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

Donnadieu-Rigole H *et al.* Addictive behaviors and liver transplantation

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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; Severe alcohol relapse; Tobacco use; Illicit drugs; Behavior management

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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 HCV infection is intravenous drug abuse. Alcoholic liver disease (ALD) is the second most common indication for LT in the United States and Europe[1]. Except for alcohol consumption, addictive behavior is poorly studied in transplant patients[2], 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 LIVER TRANSPLANTATION**

***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[3]. The survival rates in Europe are 75% at 5 years and 68% at 10 years[1].

The rates of alcohol relapse vary from 7 to 95% because of the heterogeneity of its definition[4-7]. The notion of relapse goes from "slips" to severe relapse[8,9]. The moment and the intensity of alcohol relapse are both important. DiMartini *et al*[9] 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[9,10].

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[8-12]. The frequency of severe relapse is estimated at 11% to 26%[13] and 5 years after LT this type of relapse decreases life expectancy regardless of the primary indication of surgery[14-17].

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[18-20]. These risk factors are not clearly adapted to the prediction of severe relapse. Some LT teams have suggested calculating a risk of relapse score[21],but their multicenter findings are not yet available[17]. The effect of addiction treatment before LT has been little studied as yet[22,23]; 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[24]. 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[25]. 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*[26] 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[27]. As Dom says very well[18] 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[28,29]. Diagnosis and treatment of severe relapse requires the presence of an addiction unit within the LT center[30, 31]. 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%[2]. During the pre-transplant period, 57% of patients have a lifetime prevalence of smoking, and 27% of all patients are active smokers[32]. Tobacco use is associated with graft loss and higher mortality in kidney, pancreas, lung and heart transplant patients[33]. In LT patients, tobacco use is associated with an increase in the incidence of vascular complications, but this was not found in all the series[32,34,35]. *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[36-38]. Tobacco use before transplantation seems to be a risk factor for malignancies in LT patients presenting with alcoholic liver disease[39]. 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[36, 37]. Cardiac events in LT patients also limited long-term survival[40] and tobacco is a well-known risk factor for cardiovascular diseases[39].

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

Iruzubieta *et* *al*[43] 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[44]. 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[45,46].

Patients on methadone maintenance therapy (MMT) for opiate dependence have not been well studied after LT; Weinrieb *et al*[47,48] 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[49,50]. In the general population, they reduce mortality of liver diseases[51]. Psychotherapies include Twelve-step Facilitation Therapy (TSF), which is recommended by Alcoholics Anonymous; Cognitive-Behavioral Therapy (CBT) and Motivational Enhancement Therapy (MET) can promote abstinence or help to reduce the amount of alcohol drunk[52-55].

Medication exists to treat alcohol dependence. Acamprosate is a medication that has proved its effectiveness in maintaining abstinence[55]. Naltrexone, an opioid receptor inhibitor, is effective on alcohol craving[56].These two medicinal products are poorly studied in liver disease, so they are not currently approved in LT recipients and further studies are necessary[57]. 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[52]. Baclofen is the only treatment of alcohol dependence that has been studied in patients with alcoholic cirrhosis[24]. Pharmacotherapy should be associated with psychosocial support[58].

***Treatment of opioid dependence***

Methadone-maintenance treatment (MMT) for opiate-dependent patients at any dosage is not a contraindication for transplantation[59,60] 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[59]. 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[61]. 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[62] 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[63] (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[64,65]. As well as transplant surgeons and anesthetists, addiction specialists must actively participate in the patient’s clinical journey before, and especially after, LT.

**REFERENCES**

1 **Burra P**, Senzolo M, Adam R, Delvart V, Karam V, Germani G, Neuberger J. Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). *Am J Transplant* 2010; **10**: 138-148 [PMID: 19951276 DOI: 10.1111/j.1600.6143.2009.02869.x]

2 **Ehlers SL**. Ethical analysis and consideration of health behaviors in organ allocation: focus on tobacco use. *Transplant Rev* (Orlando) 2008; **22**: 171-177 [PMID: 18631873 DOI: 10.1016/j.trre.2008.02.006]

3 **Bruha R**, Dvorak K, Petrtyl J. Alcoholic liver disease. *World J Hepatol* 2012; **4**: 81-90 [PMID: 22489260 DOI: 10.4254/wjh.v4.i3.81]

