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*WJH* covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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## Addictive behaviors in liver transplant recipients: The real problem?

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### Abstract

Liver transplantation (LT) is the gold standard treatment for end-stage liver disease. Whatever the primary indication of LT, substance abuse after surgery may decrease survival rates and quality of life. Prevalence of severe alcohol relapse is between 11 and 26%, and reduces life expectancy regardless of the primary indication of LT. Many patients on waiting lists for LT are smokers and this is a major risk factor for both malignant tumors and cardiovascular events post-surgery. The aim of this review is to describe psychoactive substance consumption after LT, and to assess the impact on liver transplant recipients. This review describes data about alcohol and illicit drug use by transplant recipients and suggests guidelines for behavior management after surgery. The presence of an addiction specialist in a LT team seems to be very important.

**Key words:** Liver transplantation; Tobacco use; Illicit drugs; Behavior management; Severe alcohol relapse

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**Core tip:** Liver transplantation is the best treatment for end-stage liver disease. However, some transplant recipients use or abuse alcohol, tobacco and illicit drugs during the post-transplant period. Given the scarcity of organs, this type of consumption, which can affect life expectancy and quality, must be addressed with kindness and without moralizing. Although specific behavior treatment does not exist in this indication, specialists in addiction should be part of the transplant team.

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## INTRODUCTION

Liver transplantation (LT) is the gold standard curative treatment for end-stage liver disease, acute liver failure and hepatocellular carcinoma. The aim of LT is to improve life expectancy and quality. Hepatitis C is the most common indication for LT, and the major risk factor for hepatitis C virus (HCV) infection is intravenous drug abuse. Alcoholic liver disease (ALD) is the second most common indication for LT in the United States and Europe<sup>[1]</sup>. Except for alcohol consumption, addictive behavior is poorly studied in transplant patients<sup>[2]</sup>, and there are many obstacles to obtaining pre- and post-transplant data for psychoactive substance consumption. Currently, the question of how to select transplant candidates is often posed; selection is intended to guarantee a survival probability of at least 50% at 5 years with good quality-of-life. How psychoactive substance consumption affects survival rates and post-surgery outcome are major questions that must be answered.

Firstly, the aim of this review is to describe psychoactive substance consumption of patients after LT; and secondly the various treatments available for patients presenting with substance abuse will be described.

## PSYCHOACTIVE SUBSTANCE CONSUMPTION AFTER LT

### *Alcohol consumption in LT patients*

Currently, ALD is the second most common indication of LT worldwide, with 30% to 50% of all LT in Europe and 17% in the United States<sup>[3]</sup>. The survival rates in Europe are 75% at 5 years and 68% at 10 years<sup>[1]</sup>.

The rates of alcohol relapse vary from 7% to 95% because of the heterogeneity of its definition<sup>[4-7]</sup>. The notion of relapse goes from "slips" to severe relapse<sup>[8,9]</sup>. The moment and the intensity of alcohol relapse are both important. DiMartini *et al*<sup>[9]</sup> identified four distinct types of alcohol consumption in liver transplant recipients. Patients who drank low amounts infrequently, patients with early moderate use that decreased over time, patients with later moderate use that increased over time and patients with early and increasing use. Patients who died of recurrent alcoholic liver diseases were in groups with early alcohol relapse after LT<sup>[9,10]</sup>.

Severe relapse consists in the consumption of more than 14 units of alcohol per week for women and more than 21 per week for men<sup>[8-12]</sup>. The frequency of severe relapse is estimated at 11% to 26%<sup>[13]</sup> and 5 years after LT this type of relapse decreases life expectancy regardless of the primary indication of surgery<sup>[14-17]</sup>.

Previous studies have attempted to identify the risk factors of alcohol relapse such as the duration of pre-transplantation abstinence, the severity of alcohol dependence, neurocognitive data, male sex, polyaddiction, and social isolation<sup>[18-20]</sup>. These risk factors are not clearly adapted to the prediction of severe relapse. Some LT teams have suggested calculating a risk of relapse score<sup>[21]</sup>, but their multicenter findings are not yet available<sup>[17]</sup>. The effect of addiction treatment before LT has been little studied as yet<sup>[22,23]</sup>; these studies used classical behavioral therapies and were limited with regard to medication, which is not indicated for patients with end-stage liver disease. More recently, baclofen, which is not metabolized by the liver, has demonstrated some effectiveness in maintaining abstinence in cirrhosis patients<sup>[24]</sup>. This pre-graft period is very special because the question of "life or death" is posed, and there is a serious deterioration in the quality-of-life. Patients on the waiting list are extremely anxious and some present symptoms of depression, stress or insomnia and are in denial of their disease<sup>[25]</sup>. Apart from a standard addictological follow-up, implementation of any new addictological procedures at this difficult time is neither suitable nor effective. Masson *et al*<sup>[26]</sup> tried to define an "alcohol contract" before LT in which patients awaiting transplant confirmed their abstinence. This contract did not have any effect on severe relapse rates after LT. In the general population there is a wide variety of alcohol use disorders (AUD), and most people with AUD go into remission after three years without any specific addiction treatment<sup>[27]</sup>. As Dom says very well<sup>[18]</sup> some patients with an AUD are more at risk of relapse than others and the course of LT tends to have selected those patients with a low risk of alcohol relapse.

