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

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Introduction

While the intent of liver transplantation (LT) is to restore health, vitality, and well-being in the recipient, the surgical process and subsequent recovery can be very stressful. Awareness of mental health issues is key to post-LT care as liver transplant patients have some of the highest rates of psychiatric disorders among all solid organ transplant patients. Additionally, evidence shows that untreated psychiatric disorders can impact post-transplant medical outcomes. As psychiatric and psychological disorders typically cross the pre- to post-transplant periods, early post-transplant identification and treatment will aid in the restoration of stable mental health and ultimately facilitate optimal recovery. Substance use issues, which are common in LT recipients, are most often considered in post-LT studies. These studies provide ample evidence of post-transplant substance use outcomes. Beyond psychiatric disorders, awareness of psychosocial outcomes is critical to understanding overall outcomes for LT recipients. It is essential to consider whether LT recipients recover adequate physical and cognitive functioning, have good quality of life (QOL), and are able to resume normal pre-LT activities and employment. Data on these types of outcomes are limited, and many studies of mental health and psychosocial outcomes include recipient cohorts of a variety of organ types. In this chapter, we will review prospective findings to the extent they are available, although the bulk of the studies are either cross-sectional or retrospective. While we will focus on the post-transplant period, some studies considering pre- to post-transplant comparisons will be used to illustrate changes over time. We will also report on meta-analytic reviews relevant to LT recipient outcomes. Although this chapter covers return to substance use and briefly reviews pharmacotherapy, additional chapters in this book (Chap. 45 Substance Use Disorders and Chap. 42 Psychopharmacology) provide further information on these issues in liver transplant recipients.

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Mental Health and Behavioral Issues

Depression and Anxiety

Mood and anxiety disorders, both new onset and recurrence of preexisting disorders, are common post-LT. Beyond the psychological stressors of the transplant experience, physiological changes and immunosuppression medications can contribute to mood and anxiety symptoms. Depression and anxiety pose significant clinical concern, as up to 30% of LT recipients experience depressive and/or anxious symptoms [1–4]. Post-traumatic stress disorder (PTSD) can occur specifically due to the life-threatening nature of the transplant process and has been identified in greater than 10% of LT patients

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[5]. The development of PTSD in LT recipients is associated with a greater severity of liver disease prior to LT, longer stay in intensive care post-transplant, acute rejection, and post-LT complications [6, 7]. PTSD symptoms are associated with poorer QOL across multiple domains [6, 7]. A history of major depressive episodes, as well as decreased availability of psychosocial support during the transplantation process, can increase risk for developing depressive and anxious symptoms following liver transplant [1, 6]. Screening for mood and anxiety symptoms and specifically PTSD is an essential part of the post-transplant follow-up for early identification and appropriate management. In the special case of patients transplanted for acetaminophen overdose, early involvement of the mental health team during the transplant hospitalization is critical to determining psychiatric care needs and whether inpatient psychiatric hospitalization is indicated (see [8] Crone 2014 for review and treatment recommendations).

Of particular importance, depression is associated with a number of adverse transplant-related outcomes. A meta-analysis of 27 transplant studies including 6 studies of liver transplant patients contributing over 1000 liver transplant subjects found that, regardless of transplant type, depression increased the relative risk of both post-transplant mortality and death-censored graft loss by 65% [9]. Although studies of liver transplant patients appeared to show a lesser relative risk compared to other organ types, this was not significant. The smaller number of studies on anxiety and transplant outcomes showed no effect between anxiety and mortality or morbidities [9].

Individual studies of LT recipients show that the presence of depression after a liver transplant predicts poorer survival in the post-transplant phase. Compared to post-LT patients without depression as measured by the Beck Depression Inventory, patients with high depression scores had a poorer survival rate after the first post-transplant year [1]. Further, depression at 3 months post-liver transplant predicts increased mortality in the long term, even after accounting for other variables which influence transplant survivability including age and recurrence of hepatitis C [2].

In a study of alcoholic liver disease (ALD) LT recipients, those with untreated or undertreated depression had a significantly higher number of encounters with healthcare providers, including hospital readmissions, and thus a higher utilization of healthcare resources, even after adjusting for variables such as MELD score and other donor/recipient characteristics known to influence post-transplant outcomes [10]. At the same time, adequate treatment of depression post-transplant normalizes use of healthcare resources to levels seen in transplant patients without a history of depression either pre- or post-transplant [10]. Thus, depression may be a modifiable risk factor and, not only may adequate treatment improve the patient's mental health outcome, some studies suggest it may reduce the risk of poorer medical outcomes.