4 **Dew MA**, DiMartini AF, Steel J, De Vito Dabbs A, Myaskovsky L, Unruh M, Greenhouse J. Meta-analysis of risk for relapse to substance use after transplantation of the liver or other solid organs. *Liver Transpl* 2008; **14**: 159-172 [PMID: 18236389 DOI: 10.1002/lt.21278]

5 **Lucey MR**, Carr K, Beresford TP, Fisher LR, Shieck V, Brown KA, Campbell DA, Appelman HD. Alcohol use after liver transplantation in alcoholics: a clinical cohort follow-up study. *Hepatology* 1997; **25**: 1223-1227 [PMID: 9141441]

6 **Lim JK**, Keeffe EB. Liver transplantation for alcoholic liver disease: current concepts and length of sobriety. *Liver Transpl* 2004; **10**: S31-S38 [PMID: 15382288 DOI: 10.1002/lt.20267]

7 **Neuberger J**, Tang H. Relapse after transplantation: European studies. *Liver Transpl Surg* 1997; **3**: 275-279 [PMID: 9346751]

8 **Tome S**, Lucey MR. Timing of liver transplantation in alcoholic cirrhosis. *J Hepatol* 2003; **39**: 302-307 [PMID: 12927913]

9 **DiMartini A**, Dew MA, Day N, Fitzgerald MG, Jones BL, deVera ME, Fontes P. Trajectories of alcohol consumption following liver transplantation. *Am J Transplant* 2010; **10**: 2305-2312 [PMID: 20726963 DOI: 10.1111/j.1600-6143.2010.03232.x]

10 **Dumortier J**, Dharancy S, Cannesson A, Lassailly G, Rolland B, Pruvot FR, Boillot O, Faure S, Guillaud O, Rigole-Donnadieu H, Herrero A, Scoazec JY, Mathurin P, Pageaux GP. Recurrent alcoholic cirrhosis in severe alcoholic relapse after liver transplantation: a frequent and serious complication. *Am J Gastroenterol* 2015; **110**: 1160-116; quiz 1167 [PMID: 26169514 DOI: 10.1038/ajg.2015.204]

11 **Pageaux GP**, Michel J, Coste V, Perney P, Possoz P, Perrigault PF, Navarro F, Fabre JM, Domergue J, Blanc P, Larrey D. Alcoholic cirrhosis is a good indication for liver transplantation, even for cases of recidivism. *Gut* 1999; **45**: 421-426 [PMID: 10446113]

12 **Poynard T**, Naveau S, Doffoel M, Boudjema K, Vanlemmens C, Mantion G, Messner M, Launois B, Samuel D, Cherqui D, Pageaux G, Bernard PH, Calmus Y, Zarski JP, Miguet JP, Chaput JC. Evaluation of efficacy of liver transplantation in alcoholic cirrhosis using matched and simulated controls: 5-year survival. Multi-centre group. *J Hepatol* 1999; **30**: 1130-1137 [PMID: 10406193]

13 **Kotlyar DS**, Burke A, Campbell MS, Weinrieb RM. A critical review of candidacy for orthotopic liver transplantation in alcoholic liver disease. *Am J Gastroenterol* 2008; **103**: 734-43; quiz 744 [PMID: 18081918]

14 **Lucey MR**. Liver transplantation for alcoholic liver disease. *Nat Rev Gastroenterol Hepatol* 2014; **11**: 300-307 [PMID: 24393837]

15 **Faure S**, Herrero A, Jung B, Duny Y, Daures JP, Mura T, Assenat E, Bismuth M, Bouyabrine H, Donnadieu-Rigole H, Navarro F, Jaber S, Larrey D, Pageaux GP. Excessive alcohol consumption after liver transplantation impacts on long-term survival, whatever the primary indication. *J Hepatol* 2012; **57**: 306-312 [PMID: 22521352 DOI: 10.1016/j.jhep.2012.03.014]

16 **Rice JP**, Eickhoff J, Agni R, Ghufran A, Brahmbhatt R, Lucey MR. Abusive drinking after liver transplantation is associated with allograft loss and advanced allograft fibrosis. *Liver Transpl* 2013; **19**: 1377-1386 [PMID: 24115392 DOI: 10.1002/lt.23762]

