

Management of Alcoholic Liver Disease

Michael R. Lucey, MD, FRCPI

KEYWORDS

- Alcohol • Alcoholism • Cirrhosis • Hepatitis
- Abstinence

ADDICTION TO ALCOHOL

Addictions usually arise from pleasurable actions, and immediate gratification is the most common foundation for addiction. In the case of alcohol, the addictive state is divided into 2 classes within a spectrum: abuse, in which drinking is excessive but does not lead to many of the physical and social harmful consequences, and dependency, wherein drinking is continued despite physical and social injury. Ask an alcoholic person why they continue to drink, despite the obvious havoc alcohol is bringing to their lives and the lives of their family, and they will often say, “I drink because I like it.”

The combination of gratification from the substance with the unwanted effects of the treatment, such as inconvenience of attending psychological therapy, embarrassment, financial disincentives, and ambivalence about the addictive behavior, can all contribute to addiction persisting. Consequently, substance abuse and addiction are disorders of remission and relapse.

Most reviews of alcoholic liver disease concentrate on treatment of the liver disease and do not address the underlying addiction. In practice, understanding the addiction is the key to understanding the continuum from alcoholic fatty liver to alcoholic cirrhosis. Furthermore, abstinence leads to resolution of alcoholic fatty liver and alcoholic hepatitis,^{1,2} and, as shown by the classic studies of Powell and Klatskin, is associated with improved survival in alcoholic cirrhotic patients with decompensated liver function (**Fig. 1**).³ Consequently, there is every reason to encourage alcoholic patients with liver disease to become abstinent.

When counseling an alcoholic patient, addiction specialists distinguish between a slip and a relapse.⁴ A slip is a temporary return to drinking, which is recognized by the patient as potentially harmful, and leads to renewed efforts toward abstinence. A relapse suggests a more sustained resumption of drinking. These events are sometimes characterized as “harmful,” “abusive,” or “addictive drinking,” whereas the term “recidivism” is abjured on account of its pejorative connotations.

Section of Gastroenterology and Hepatology, Department of Medicine, University of Wisconsin School of Medicine and Public Health, H6/516 CSC, 600 Highland Avenue, Madison, WI 53792, USA
E-mail address: mrl@medicine.wisc.edu

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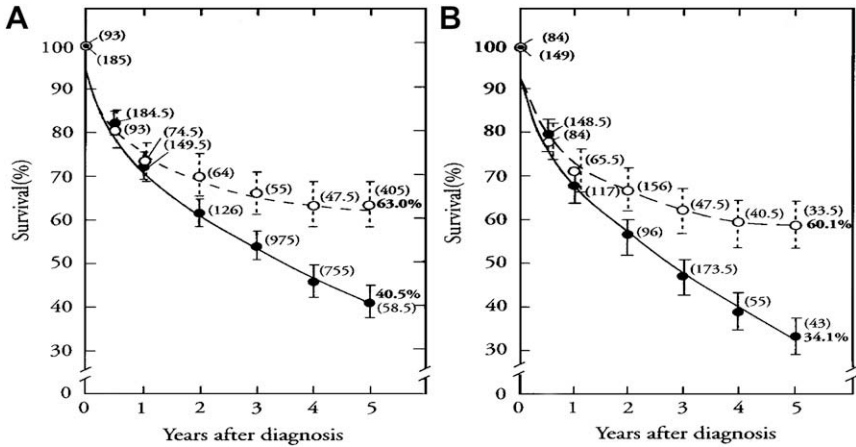


Fig. 1. Survival after diagnosis of alcoholic cirrhosis ($n = 278$) and from onset of decompensation ($n = 233$) according to continued alcohol use or abstinence. (From Powell WJ Jr., Klatskin G. Duration of survival in patients with Laennec's cirrhosis. Influence of alcohol withdrawal, and possible effects of recent changes in general management of the disease. *Am J Med* 1968;44(3):406-20; with permission.)

Treatment of addiction is directed at establishing and maintaining abstinence from the addictive behavior. Although continuing drinking that is less frequent or of reduced amounts is less than ideal, it is better than continuing harmful drinking. In contrast, in the world of hepatology, especially transplant, absolute abstinence is considered the only acceptable outcome, and any slip is judged to be a treatment failure. Many addiction specialists think that this is an unreasonable and unrealistic standard.⁴ Furthermore, some specialists believe that this preoccupation with complete abstinence works against the best interests of the alcoholic patient with liver failure, since the patient may be frightened to seek help when he or she experiences a slip.⁵ Recent long-term follow-up data suggest that relapse to harmful drinking affects survival after transplantation, whereas a history of a slip alone does not, further emphasizing the importance of this clinical distinction.⁶

TREATMENT OF ALCOHOLISM IN PATIENTS WITH LIVER DISEASE

Many alcoholic patients resume alcohol use despite life-threatening events such as variceal hemorrhage.⁷ However, we understand only poorly what drives an alcoholic patient with liver disease to maintain abstinence, to slip and regain sobriety, or to relapse to harmful drinking. It is probable that alcoholic patients attending liver clinics or admitted as inpatients do not constitute a homogenous group but rather are a heterogeneous group determined in large part by selection biases. For example, both patients with alcoholic hepatitis and many alcoholic patients who present with acute variceal hemorrhage report recent alcohol use. In contrast, many alcoholic patients undergoing evaluation for liver transplantation usually report extended intervals of abstinence, often many years in duration.