Psychotic Disorders

Transplant teams can demonstrate significant reservations about considering patients with schizophrenia as candidates for organ transplantation. Much of this is related to concerns about these patients' ability to adhere to post-transplant immunosuppressive regimens and fears about their susceptibility to steroid-induced neuropsychiatric side effects. Nevertheless, individual case reports and small case series suggest that with good management, patients with serious mental health conditions can have successful outcomes [11]. Because of the rarity of psychotic disorders in the general population and the likely underrepresentation of persons with psychotic disorders referred for liver transplantation, it is difficult to study post-transplant outcomes. Much of available literature relies on mixed organ transplant samples. Despite this limitation, a case series of ten patients with pre-existing psychotic disorders who underwent transplantation, with four receiving livers and one combined kidney-liver, demonstrated that none had episodes of nonadherence to medical or psychiatric treatment after transplant and none suffered graft loss [12]. In another mixed organ transplant series from the Veterans Health Administration, 20 patients with psychotic disorders (schizophrenia or bipolar disorder) who received a transplant had no difference in survival rates over the first 3 years post-transplant compared to patients with no history of mental illness or other nonpsychotic mental illnesses [13].

Although post-transplant liver data are limited, it appears to indicate that persons with psychotic disorders can have comparable medical outcomes to those without psychosis. However, there may be a need to carefully consider potential risk factors pre-transplant and determine whether they can be addressed prior to transplant or managed following transplant. A survey of transplant programs identified 35 cases of patients with psychotic disorders, many of whom were liver transplant patients, and identified potential risk factors affecting post-transplant outcomes. Living alone or being homeless, positive psychotic symptoms 1 year prior to transplant, history of assault, family history of schizophrenia, and borderline or antisocial features appeared to be linked to post-transplant psychiatric complications and nonadherence [14]. In some cases, helping pre-transplant patients to establish stable housing, ongoing mental healthcare, and identifying an available support system may increase chances of successful post-transplant outcome. After transplant, teams should plan on closer follow-up for patients with psychotic disorders and make efforts to collaborate with patients' mental health providers and supports.

Despite concerns about the risk of administering steroids to patients with psychotic disorders, there is a lack of prospective studies identifying a clear increased risk of neuropsychiatric complications. While higher steroid doses

contribute to increased risk for all patients, there is equivocal evidence as to whether patients with premorbid psychiatric disorders are at increased risk [15–17]. However, clinical experience reveals that some patients are highly sensitive to steroids and have repeated history of developing serious neuropsychiatric side effects. For such patients, prophylactic use of antipsychotic agents such as olanzapine or lithium may prove helpful [18].

Substance Use Disorders

Alcohol Use

Alcohol and other substance use disorders are common among LT recipients as excess alcohol and viral hepatitis incurred from illicit drug use are more likely to result in the need for LT than for other types of transplantation. Preparation for post-LT addiction stability begins during the pre-LT phase as potential candidates are carefully evaluated and addiction rehabilitation may be required to improve abstinence stability. However, because substance use disorders are chronic medical illnesses requiring long-term management, it should not be assumed that transplantation cures an addiction or that addiction issues are no longer relevant following transplantation. To the contrary, rates of alcohol use for ALD LT recipients are significant (see below), and optimal treatment planning should encompass a longitudinal perspective for which LT is not the terminus. Studies examining the timing of addiction treatment demonstrate that LT recipients with alcohol use disorders who receive addiction treatment both before *and after* LT have the lowest relapse rates compared to those who receive addiction treatment only prior to LT or not at all [19, 20]. At one LT center, the introduction of an embedded alcohol addiction unit that provided intensive treatment and monitoring across the pre- to post-LT period was associated with reduced post-LT relapse rates compared to those patients not in the program (16.4% vs. 35.1%) and an improvement in the 5-year mortality rate [20]. Ongoing addiction treatment is especially pertinent post-LT as the early recovery period can be very stressful and physical stress and emotional distress during this period are associated with increased risk for alcohol relapse [21]. In one study, the use of an "alcohol contract" signed prior to transplant confirming a commitment to abstinence following transplant and agreement to attend addiction rehabilitation did not reduce the rates or amounts of alcohol use following LT [22].