17 **Dom G**, Peuskens H. Addiction specialist's role in liver transplantation procedures for alcoholic liver disease. *World J Hepatol* 2015; **7**: 2091-2099 [PMID: 26301051 DOI: 10.4254/wjh.v7.i17.2091]

18 **Pageaux GP**, Bismuth M, Perney P, Costes V, Jaber S, Possoz P, Fabre JM, Navarro F, Blanc P, Domergue J, Eledjam JJ, Larrey D. Alcohol relapse after liver transplantation for alcoholic liver disease: does it matter? *J Hepatol* 2003; **38**: 629-634 [PMID: 12713874]

19 **Karim Z**, Intaraprasong P, Scudamore CH, Erb SR, Soos JG, Cheung E, Cooper P, Buzckowski AK, Chung SW, Steinbrecher UP, Yoshida EM. Predictors of relapse to significant alcohol drinking after liver transplantation. *Can J Gastroenterol* 2010; **24**: 245-250 [PMID: 20431813]

20 **Rodrigue JR**, Hanto DW, Curry MP. Substance abuse treatment and its association with relapse to alcohol use after liver transplantation. *Liver Transpl* 2013; **19**: 1387-1395 [PMID: 24123780 DOI: 10.1002/lt.23747]

21 **De Gottardi A**, Spahr L, Gelez P, Morard I, Mentha G, Guillaud O, Majno P, Morel P, Hadengue A, Paliard P, Scoazec JY, Boillot O, Giostra E, Dumortier J. A simple score for predicting alcohol relapse after liver transplantation: results from 387 patients over 15 years. *Arch Intern Med* 2007; **167**: 1183-1188 [PMID: 17563028 DOI: 10.1001/archinte.167.11.1183]

22 **Weinrieb RM**, Van Horn DH, Lynch KG, Lucey MR. A randomized, controlled study of treatment for alcohol dependence in patients awaiting liver transplantation. *Liver Transpl* 2011; **17**: 539-547 [PMID: 21506242 DOI: 10.1002/lt.22259]

23 **Erim Y**, Beckmann M, Tagay S, Beckebaum S, Gerken G, Broelsch CE, Senf W. [Stabilisation of abstinence by means of psychoeducation for patients with alcoholic liver disease awaiting liver transplantation]. *Z Psychosom Med Psychother* 2006; **52**: 341-357 [PMID: 17156604]

24 **Addolorato G**, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, Abenavoli L, D'Angelo C, Caputo F, Zambon A, Haber PS, Gasbarrini G. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet* 2007; **370**: 1915-1922 [PMID: 18068515]

25 **Ramírez P**, Febrero B, Martínez-Alarcón L, Abete C, Galera M, Cascales P, López-Navas AI, González MR, Ríos A, Pons JA, Parrilla P. Benefits of Group Psychotherapy in Cirrhotic Patients on the Liver Transplant Waiting List. *Transplant Proc* 2015; **47**: 2382-2384 [PMID: 26518934 DOI: 10.1016/j.transproceed.2015.08.033]

26 **Masson S**, Marrow B, Kendrick S, Elsharkawy AM, Latimer S, Hudson M. An 'alcohol contract' has no significant effect on return to drinking after liver transplantation for alcoholic liver disease. *Transpl Int* 2014; **27**: 475-481 [PMID: 24533687 DOI: 10.1111/tri.12283]

27 **Tuithof M**, Ten Have M, van den Brink W, Vollebergh W, de Graaf R. Predicting persistency of DSM-5 alcohol use disorder and examining drinking patterns of recently remitted individuals: a prospective general population study. *Addiction* 2013; **108**: 2091-2099 [PMID: 23889861 DOI: 10.1111/add.12309]

28 **DiMartini A**, Day N, Dew MA, Lane T, Fitzgerald MG, Magill J, Jain A. Alcohol use following liver transplantation: a comparison of follow-up methods. *Psychosomatics* 2001; **42**: 55-62 [PMID: 11161122 DOI: 10.1176/appi.psy.421.55]

