

# The psychiatrist's role in liver transplantation

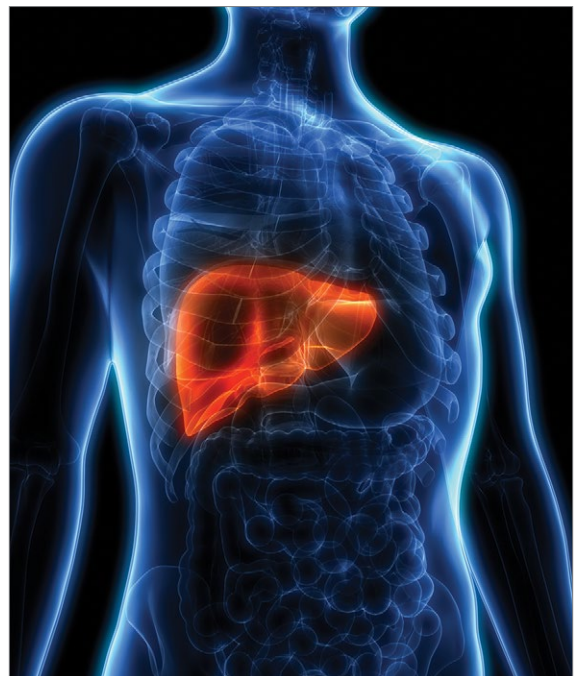
## A thorough pre-transplant assessment and careful follow-up can maximize patient outcomes

Since the first liver transplant (LT) was performed in 1963 by Starzl et al, there have been considerable advances in the field, with improvements in post-transplant survival.<sup>1</sup> There are multiple indications for LT, including acute liver failure and index complications of cirrhosis such as ascites, encephalopathy, and hepatopulmonary syndrome.<sup>2</sup> Once a patient develops one of these conditions, he/she is evaluated for LT, even as the complications of liver failure are being managed.

Although the number of LTs has risen, the demand for transplant continues to exceed availability. In 2015, chronic liver disease and cirrhosis was the 12th leading cause of death in the United States.<sup>3</sup> In 2016, approximately 50% of waitlisted candidates received a transplant.<sup>4</sup> There is also a donor shortage. In part, this shortage may be due to longer life spans and the subsequent increase in the age of the potential donor.<sup>5</sup> In light of this shortage and increased demand, the pre-LT workup is comprehensive. The pre-transplant assessment typically consists of cardiology, surgery, hepatology, and psychosocial evaluations, and hence requires a team of experts to determine who is an ideal candidate for transplant.

Psychiatrists play a key role in the pre-transplant psychosocial evaluations. This article describes the elements of these evaluations, and what psychiatrists can do to help patients both before and after they undergo LT.

continued



MAGIC MINE

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## Liver transplantation

### Clinical Point

Studies have found that patients with higher education are more at risk for post-transplant medication nonadherence

## Elements of the pre-transplant evaluation

The psychosocial evaluation is a critical component of the pre-transplant assessment. As part of the evaluation, patients are screened for psychosocial limitations that may complicate transplantation, such as demonstrated noncompliance, ongoing alcohol or drug use, and lack of social support (*Table 1, page 11*). Other goals of the psychosocial evaluation are to identify in the pre-transplant period patients with possible risk factors, such as substance use or psychiatric disorders, and develop treatment plans to optimize transplant outcomes (*Table 2, page 13*). There are relative contraindications to LT (*Table 3, page 14*) but no absolute psychiatric contraindications, according to the 2013 American Association for the Study of Liver Diseases (AASLD) practice guideline for transplantation.<sup>2</sup>

**Adherence.** The 2013 AASLD practice guideline states that patients “should be evaluated for and meet reasonable expectations for adherence to medical directives and mental health stability as determined by the psychosocial evaluation.”<sup>2</sup> In the transplant setting, adherence is complex. It requires compliance with complicated medication regimens and laboratory testing, frequent follow-up appointments, and close, prompt communication of concerns to the health care team. Patient adherence to medication regimens plays an important role in transplant outcomes.<sup>8</sup> In fact, in patients who have undergone renal transplant, nonadherence to therapy is considered the leading cause of avoidable graft failure.<sup>9</sup>