For a minority of transplanted patients, severe relapse exists. The diagnosis of severe alcohol relapse after LT is very difficult for the transplant team. It can be made using several tools such as clinical, blood or urinary analysis, an interview with an addiction specialist or histological data<sup>[28,29]</sup>. Diagnosis and treatment of severe relapse requires the presence of an addiction unit within the LT center<sup>[30,31]</sup>. In Table 1, previous significant reports on alcohol relapse are given.

### *Tobacco consumption in LT patients*

Tobacco use is the first preventable cause of mortality in the general population of the United States with a prevalence of 20.9%<sup>[2]</sup>. During the pre-transplant period, 57% of patients have a lifetime prevalence of smoking, and 27% of all patients are active smokers<sup>[32]</sup>. Tobacco use is associated with graft loss and higher mortality in kidney, pancreas, lung and heart transplant patients<sup>[33]</sup>. In LT patients, tobacco use is associated with an increase in the incidence of vascular complications, but this was not found in



**Table 1** Previous significant reports on alcohol relapse after liver transplantation

Theme	Ref.	Year	Journal
Risk factors of alcohol relapse	De Gottardi <i>et al</i> <sup>[22]</sup>	2007	<i>Arch Intern Med</i>
	Dew <i>et al</i> <sup>[4]</sup>	2008	<i>Liver Transpl</i>
Types of relapse	Tome <i>et al</i> <sup>[8]</sup>	2003	<i>J Hepatol</i>
	DiMartini <i>et al</i> <sup>[9]</sup>	2010	<i>Am J Transplant</i>
	Faure <i>et al</i> <sup>[15]</sup>	2012	<i>Journal of Hepatology</i>
	Dumortier <i>et al</i> <sup>[10]</sup>	2015	<i>Am J Gastroenterol</i>
Treatment of alcohol relapses	Dimartini <i>et al</i> <sup>[28]</sup>	2001	<i>Psychosomatics</i>
	Weinrieb <i>et al</i> <sup>[23]</sup>	2007	<i>Liver Transpl</i>
	Addolorato <i>et al</i> <sup>[31]</sup>	2013	<i>Alcohol Clin Exp Res</i>
	Dom <i>et al</i> <sup>[17]</sup>	2015	<i>World J Hepatol</i>
	Donnadieu-Rigole <i>et al</i> <sup>[30]</sup>	2017	<i>Alcohol Clin Exp Res</i>

all the series<sup>[32,34,35]</sup>. *De novo* cancers are the second cause of late mortality after LT; during recent years, series of LT patients have shown an increase in upper aerodigestive tract, colon and kidney tumors<sup>[36-38]</sup>. Tobacco use before transplantation seems to be a risk factor for malignancies in LT patients presenting with alcoholic liver disease<sup>[39]</sup>. Other risk factors for malignancies are advanced age, alcohol consumption pre-and post-transplantation, viral infections, sun exposure, obesity, premalignant lesions and tacrolimus exposure levels<sup>[36,37]</sup>. Cardiac events in LT patients also limited long-term survival<sup>[40]</sup> and tobacco is a well-known risk factor for cardiovascular diseases<sup>[39]</sup>.

Some authors believe that tobacco use should be a contraindication to organ allocation demanding smoking cessation before transplantation; other authors just recommended abstinence<sup>[41]</sup>. For kidney transplant recipients, a program for treating tobacco use was designed by Ehlers *et al*<sup>[42]</sup>. This program could be adapted to LT patients with systematic addiction consultations before and after LT.

Iruzubieta *et al*<sup>[43]</sup> proposed pre- and post-transplant follow-up during which tobacco use after LT should be taken care of.

### Polysubstance abuse in LT patients

There are very few exact descriptions of the prevalence of polysubstance use in LT patients during pre- or post-transplant periods.

