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Management of Alcohol Use Disorder in Patients Requiring Liver Transplant

Mary R. Lee, M.D.[1] and **Lorenzo Leggio, M.D., Ph.D., M.S.c.**[1,2,*]

[1]Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology, National Institute on Alcohol Abuse and Alcoholism and National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD

[2]Center for Alcohol and Addiction Studies, Department of Behavioral and Social Sciences, Brown University, Providence, RI

Abstract

Alcoholic liver disease is the second most common indication for orthotopic liver transplantation in western countries. The majority of patients with alcoholic liver disease, however, are not referred for transplant evaluation. If evaluated, a 6 month period of sobriety is required before waitlisting for transplant. The consequences of relapse to alcohol use in patients on the waitlist are usually removal from the list. Therefore, identification and treatment of alcohol use disorder in patients with end-stage liver disease greatly impacts quality of life, treatment options and survival in patients' course with this grave illness. Psychosocial and behavioral interventions prior to transplant appear to reduce drinking in the period before the surgery as well as reduce relapse rates post-transplant. Only one of the three medications approved by the Food and Drug Administration, acamprosate, seems feasible for use in patients with end-stage liver disease, while several other medications currently under investigation for the treatment of alcohol use disorder can be considered for use in this population. While only baclofen has been formally studied in alcoholic patients with end-stage liver disease with positive results for safety and efficacy, other medications also hold promise to treat alcohol use disorder in this population. Transplant programs with addictions specialists who function as an integral part of the treatment team may offer better outcomes to patients in terms of success of maintaining sobriety both pre- and post-transplant.

A woman with alcohol use disorder presenting with jaundice, enlargement of the abdomen, severe fatigue and malaise

"Ms. W." is a 48-year-old divorced Caucasian female with a history of alcohol use disorder who presents to the emergency department with complaints of increasing fatigue, shortness of breath and abdominal girth. Upon initial evaluation, she is awake and alert with blood pressure of 95/65 mmHg and pulse 105 bpm. She

*Contact information: Lorenzo Leggio, M.D., Ph.D., M.Sc., Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology, NIAAA & NIDA, NIH, 10 Center Drive (10CRC/15330) MSC 1108; Room 1-5429, Bethesda, MD 20892-1108, Phone: +1 301 435 9398; Fax: + 1 301 402 0445, lorenzo.leggio@nih.gov.

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reports daily alcohol drinking, usually 1 to 2 bottles of wine per day. She also reports a history of depression dating back to her late teens and early 20's preceding her alcohol use and then, again, shortly after her divorce several years ago. On physical exam she appears jaundiced with distended abdomen and pedal edema. Laboratory tests show albumin 2.6 g/dL, total bilirubin 4.4 mg/dl, total cholesterol 95 mg/dL, AST 23 U/L, ALT 30 U/L, GGT 98 U/L, international normalized ratio 2.2, Creatinine 1.2 mg/dl, Hb 10.9 g/dL. Her breath alcohol level is 0.04%. Serum serologies are negative for hepatitis B or C. Abdominal ultrasound indicates presence of a nodular liver surface, increased caudate-right lobe ratio, portal hypertension and splenomegaly.

Psychiatry consult is called to address her alcohol use and past depression. The patient reports drinking heavily for the past 20 years. Her longest time of sobriety has been for 3 months following a brief hospital stay for alcohol detoxification 7 years ago. She intermittently attends Alcoholics Anonymous meetings. She has been mandated to outpatient alcohol rehabilitation multiple times after driving while intoxicated. She smokes 20 cigarettes daily for the past 20 years.

