

# Hepatitis C in Alcohol Dependence: Drinking versus Disulfiram

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**ABSTRACT.** Hepatitis C virus (HCV) infects alcohol dependent (AD) individuals disproportionately. Disulfiram for timely abstinence in HCV+AD cases remains controversial. Our literature review suggests that (1) active drinking accelerates HCV-related liver damage and that abstinence is associated both (2) with a slower course of HCV+ hepatic deterioration and (3) with enhanced response to antiviral HCV treatment. Further, (4) the risk of disulfiram liver injury appears much lower than that from alcohol, (5) HCV+AD individuals require close monitoring during the first 6 months of disulfiram treatment, and (6) early discontinuation of disulfiram usually reverses harmful effects when these occur. Although systematic data are sparse, continued drinking appears much more liver toxic than does disulfiram in this group. Disulfiram

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therapy may allow (1) prolonged abstinence leading to successful antiviral therapy for HCV, and (2) time to begin behavioral treatments that facilitate long-term abstinence. Sizeable prospective studies of HCV+ AD treatment are badly needed. [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <<http://www.HaworthPress.com>> © 2005 by The Haworth Press, Inc. All rights reserved.]

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### INTRODUCTION

Already at risk for alcoholic liver disease, alcohol dependent (AD) persons are more frequently found to be infected with hepatitis C virus (HCV) than non-dependent individuals.<sup>1</sup> This suggests an apparent vulnerability to the virus (the mechanisms of which have yet to be elucidated) and/or the presence of risk factors for infection that are associated with alcoholism. Clinicians must face the task of assisting HCV-infected (HCV+), AD patients in reaching and maintaining a state of stable abstinence. The first clinical aim is to improve prognosis by lessening the inflammatory effects that alcohol exposure causes in the liver. The second is rendering more patients eligible for antiviral therapy, which, according to standards of practice,<sup>2</sup> requires an abstinent state in order to promote both compliance and medicinal efficacy.

At present, there are essentially two avenues for achieving abstinence from ethanol in HCV+, AD patients. The first is through standard psychosocial treatment for AD, as for example 12-Step, motivational enhancement or cognitive-behavioral therapies. The second is to prescribe disulfiram with or without psychosocial AD treatment. While other medicinal agents are currently approved for treating alcoholism, only disulfiram targets *immediate* cessation of alcohol use. Naltrexone, for example, has not demonstrated a direct effect on establishing abstinence but can limit the extent of alcohol relapses, if not their frequencies.<sup>3,4</sup>

Behavioral treatment is most often a lengthy process that expects drinking relapses and results in total abstinence in about 40% of cases through follow-up periods of 6 months to one year.<sup>5</sup> Disulfiram, by contrast, when properly monitored, decreases both frequency of drinking and volumes consumed during the time the AD patient takes the medicine.<sup>6,7</sup> The behavioral reinforcement of imminent disulfiram-ethanol

reaction should drinking return, along with the patient's ability to maintain hope, appear to account for this.<sup>8</sup> Two clinical concerns persist, however. First, unsupervised patients are frequently non-compliant with disulfiram,<sup>9</sup> and often stop it before resuming alcohol use. Second, disulfiram itself can be injurious to the liver.<sup>10</sup>

The first concern can be addressed clinically by administering disulfiram in a supervised manner. In the setting of a mandate from the judicial system, our experience suggests that supervised administration may yield a compliance rate of more than 80%.<sup>11</sup>

The second, that of safety of use, constitutes the focus of this review. Although disulfiram-induced acute hepatic failure is relatively rare, experienced hepatologists may see cases that can color their view of this agent, especially when other liver diseases such as HCV complicate matters. The Hepatology Service at our medical center for example, located in a large metropolitan area, has seen only five such cases in the past twelve years, all requiring liver transplantation. This raises questions about the consensus experience of disulfiram's safety, its drawbacks balanced against those of uncontrolled alcohol use, and its effects in the setting of HCV.

We will focus on the clinical concerns surrounding disulfiram as an agent that can bring about immediate abstinence from ethanol. Faced with the difficult choice between alcohol-related liver injury in HCV+ patients who continue drinking versus the risk of disulfiram induced liver injury in those who reach abstinence by this route, we ask what the preponderance of evidence would recommend.

We will briefly review the epidemiology of HCV infection in alcoholics, highlighting evidence of the detrimental effects of alcohol consumption in HCV+ individuals. This will include the relationship of HCV and alcohol in the areas of mortality, of the occurrence of cirrhosis and hepatocellular carcinoma, and of the response to interferon-based therapy. Next, we will review clinical studies of disulfiram, focusing on the areas of efficacy and hepatotoxicity. Finally, we will discuss a possible treatment path for HCV+, AD individuals.