29 **Ursic-Bedoya J**, Faure S, Donnadieu-Rigole H, Pageaux GP. Liver transplantation for alcoholic liver disease: Lessons learned and unresolved issues. *World J Gastroenterol* 2015; **21**: 10994-11002 [PMID: 26494956 DOI: 10.3748/wjg.v21.i39.10994]

30 **Donnadieu-Rigole H**, Olive L, Nalpas B, Winter A, Ursic-Bedoya J, Faure S, Pageaux GP, Perney P. Follow-Up of Alcohol Consumption After Liver Transplantation: Interest of an Addiction Team? *Alcohol Clin Exp Res* 2017; **41**: 165-170 [PMID: 27936489 DOI: 10.1111/acer.13276]

31 **Addolorato G**, Mirijello A, Leggio L, Ferrulli A, D'Angelo C, Vassallo G, Cossari A, Gasbarrini G, Landolfi R, Agnes S, Gasbarrini A. Liver transplantation in alcoholic patients: impact of an alcohol addiction unit within a liver transplant center. *Alcohol Clin Exp Res* 2013; **37**: 1601-1608 [PMID: 23578009 DOI: 10.1111/acer.12117]

32 **Pungpapong S**, Manzarbeitia C, Ortiz J, Reich DJ, Araya V, Rothstein KD, Muñoz SJ. Cigarette smoking is associated with an increased incidence of vascular complications after liver transplantation. *Liver Transpl* 2002; **8**: 582-587 [PMID: 12089709 DOI: 10.1053/jlts.2002.34150]

33 **Ehlers SL**, Rodrigue JR, Widows MR, Reed AI, Nelson DR. Tobacco use before and after liver transplantation: a single center survey and implications for clinical practice and research. *Liver Transpl* 2004; **10**: 412-417 [PMID: 15004770 DOI: 10.1002/lt.20087]

34 **Perney P**, Segalas F, Nalpas B, Chanques G, Rigole H, Duny Y, Blanc F, Jaber S, Pageaux GP. Impact of tobacco and alcohol consumption in patients registered on waiting list on early morbidity following liver transplantation. *Clin Res Hepatol Gastroenterol* 2013; **37**: 473-478 [PMID: 23522692 DOI: 10.1016/j.clinre.2013.01.009]

35 **Leithead JA**, Ferguson JW, Hayes PC. Smoking-related morbidity and mortality following liver transplantation. *Liver Transpl* 2008; **14**: 1159-1164 [PMID: 18668649 DOI: 10.1002/lt.21471]

36 **Jiménez-Romero C**, Justo-Alonso I, Cambra-Molero F, Calvo-Pulido J, García-Sesma Á, Abradelo-Usera M, Caso-Maestro O, Manrique-Municio A. Incidence, risk factors and outcome of de novo tumors in liver transplant recipients focusing on alcoholic cirrhosis. *World J Hepatol* 2015; **7**: 942-953 [PMID: 25954477 DOI: 10.4254/wjh.v7.i7.942]

37 **Carenco C**, Faure S, Herrero A, Assenat E, Duny Y, Danan G, Bismuth M, Chanques G, Ursic-Bedoya J, Jaber S, Larrey D, Navarro F, Pageaux GP. Incidence of solid organ cancers after liver transplantation: comparison with regional cancer incidence rates and risk factors. *Liver Int* 2015; **35**: 1748-1755 [PMID: 25488375 DOI: 10.1111/liv.12758]

38 **Mangus RS**, Fridell JA, Kubal CA, Loeffler AL, Krause AA, Bell JA, Tiwari S, Tector J. Worse Long-term Patient Survival and Higher Cancer Rates in Liver Transplant Recipients With a History of Smoking. *Transplantation* 2015; **99**: 1862-1868 [PMID: 26308417 DOI: 10.1097/TP.0000000000000671]

39 **van der Heide F**, Dijkstra G, Porte RJ, Kleibeuker JH, Haagsma EB. Smoking behavior in liver transplant recipients. *Liver Transpl* 2009; **15**: 648-655 [PMID: 19479809 DOI: 10.1002/lt.21722]