She is admitted to the medical service for alcohol detoxification, further evaluation and treatment of presumptive alcoholic liver disease. Signs and symptoms of alcohol withdrawal are monitored via the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) and lorazepam is administered on a symptom-triggered regimen. Thiamine and B-group vitamins are also administered. An upper endoscopy indicates the presence of esophageal varices, and a CT scan confirms the presence of liver cirrhosis and portal hypertension with no evidence of hepatocellular carcinoma. A more comprehensive psychiatric evaluation confirms DSM-5 diagnosis of severe alcohol use disorder, tobacco use disorder, and past Major Depressive Disorder. The internist and psychiatrist meet with the patient and explain the diagnosis of end-stage liver disease, its etiology and the indication for orthotopic liver transplantation. The patient agrees to begin outpatient alcohol rehabilitation. She will also be followed by her hepatologist who will begin the process of waitlisting for liver transplant. The psychiatrist and the patient discuss alcohol rehabilitation options and agree to start a combined treatment that includes a behavioral treatment with adjunctive pharmacotherapy in order to maximize her chance of maintaining alcohol abstinence. For the behavioral treatment, the patient meets with a clinical psychologist to start motivational interviewing sessions that will continue during outpatient rehabilitation. For the pharmacotherapy, the psychiatrist discusses options with the patient, including both medications approved by the Food and Drug Administration (FDA) for alcoholism (disulfiram, naltrexone, acamprosate), as well as other non-approved medications that have some evidence of efficacy that may be considered (topiramate, ondansetron, baclofen, gabapentin and varenicline). Disulfiram and naltrexone are excluded, given the risk of liver toxicity. The hepatotoxic risk of ondansetron is uncertain, so this option is also excluded. The FDA-approved medication, acamprosate, and the possible off-label prescription of topiramate, baclofen, gabapentin or varenicline are considered. Topiramate is ruled out as cognitive side-effects might confound onset of hepatic encephalopathy for which the patient is being treated prophylactically with lactulose. Acamprosate is avoided as it may worsen diarrhea associated with lactulose. The remaining three options (baclofen, gabapentin and

varenicline) are discussed. As the patient is a smoker, and is willing to consider quitting now learning of her new diagnosis of severe liver disease, varenicline is started. Either baclofen or gabapentin will be considered, should she not respond to varenicline (e.g., alcohol relapse and/or reported high cravings).

This case is discussed by the liver transplant team along with her internist and psychiatrist. Some members of the liver transplant team argue that the patient should only be considered for the wait list when and if a documented 6-month period of sobriety is achieved. The psychiatrist and internist observe that the patient has agreed to begin alcohol rehabilitation and advocate that she be waitlisted presently as her Model For End-Stage Liver Disease (MELD) score of 23 carries a ~60% 90-day mortality rate. It is agreed to include the patient in the liver transplant waiting list. The patient receives liver transplant 49 days after waitlisting and has now been followed by the internist, the psychiatrist and the rest of the liver transplant team for 12 months after the surgery, during which “Ms. W.” remains abstinent from alcohol.

Data were obtained for the Review by searching the published medical literature from the late 1940’s to February 19, 2015. The searches were conducted in Medline (PubMed), Embase, and PsycInfo. There were no language restrictions; the search was limited to Humans. The search terms used were alcoholism or alcohol use disorder AND alcoholic liver diseases or alcoholic liver cirrhosis or alcoholic hepatitis or alcoholic fatty liver or end-stage liver disease AND liver transplantation.

Alcohol Use Disorder

Epidemiology of Alcohol Use Disorder—Approximately 17 million adults ages ≥ 18 (7.2% of this age group) had an alcohol use disorder in 2012(1). About 1.4 million adults received treatment for alcohol use disorder in 2012 (8.4% of adults in need) which included 416,000 women (7.3% in need) and 1.0 million men (8.9% in need)(1). Alcohol misuse represents the third largest risk factor for disease burden worldwide, including end-organ damage(2).

Diagnosis and Evaluation of Alcohol Use Disorder—The CAGE and the Alcohol Use Disorders Identification Test questionnaires may be used to screen for consequences of drinking and hazardous alcohol consumption. The Fifth Edition of the Diagnostic and Statistical Manual(3), is used to diagnose alcohol use disorder using a list of 11 symptoms, with mild (2–3 symptoms), moderate (4–5 symptoms) and severe (6+ symptoms) sub classifications. As such, the DSM-5 provides a different apportioning of severity compared to the DSM-IV abuse/dependence dichotomy.

The DSM-5 criteria do not quantify alcohol use. A semi-structured interview, the Time-Line Follow-Back(4), has become the “gold standard” for obtaining quantitative drinking information allowing the interviewer to guide the patient to obtain more accurate information compared to self-report measures.. Objective biomarkers have been sought though no one has the sensitivity to reliably detect heavy drinking. Mean corpuscular volume is a poor indicator of excessive alcohol use. Other objective candidate biomarkers

include ethyl glucuronide, ethyl sulphate and carbohydrate-deficient transferrin but none of them has reached standard point-of-care in clinical practice(5). Notably, a combination of carbohydrate-deficient transferrin and GGT using a formulated equation improves the sensitivity of detecting heavy drinking without a loss in assay specificity(6).