## **METHODS**

A MEDLINE search for references from June, 1996, to October, 2003, identified English-language articles that focused on alcohol or ethanol, and HCV or hepatitis C. This time period was chosen arbitrarily to focus on relatively recent articles. Key search words also in-

cluded disulfiram and hepatitis. We also searched under the heading hepatitis C, limiting to English-language reviews published from 1996 to 2003. From these, any citations mentioning alcohol were obtained. A total of 272 citations were reviewed and synthesized, with emphasis on randomized, controlled data and prospective epidemiological studies when available. From these, articles with the strongest data and those describing data directly relevant to our topic were included in this article.

### **COMBINED EFFECTS OF HCV AND ALCOHOL ON THE LIVER**

An estimated 170 million people worldwide are infected with HCV, which is five times the number of those infected with human immunodeficiency virus type-1. In the US, 1.8% of the population has been infected with HCV. More than three quarters of these do not clear the virus and have chronic infection.<sup>12</sup> Reverse transcription polymerase chain reaction shows that 11-29% of chronic alcoholics are HCV+ in reported samples.<sup>1,13</sup> In patients with alcoholic liver disease, the percentage with detectable HCV RNA increases to 18-48%.<sup>14,15</sup>

According to one study, drinking habits alone may have not explained a sharp increase in deaths related to alcoholic liver damage in the UK in the 1990s.<sup>16</sup> The authors suggested that it probably resulted from the rapid progression of alcoholic cirrhosis in people who had acquired HCV infection through intravenous drug use.

Alternatively, a fourfold increase in cirrhosis has been found in individuals with heavy alcohol exposure.<sup>17</sup> HCV infection and heavy alcohol use together yielded a 31-fold higher risk for cirrhosis compared with controls, which demonstrated the multiplicative effect of the two insults on the liver.<sup>17</sup> "Heavy use" in this study was defined as more than 80 g alcohol/day (roughly 7 standard drinks); loss of family, friends or a job related to alcohol use; admitting to an alcohol use problem; or evidence of "heavy drinking" from the medical record. One standard alcoholic drink equates to 12 g ethanol, according to the United States Department of Agriculture.<sup>18</sup> Another recent follow-up study of 122 heavy drinkers with liver cirrhosis similarly found that concomitant HCV infection exerted an independent worsening effect on five-year survival rates.<sup>19</sup>

The dramatic effect of alcohol on the course of HCV infection was shown in the Italian Dionysos study. Approximately 7,000 of 10,000

people in 2 Northern Italian towns took part in a 3-year prospective, cross-sectional study.<sup>20</sup> In HCV+ individuals who drank < 30 g/day, 10% developed cirrhosis or hepatocellular carcinoma (HCC), compared with 32% of those who drank > 30 g/day. The average daily alcohol intake was 122 g/day in 5 subjects who developed HCC (all were HCV+), versus 46 g/day in other subjects with cirrhosis. The incidence rate of HCC was 3% per year.<sup>20</sup>

In a study from Japan, clearance of virus from the blood with interferon therapy was noted in 58.3% of non-drinkers, compared with 20% for those who drank < 70 g/day and only 12.5% for those who drank > 70 g/day for at least 10 years.<sup>21</sup> All groups abstained during interferon therapy. No individual who continued to drink at least 5 drinks per day cleared viral RNA from the blood in another study.<sup>22</sup> These poor response rates, along with numerous potential adverse effects of interferon-based therapy, have led to the standard of care being not to offer antiviral treatment to those who are actively drinking.<sup>2,23-25</sup> Clinical priority has shifted to the cessation of alcohol use first, since alcohol use in large numbers of HCV+ individuals has eliminated them from candidacy for interferon therapy.

### ***EFFICACY OF DISULFIRAM***

Little data exist on treatment methods for alcoholism that coexists with chronic HCV infection. A large body of data has shown that behavioral treatments specific to alcoholism are effective in assisting AD patients to reach stable abstinence from alcohol.<sup>8</sup> Such treatments, however, often include recognition of the relapsing-remitting course of AD that may take months or years. This time frame may be much longer than that dictated by a necessity of stabilizing liver disease immediately. HCV+ alcoholics need assistance in immediate cessation of alcohol use plus ongoing behavioral treatment. Disulfiram is one of the options available to aid in immediate abstinence.

Disulfiram has had a checkered history in clinical medicine, despite its status as one of the only effective pharmacological methods of decreasing alcohol use<sup>9</sup> and its usefulness over a longer term in conjunction with behavioral therapy.<sup>6</sup> Those who believe disulfiram has little to offer alcoholics note that it does not address the underlying complexity of alcohol dependence, that it has poor efficacy, and that it can be potentially fatally hepatotoxic. There are reasonable data with which to address each of these points.

