentional fusion of these concepts.

As demonstrated by this case, providers must take care to avoid conflating the high prevalence of psychiatric disorders in TGNC populations with the distress of gender dysphoria and gender non-conformity itself. Diagnostic clarification required careful communication to avoid either reinforcing this conflation or minimizing the real sociocultural marginalization impacting the mental health of TGNC individuals. The diagnosis "gender dysphoria" in the DSM-5 replaced "gender identity disorder" in the DSM-IV-TR in an effort to destigmatize gender diversity and shift the focus to the distress experienced by TGNC individuals, similarly to the paradigm shift within the Somatic Symptom and Related Disorders [21]. The complexities of this issue contribute to controversy over "gatekeeping" within the medical community: in order to access some gender-affirming care, current standards and guidelines recommend psychiatric evaluation and a diagnosis of "gender dysphoria" [23, 24]. However, some argue that a psychiatric diagnosis should not be universally required in order to obtain gender-affirming medical interventions [25], as it can lead to the presumption that all TGNC people experience some level of impairment, thus propagating stigma rather than counteracting it.

Unconscious bias manifesting as the attribution of psychiatric distress or mental illness to all TGNC individuals can have other unintentional consequences, such as automatic referral for additional psychiatric evaluation of TGNC individuals despite lack of psychiatric risk factors, or even the assumption that all TGNC individuals are at higher psychiatric risk solely on the basis of TGNC identity. While the insights generated from dedicated psychiatric evaluation ultimately enriched understanding of MK's donor candidacy, it is our hope that these insights will arise from the evaluation process at large as the knowledge and understanding of TGNC donor needs continue to grow.

Risk Mitigation

MK's donor candidacy was deferred for other medical reasons. However, had he been accepted as a donor, implicit bias, and limited understanding of TGNC health needs may have continued to affect management choices and clinical outcomes. Transplant surgeons initially recommended that MK discontinue what they presumed were elective testosterone injections due to the increased risk of VTE and cardiac morbidity [26, 27]. In contrast, transplant psychiatrists had advised that testosterone injections be continued through the transplant process, given the integral role that gender-affirming interventions had played in the resolution of his severe psychiatric symptoms.

During multidisciplinary selection discussion, it became clear that both the psychiatry and surgery teams had assumed that their respective recommendations were straightforward and did not need to be explicitly discussed. Rather, the contradictory recommendations came to light only by chance mention within the selection meeting. After gaining more understanding of the VTE risk, the psychiatric team discussed concern for increased risk of psychiatric decompensation both pre- and post-operatively, comparing level of concern to that of discontinuing an antidepressant or other long-term psychotropic. All members of the team appreciated the validity of both major risks. As there was no concern for decisional capacity, the transplant team agreed to prioritize MK's autonomy and provided a risk–benefit discussion to support him in making an informed decision.

Unfortunately, providers may underestimate the importance of gender-affirming treatments, like testosterone injections. Often, providers unintentionally undervalue gender-affirming treatments because the risk is not as evident to them. For example, as in our case, providers may simply not realize that a particular intervention is part of gender-affirming care, as many interventions can be elective treatments in other contexts. Once highlighted and discussed, it is our experience that providers quickly grasp the seriousness of the issue and adjust management plans accordingly.

Regardless of the reason, the perception that gender-affirming interventions are "elective" inadvertently communicates and reinforces a pervasive sociocultural sentiment that underlies transgender stigma: that TGNC identity itself is "elective." Without challenging this fundamental predisposition, it easily follows that discontinuing gender-affirming interventions would be minimally impactful to the donor's overall risk. Beyond the direct impact on risk mitigation strategies, the implication that TGNC identity itself is "elective" can inflict lasting psychological harm to TGNC individuals, and negatively impact the TGNC donor's alliances with medical providers and likelihood to engage with follow-up post-donation.

It is important to note that all providers involved were well intentioned and had made good faith efforts to provide transgender-affirming care (e.g., using correct pronouns in both conversation and in charting, avoiding misgendering language in the physical exam). Yet, the influence and tangible impact of implicit biases and conventions at the individual, systemic, and societal levels are undeniable in MK's case. This experience underscores the importance of maintaining vigilance for subtle or unexpected ways in which TGNC donors may be marginalized or impacted.