The likelihood of alcoholic relapse and the motivation for treatment of alcoholism vary in these subgroups also. Thus, when a group of alcoholic patients undergoing transplant evaluation were compared with a matched group of alcoholics recruited to outpatient trials of alcoholism treatment, the liver clinic cohort reported significantly

longer sobriety, little craving for alcohol, and low interest in treatment of alcoholism, whereas the group without liver disease reported significantly greater craving for alcohol and desire for treatment of alcoholism.⁸ The perception that alcoholism is no longer a problem is common among alcoholic liver transplant recipients and limits their support for treatment.⁹

A comprehensive review of all interventions, psychological and medicinal, designed to ameliorate drinking behavior in alcoholic persons is beyond the scope of this review. Suffice it to say that few studies of treatment of alcohol abuse or dependence have included patients with alcoholic liver disease. Many use nuanced qualitative measures of reduced drinking, such as proportion of abstinent days and number of days with addictive drinking, as primary outcomes.^{10,11} Harder endpoints, such as survival, or measures of liver health, such as the model for end-stage liver disease score, have rarely been assessed. There are few studies of psychological therapies directed at patients with significant liver injury. In one such example, the present author in conjunction with Robert Weinrieb of the University of Pennsylvania conducted a randomized study of motivational enhancement therapy (MET) versus treatment as usual in patients undergoing evaluation for liver transplantation (unpublished observations). Approximately 25% of subjects in either group admitted to some drinking in the period of follow-up, without any apparent benefit from MET.

As Garbutt and Flannery noted in 2007, “pharmacotherapy for alcoholism is undergoing a period of growth and scientific excitement.”¹² However, there is a paucity of studies on the use of medications to deter patients with alcoholic liver injury or cirrhosis from drinking. Disulfiram, an antagonist of acetaldehyde dehydrogenase, has the longest period of approval for use in treating alcoholism. Hepatotoxicity and liver failure have been reported with use of disulfiram.^{13,14} Furthermore, evidence of its efficacy is conflicting, and it has not been studied in a controlled fashion in patients with liver disease.

New drugs, such as oral or depot naltrexone and oral acamprosate, have been approved for use in alcoholic patients, whereas agents approved for other indications, such as baclofen or topiramate, have shown promise in controlling drinking behavior in alcoholic persons. Apart from baclofen, each of the studies mentioned below eschewed patients with known alcoholic cirrhosis. Concern remains about hepatotoxicity with naltrexone, which has a “black box” warning on this account. In the studies of agents designed to reduce the craving for alcohol described later, the observed effects have been modest reductions in total drinking, rather than substantial increases in total abstinence. Whether these qualitative effects would be accompanied by salutary effects on liver function, injury, or repair has not been shown, and therefore, it is too early to advocate their use in cirrhotic patients.

Several American multicenter clinical trials of the opioid receptor antagonist naltrexone have yielded conflicting results on drinking behavior.¹⁵ For example, a study of 627 alcoholic subjects in the Veterans Affairs system failed to demonstrate an advantage in the treated group. In contrast, the Combined Pharmacotherapies and Behavioral Interventions (COMBINE) study, which comprised 1383 patients with alcohol dependence and at least 4 days of abstinence, showed a benefit for patients receiving naltrexone, but none for those receiving acamprosate (see below).^{16,17} A multicenter study used a monthly injectable, extended-release naltrexone in comparison with placebo injections for 6 months in 624 alcohol subjects in whom alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels did not exceed 3 times the upper limit of normal ($>3 \cdot \text{ULN}$) and found that depot naltrexone significantly decreased drinking.¹⁸ A post hoc analysis of potential hepatotoxicity showed no significant differences in AST, ALT, or bilirubin levels between the study groups at

study initiation or at subsequent assessments, whereas gamma-glutamyltransferase levels declined in the naltrexone group. Furthermore, there was no increase in frequency of high liver chemistry tests or hepatic-related adverse events in naltrexone-treated subjects who were drinking heavily throughout the study, in obese subjects, or in those taking nonsteroidal anti-inflammatory medicines.¹⁹ In summary, although the data suggest that naltrexone may enhance sobriety, and the depot preparation, which promotes adherence at lower doses, appears safe in actively drinking alcoholics, neither preparation of naltrexone can be recommended for cirrhotic patients until they have been tested in this population.