Disulfiram used as a sole therapeutic measure for the treatment of alcohol dependence, without behavioral therapy to improve the long-term predictors of abstinence, is a suboptimal attempt at a "quick fix." However, disulfiram likely promotes fertile ground for behavioral therapy by enabling a short-term abstinent period. As Brewer remarked, disulfiram is sometimes regarded as a "crutch," but what is wrong with using a temporary crutch if the long-term goals are more likely to be obtained?<sup>26</sup> Compliance with behavioral therapy and actual behavioral change are far less likely with ongoing drinking.

Efficacy of disulfiram treatment depends largely on supervised administration, preferably with the dose dissolved in a glass of water, which makes pill hiding and regurgitation less likely. *Because patients may surreptitiously denature the medication by baking it, tablets should not be under their control in most cases.* Rather, disulfiram should be left in the possession of the clinic staff. Patients who are not supervised discontinue disulfiram within a few weeks,<sup>6,27</sup> and this was demonstrated in a large VA cooperative study with unsupervised disulfiram administration. In this study, 438 (72%) of 605 subjects did not achieve abstinence.<sup>9</sup> The abstinence rates were approximately 20% in the group with unsupervised disulfiram therapy and in the control group, less than those reported for behavioral therapy.<sup>5</sup> There was a significant relationship between adherence to the study drug regimen (placebo or disulfiram) and complete abstinence in the 3 groups, which suggests that those who voluntarily comply with therapy are more likely to do well with disulfiram or any other treatment.

Studies of supervised administration of disulfiram have yielded compliance rates as high as 86%<sup>11</sup> abstinence rates of 50-70%,<sup>28,29</sup> and lessened occupational absenteeism.<sup>30</sup> However, it is difficult to differentiate the effect of external motivators, such as court mandates, from that of the medication in these studies. The diagnosis of HCV infection may be a similar external motivation. Indeed, participants in one study who were made aware of their HCV+ status were more likely to reduce their alcohol intake than those not infected.<sup>31</sup>

One of the best-designed studies of disulfiram was unfortunately limited by small sample size of only 42 subjects randomized to 3 groups: unsupervised disulfiram, supervised disulfiram, and supervised disulfiram with behavioral therapy.<sup>32</sup> Both disulfiram and behavioral therapy were significantly associated with decreased drinking, absenteeism, and illness. Behavioral therapy offered no additional benefit to supervised disulfiram therapy in married or cohabiting individuals: these had 30 out of 30 sober days in the 6th month of the study with supervised

disulfiram only. On the other hand, single drinkers showed a poor response to supervised and unsupervised disulfiram administration, but near total sobriety when behavioral therapy was added. In a broad review of the above and other clinical studies, Wright and colleagues state that “disulfiram is probably effective in reducing the frequency of alcohol consumption in the compliant patient over the short term (e.g., 6 months),” which is key in rendering the individual more likely to respond to concomitant behavioral therapy.<sup>33</sup> A large randomized, controlled trial with *supervised* administration of disulfiram in HCV+ alcoholics is needed to demonstrate efficacy in this regard.

### ***DISULFIRAM LIVER INJURY***

The first case of hepatotoxicity associated with disulfiram was published in 1949, two years after this agent’s introduction for treatment of alcohol dependence.<sup>10</sup> Since then, hepatic inflammation and clinical hepatitis have been noted as the most common adverse outcomes related to disulfiram treatment.<sup>34</sup> A range of outcomes, from asymptomatic aminotransferase elevation (usually < 3 times the upper limit of normal) to hepatic failure and death, has been linked to disulfiram therapy.

Serum biochemical changes associated with disulfiram hepatitis are indistinguishable from alcoholic hepatitis,<sup>34</sup> which often makes the etiology of liver test abnormalities difficult to discern in disulfiram treated alcoholics. However, in a large study undertaken to assess disulfiram safety, there were 201 liver test elevations in 453 alcoholics treated with disulfiram.<sup>35</sup> Of those, 179 elevations (40%) were attributed to ongoing drinking, which underscores the effect of lack of supervised disulfiram administration in that trial. The same authors reported no relationship between liver test elevation and disulfiram therapy.<sup>35</sup>

Another group that ensured compliance through supervision reported a similar lack of correlation between abnormalities in liver tests and disulfiram treatment.<sup>7</sup> They also noted an improvement in the liver tests of the disulfiram group, compared to a deterioration (associated with drinking) in the controls. In a study of 50 male inpatients randomized to receive placebo, disulfiram 250 mg/day or disulfiram 500 mg/day, no differences in liver biochemistry were noted among the 3 groups over 3 weeks.<sup>36</sup> One clinician reported disulfiram treatment of 1500 consecutive alcoholics “without long term ill effects.”<sup>37</sup>

