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Liver disease and pharmacotherapy for alcoholism

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Abstract

A common clinical question to addiction specialists concerns whether a medication to treat a patient???s alcoholism should be used and if so, when could such be commenced given the patient has liver disease. Alcohol consumption itself is a principal driver of alcoholic liver disease and as such, should prompt treatment intervention. While there is a reasonable evidence for medications that treat alcoholism, very little evidence exists to guide the decision to use such medication in the presence of clinically significant liver disease. This presentation reviews recent literature on pharmacotherapy for alcohol dependence relating particularly to patients having comorbid liver disease and alcoholism. It concludes with an outline for a Risk versus Benefit approach to pharmacotherapy decision-making.

Alcoholic liver disease (ALD), which ranges from simple steatosis to cirrhosis and hepatocellular carcinoma (HCC), continues to represent a major health issue in the United States and abroad. Despite significant advances in the understanding of the pathogenesis of alcohol-related liver injury, there are no FDA-approved treatments for ALD. The purpose of this review is to examine the diagnosis and current modalities of treatment for ALD. At present, abstinence remains the cornerstone for successful treatment of ALD. Aside from treatment of the underlying addiction, aggressive nutritional intervention and 'off-label' use of various pharmacotherapies aimed at the underlying mechanisms of injury (e.g., cytokine dysregulation, endotoxin translocation and oxidative stress) represent our approach to treating ALD.

Although alcohol abuse and/or dependency are not prerequisites to the development of ALD, the two often correlate with one another. Alcohol addiction is divided into two categories: abuse and dependence. Alcohol abuse is defined as excessive drinking without harmful physical and social consequences. In contrast, alcohol dependence is defined as continued drinking despite physical and social harms [Lucey, 2009]. These diagnoses are commonly based on history and evidence of harm (e.g., organ damage, legal/social difficulties and/or increased injuries secondary to intoxication). Only 24% of problem drinkers will actively seek assistance, and just 13% will receive specialized addiction treatments. Primary care physicians represent the first line of detection, but only 50% of problem drinkers were identified by their physicians. In light of this, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) published guidelines in 2007 to assist primary care physicians in screening for problematic drinking. Methods as basic as a single question inquiring how often has the maximum daily alcohol limit been exceeded in the past year have greatly improved diagnosis of alcohol abuse and dependence. Other screening tools such as the CAGE (need to cut down, annoyed by criticism, guilty about drinking, need for an eye-opener in the morning) and the AUDIT-C (Alcohol Use Disorders Identification Test) have also increased detection of problem drinking in the physician's office [Bradley et al. 2007]. On the CAGE questionnaire, two positive answers indicate alcohol dependency with a sensitivity of more than 70% and specificity of more than 90%.

A large obstacle in making the diagnosis of alcohol abuse is patient reluctance to openly share a drinking history if it may be viewed as excessive or problematic. A recent study reiterated this by demonstrating that electronic administration of the AUDIT-C was more likely to identify at-risk drinking than the same screening questionnaire administered orally or on paper.Alcoholic cirrhosis is a leading indication for OLT in North America. Multiple studies consistently indicate improved survival in severe ALD, and similar outcomes in patients receiving liver transplantation for ALD and other etiologies. A recent case–control study comparing long-term outcomes of OLT in patients with ALD versus hepatitis C virus (HCV) infection confirmed 9-year survival rates in patients with ALD is comparable to HCV. Another recent comparison of ALD and HCV as indications for OLT, evaluated the effects of ALD and HCV infection on waiting list mortality, posttransplant mortality, and the survival benefit. The study revealed that the presence of ALD does not influence liver transplant survival benefit. Patients grafted for ALD do appear to have a higher incidence of some malignancies following liver transplantation (e.g., upper airway and upper gastrointestinal track).

Finally, quality of life appears to improve in patients who undergo OLT for ALD and this rate of improvement is similar to that associated with other forms of liver disease
Regarding the severity of liver disease and transplantation, a recent randomized trial compared immediate listing for liver transplantation versus standard care for Child-Pugh stage B alcoholic cirrhosis.Furthermore, there was an increased the risk for extrahepatic cancer in patients in the immediate listing arm Importantly, other studies have

likewise indicated that patients with more severe disease are more likely to benefit from OLT.Among the major concerns regarding liver transplantation for ALD, a return to drinking after transplant is perhaps the most vexing. Extensive attempts at identifying potential pretransplant predictors of recidivism have revealed conflicting results.

In addition, studies examining the likelihood of posttransplant drinking on survival and graft failure are equally inconsistent. The current practice in most transplant centers is to require a 6-month period of abstinence prior to listing for OLT. The 6-month period is not based on prospectively gathered data but rather on custom and practice [Neuberger et al. 2002]. As to pretransplant predictors of recidivism, several factors have been studied including: mental illness, the lack of a stable partner, grams per day consumed in the years before assessment for transplant, reliance on 'family or friends' for posttransplant support, tobacco consumption at time of assessment, lack of insight into the alcohol etiology, duration of pretransplant abstinence, number of prior alcoholism inpatient treatment experiences, a family history of alcoholism and others.

Results from the multitude of studies have failed to show consistent. While some patients will inevitably return to some level of alcohol use, there is conflicting evidence that this has a significant influence on either patient or graft survival.

One important distinction appears to be in differentiating abusive from nonabusive drinking when examining outcomes. For example, in a recent retrospective analysis studying survival and alcohol use in 300 patients transplanted for ALD, survival rates of patients who resumed abusive drinking were significantly lower than survival rates of abstinent patients or patients with minor lapses. In contrast, in the aforementioned study comparing long-term outcomes of OLT in patients with ALD versus HCV infection, the alcoholic recidivism rate was 28% without influence on patients or graft survival. The study did not differentiate patterns of recidivism (abusive versus nonabusive drinking). ALD remains a major cause of liver related mortality in the US and worldwide. Clinicians should be well versed on the diagnosis and treatment of the wide spectrum of hepatologic conditions associated with ethanol intake. In conjunction with the 2010 AASLD/ACG guidelines on the treatment of severe alcoholic hepatitis, PTX should be considered an alternative to corticosteroids and appears to especially effective in ALD patients with renal dysfunction/hepatorenal syndrome. Biologics, such as specific anti-TNFs, have been disappointing and should probably not be used outside the clinical trial setting. Future areas of research include the safety, efficacy, and ethical considerations of liver transplant in severe ASH for patients who are not responding to medical therapy.

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