For these reasons, transplant clinicians should monitor for alcohol use early on and reengage recipients in psychiatric and/or addiction counseling as indicated. Optimally the recipient would resume addiction counseling therapy early post-LT as a preventative measure. However, this can be challenging as patients have many competing medical priorities and may not feel fully recovered in the early postoperative period. Among these priorities, they may not see the need or value in resuming counseling. This is especially true if the patient was resistant to addiction counseling prior to LT. The intensity of the post-LT counseling will depend on where the patient is in their recovery treatment plan. Some may only require maintenance therapy, while others with short sobriety and little pre-LT counseling who proceeded to transplantation quickly due to the urgency of their condition may require intensive counseling post-LT. Motivational interviewing may facilitate reengagement in addiction counseling. Although most transplant programs do not have embedded addiction clinicians, if psychiatric consultants are available in the outpatient transplant clinic, these specialists may be able to see the patient during the early postoperative transplant clinic appointments and bridge the eventual transition back to community addiction services. Psychiatric consultation can provide a thorough post-LT reevaluation of the patient's recovery stability, understanding of his/her addiction, commitment to lifelong abstinence, family and social support for continued abstinence, and the presence of other psychiatric disorders.

Monitoring of alcohol use is commonly done through self-report during transplant team clinic appointments [23–25]. Maintaining an open, nonjudgmental approach during the interview can facilitate disclosure. In one study, three methods were used to monitor alcohol use post-LT (addiction specialist interview, hepatologist interview, and the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C)). In patients who had not yet developed liver test abnormalities due to their drinking, the addiction specialist not only identified more patients drinking alcohol but also uncovered significantly higher consumption amounts than were discovered by the hepatologist interview or AUDIT-C [26]. The authors hypothesized this was in part due to the focus of the hepatologist interview more on transplant specific issues but also perhaps due to denial and shame on the part of the patient [26]. It was also suggested that the addiction specialist's expertise and the provision of confidentially without sharing information with the transplant program facilitated more open disclosure. However, whether transplant teams would agree to this arrangement for post-LT follow-up is unknown [27]. Following LT, while some disincentives to reveal alcohol use prior to transplant (e.g., fear of removal from transplant waitlist) may no longer exist, continued psychological obstacles of shame, guilt, and denial can make revelation of alcohol consumption to transplant clinicians difficult. Some patients may be concerned about how the transplant team will respond to their resumption of alcohol use and may need to know that the transplant team will not abandon them. Nevertheless, transplant teams should be careful not to condone or dismiss small amounts of alcohol use as these can quickly lead to a

relapse as noted below. Although we found that our transplant clinical interviews with a psychiatrist who was part of the team at the University of Pittsburgh revealed the most episodes of post-LT alcohol use in comparison to other monitoring methods, using a combination of methods provides the greatest yield [28]. One study conducted in an LT clinic found among several biomarkers, urinary ethyl glucuronide was the strongest marker of alcohol consumption and provided a more accurate prediction rate of alcohol consumption than the AUDIT-C or carbohydrate-deficient transferrin [23]. Blood alcohol level is the most commonly used biomarker for monitoring alcohol use due to widespread availability of this test. In some cases, a review of liver enzymes and biopsy results along with a candid discussion with the LT recipient can provide opportunity to overcome denial of the damaging consequences of their alcohol use [29].

One of the most highly investigated outcomes for LT recipients is alcohol use after LT. A meta-analysis that included 50 LT studies of patients who received LT for ALD showed the cumulative incidence rate of any alcohol use was 5.6% of patients per year and heavy use was 2.5% per year [25]. Some studies identified return to alcohol use beginning many years after LT, suggesting that relapse rates are unlikely to level off over time [25]. While these rates may appear low cumulatively, by 10 years, over 50% will have had any alcohol, and 25% will have engaged in heavy drinking. Among 12 possible psychosocial risk factors for alcohol use (e.g., demographics and pre-LT characteristics), only 3 variables were significantly associated with relapse: poorer social support, family history of alcohol abuse/dependence, and pre-LT abstinence of less than 6 months [25]. However, a 6-month cut point for pre-LT sobriety, although used in clinical practice, is an arbitrary value. Cumulatively each additional month sober confers less risk to drink [30]. A study using cluster analysis of the DSM-IV criteria for alcohol abuse/dependence disorders found whereas the patient's subcategory of alcohol dependence identified by the cluster analysis was unimportant for risk stratification with respect to post-LT relapse, it was the diagnosis of alcohol dependence compared to alcohol abuse that most accurately predicted relapse [31].