Medical Evaluation

There was question as to MK's donor acceptability based on kidney function. His eGFR appeared inadequate when calculated with "female" reference standards, but within a normal range when recalculated within "male" reference standards. Despite extensive discussion, there remained uncertainty regarding which sex-specific interpretation to accept. Ultimately, the nephrology team recommended nuclear GFR testing, a sex-independent measurement, if MK moved forward with evaluation.

Gender transition is not a uniform process: TGNC people undergo variable combinations of social transition, surgical interventions, and hormone therapy (including hormone antagonists and exogenous sex steroids). While not everyone undergoes hormone therapy, those who do experience alterations in physiology may influence laboratory tests. Laboratory values such as hematocrit, liver enzymes, lipid concentrations, and creatinine vary between "male" and "female" due to a variety of factors, with hormonal profile, puberty, muscle mass, and other identity categories, such as race and age contributing to variations [28–30]. No official guidelines have addressed how to approach such laboratory values in the context of hormone treatment, though some recommend using reference values that reflect the hormonal profile of the individual instead of their assigned sex [31].

The EMR has been shown to be another systemic factor confounding accurate assessment of a TGNC patient's health status. Even when the recorded sex is concordant with the patient's identification, preventive healthcare based on binary gender categories (e.g., cervical and breast cancer screening for women, prostate cancer screening for men) may not be accurate, though it is not known how or if exogenous hormones alter these health risks in a clinically significant manner [13, 32]. Likewise, diagnostic results, such as biopsy specimens and radiologic findings, can be more difficult to interpret [15]. While research is generally lacking regarding these discrepancies and outside the clinical realm of psychiatrists, we bring attention to this topic as an example of unanticipated complications that may emerge during transplant evaluations and in which a psychiatrist can act as an advocate and/or a liaison for both transplant team and donor.

Supporting the TGNC Living Organ Donor Candidate

Due to their unique role, transplant psychiatrists have both an opportunity and a duty to be leaders in championing transgender-affirming care throughout organ donor evaluation and care. MK's case highlights just a few examples of the variety of unexpected issues that can arise and complicate the care of TGNC donors, both pre- and post-transplantation.

Proactive and pre-emptive education can raise awareness of concerns regarding common issues in TGNC health, such as confusion between psychiatric distress and disorders and general mental health disparities faced by the TGNC population. An example of such psychoeducation could be through insights on TGNC donor cases that have not been referred for further psychiatric evaluation. However, care must be taken to emphasize that TGNC identity is not an appropriate reason for referral in the absence of other risks or concerns. Additionally, it is our experience that disagreements with other providers' assessment and recommendations are not to be avoided, but rather are positive opportunities to learn from each other and to improve patient care, as in our case above.

A powerful means of implementing gender-affirming care is for transplant psychiatrists to model care for other providers. The discomfort many providers feel in offering TGNC-affirming care may be rooted in fear of appearing, or perhaps feeling, incompetent. As psychiatrists, we are often more comfortable with uncertainty and utilizing curiosity in the service of respecting and validating our patients' unique experiences. Sharing these strategies with providers can help encourage them and manage their concerns. Other important behaviors to model are humility and acknowledging when mistakes are made. While physicians are accustomed to roles of authority and expertise, TGNC individuals are the experts on their experience and often welcome the opportunity to educate providers on TGNC-affirming care. Similarly, it is powerful to model acknowledging one's error or misstep with our TGNC patients and equally important to then learn from the interaction.

In our experience, efforts of individual providers are necessary, but not sufficient to effect lasting positive changes in TGNC care. Transplant psychiatrists involved in administration and policy have a wide range of influence to advocate for TGNC care, which could lead to improved physical and mental health outcomes [33, 34]. In advocating for optimal TGNC-affirming evaluation and care, transplant psychiatrists can advocate not only for the potential donor but for the advancement of transplant medicine itself.

Take Home Points

1. TGNC organ donors face a variety of unexpected complications and disparities, ranging from inaccurate psychiatric diagnosis and risk stratification, suboptimal risk mitigation recommendations, and even inconclusive interpretation of diagnostic information. Psychiatric evaluation of TGNC donors should evaluate concerning symptoms and history in context of stigma, taking care to avoid attributing psychiatric symptoms and gender dysphoria to gender nonconformity itself. While there are some potential health risks associated with hormone therapy and other gender-affirming interventions, providers must ensure that the value of these treatments is appropriately considered and weighed against risks of discontinuation. In advocating for TGNC-affirming approaches to potential organ donors, psychiatrists have the opportunity to educate others and improve TGNC care in transplant medicine.

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