When a patient is dependent on a psychoactive substance they are at higher risk of being dependent on another one; this is true for tobacco and cannabis, so any detection of cannabis use must be systematically investigated in pre- and post-LT patients. Cannabis use is often associated with other psychoactive substance consumption in a context of polysubstance abuse<sup>[44]</sup>. In this series of polysubstance abuse in LT patients, the mean number of substances consumed was 3 before LT. The etiology of the end-stage liver disease was HCV infection and substance abuse had no impact on survival rates after LT. In the event of HCV infection as the primary indication, lifelong abuse of alcohol or other substances is often missed by the referent physician<sup>[45,46]</sup>.

Patients on methadone maintenance therapy (MMT) for opiate dependence have not been well studied after LT; Weinrieb *et al*<sup>[47]</sup> and Tome *et al*<sup>[48]</sup> described more severe recurrent HCV infection and 20% of alcohol or illicit drug use after LT in these patients, but larger studies are necessary.

## TREATMENT OF ADDICTIVE BEHAVIORS IN LT PATIENTS

### Treatment of alcohol relapses

Although LT is the treatment of choice in the event of liver failure, some patients need specific follow-up post-surgery. No specific follow-up treatment is recommended for transplant recipients with addiction disorders, but motivational therapies have proved their effectiveness in this indication<sup>[49,50]</sup>. In the general population, they reduce mortality of liver diseases<sup>[51]</sup>. Psychotherapies include Twelve-step Facilitation Therapy, which is recommended by Alcoholics Anonymous; Cognitive-Behavioral Therapy and Motivational Enhancement Therapy can promote abstinence or help to reduce the amount of alcohol drunk<sup>[52-55]</sup>.

Medication exists to treat alcohol dependence. Acamprosate is a medication that has proved its effectiveness in maintaining abstinence<sup>[55]</sup>. Naltrexone, an opioid receptor inhibitor, is effective on alcohol craving<sup>[56]</sup>. These two medicinal products are poorly studied in liver disease, so they are not currently approved in LT recipients and further studies are necessary<sup>[57]</sup>. Disulfiram (an acetaldehyde dehydrogenase) is a treatment which causes unpleasant sensations that prevent alcohol consumption. This treatment is potentially hepatotoxic and must be used with caution in LT patients<sup>[52]</sup>. Baclofen is the only treatment of alcohol dependence that has been studied in patients with alcoholic cirrhosis<sup>[24]</sup>. Pharmacotherapy should be associated with psychosocial support<sup>[58]</sup>.

### Treatment of opioid dependence

MMT for opiate-dependent patients at any dosage is not a contraindication for transplantation<sup>[59,60]</sup> but MMT patients continue to be discriminated against and it is very important to repeat that patients

should not be weaned from methadone before liver transplantation<sup>[59]</sup>. This treatment may be associated with anti-rejection drugs without specific supervision.

### Treatment of tobacco cessation

For tobacco, patients transplanted for alcoholic liver disease often resume smoking very soon after surgery and the number of cigarettes smoked increases rapidly with patients smoking more than during the pre-transplantation period<sup>[61]</sup>. Nicotine replacement therapies can be used after LT. Bupropion should be used with caution in patients with liver disease and there are no contraindications for varenicline except allergy<sup>[62]</sup> but these medicinal products have not been studied in LT recipients.

In our LT center a systematic addiction consultation was made before LT and follow-up was proposed to patients with a high level of risk factors, but this did not result in the reduction of severe alcohol relapse.

A structured addiction consultation such as BRENDA<sup>[63]</sup> (B for biopsychosocial evaluation, R for restitution, E for Empathy, N for Needs identification, D for Direct counseling, A for Assess) in order to prevent and diagnose any alcohol relapse as soon as possible is now proposed systematically one month after LT.

Furthermore, these addiction consultations will promote tobacco cessation and/or prevention and treatment of psychoactive substance consumption.

## CONCLUSION

There are many barriers to obtaining and documenting data about alcohol and illicit drug use by transplant recipients. One such barrier is the fear of patients and their referent physicians of judgment and medical sanction. But the objectives of addiction specialists are to improve life expectancy and quality without automatically obtaining total abstinence in patients. For all patients the period of LT surgery is a real "psychological earthquake" and causes behavioral changes that should be systematically evaluated after a few weeks of convalescence. Whatever the primary indication of LT, all transplanted patients should be seen at least once during the post-transplantation period to document present or past use of tobacco, alcohol, opiates, marijuana, cocaine and other drugs. There are no specific guidelines for behavioral management in LT patients, but non-judgmental care and a fostering attitude by the transplant team is recommended<sup>[64,65]</sup>. As well as transplant surgeons and anesthesiologists, addiction specialists must actively participate in the patient's clinical journey before, and especially after, LT.

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