A prospective study of 208 ALD LT recipients found that, of those who drank, 40% (20% of the total cohort) progressed to a binge episode (6 drinks or more on a single occasion)—many within 6 months of their first drink [30]. This suggests that any exposure to alcohol is dangerous with the recipient quickly losing control over their consumption. In addition, moderate to heavy persisting patterns of alcohol consumption were identified in 20% of the cohort. These recipients tended to resume alcohol early postoperatively within the first months following LT. They were also significantly more likely to experience poorer early outcomes, with more frequent evidence of acute rejection or steatohepatitis on biopsy, and higher likelihood of graft failure or death from recurrent ALD [21]. Those most likely to drink in these early problematic patterns also reported experiencing more stress, more pain, and less vitality, and they felt their health was worse after LT.

Overall patients transplanted for ALD as a group have survival comparable or better than patients transplanted for other types of liver diseases. However, not surprisingly, those who relapse, especially those who return to abusive drinking, have poorer 10-year survival rates (45.1% vs. 85.5%) [32] and decreased survival related to both recurrent ALD [33] and acute alcoholic hepatitis [34]. A meta-analysis of the impact of alcohol use on outcomes showed that, compared to those who did not drink, those who drank had nearly 4 times higher odds of graft steatosis, had 7 times higher odds of graft fibrosis, were 4.6 times more likely to develop worse histological findings on biopsy, and were 3.7 times more likely to die by 10 years [35].

Marijuana Use

In a recent survey, only 43% of liver transplant programs considered pre-LT marijuana use an absolute contraindication to transplantation [36], and thus LT programs may not require discontinuation as a prerequisite for transplantation. In addition, some states have passed laws protecting organ transplantation for medicinal marijuana users. For example, in 2015, the state of California passed the Medical Cannabis Organ Transplant Act prohibiting discrimination against patients using legally prescribed medical cannabis in the organ transplant process, unless a surgeon or other physician has determined that medical cannabis use is clinically significant to the transplant process. Consequently LT programs may be caring for recipients who are using marijuana following LT. Specific rates of post-LT marijuana use have not been investigated, and there are no large studies of marijuana use in transplant recipients to examine the actual impact on outcomes. However, a number of case reports of fungal lung infections in cannabis smoking transplant recipients indicate that smoked cannabis may expose immunocompromised patients to infectious agents [37, 38]. New evidence suggests inhaled/vaporized marijuana may be the source of these infections [39]. More worrisome is the fact that a recent study of medicinal dispensaries cultured multiple fungi (*Aspergillus* and *Penicillium* spp.) and bacteria (*Klebsiella*, *Enterobacter*, *Salmonella*, and *Bacillus*) from dispensary cannabis samples [39]. This underscores the fact that viable infectious organisms can be recovered from cannabis, even medicinal grade marijuana. Patients and clinicians are likely unaware that medicinal dispensaries do not have governmental quality or purity oversight [40], which raises risks specifically for immunocompromised patients. It is notable that clinical studies demonstrating the medicinal benefits of

cannabinoids used synthetic pharmaceutical grade cannabinoids, not smoked marijuana [41]. Additionally the Institute of Medicine maintains there is no medicinal role for smoked marijuana and no other medication is smoked [41]. This suggests if medicinal cannabinoids are to be used, the best choice, to avoid these risks, would be the cannabinoid medications approved by the FDA (dronabinol and nabilone).

Other Non-alcohol Substance Use

While there is a limited literature on LT patients with other nonalcohol substance use disorders, the same post-LT clinical management and treatment as discussed above with alcohol use disorders would similarly apply to LT recipients with other substance use disorders. A few studies have addressed substance use in LT recipients who had comorbid alcohol and substance use. One study of ALD LT recipients with a median follow-up of 41 months found that 47% additionally used illicit drugs prior to LT with 17.2% of the total group using substances after LT [42]. Another study of LT patients with a pre-LT history of polysubstance use found that not only did polysubstance users have a higher rate of post-LT alcohol use but the majority also had ongoing substance use following LT [43]. The majority of post-LT substance use was marijuana, with pre-LT substance use being the only independent predictor of substance use after LT [42]. A meta-analysis including 4 studies of illicit drug use in LT recipients showed illicit drug relapse among all organ types averaged 3.7 cases per 100 patients per year, with a significantly lower rate in liver versus other recipients (1.9 vs. 6.1 cases) [25].