A retrospective study of adult LT recipients found that pre-transplant chart evidence of nonadherence, such as missed laboratory testing and clinic visits, was a significant predictor of post-transplant nonadherence with immunosuppressant therapy. Pre-transplant unemployment status and a history of substance abuse also were associated with nonadherence.<sup>9</sup>

Dobbels et al<sup>10</sup> found that patients with a self-reported history of pre-transplant nonadherence had a higher risk of being nonadherent with their immunosuppressive

therapy after transplant (odds ratio [OR]: 7.9). Their self-report adherence questionnaire included questions that addressed pre-transplant smoking status, alcohol use, and adherence with medication. In this prospective study, researchers also found that patients with a low “conscientiousness” score were at a higher risk for post-transplant medication nonadherence (OR: 0.8).

Studies have also found that patients with higher education are more at risk for post-transplant medication nonadherence. Higher education may be associated with higher employment status resulting in a busier lifestyle, a known risk factor that may prevent patients from regular medication adherence.<sup>11,12</sup> Alternatively, it is possible that higher educated patients are “decisive” nonadherers who prefer independent decision-making regarding their disease and treatment.<sup>13</sup>

**Substance use.** The 2013 AASLD practice guideline lists “ongoing alcohol or illicit substance abuse” as one of the contraindications to LT.<sup>2</sup> In guidelines from the Austrian Society for Gastroenterology and Hepatology, Graziadei et al<sup>14</sup> listed “alcohol addiction without motivation for alcohol abstinence and untreated/ongoing substance abuse” as absolute contraindications and “untreated alcohol abuse and other drug-related addiction” as relative contraindications. Hence, the pre-transplant evaluation should include a thorough substance use history, including duration, amount, previous attempts to quit, and motivation for abstinence.

Substance use history is especially important because alcoholic liver disease is the second most common indication for LT.<sup>2</sup> Most LT programs require 6 months of abstinence before a patient can be considered for transplant.<sup>15</sup> The 6-month period was based on studies demonstrating that pre-transplant abstinence from alcohol for <6 months is a risk factor for relapse.<sup>15</sup> However, this guideline remains controversial because the transplant referral and workup may be delayed as the patient’s liver disease worsens. Other risk factors for substance relapse should also be taken into consideration, such as depression,



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**Table 1**

## Practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation

Recommendation	Grading of evidence (strength and quality)
#26: Patients should be evaluated for and meet reasonable expectations for adherence to medical directives and mental health stability as determined by the psychosocial evaluation	Strong recommendation High quality
#27: Methadone-maintained patients should not be denied transplantation based on methadone use alone, and expectations of methadone reduction or discontinuation should not be a requirement for transplant listing	Strong recommendation Moderate quality
#28: Patients should have adequate social/caregiver support to provide the necessary assistance both while waitlisted and until independently functioning in the postoperative period	Strong recommendation Moderate quality

**Source:** Reference 2

### Clinical Point

**Evaluation for transplant should not be delayed until a patient has achieved 6 months of abstinence from alcohol**

personality disorders, lack of social support, severity of alcohol use, and family history of alcoholism.<sup>16</sup> Lee and Leggio<sup>16</sup> developed the Sustained Alcohol Use Post-Liver Transplant (SALT) score to identify patients who were at risk for sustained alcohol use posttransplant. The 4 SALT criteria are:

- >10 drinks per day at initial hospitalization (+4 points)
- multiple prior rehabilitation attempts (+4 points)
- prior alcohol-related legal issues (+2 points), and
- prior illicit substance abuse (+1 point).