Alcoholic Liver Disease

Alcohol is a major risk factor for all liver diseases, including cirrhosis(7). Worldwide in 2010, alcohol was one of the top 5 risk factors responsible for Disability Adjusted Life Years lost and this represents an increase from ranking 8th in 1990(8). While the amount of alcohol consumed over time is the most important risk factor for developing alcoholic liver disease, the relationship is not entirely dose dependent(9). Other major risk factors play a role, including nutritional status, female sex, hepatitis viral infection, genetic predisposition, age and others(10, 11). Factors that increase the risk of alcohol use disorder and those that increase susceptibility to alcoholic liver disease are not necessarily the same. While genetic variation of the alcohol dehydrogenase, aldehyde dehydrogenase and gamma-aminobutyric acid pathways may be associated with alcohol use disorder, they do not increase the risk of alcoholic liver disease(12). By contrast, genetic polymorphisms of the tumor necrosis factor-α gene and the patatin-like phospholipase domain-containing 3 (*PNPLA3*) gene have been found to modulate liver steatosis, inflammation and fibrosis.

Role of Liver Transplantation in Treating End-Stage Liver Disease in Patients with Alcohol Use Disorder

General Indication for Orthotopic Liver Transplant

Liver transplant is a standard treatment for end-stage liver disease and successful liver transplant extends life expectancy and enhances quality of life. The American Association for the Study of Liver Diseases guideline states that patients with cirrhosis should be referred for transplantation when they develop evidence of hepatic dysfunction, quantified as a Model for End-stage Liver Disease (MELD) score >10 or with onset of ascites, variceal bleeding and/or hepatic encephalopathy(13). The MELD is a mathematical model that incorporates serum creatinine and bilirubin levels with the international normalized ratio and is the main measure used to place patients on the waitlist and to prioritize their rank therein.

Patients with alcohol use disorder and end-stage liver disease: Referral for liver transplant

Either alone or in combination with hepatitis C infection, alcoholic liver disease accounted for 20% of all the primary liver transplants in the US over 1988–2009 accounting for >19,000 recipients and is the second most common indication for liver transplantation(14).

Without transplant, 5-year patient survival is as low as 23% in end-stage alcoholic liver disease, however 5 year survival with liver transplant is as much as 88%(15). For end-stage alcoholic liver disease, there is an estimated 95% of patients who are not referred for evaluation even when American Association for the Study of Liver Diseases guidelines for referral are met(16), in addition to disparities in rates of wait listing for liver transplant based on geography, sex, acuity of illness and ethnicity(17).

One important reason for this low referral rate is the bias held against alcoholic patients as candidates for liver transplantation particularly by community practitioners(18) who may be reluctant to consider giving a scarce resource to those who have failed to treat their alcoholism but who develop end-stage liver disease for reasons beyond their control(19). The probability of referral for alcohol etiologies of end-stage liver disease remains significantly less compared to non-alcoholic etiology regardless of current drinking status(20). Nevertheless, patients who are transplanted for alcoholic liver disease have graft survival rates comparable or even higher than those of patients with other etiologies for their liver diseases(21). Furthermore, judgments of moral responsibility are not made for other addictions, such as smoking(21).

Current drinking is another major reason for not referring a patient for liver transplant evaluation. A 6 month minimum period of abstinence (the “6-month rule”) before being considered eligible for liver transplant is commonly enforced and required by most insurance companies(22). Evaluating sobriety is challenging as the accuracy of self-report measures is questionable and most objective measures have limited specificity and only reflect recent use of alcohol. The 6-month abstinence rule is controversial as there is evidence that a threshold of 6 month’s abstinence is a poor indicator for future abstinence even though there is an inverse correlation between time of sobriety and risk of relapse(23). In cases where patients are transplanted before being required to be abstinent for 6 months, as in patients with severe alcoholic hepatitis unresponsive to medical therapy, there is a long-term survival advantage(24). Importantly, only return to excessive drinking impacts survival post-transplant while return to occasional or moderate drinking does not affect outcomes post-transplant(14). Therefore, instead of evaluating drinking as abstinence or not, it is important to evaluate severity of drinking in order for this parameter to be clinically relevant. Furthermore, there are multiple factors that predict relapse, post-transplant, including absence of social support, family history of alcoholism, presence of psychiatric comorbidity among others(25).