Tobacco Use

While there is no doubt of the well-established negative effect of tobacco use on post-LT outcomes, only a quarter of LT programs consider tobacco use to be an absolute contraindication to transplantation [36]. Both current and prior smokers have an increased risk of post-LT morbidity, including biliary and vascular complications, cardiovascular disease, increased rates of de novo cancer as well as recurrence of hepatocellular carcinoma, and poorer graft and patient survival [44–46]. Efforts toward tobacco use cessation, for both smoked and chewed tobacco, should be vigorously pursued. Unfortunately, many LT recipients who stopped smoking as a condition for transplant resume afterwards, ≥60% in two studies [47, 48]. In addition, a meta-analysis found that of patients with a prior substance use history, LT cohorts had the highest prevalence rate of post-LT tobacco use, with a rate of nearly 10% per year [25] as compared to 3.4% per year for all solid-organ transplant recipients [49].

Not surprisingly, those who resumed smoking had a shorter period of abstinence pre-LT and a longer history of smoking [48]. In addition those who smoked were also more likely to drink alcohol post-LT (OR, 1.79; 95% CI, 0.75–4.27; $P = 0.026$) [48]. Resumption of smoking can occur very early on within the first months after LT and can quickly increase in amount and frequency of use [47]. Thus, close monitoring, assessment of relapse risk, and assistance with smoking cessation are essential parts of the post-LT clinical care. In addition to pharmacotherapies that transplant clinicians/psychiatrists can prescribe (see Chap. 42), many states have smokers assistance programs including free nicotine replacement therapies and health coaches. The American Lung Association has a web-based smoking cessation program with a number of assistance options (e.g., American Lung Association's Freedom From Smoking Online). Similar to alcohol and other substance use, random biochemical monitoring for nicotine and cotinine is suggested to supplement self-reported use [48].

Methadone-Maintained LT Recipients

For patients on methadone maintenance therapy (MMT), higher doses may be required after LT when hepatic metabolic function becomes normalized. In one study, the post-LT dose of methadone was increased an average of 60% from baseline [50]. LT teams often use methadone as the postoperative pain medication to avoid patient exposure to other narcotics that could precipitate relapse. MMT programs do not treat chronic pain, but following postoperative recovery when the patient transitions back to the MMT program, a methadone increase can be justified to provide adequate coverage for opioid addiction with improved liver functioning. Coordination of such dose increases with the MMT program is required so as not to interfere with the agreed upon treatment plan. Although MMT patients may see LT as a new chapter in their life and wish to discontinue methadone, in the stressful early recovery period, this should not be undertaken, as it can increase the risk for relapse. In a study of 36 MMT LT recipients, 4 (11%) relapsed to heroin, and 2 had their methadone increased to address their addiction [51]. Relapses were brief and did not appear to affect outcomes [51].

Although several small cohort studies have reported similar medical outcomes for MMT LT recipients compared to non-MMT recipients [51], several other studies suggest these patients may have higher perioperative morbidity, longer hospital stays, and more severe recurrent hepatitis C infections [50, 52].

Treatment Adherence

Lifelong adherence to medical treatment and self-management is crucial to successful liver transplantation. Unfortunately, nonadherence is emerging as a major cause of transplant patient morbidity and graft loss. Adherence includes perpetual daily self-administration of at least one

antirejection medication, frequent self-monitoring (e.g., vital signs, weight) and reporting of symptoms as indicated to the transplant team, as well as follow-up appointments, laboratory testing, and general self-care. The concept of adherence also includes following prescribed diet and exercise regimens. A meta-analysis of adherence behaviors across all organ types showed that liver recipients had some of the lowest rates of nonadherence when compared to kidney, heart, pancreas, and lung recipients including the lowest rates of medication nonadherence; 6.7 cases per 100 persons per year of follow-up (PPY) compared to 14.5 PPY for heart and 35.6 PPY for kidney recipients [49]. Liver recipients were the least likely to be nonadherent to an exercise regimen and interestingly had similar, not higher, rates of substance use including alcohol, tobacco, and illicit drugs compared to other organ recipients [49].

While many liver transplant patients have a history of medical illness from which a pattern of adherence (or nonadherence) can be established, it remains difficult to predict based on pre-transplant evaluation which patients will have nonadherence behaviors and resulting complications post-transplant. Across all organ types, in addition to pre-transplant nonadherent behaviors, depression and anxiety, substance use, poor support, low health literacy, lower socioeconomic status, and greater complexity of the treatment regimen have been associated with poorer adherence following transplant [53, 54]. A single study comparing adherence rates between kidney and liver recipients showed symptoms of depression were associated with lower rates of immunosuppressive medication adherence in renal but not liver transplant recipients [55]. However, another study examining treated versus untreated depression in LT recipients found higher rates of acute rejection in the untreated depressed group suggesting acute rejection may have been mediated by depression-related nonadherence [56].