40 **Malik MU**, Russell SD, Pustavoitau A, Chacko M, Cosar AM, Thompson CB, Trilianos P, Dagher NN, Cameron AM, Gurakar A. The predictors of post-transplant coronary events among liver transplant recipients. *Hepatol Int* 2016; **10**: 974-982 [PMID: 27311889 DOI: 10.1007/s12072-016-9742-5]

41 **Fleetwood VA**, Hertl M, Chan EY. Liver Transplantation to the Active Smoker: Transplant Provider Opinions and How They Have Changed: Transplantation in Smokers: A Survey. *J Gastrointest Surg* 2015; **19**: 2223-2227 [PMID: 26358276 DOI: 10.1007/s11605-015-2935-8]

42 **Ehlers SL**, Rodrigue JR, Patton PR, Lloyd-Turner J, Kaplan B, Howard RJ. Treating tobacco use and dependence in kidney transplant recipients: development and implementation of a program. *Prog Transplant* 2006; **16**: 33-37 [PMID: 16676672]

43 **Iruzubieta P**, Crespo J, Fábrega E. Long-term survival after liver transplantation for alcoholic liver disease. *World J Gastroenterol* 2013; **19**: 9198-9208 [PMID: 24409048 DOI: 10.3748/wjg.v19.i48.9198]

44 **Nickels M**, Jain A, Sharma R, Orloff M, Tsoulfas G, Kashyap R, Bozorgzadeh A. Polysubstance abuse in liver transplant patients and its impact on survival outcome. *Exp Clin Transplant* 2007; **5**: 680-685 [PMID: 18194121]

45 **Day E**, Best D, Sweeting R, Russell R, Webb K, Georgiou G, Neuberger J. Detecting lifetime alcohol problems in individuals referred for liver transplantation for nonalcoholic liver failure. *Liver Transpl* 2008; **14**: 1609-1613 [PMID: 18975295 DOI: 10.1002/lt.21528]

46 **Webzell I**, Ball D, Bell J, Sherwood RA, Marsh A, O'Grady JG, Heaton ND. Substance use by liver transplant candidates: an anonymous urinalysis study. *Liver Transpl* 2011; **17**: 1200-1204 [PMID: 21744466 DOI: 10.1002/lt.22370]

47 **Weinrieb RM**, Barnett R, Lynch KG, DePiano M, Atanda A, Olthoff KM. A matched comparison study of medical and psychiatric complications and anesthesia and analgesia requirements in methadone-maintained liver transplant recipients. *Liver Transpl* 2004; **10**: 97-106 [PMID: 14755785 DOI: 10.1002/lt.20003]

48 **Tome S**, Said A, Lucey MR. Addictive behavior after solid organ transplantation: what do we know already and what do we need to know? *Liver Transpl* 2008; **14**: 127-129 [PMID: 18236443 DOI: 10.1002/lt.21311]

49 **Georgiou G**, Webb K, Griggs K, Copello A, Neuberger J, Day E. First report of a psychosocial intervention for patients with alcohol-related liver disease undergoing liver transplantation. *Liver Transpl* 2003; **9**: 772-775 [PMID: 12827568 DOI: 10.1054/jlts.2003.50152]

50 **Weinrieb RM**, Lucey MR. Treatment of addictive behaviors in liver transplant patients. *Liver Transpl* 2007; **13**: S79-S82 [PMID: 17969092 DOI: 10.1002/lt.21340]

51 **Xie YD**, Feng B, Gao Y, Wei L. Effect of abstinence from alcohol on survival of patients with alcoholic cirrhosis: A systematic review and meta-analysis. *Hepatol Res* 2014; **44**: 436-449 [PMID: 23607793 DOI: 10.1111/hepr.12131]

52 **Jaurigue MM**, Cappell MS. Therapy for alcoholic liver disease. *World J Gastroenterol* 2014; **20**: 2143-2158 [PMID: 24605013 DOI: 10.3748/wjg.v20.i9.2143]

53 Matching Alcoholism Treatments to Client Heterogeneity: Project MATCH posttreatment drinking outcomes. *J Stud Alcohol* 1997; **58**: 7-29 [PMID: 8979210]

54 **Leggio L**, Lee MR. Treatment of Alcohol Use Disorder in Patients with Alcoholic Liver Disease. *Am J Med* 2017; **130**: 124-134 [PMID: 27984008 DOI: 10.1016/j.amjmed.2016.10.004]