In the majority of transplant centers in the US, resumption of drinking after listing for a liver transplant, results in removal from the list either permanently, in 15% of centers or temporarily with almost half removing a patient for an additional 6 months, potentially compromising survival in severely ill patients(22). In addition, only a small number (<10%) of centers, require treatment for those patients who relapse(22).

Nevertheless, according to the American Association for the Study of Liver Diseases guidelines for liver transplantation, it is optimal to refer patients with alcoholic liver disease early for evaluation of liver transplant to provide time for psychosocial assessment and to set addiction treatment goals in addition to 6 months abstinence and compliance with an addictions specialist’s recommendations(13).

Gender differences in waitlisting and transplantation that are relevant to management of alcohol use disorder

There are fewer women than men on the liver transplant waitlist (38 vs. 62%, respectively). Women have a higher risk of hepatic damage at lower doses of alcohol exposure(26). Once diagnosed with alcoholic liver disease, women have more rapid acceleration to liver fibrosis

than men(27). In accordance with this, while women may have greater access to the transplant list(17), they have worse waitlist outcomes with longer waitlist times: women are 30% less likely than men to receive a transplant within 3 years of listing(28). They also are at higher risk of death or becoming too sick for liver transplant(29). To some extent this has been linked to lower MELD scores due to lower serum creatinine levels in women, thereby underestimating reduction in true renal function in female patients compared to men(30). Longer waitlist times necessitate more careful treatment to minimize the risk of removal from the waitlist for relapse to drinking. Post-transplant, there is evidence of increased relapse rates and poorer psychosocial outcomes in women(31), highlighting the particular need for ongoing relapse prevention treatment in this group.

Pre-transplant psychiatric assessment

According to the American Association for the Study of Liver Diseases guidelines, the evaluation for liver transplantation in adults, requires a psychosocial evaluation(13). The major issues to be addressed are ability to comply with medical directives, existence of social supports particularly in the peritransplant period, and existence of psychiatric disorders including drug and alcohol use disorders that can compromise well-being and adherence to medical directives(13).

Factors predicting relapse have been recently reviewed comprehensively in(32). Important factors to assess that are associated with a higher risk of alcohol relapse are inability to remain abstinent pre-transplant, presence of alcohol dependence vs. abuse, longer duration of heavy drinking and number of drinks per drinking day, family history of alcoholism, previous unsuccessful attempts to treat alcoholism, lack of social supports, and psychiatric comorbidity. There is no psychiatric disorder that is an absolute contraindication to liver transplant including psychosis or mental retardation(13). A diagnosis of depression has been associated with increased risk of relapse to drinking post-transplant, however, it does not appear to be associated with poorer post-transplant morbidity or mortality; rather, depression in the immediate post-transplant period is associated with a higher risk of morbidity and mortality(33). Again, this supports the important role for careful, close post-transplant psychiatric monitoring and care.

Management of patients with alcohol use disorder who are candidates for liver transplant

Abstinence from alcohol is the most important therapeutic goal for patients with alcoholic liver disease because it can improve outcome at all stages of alcoholic liver disease including overall survival(34)., Established treatment for the liver damage itself may not be effective, if alcohol consumption continues. For example, a recent multisite trial in the UK failed to show an effect of medications for alcoholic hepatitis, prednisolone and pentoxifylline (either alone or combined) on outcome, mortality and liver transplant(35). However, no formal treatment for relapse prevention was integrated in the outpatient phase of this trial, highlighting again the need for adjunct long-term rehabilitation treatments for these patients.

Management of Alcohol detoxification in End-Stage Liver Disease

While up to 50% of patients with alcohol use disorder manifest withdrawal symptoms upon alcohol discontinuation, only a small percentage of them develops clinically significant symptoms requiring medical treatment. Patients are more likely to present with hypoglycemia and electrolyte disturbances secondary to the neurohormonal changes that occur in liver failure including hepato-renal syndrome. Concomitant medications for end-stage liver disease, such as furosemide and/or spironolactone also contribute to fluid management problems.