Transplant recipients tend to underestimate their level of nonadherence to medications [57]. Given that self-report of adherence is not always reliable, other methods are sometimes used to monitor adherence. Most commonly, immunosuppressive medication blood levels are used. A higher variability in successive blood levels between blood draws indicates a non-steady state of immunosuppression coverage in the transplant recipient and can be used as a marker for nonadherence and can also be used as a predictor of graft rejection [58].

In a study of LT recipients' treatment, knowledge of prescribed medication regimen (defined as a patient's ability to describe each medication's indication and dosing schedule) showed factors correlated with lower treatment knowledge were lower income, less time since transplant, a higher number of medications in the regimen, and low health literacy. A higher level of treatment knowledge was associated with fewer rehospitalizations after transplant [59]. These findings highlight the importance of ongoing assessment of LT recipients' understanding of prescribed medication regimen as well as reeducation around the time of changes in the regimen. Possible measures toward increasing treatment knowledge would be complete medication reconciliation at every appointment, counseling with a pharmacist about medications at every refill visit and frequently providing the most up-to-date medication list for patients. The use of drug-reminder (blister pack) packaging was also shown to improve medication adherence and could be recommended and facilitated by providers for those patients at high risk of nonadherence [60].

A systematic review including three studies of LT recipients examined interventions intended to improve medication adherence [61]. A combination of cognitive, educational, counseling, and psychological interventions at the patient, provider, and system levels were more likely to be effective than single interventions [61]. Improving patient education and encouraging an active role in treatment may improve patient adherence [62]. In addition to education assessment of barriers, involving the patient in the selection of strategies to improve adherence, and allowing them with support to make their own decisions about their care, is most likely to produce the best results [63, 64]. Motivational interviewing or problem-solving therapies can be used to address barriers to adherence. However, because adherence tends to deteriorate over time [53], ongoing assessment of adherence behaviors with booster intervention sessions will likely be required over the long term.

Cognitive Recovery Post-Liver Transplantation

Cognitive impairment is common prior to LT due to physiological consequences of end-stage liver disease, specifically hepatic encephalopathy (HE), but comorbid diseases (e.g., diabetes, vascular disease), prior trauma, or the effects of substance use (e.g., alcohol or drugs) may also contribute to pre-LT deficits. Hepatic encephalopathy is common pre-LT with 70% of patients demonstrating subtle symptoms, but nearly 50% having overt motor and neuropsychological impairment [65]. While successful treatment of HE improves cognitive functioning, several studies show even one episode of overt HE can result in persistent cognitive deficits in the areas of working memory, response inhibition, and learning [66, 67]. Thus, the reversibility of cognitive impairment or the potential for worsening cognitive symptoms following LT depends on a variety of factors influencing the vulnerability of the brain including age, prior central nervous system damage, severity of pre-LT hepatic encephalopathy, homeostatic reserve of the brain, and the ability to withstand transplant-related stressors (e.g., hemodynamic changes, operative stresses, immunosuppressive medications).

The incidence of postoperative cognitive dysfunction, defined as a "more than expected" postoperative deterioration in cognitive areas such as short-term and long-term memory, consciousness, mood, and circadian rhythm, is estimated at 44% [68]. It is associated with several factors including the severity of hepatic failure before transplantation, alcohol abuse, use of immunosuppressants and corticosteroids, neuroinflammation, ischemia-reperfusion syndrome, and postoperative infections [68]. In terms of long-term cognitive recovery, the literature indicates that improvement in pre-LT cognitive deficits is possible, though complete resolution of these deficits may not be. Moreover, pre-LT cognitive status based largely on the presence of HE may play a significant role in post-LT cognitive outcomes. In a prospective study of 66 patients who underwent neuropsychological testing before and 6 months after LT, the percentage of patients who exhibited cognitive impairment as determined by psychometric hepatic encephalopathy scores was significantly reduced from 67% pre-transplant to 21% post-transplant. However, the researchers also found that patients with pre-LT cognitive impairment performed worst in almost all areas of cognitive testing except for block design and line tracing after LT compared to the cognitively unimpaired pre-transplant patients [69].

The connection between post-LT cognitive recovery and severity of pre-transplant HE was explored by comparing the post-LT cognitive functioning of three groups: those with HE pre-LT, those without HE pre-LT, and matched controls. Compared to the control group and those without HE pre-LT, patients who had HE pre-LT demonstrated significantly worse performance 18 months post-LT on several domains of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) exam, Psychometric Hepatic Encephalopathy Score subtests, and critical flicker frequency test [70]. Additionally, a study involving 65 LT recipients found that 1-year post-transplant EEG normalization was similar between patients with and without history of overt HE. On neuropsychological testing though, patients with a history of overt HE showed the most improvement in cognitive functioning from their pre-transplant baseline but continued to perform worse on cognitive testing compared to those without a history of overt HE. In terms of predictors of cognitive dysfunction post-transplantation, only age was found to be significant predictor [71].