A SALT score can range from 0 to 11. Lee et al<sup>17</sup> found a SALT score  $\geq 5$  had a 25% positive predictive value (95% confidence interval [CI]: 10% to 47%) and a SALT score of  $< 5$  had a 95% negative predictive value (95% CI: 89% to 98%) for sustained alcohol use post-LT. Thus, the 2013 AASLD guideline cautions against delaying evaluation based on the 6-month abstinence rule, and instead recommends early transplant referral for patients with alcoholic liver disease to encourage such patients to begin addiction treatment.<sup>2</sup>

As part of the substance use history, it is important to ask about the patient's smoking history. Approximately 60% of LT candidates have a history of smoking cigarettes.<sup>18</sup> Tobacco use history is associated with increased post-transplant vascular complications, such as hepatic artery thrombosis or stenosis, portal vein thrombosis, and deep

vein thrombosis.<sup>19</sup> The 2013 AASLD guideline recommends that tobacco use should be prohibited in LT candidates.<sup>2</sup> Pungpapong et al<sup>19</sup> reported that smoking cessation for at least 2 years prior to transplant led to a significantly decreased risk of developing arterial complications, with an absolute risk reduction of approximately 16%.

Liver cirrhosis due to chronic hepatitis C virus (HCV) infection is one of the leading causes for LT. In the United States, HCV is commonly transmitted during injection drug use. According to the 2013 AASLD guideline, ongoing illicit substance use is a relative contraindication to LT.<sup>2</sup> It is important to note, however, that methadone maintenance therapy (MMT) is not a contraindication to LT. In fact, the 2013 AASLD guideline recommends that patients receiving MMT should not be required to reduce or stop therapy in order to be listed for transplant.<sup>2</sup> Studies have shown that in 80% of patients, tapering MMT leads to illicit opiate relapse.<sup>20</sup> Currently, there is no evidence that patients receiving MMT have poorer post-transplant outcomes compared with patients not receiving MMT.<sup>21</sup>

Whether cannabis use is a relative contraindication to LT remains controversial.<sup>22</sup> Possible adverse effects of cannabis use in transplant patients include drug-drug interactions and infections. Hézode et al<sup>23</sup> reported that daily cannabis use is significantly associated with an increased fibrosis progression rate in patients with



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**Patients with a serious mental illness such as schizophrenia can have successful transplant outcomes with proper evaluation and preparation**

chronic HCV infection. Another recent study found that a history of cannabis use was not associated with worse outcomes among patients on the LT waitlist.<sup>24</sup> With the increased legalization of cannabis, more studies are needed to assess ongoing cannabis use in patients on the LT waitlist and post-LT outcomes.

**Psychiatric history.** When assessing a patient for possible LT, no psychiatric disorder is considered an absolute contraindication. Patients with a serious mental illness, such as schizophrenia, and those with intellectual disability can have successful, long-term outcomes with proper evaluation and preparation, including social support. However, empirical literature regarding transplant outcomes and predictive factors in patients with serious mental illness is scarce.<sup>2</sup>

Studies examining the predictive value of pre-transplant depression on post-transplant outcomes have had mixed results.<sup>25</sup> Depression may predict lower post-transplant quality of life. Pre-LT suicidal thoughts (as noted on the Beck Depression Inventory, for example) are associated with post-LT depression.<sup>25</sup> In contrast, available data show no significant effect of pre-transplant anxiety on post-LT outcomes. Similarly, pre-transplant cognitive performance appears not to predict survival or other post-transplant outcomes, but may predict poorer quality of life after transplant.<sup>25</sup>

A few psychiatric factors are considered relative contraindications for LT. These include severe personality disorders, active substance use with no motivation for treatment or abstinence, active psychosis, severe neurocognitive disorders, suicidality, and factitious disorder.<sup>7</sup>

**Social support.** Assessing a pre-LT patient's level of social support is an essential part of the psychosocial evaluation. According to the 2013 AASLD guideline, patients should have "adequate" social support both during the waitlist and post-operative periods.<sup>2</sup> Lack of partnership is a significant predictor of poor post-transplant outcomes, such as late graft loss.<sup>10</sup> Satapathy and Sanyal<sup>26</sup> reported that among patients who receive an LT for alcoholic liver disease, those with

immediate family support were less likely to relapse to using alcohol after transplant. Poor social support was also a predictor of post-transplant medication nonadherence.<sup>10</sup> Thus, the patient needs enough social support to engage in the pre-transplant health care requirements and to participate in post-transplant recommendations until he/she is functioning independently post-transplant.