General supportive care should correct fluid balance and electrolyte disturbances, hypoglycemia and should include hydration and vitamin supplementation including folate and thiamine. Since prolonged glucose supplementation without the addition of thiamine can be a risk factor for the development of Wernieke's Encephalopathy, thiamine supplementation should be given promptly(36).

The severity of withdrawal is typically measured by using ranked scales, most commonly, the Clinical Institute Withdrawal Assessment for Alcohol—revised (CIWA-Ar) scale. While scores > 8 but < 15 indicate a potential need for a pharmacological treatment, an alcohol withdrawal syndrome with a CIWA-Ar score > 15 must be treated pharmacologically. Benzodiazepines are considered the gold-standard treatment for alcohol withdrawal syndrome since they also educe n the risk of withdrawal seizures and/or delirium tremens. Benzodiazepines may be delivered as a fixed dose or triggered by CIWA-Ar score. The latter is usually preferred as it minimizes unnecessary dosing of benzodiazepines whose clearance is compromised in end-stage liver disease. There is no evidence that any benzodiazepine is significantly superior to the others in the treatment of alcohol withdrawal syndrome. However, while long-acting benzodiazepines such as diazepam and chlordiazepoxide provide more protection against seizures and delirium tremens due to their long half-lives, shorter-acting benzodiazepines, such as lorazepam, temazepam and oxazepam are preferable in patients with reduced liver function due to their primary urinary excretion.

Finally, several other medications have been investigated for use in this population to treat alcohol withdrawal syndrome such as clonidine, atenolol, carbamazepine, valporic acid, topiramate, baclofen, gabapentin and pregabalin(36). Among them, gabapentin, topiramate and baclofen have the advantages of having no or little hepatic metabolism and being able to be continued through the post-withdrawal period to prevent relapse [reviewed in:(10)]. However, unlike benzodiazepines, none of these medications has proven their efficacy in preventing the complications such as seizures and delirium tremens.

Psychosocial treatment to promote abstinence and prevent relapse in end-stage liver disease patients

Psychosocial interventions prior to transplant appear to reduce drinking in the period before the surgery. In a recent randomized study, motivational enhancement therapy combined with contingency management was superior to treatment as usual with respect to daily drinking during the wait list period(37). Recently, a retrospective study(38) compared the alcohol outcomes of patients being offered addiction counseling by a provider outside the transplant

unit versus those who received treatment by addiction specialists integrated within the transplant unit. The latter group showed less alcohol recidivism and lower mortality rates after liver transplant, emphasizing the utility of an integrated team caring for this population. Timing of the intervention seems to be important as treatment before and after transplant reduced relapse rates post-transplant compared to those receiving treatment only pre-transplant or not at all(39). Lastly abstinence contracts do not seem to impact relapse rates(40), although more work needs to be done on this approach as a potential effective intervention.

Pharmacological treatment to promote abstinence and prevent relapse in end-stage liver disease patients

Consistent with the increasing knowledge of the neurobiology of addictions, treatment options for alcohol use disorder have been expanded from psychosocial and behavioral approaches alone to ‘adjunct’ pharmacotherapy interventions(Table 1). Of the three medications approved by the Food and Drug Administration (FDA) to treat alcohol use disorder (disulfiram, naltrexone, acamprosate), acamprosate, which undergoes minimal hepatic metabolism, has few, mild side-effects and no liver-related side-effects. Thus, its use in alcoholic patients with end-stage liver disease should be safe.

Other promising medications that are FDA-approved for other indications have been tested in phase 2/3 trials and some of them are often used off-label for alcohol use disorder, including topiramate, ondansetron, baclofen, gabapentin and varenicline [Table 1; for review, see (10)]. Most of these medications have no evidence of liver toxicity, although only baclofen has been formally tested for safety and efficacy in alcoholic patients with end-stage liver disease [for review, see: (10)]. Baclofen titrated up to 30 mg/day in three divided doses was tested in a 12-week randomized clinical trial with alcoholic patients with liver cirrhosis (n = 84). Treatment with baclofen, compared to placebo, resulted in significant increase in number of abstinent patients and total days of alcohol abstinence, and significant decrease in alcohol craving. Additionally, baclofen treatment, compared to placebo, was associated with improved liver function tests and was safe, including in a sub-set of patients with hepatitis C virus co-infection [for review, see (10)]. Further open-label studies have shown that baclofen promotes alcohol abstinence and improves liver function in alcoholic patients with liver damage and in a group, albeit very small, of post-transplant alcoholic patients(38).