While most studies show global cognitive improvement, at least one study found discrepancies in specific areas of cognitive recovery. In a prospective study, patients with prior minimal HE failed to reach the functional level of controls on visuomotor performance testing conducted on average 21 months post-LT. In fact, 7 of the 14 patients with prior minimal HE showed no improvement in this cognitive area [72]. Knowledge that post-LT patients may have continued cognitive impairment should be shared with patients and their support system prior to LT to provide them with reasonable expectations. It may also suggest the need for continued engagement of patient's support system at post-LT follow-up, especially when significant medication adjustments or patient education need to be provided. In some cases, patients may also be considered for cognitive rehabilitation to help optimize their functioning post-LT.

Pharmacologic Considerations

In addition to psychotherapy (see Chap. 43), pharmacotherapy is an essential treatment component in the psychiatric care of LT recipients. Here we will briefly touch on liver-specific metabolic issues and refer the reader to Chap. 42 on psychopharmacology in transplant patients. Psychotropic medications are often inadvertently discontinued in the early post-LT recovery period due to oversight, lack of awareness of the need of ongoing treatment by nonpsychiatric providers, or concern over the patients' medical fragility and the potential risks of psychotropic medications. Although the treatment of transplant recipients can be complicated, withholding needed psychotropic medications can lead to onset/recurrence of psychiatric disorders and, as noted above, result in poorer patient outcomes.

As most psychotropic medications are hepatically metabolized, it is critical to establish the restoration of normal organ functioning during the early recovery period after LT. For the majority of recipients, the newly transplanted organ functions immediately, so that normal physiological parameters are quickly restored and pharmacokinetic abnormalities resolve. However delayed graft function (DGF) is the most common allograft complication affecting pharmacokinetics in the immediate post-transplantation period. DGF occurs in 10%–25% of liver recipients but can reach 50% if marginal organs are counted [73, 74]. Although the pharmacokinetics of psychotropic medications in DGF have not been examined, studies of immunosuppressive medication metabolism suggest recipients with DGF may require one-half of the typical dose [75, 76]. Acute cellular rejection with resulting transient graft dysfunction occurs in 20–70% of LT recipients, typically within the first 3 weeks post-transplant. Most cases are effectively treated, do not lead to clinically significant alteration in liver histology or architecture [77], and require no specific change to psychotropic dosages. However, chronic rejection that evolves over time in 5%–10% of liver recipients eventually leads to chronic liver dysfunction and loss of metabolic capacity [77]. In these cases, precautions similar to pre-LT cirrhosis should be taken.

In addition to graft status, the patient's total physiologic status should be considered in drug choice and dosing. Resolving hepatorenal syndrome, lingering ascites, or liver congestion can affect pharmacokinetics. In the absence of

these issues within the first month following LT, patients with stable liver functioning can have the clearance and steady-state volume of distribution of drugs similar to healthy volunteers [75]. Following the surgical recovery and resolution of immediate postoperative complications (e.g., sedation, intestinal paralysis), patients can be treated with normal therapeutic dosing. An additional consideration is whether the pre-LT dosing of a psychotropic medication may require an increase to accommodate the improved functioning of the liver.

Post-transplant Quality of Life and Employment

Improving mental health outcomes requires not only understanding and lessening the impact of mental health disorders on transplant outcomes but also an awareness of the role of quality of life (QOL) and functional status. Ideally, following a period of postoperative recovery, rehabilitation, and adjustment to a new self-care regimen, patients would resume their roles within their family, community, and workplace. There is substantial evidence that QOL across many domains improves pre- to post-transplant [78]. Unfortunately, liver transplant recipients do not achieve the QOL of healthy controls [78]. The degree of improvement appears largely driven by the severity of illness at the point of transplant rather than the primary liver disease [78, 79]. While LT recipients' QOL can dramatically improve in the early period following transplant and largely be sustained over a decade following transplant, there are gradual and consistent decrements in QOL over time [80]. Additionally, those with combined ALD and hepatitis C reported the worst quality of life compared to others and had the greatest rate of physical decline compared to those with either etiology alone or other etiologies of liver disease [80]. Whether these outcomes will improve with the newer antiviral therapies is yet unknown.