55 **Mann K**, Lehert P, Morgan MY. The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: results of a meta-analysis. *Alcohol Clin Exp Res* 2004; **28**: 51-63 [PMID: 14745302 DOI: 10.1097/01.ALC.0000108656.81563.05]

56 **Rösner S**, Hackl-Herrwerth A, Leucht S, Vecchi S, Srisurapanont M, Soyka M. Opioid antagonists for alcohol dependence. *Cochrane Database Syst Rev* 2010; **(12)**: CD001867 [PMID: 21154349]

57 **Vuittonet CL**, Halse M, Leggio L, Fricchione SB, Brickley M, Haass-Koffler CL, Tavares T, Swift RM, Kenna GA. Pharmacotherapy for alcoholic patients with alcoholic liver disease. *Am J Health Syst Pharm* 2014; **71**: 1265-1276 [PMID: 25027533 DOI: 10.2146/ajhp140028]

58 **Mann K**. Pharmacotherapy of alcohol dependence: a review of the clinical data. *CNS Drugs* 2004; **18**: 485-504 [PMID: 15182219]

59 **Kanchana TP**, Kaul V, Manzarbeitia C, Reich DJ, Hails KC, Munoz SJ, Rothstein KD. Liver transplantation for patients on methadone maintenance. *Liver Transpl* 2002; **8**: 778-782 [PMID: 12200777 DOI: 10.1053/jlts.2002.33976]

60 **Liu LU**, Schiano TD, Lau N, O'Rourke M, Min AD, Sigal SH, Drooker M, Bodenheimer HC. Survival and risk of recidivism in methadone-dependent patients undergoing liver transplantation. *Am J Transplant* 2003; **3**: 1273-1277 [PMID: 14510701]

61 **DiMartini A**, Javed L, Russell S, Dew MA, Fitzgerald MG, Jain A, Fung J. Tobacco use following liver transplantation for alcoholic liver disease: an underestimated problem. *Liver Transpl* 2005; **11**: 679-683 [PMID: 15915490 DOI: 10.1002/lt.20385]

62 **Little MA**, Ebbert JO. The safety of treatments for tobacco use disorder. *Expert Opin Drug Saf* 2016; **15**: 333-341 [PMID: 26715118 DOI: 10.1517/14740338.2016.1131817]

63 **Starosta AN**, Leeman RF, Volpicelli JR. The BRENDA model: integrating psychosocial treatment and pharmacotherapy for the treatment of alcohol use disorders. *J Psychiatr Pract* 2006; **12**: 80-89 [PMID: 16728904]

64 **Weinrieb RM**, Van Horn DH, McLellan AT, Lucey MR. Interpreting the significance of drinking by alcohol-dependent liver transplant patients: fostering candor is the key to recovery. *Liver Transpl* 2000; **6**: 769-776 [PMID: 11084066 DOI: 10.1053/jlts.2000.18497]

65 **Parker R**, Armstrong MJ, Corbett C, Day EJ, Neuberger JM. Alcohol and substance abuse in solid-organ transplant recipients. *Transplantation* 2013; **96**: 1015-1024 [PMID: 24025323 DOI: 10.1097/TP.0b013e31829f7579]

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Theme** | **Authors** | **Years** | **Journal** |
| Risk factors of alcohol relapse | De Gottardi *et al*[21]  | 2007 | *Arch Intern Med* |
| Dew *et al*[4] | 2008 | *Liver Transpl.*  |
| Types of relapse | Tome[8] | 2003 | *J Hepatol.* |
| DiMartini *et al*[9] | 2010 | *Am J Transplant.* |
| Faure *et al*[15] | 2012 | *Journal of Hepatology* |
| Dumortier *et al*[10] | 2015 | *Am J Gastroenterol.* |
| Treatment of alcohol relapses | Dimartini *et al*[28] | 2001 | *Psychosomatics* |
| Weinrieb[23] | 2007 | *Liver Transpl.* |
| Addolorato *et al*[31] | 2013 | *Alcohol Clin Exp Res.* |
| Dom | 2015 | *World J Hepatol* |
| Donnadieu-Rigole *et al*[30] | 2017 | *Alcohol Clin Exp Res.* |