Finally, combined pharmacotherapies for alcohol use disorder have been studied and may offer advantages using potentially hepatotoxic drugs at lower doses in combination with drugs that have shown some efficacy that do not undergo hepatic metabolism [for review, see: (41)].

Special Issues in Patients with Alcoholic Liver Disease and Liver Transplant

Smoking cessation treatment in patients with alcoholic liver disease

Up to 60% of liver transplant candidates have a lifetime history of smoking and the prevalence in alcoholic liver disease is up to 70%(42). Smoking is considered to be

responsible for morbidity and mortality after liver transplant, contributing to the increased incidence of cardiovascular disease and cancers in this group(21, 43). Therefore, ongoing treatment for cormorbid nicotine addiction when managing liver transplant candidates is important. Varenicline, FDA-approved for smoking cessation, with minimal hepatic metabolism has been shown to reduce drinking and smoking in a recent randomized controlled trial with alcoholic patients (n = 200)(44). As such, varenicline may represent a promising addition to potential pharmacologic treatment for this comorbidity, including in the context of liver transplant.

Effect of liver transplant on mental health and drinking outcomes

DiMartini and colleagues(45)assessed trajectories of depressive symptoms in the first year after transplant. Identifying three distinct patterns of symptoms, patients with persistently high levels of depression and patients with increasing levels of depression were more than twice as likely to die on follow up compared to the group with consistently low depression scores. Of note, 50 % of each group abstained from alcohol and there were no significant differences in these 3 groups in alcohol consumption or death due to recurrent alcoholic liver disease. In another study, early return to problematic drinking post-transplant was associated with poorer health, more stress, pain and demoralization that the transplant did not restore feelings of well-being(46).

Viral complications in end stage alcoholic liver disease and the effect on transplant outcomes for alcoholic liver disease

There is considerable comorbidity between alcoholic liver disease and hepatitis C infection; alcohol use worsens the course of hepatitis C infection(47). In addition, waitlist mortality for those with both liver disease etiologies is higher than for those with either etiology alone(48). Liver transplant graft and patient survival outcomes for hepatitis C, hepatitis C and alcohol along with hepatocellular carcinoma are the lowest of all the etiologies for liver transplant(49) with patients transplanted for alcoholic and hepatitis C etiologies having lower survival compared to those with alcoholic and hepatitis B etiologies(21). There is no evidence that there is increased recurrence of hepatitis C post-transplant in those transplanted for combined etiologies compared to hepatitis C alone(50) or that return to alcohol drinking post-transplant worsens liver function(51). By contrast, comparing quality of life benefits by pre-transplant etiology(52), at 1 year follow up, those transplanted for combined etiologies of alcohol and hepatitis C had worse quality of life measured in all domains. Over 12 years follow up, the scores for physical functioning and symptoms continued to decrease. These differences remained after controlling for medical factors before transplant and there were no group differences in alcohol or tobacco use. According to these results, patients transplanted for both hepatitis C and alcoholic liver disease realize fewer improvements in quality of life compared to patients who are transplanted for other etiologies. Special efforts should be made in post-transplant rehabilitation programs for this at-risk group to restore quality of life and to maintain maximal quality of life levels attained.