### Screening tools

Various screening tools may be useful in a pre-LT evaluation. Three standardized assessment tools available specifically for pre-transplant psychosocial assessments are the Stanford Integrated Psychosocial Assessment for Transplantation (*Table 2,*<sup>6</sup> *page 13*), the Psychosocial Assessment of Candidates for Transplantation,<sup>27</sup> and the Transplant Evaluation Rating Scale.<sup>28</sup> Instruments to aid in the assessment of depression, anxiety, and delirium,<sup>29-31</sup> a structured personality assessment,<sup>32</sup> coping inventories,<sup>33</sup> neuropsychological batteries,<sup>34</sup> and others also have been used to evaluate patients before LT. The self-rated Beck Depression Inventory and the clinician-rated Hamilton Depression Rating Scale are commonly used.<sup>7</sup> Other tools, such as the LEIPAD quality of life instrument and the Brief Symptom Inventory (BSI), have been used to assess for perceived quality of life and psychological distress, respectively.<sup>35</sup> These screening tools can be helpful as aids for the pre-LT evaluation; however, diagnoses and treatment plan recommendations require a psychiatric evaluation conducted by a trained clinician.

### Treatment after liver transplant

**Psychiatric issues.** After LT, various psychiatric complications may arise, including (but not limited to) delirium<sup>7</sup> and "paradoxical psychiatric syndrome" (PPS).<sup>36</sup> Delirium can be managed by administering low-dose antipsychotic medications, limiting the use of benzodiazepines and medications with anticholinergic effects, implementing behavioral interventions (frequent orientation, maintaining sleep/wake cycle, limiting noise, presence of a family member or

Table 2

## Psychosocial domains and factors measured by the Stanford Integrated Psychosocial Assessment for Transplantation

Patient's readiness level and illness management	
Item 1	Knowledge and understanding of medical illness process (that caused specific organ failure)
Item 2	Knowledge and understanding of the process of transplantation
Item 3	Willingness/desire for treatment (transplant)
Item 4	History of treatment adherence/compliance (pertinent to medical issues)
Item 5	Lifestyle factors (including diet, exercise, fluid restrictions, and habits according to organ system)
Social support system level of readiness	
Item 6	Availability of social support system
Item 7	Functionality of social support system
Item 8	Appropriateness of physical living space and environment
Psychological stability and psychopathology	
Item 9	Presence of psychopathology (other than personality disorders and organic psychopathology)
Item 10	History of organic psychopathology or neurocognitive impairment (ie, illness or medication-induced psychopathology)
Item 11	Influence of personality traits vs disorder
Item 12	Effect of truthfulness vs deceptive behavior
Item 13	Overall risk for psychopathology
Lifestyle and effect of substance use	
Item 14	Alcohol use, abuse, and dependence
Item 15	Alcohol abuse, risk for recidivism
Item 16	Illicit substance, abuse and dependence
Item 17	Illicit substance abuse, risk for recidivism
Item 18	Nicotine use, abuse, and dependence
Source: Reference 6	

a sitter at bedside),<sup>37</sup> and addressing the underlying etiology. Paradoxical psychiatric syndrome is defined as psychiatric symptoms that occur despite a successful LT. It develops within the first year of transplantation and is characterized by recipients having strong guilt feelings toward their donors.<sup>38</sup>

**Drug interactions.** In the post-transplant period, antipsychotics are used for management of delirium and psychosis, antidepressants for anxiety and depression, and benzodiazepines for anxiety and sleep problems.<sup>7</sup> Drug–drug interactions between psychotropic medications and the immunosuppressants required after LT must be closely monitored. First-generation antipsychotics should be avoided in

post-transplant patients taking tacrolimus due to the increased risk of QTc prolongation. Tacrolimus can also increase the risk of nephrotoxicity when co-administered with lithium. Post-LT patients taking steroids and bupropion have an increased risk of seizure. Carbamazepine may decrease blood levels of cyclosporine due to the induction of hepatic metabolism.<sup>39,40</sup> The psychiatrist should review and update the patient's complete medication list at each visit, checking for possible medication interactions.