Following LT, employment rates are significantly lower than the general population. Across studies, rates range from 22% to 60%, with an average employment rate of 37% from studies published after 2000 [81, 82]. A considerable portion of recipients pursue early retirement, but this does not fully explain the low rates among younger patients. Even compared against renal transplant recipients, rates are below expected, and efforts have been made to understand what factors influence post-LT employment [82, 83]. Results from several studies have shown that the most consistent factors associated with employment include pre-LT employment, younger age (18–40), higher education, functional/health status, and subjective work ability [82, 84, 85]. Although some report higher employment rates with males, it is unclear if this is due to females being more likely to be doing unsalaried work as homemakers [82, 84]. Racial differences have also been suggested, but have not been adequately studied [84]. Interestingly, severity of pre-LT liver disease as measured by MELD has not seemed to influence post-LT employment [82]. A recent study looking at pre-LT hepatic encephalopathy suggested similar findings [86]. Even if there is a desire to return to work, patients may not be able to return to their pre-LT level of employment [87]. For others, fear of losing health insurance coverage tied to disability benefits dissuades efforts at seeking employment [82, 84].

Existing studies of post-LT employment are mostly cross-sectional and descriptive in nature. There is also considerable heterogeneity among studies regarding the definition of employment, approaches to assessing work experience, the time point of assessment, as well as other factors, making broad conclusions about findings challenging [82, 84]. Nonetheless, some studies bear greater attention due to large sample size or use of a control group [81, 85, 88]. Huda et al. obtained United Network for Organ Sharing (UNOS) employment data on recipients within 24 months after LT between 2002 and 2008. Of approximately 22,000 patients, only 24% were employed within 24 months after LT, and those employed had significantly better functional status than those not employed [81]. Another study examined UNOS data on approximately 13,000 recipients 5 years after LT and divided those employed based on level of continuity of post-LT employment and timing of return to work [85]. Lower socioeconomic status, higher local unemployment rates, and post-transplant complications and comorbidities were predictors of less than continuous post-LT employment. Of note, nearly half who resumed work within 2 years after LT later became unemployed [85]. A Finnish study utilized an age and gender-standardized community-based control group for comparison against 353 LT recipients [88]. Assessments included health-related quality of life (HRQOL), which was slightly lower than the control group. Recipients who were employed reported significantly better HRQOL compared to those unemployed. This finding is similar to an earlier study of 308 LT recipients that found better SF-36 scores on role physical and physical functioning, indicating less limitation in these areas due to health problems, were independently associated with post-LT employment [89]. Beyond a positive impact of physical well-being on post-LT employment, separate studies have reported a negative impact from depression [90, 91].

A recent review of post-LT employment studies stressed the need for transplant programs and clinical studies to incorporate efforts at providing job rehabilitation post-LT [82]. Additionally, as a consistent finding across studies is the positive influence of pre-LT employment, it was also recommended that transplant candidates be provided with assistance in maintaining employment. Reducing pre-LT disability by managing minimal HE, maintaining mobility, and helping to plan for work adjustments was encouraged.

Post-LT, physical rehabilitation, encouragement, self-efficacy measures, and depression management were recommended to facilitate recipients' return to employment [82]. Although social functioning is another factor contributing to post-LT QOL, studies are lacking. Usually mentioned in employment or QOL studies, there is indication that social functioning may not improve significantly post-LT [88, 91, 92].

Conclusions

Liver transplant recipients represent a complex patient population who among solid organ recipients have some of the highest prevalences of mental health disorders. Patients with mental health disorders can successfully undergo transplantation and have good outcomes, especially if they are identified and adequately psychiatrically managed. Those with serious mental health disorders can also achieve good outcomes, if expert management, good caregiver support, and collaboration with the transplant team are established. Substance use, especially alcohol and tobacco use, and nonadherence to medications continue to represent significant issues following LT. Clinicians should consistently monitor for these behaviors, including self-report and biochemical screening for substances and immunosuppressive medication levels. With all mental health disorders, continuity of psychiatric care from pre- to post-LT is essential for optimal mental health and medical outcomes to be achieved. In the early postoperative period assessment, identification and treatment of emerging psychiatric and behavioral issues are critical. Reinstitution and adjustment of psychotropic medications may be indicated. If nonadherent behaviors are identified, the use of psychotherapeutic techniques including education, motivation, and problem-solving may alleviate poor adherence behaviors. Beyond mental health outcomes, whether strategies to improve quality of life and social reintegration can additionally improve medical outcomes can be considered, but studies of such interventions are lacking.

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