Encephalopathy, Cognitive Fluctuations, Psychotropic Dosing

Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and/or porto-systemic shunting. It is recurrent, episodic and manifests as a wide spectrum of neurological

or psychiatric abnormalities ranging from subclinical findings (unimpaired) to Grade IV or coma(53). It does generally resolve after liver transplant. Hepatic encephalopathy will occur in 30–40% of those with cirrhosis at some time in their clinical course and is one of the factors in advancing the MELD score for those on the liver transplant waitlist as it carries a poor prognosis. On one end of the clinical spectrum, minimal hepatic encephalopathy is found in the setting of normal clinical exams but manifests as abnormalities in neuropsychological tests probing attention, working memory, visual spatial processing, electroencephalography(54). Overt hepatic encephalopathy, presents with a panoply of neuropsychiatric symptoms in the domains of neurological, cognitive, affective, behavioral and bioregulatory symptoms. When evaluating cognitive fluctuations in patients awaiting transplant, it is important to consider factors that precipitate mental status changes such as gastrointestinal bleeding, electrolyte disturbances, medications, infections, among others [for review, see: (53)]. It is important to distinguish alcohol-related dementia from hepatic encephalopathy as the former is irreversible, thus constituting a consideration for waitlisting. Of particular relevance, given the high incidence of neuropsychiatric disturbances in this population, psychotropic medications especially those undergoing hepatic metabolism must be administered with caution. Whenever possible, psychotropic medications that are renally excreted should be used such as lithium, topiramate, gabapentin or pregabalin. Overall, drugs that undergo glucuronidation rather than oxidation as it primary hepatic metabolism should be favored as this is relatively preserved late in hepatic failure(55).

Final Recommendations

Given that alcohol use disorder is the second most common etiology for liver transplant, management of the antecedent disorder is of paramount importance. Indeed, given the recent development of highly effective interferon-free treatments for hepatitis C virus, alcohol as well as nonalcoholic steatohepatitis will emerge as the two major etiologies for liver transplant. Provision of integrated psychosocial and pharmacologic treatment administered by addictions specialists who are integral members of the transplant team is strongly needed and recommended. This allows for consistent treatment by addiction specialists who can optimize medication and psychosocial management. Experience to date shows that the integrated team approach, comprehensive, contextual evaluation of substance use, instituting behavioral, psychosocial and pharmacologic interventions pre-transplant, and continuing these after surgery are strategies that optimize outcomes in patients with alcohol use disorder awaiting for and after liver transplant.

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Table 1

Medications that may be used for alcohol use disorder patients and their potential use in alcoholic patients with End-Stage Liver Disease

Medication	Dosage	Pharmacological Target(s)/Action	Metabolism/Excretion	Consider for use in alcohol use disorder / end-stage liver disease	Additional Information
FDA-approved Medications:					
Disulfiram	250–500mg QD	Acetaldehyde Dehydrogenase Inhibitor	Hepatic/Hepatic	No	"*Disulfiram reaction*" within 15 minutes from alcohol ingestion: flushing, headache, nausea, vomiting, sweating thirst, palpitations, etc.
Naltrexone	50 mg P.O. QD 380 mg I.M. monthly	μ-opioid receptor antagonist	Hepatic/Renal	No	Perceptions of liver toxicity limit use in end-stage liver disease. Caution if given with opiate medication: precipitate withdrawal.
Acamprosate	666mg TID	Unclear (possibly NMDA agonist)	Minimal/Renal	Yes	
***Not FDA-approved Medications:**					
Topiramate	300 mg QD	Several targets ($GABA_A$, AMPA/kainite glutamate, Ca and Na channels)	Hepatic/Renal	Possibly	Caution especially in end-stage liver disease patients with hepatic encephalopathy
Ondansetron	1–16 mcg/kg BID	$5HT_3$ antagonist	Hepatic/Renal	Possibly	Reported hepatotoxicity, although relationship with ondansetron cannot be clearly determined
Baclofen	10mg TID; 80 mg QD max	$GABA_B$ receptor agonist	Minimal/Renal	Yes	Formally tested in a randomized clinical trial with alcoholic patients with liver cirrhosis (see text for details)
Gabapentin	900–1800 mg QD	Unclear (Possibly modulates GABA transmission)	Minimal/Renal	Yes	

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Medication	Dosage	Pharmacological Target(s)/Action	Metabolism/Excretion	Consider for use in alcohol use disorder / end-stage liver disease	Additional Information
Varenicline	2 mg QD	Nicotinic acetylcholine receptor partial agonist	Minimal/Renal	Yes	FDA approved for smoking cessation(see text for the importance of addressing smoking in liver transplant)

*These medications are approved by the Food and Drug Administration (FDA) for other indications but not for alcohol use disorder