**Quality of life.** In the first 6 months post-transplant, patients typically experience improved quality of life in both physical and psychological domains. However, this improvement vacillates as the patient

### Clinical Point

**Patients need enough social support to engage in pre-transplant health care requirements and post-transplant recommendations**



## Liver transplantation

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After liver transplant, potential psychiatric complications include delirium and 'paradoxical psychiatric syndrome'

Table 3

### Relative contraindications for liver transplantation

Psychiatric	Social
Severe personality disorders	Absent or inadequate psychosocial supports
Active substance use	Demonstrated poor adherence
Active psychosis	
Severe neurocognitive disorders	
Suicidality	
Factitious disorder	

Source: Reference 7

adjusts to post-transplant life. A reduction in BSI score 1 year after transplant has been reported. The BSI evaluates psychopathological symptoms, which are early indicators of psychological discomfort. One study noted a reduction in the LEIPAD quality of life score, which measures overall quality of life, 2 years after transplant.<sup>35</sup> This decline may reflect the difficulties associated with the new challenges after transplant. Patients may endure both physical changes due to medical complications as well as psychological problems as they adjust to their new bodily integrity, their dependence on medications and medical staff, and other changes in function. Three to 5 years after transplant, patients reached a new psychological stability, with reported improvements in quality of life and decreased psychological distress.<sup>35</sup>

### Special populations

**HCV infection.** Recurrent HCV infection and liver disease after transplantation are associated with psychological distress. This is particularly evident in patients 6 months after transplantation. Depression and psychological distress have been reported in male patients with recurrent HCV infection within the first year after transplantation.<sup>35</sup>

**Acetaminophen overdose.** Patients who receive a transplant for acetaminophen-induced acute liver failure (ALF) had a greater prevalence of psychiatric comorbidity

as reflected by predefined diagnoses, medication, and previous suicide attempts.<sup>41</sup> Despite this, outcomes for patients transplanted emergently for acetaminophen-induced ALF were comparable to those transplanted for non-acetaminophen-induced ALF and for chronic liver disease. Multidisciplinary approaches with long-term psychiatric follow-up may contribute to low post-transplant suicide rates and low rates of graft loss because of noncompliance.<sup>41</sup>

### CASE REPORT

#### A complicated presentation

Ms. A, age 45, a married woman with history of chronic back pain and self-reported bipolar disorder, presented to our hospital with acute liver failure secondary to acetaminophen overdose. Her Model for End-Stage Liver Disease (MELD) score on presentation was 38 (range: 0 to 40 with higher scores indicating increased likelihood of mortality). Her urine drug screen was positive for benzodiazepines and opiates. On hospital Day 2, the primary team consulted psychiatry for a pre-transplant evaluation and consideration of suicidality. Hepatology, toxicology, and transplant surgery services also were consulted.

Because Ms. A was intubated for acute respiratory failure, the initial history was gathered from family, a review of the medical record, consultation with her pharmacy, and collateral from her outpatient physician. Ms. A had been taking diazepam and hydromorphone as prescribed by her primary care physician for several years for chronic back pain.

Four days before presenting with acute liver failure, Ms. A had visited another hospital for lethargy. Benzodiazepines and opiates were stopped abruptly, and she was discharged with the recommendation to take acetaminophen for her pain. Approximately 24 hours after returning home, Ms. A began having auditory and visual hallucinations, and she did not sleep for days. She continued to complain of pain and was taking acetaminophen as recommended by the outside hospital. Her husband notes that she was intermittently confused. He was unsure how much acetaminophen she was taking.

Her family noted Ms. A had been diagnosed with bipolar disorder "years ago" but

was unable to describe any manic episodes, and Ms. A had been treated only with an antidepressant from her primary care physician. She had persistent low mood and increased sleep since developing chronic back pain that severely limited her functioning. Ms. A attempted suicide once years ago by cutting her wrists. She had 2 prior psychiatric hospitalizations for suicidal ideation and the suicide attempt; however, she had not recently voiced suicidal ideation to her husband or family. She was adherent to psychotropic medications and follow-up appointments. Ms. A is a current smoker. She had used marijuana in the past, but her family denies current use, as well as any alcohol use or illicit substance use.