In a large multicenter study, comparing acamprosate with placebo, acamprosate was associated with a modest improvement in days without drinking and in percentage of complete abstainers over a 1-year observation period.²⁰ Apart from mild diarrhea, there was no increase in side effects in the acamprosate subjects. It is interesting that the COMBINE study, mentioned above, failed to find a benefit of acamprosate in reducing drinking behavior in a study in which naltrexone was associated with a modest reduction in frequency and severity of drinking.¹⁷

Topiramate, which is approved as an anticonvulsant, has been studied in alcoholism. Although its exact mechanism of action is unknown, it is proposed to reduce alcohol's reinforcing influence on continued drinking through enhancement of γ -aminobutyric acid and inhibition of glutaminergic central neurologic pathways. Topiramate has been shown to improve drinking outcomes in a randomized, multicenter, placebo-controlled study lasting 14 weeks among 371 alcohol-dependent subjects who had normal liver chemistries and were not known to have cirrhosis.²¹ Further analysis of this study showed a minor improvement in serum aminotransferase levels in the topiramate-treated cohort.²²

Addolorato and co-workers²³ reported a randomized clinical trial in which 84 patients with alcoholic cirrhosis received oral baclofen or placebo for 12 weeks with 4 weeks' follow-up. They showed that 30 of 42 (71%) of the baclofen-treated patients achieved and maintained abstinence compared with only 12 of 42 (29%) in the placebo arm. The study is exceptional in that it enrolled patients with alcoholic cirrhosis, who are usually excluded from such studies. It will be necessary to see further studies such as this in patients with known liver disease, with greater power, and longer duration of treatment to define baclofen's role.

TREATMENT OF ALCOHOLIC HEPATITIS

Corticosteroids have become the standard of care in selected patients with alcoholic hepatitis. Selected patients should have severe alcoholic hepatitis, as shown by a Maddrey discriminant function greater than or equal to 32, no or controlled infection, and no major contraindication to use of corticosteroids. This consensus is based on a number of key publications. Principal among them is the reanalysis by Mathurin and colleagues²⁴ of the original data from 3 prior randomized, clinical trials of prednisolone in patients with acute alcoholic hepatitis. All subjects had a Maddrey discriminant function greater than or equal to 32. At 28 days, 113 corticosteroid patients had significantly higher survival ($84.6\% \pm 3.4\%$) compared with a survival of $65.1\% \pm 4.8\%$ in 102 placebo-treated patients. In multivariate analysis, age ($P = .0001$), serum creatinine ($P < .002$), and corticosteroid treatment ($P = .002$) were independent prognostic variables.

In a series of important papers, Mathurin's group has defined a stopping rule to determine whether to continue or stop corticosteroids. In 2003, they observed that patients who had a reduction in total bilirubin within the first 7 days of treatment had a good

6-month survival, whereas those who did not had a very poor outcome.²⁵ They have further refined this observation to form the so-called Lille model, which combines 6 reproducible variables (age, renal insufficiency, albumin, prothrombin time, bilirubin, and evolution of bilirubin at day 7) to provide a very accurate prognostic marker of 6-month survival.²⁶ The formula is available online at <http://www.lillemodel.com>. Unfortunately, the anticipated survival is only 25% among patients with alcoholic hepatitis treated for 7 days compared with a 6-month survival of 85% \pm 2.5% in the remainder. The recommendation is to start corticosteroids in patients with severe alcoholic hepatitis who are not septic, and then assess at day 7. If the Lille score is less than 0.45, the patient should complete 28 days of corticosteroid therapy. If the Lille score is above the threshold, the corticosteroids should be stopped at day 7. It has not been determined whether it is better to taper or stop the corticosteroids without a taper. Although the Lille score is a useful parameter, it underscores the dire outcome in those patients who fail to respond to the first 7 days of corticosteroid therapy.

A Cochrane systematic review concluded that the available evidence does not support the use of anabolic-androgenic steroids in patients with severe alcoholic hepatitis.²⁷

Two anti-tumor necrosis factor alpha (TNF- α) agents have been studied in patients with alcoholic hepatitis: infliximab and etanercept. Infliximab is a chimeric, monoclonal antibody to TNF- α . A recent randomized, controlled trial comparing intravenous infusion of infliximab plus prednisone with placebo plus prednisolone in patients with severe alcoholic hepatitis was stopped prematurely by the independent data safety monitoring board on account of a significantly greater number of severe infections and a nonsignificant increase in deaths in the infliximab plus prednisolone cohort.²⁸ Etanercept, which consists of 2 units of human recombinant, soluble TNF- α receptor type 11 (p 75) fused with the Fc domain of human IgG1, binds soluble TNF- α . Although etanercept appeared to increase short-term survival in a small pilot study,²⁹ a more recent formal, randomized, clinical trial in patients with severe alcoholic hepatitis, conducted by the same investigators, failed to confirm this benefit.

Pentoxifylline is a phosphodiesterase inhibitor approved for the treatment of intermittent claudication. The modulation of the transcription of the TNF- α gene is one putative mechanism for the salutary effect of pentoxifylline in alcoholic hepatitis, although other actions on vascular function are also of potential importance. Akriviadis and colleagues³⁰ compared the effect of either pentoxifylline (400 mg orally 3 times daily for 4 weeks) or placebo in 101 patients with severe alcoholic hepatitis. Patients with active gastrointestinal hemorrhage, systemic infection, or severe cardiopulmonary disease, as well as patients who appeared to be improving rapidly or patients with features of advanced cirrhosis were excluded. Corticosteroids were not used. The primary end points were 28-day mortality or progression to hepatorenal syndrome. Twelve (24.5%) of the 49 pentoxifylline patients and 24 (46.1%) of the 52 placebo patients died during the initial hospitalization. Hepatorenal syndrome was implicated as a cause of death in 6 of 12 deaths (50%) in the treated group and 22 of 24 deaths (91.7%) among the placebo patients. Thus, Akriviadis' study provides the best evidence to date that pentoxifylline improves mortality in patients with alcoholic hepatitis. In contrast, Mathurin and colleagues³¹ found that adding pentoxifylline as a rescue agent was ineffective in patients with severe alcoholic hepatitis who did not respond to initial corticosteroid therapy.

Although nutritional support improves nutritional status, it does not decrease early mortality in patients with alcoholic hepatitis.³²

Despite the evidence that alcoholic liver disease is associated with enhanced oxidative stress, studies have failed to show that antioxidants confer any benefit in alcoholic hepatitis or alcoholic cirrhosis.^{33,34}

TREATMENT OF CIRRHOSIS

Therapeutic approaches to the common complications of alcoholic cirrhosis, such as ascites, variceal hemorrhage, and encephalopathy, are addressed elsewhere in this issue. As already discussed, the most common cause of decompensation of alcoholic cirrhosis is recent excessive use of alcohol. Similarly, the most important therapeutic factor in recovery is abstinence, and the most common reason for failure of recovery is that the patient resumes drinking.³⁵ The progression of fibrosis in alcoholic patients is exacerbated by the presence of viral hepatitis B or C.^{36,37} Although the treatment of viral hepatitis has not been studied extensively in patients with alcoholism and liver disease, it is possible that antiviral therapy would arrest the progression of fibrosis in some patients.

Several medications, including propylthiouracil (PTU), colchicine, S-adenosylmethionine (SAME), milk thistle or silymarin, and polyenylphosphatidylcholine, have been proposed for treatment of alcoholic fibrosis and cirrhosis. Although favorable clinical trial results have been reported for PTU, colchicine, and SAME, none has become established as a standard therapy.³⁸⁻⁴⁰ The reasons differ depending on the agent under review. Regarding PTU, despite the thoughtful advocacy of the authors, including showing that hypothyroidism is rare and that PTU improves mortality even when the patient continues to drink occasionally, fear of side effects has limited the acceptance of this agent.⁴¹ Colchicine has been the focus of a well-designed placebo-controlled multicenter study in 549 patients with advanced alcoholic cirrhosis that failed to reproduce the previously reported favorable effect on mortality.⁴² In a study limited by relative lack of power, administration of SAME or placebo to 123 patients with alcoholic cirrhosis for 2 years showed a trend for improved survival, which was not statistically significant.⁴⁰ Well-designed clinical trials using silymarin or phosphatidylcholine have been reported in the treatment of alcoholic liver disease.^{43,44} Silymarin administered to alcoholic patients with liver cirrhosis showed no effect on either survival or the clinical course. Polyenylphosphatidylcholine administered to alcoholic patients with liver fibrosis did not improve survival nor prevent the progression of fibrosis.

LIVER TRANSPLANTATION

Liver transplantation has become an accepted therapy for selected patients with liver failure or hepatocellular carcinoma associated with alcoholic cirrhosis.⁴⁵ In addition to the standard elements of liver transplantation, these patients undergo careful assessment of psychosocial health and their capacity to maintain abstinence from future alcohol use. Many programs use an arbitrary minimal criterion of 6 months' abstinence as a requirement for placement on the transplant waiting list, although the utility of this "rule" as a predictor of future drinking has been challenged. Post-transplant graft and patient survival for alcoholic patients is similar to that for nonalcoholic liver transplant recipient, although patients who return to abusive drinking are at risk of liver injury and reduced survival in the longer term.⁶

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