Ms. A's diagnosis was consistent with tobacco use disorder and major depressive disorder (MDD). She likely developed withdrawal after abrupt cessation of diazepam, which she had been taking as prescribed for years. There was no evidence at the time of her initial psychiatric evaluation that the acetaminophen overdose was a suicide attempt; however, because Ms. A was intubated and sedated at that time, the consultation team recommended direct observation until she could participate in a risk assessment.

For the pre-transplant psychiatric evaluation, our consultation-liaison team noted Ms. A's history of MDD, with recent active symptoms, chronic pain, and a past suicide attempt. She was a current tobacco smoker, which increases the risk of post-transplant vascular problems. However, she had been adherent to medications and follow-up, had very close family support, and there was no clear evidence that this acetaminophen ingestion was a suicide attempt. We noted that outpatient psychiatric follow-up and better chronic pain management would be helpful post-transplant. We would have to

## Related Resources

- Beresford TP, Lucey MR. Towards standardizing the alcoholism evaluation of potential liver transplant recipients. *Alcohol Alcohol*. 2018;53(2):135-144.
- Marcangelo MJ, Crone C. Tools, techniques to assess organ transplant candidates. *Current Psychiatry*. 2007;6(9):56-66.

### Drug Brand Names

Bupropion • Wellbutrin, Zyban	Diazepam • Valium
Carbamazepine • Carbatrol, Tegretol	Hydromorphone • Dilaudid
Cyclosporine • Gengraf, Neoral	Lithium • Eskalith, Lithobid
	Tacrolimus • Astagraf XL, Envarsus XR

re-evaluate Ms. A when she was medically stable enough to communicate before making any further recommendations. Due to medical complications that developed after our evaluation, the transplant team noted Ms. A was no longer a transplant candidate.

Fortunately, Ms. A recovered with medical management over the next 2 weeks. She denied any suicidal ideation throughout her hospitalization. She was restarted on an antidepressant and received supportive therapy until discharge. Outpatient psychiatry follow-up and pain management was set up before Ms. A was discharged. Inpatient psychiatric hospitalization was not recommended. Per available records, Ms. A followed up with all outpatient appointments, including with her psychiatrist, since discharge.

## Avoiding problems, maximizing outcomes

In addition to medical factors, psychosocial factors may affect the success of LT, although empirical data regarding which factors are most predictive of post-transplant outcomes is lacking, especially in patients with serious mental illness. The goals of a psychosocial pre-transplant evaluation are to

## Clinical Point

**Drug–drug interactions between psychotropics and the immunosuppressants required after liver transplant must be closely monitored**

## Bottom Line

Psychiatrists can help patients who are candidates for liver transplantation (LT) by performing a pre-transplant psychosocial assessment to identify factors that might complicate transplantation or recovery. After LT, patients require careful monitoring for psychiatric comorbidities, drug interactions, and other factors that can affect quality of life.



## Liver transplantation

### Clinical Point

Post-transplant, patients' quality of life often improves, again declines, and then stabilizes over years

promote fairness and equal access to care, maximize optimal outcomes, wisely use scarce resources, and ensure that the potential for benefits outweigh surgical risks to the patient. Identifying potential complicating factors (ie, substance abuse, nonadherence, serious psychopathology) can help guide the medical and psychiatric treatment plan and help minimize preventable problems both before and after transplant.<sup>42</sup>

In patients who have a history of alcohol use and alcohol liver disease, relapse to alcohol is a significant problem. Relapse rates vary from 10% to 30%.<sup>7</sup> The duration of abstinence before LT appears to be a poor predictor of abstinence after LT.<sup>43</sup> Polysubstance use also adversely affects outcomes in patients with alcohol liver disease. Approximately one-third of patients with polysubstance use who receive a LT relapse to substance use.<sup>44</sup> Coffman et al<sup>45</sup> showed that the presence of antisocial behavior and eating disorders may increase the risk of relapse after LT.

The psychiatrist's role in the setting of LT spans from the pre-transplant assessment to post-transplant management and follow-up. Clarifying specific psychiatric diagnoses, psychosocial factors that need to be addressed before transplant, and substance use diagnoses and treatment recommendations can help the transplant team clearly identify modifiable factors that can affect transplant outcomes.

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### Clinical Point

**For patients with a history of alcohol use and alcohol liver disease, relapse to alcohol use should be closely monitored**