Conversely, a review of disulfiram toxicity noted that 15 of 17 reported cases of fatal fulminant hepatitis due to disulfiram presented symptoms from 2 weeks to 2 months after starting the therapy.<sup>38</sup> The Danish Committee on Adverse Drug Reactions, which reported data collected over a 23 year period, noted a similar pattern; the majority of hepatitis cases due to disulfiram occurred between 2 weeks and 3 months of therapy.<sup>34</sup> The same committee reported a mortality rate of 1:30,000 patient-treatment-years, an intermediate risk level by their criteria. In another review of cases of disulfiram induced hepatitis, all patients survived when the medication was stopped shortly after jaundice occurred.<sup>35</sup> Nearly all of the 27 patients had nausea, malaise, and fatigue, and many had fever preceding clinical jaundice by 3-7 days.<sup>35</sup> This underscores the importance of early, careful symptom monitoring and possibly laboratory monitoring of disulfiram therapy.

In another study of 108 patients with normal baseline liver tests, disulfiram was discontinued after 4 weeks in 43 cases for liver test elevations above the upper limit of normal.<sup>39</sup> Of the 43, only 2 subjects had liver test elevations > 3 times normal; the remainder had elevations from 1 to 3 times normal. Unfortunately, HCV status, which could explain this large percentage of mild liver test elevations, was not documented. More recently, another group reported that two weeks of disulfiram exposure had no significant effect on serum liver enzymes. However, a subset of three previously diagnosed cirrhotic patients was identified as having transaminase elevations greater than 1.5 times their baseline values.<sup>40</sup> It is not known whether this conservative threshold for discontinuing therapy leads to less morbidity. Other investigators report discontinuing disulfiram only when aminotransferase elevations reached either > 3 times the upper limit of normal or twice the baseline value, with no ill effects.<sup>41</sup> The degree of liver fibrosis may predispose to disulfiram hepatitis, regardless of HCV status, but unfortunately, histological information is lacking in most disulfiram toxicity studies.

#### ***DISULFIRAM THERAPY IN PATIENTS WITH ABNORMAL LIVER TESTS AND HCV INFECTION***

The concern over the safety of disulfiram in patients with abnormal liver tests appears to have deprived some patients of potentially effective treatment.<sup>42,43</sup> Many of the investigations into the hepatic effects of disulfiram occurred prior to the availability of assays for HCV, which is often associated with aminotransferase fluctuation. We found only one

pioneering study on the effects of disulfiram in HCV+ patients,<sup>41</sup> and it has several limitations. First, the study group did not take disulfiram in a supervised fashion; thus changes in the liver tests could be due to HCV, disulfiram, or continued alcohol use. In fact, 1 of the 4 HCV+ subjects with marked liver enzyme elevation reported alcohol consumption during the period in question. Secondly, the report provided little data on the effect that disulfiram therapy had on HCV+ individuals. It is not known what percentage of HCV+ subjects had mild or moderate aminotransferase elevations (only marked elevations were reported) or what characteristics in HCV+ individuals suggest a higher risk of complications with disulfiram therapy.

Finally, the sample size was very small. The report suggested that subjects with HCV were more likely than those without to show aminotransferase elevations. Specifically, 3 of 18 HCV+ subjects exhibited aminotransferase levels greater than twice baseline or 3 times normal, whereas 1 of 39 without HCV had elevations in this range. The authors concluded that in only 1 subject did elevations in alanine aminotransferase (ALT) appear to be directly related to disulfiram. Also, no subject with liver enzymes in the normal range at baseline had elevations while on disulfiram. This supports disulfiram treatment of alcoholic HCV “carriers” with normal liver tests, a category which includes up to one third of HCV+ individuals. With only this one clinical study at hand, systematically gathered data that address the safety and potential benefit of using disulfiram in HCV+, AD individuals must await further research.

In the meantime, we recommend checking liver-associated enzymes twice weekly for the first 3 months and monthly thereafter as the safest course. This, however, has been deemed unnecessary by some authors, in part due to the rarity of disulfiram-induced hepatitis and the rapidity with which it takes place.<sup>43,44</sup> Such may not be the case in HCV+ alcoholics because of an intra-hepatic environment that may already be sensitive to exogenous insult. Frequent biochemical and symptomatic monitoring can be easily incorporated into visits for supervised administration. Reported experience suggests that ALT may be a more sensitive and specific indicator of liver abnormality in patients being treated with disulfiram, when compared with aspartate aminotransferase, gamma glutamyl transferase, and alkaline phosphatase.<sup>39</sup> Regarding dosing, 500 mg three times weekly or 250 mg once per day is recommended. In rare instances, 750 mg twice a week is used. In the event that a patient experiences a mild adverse reaction that does not cease (i.e., drowsiness), 250 mg three times a week may be prescribed. Compliance with

at least two visits for psychosocial treatment should be ensured before embarking on a course of disulfiram therapy. We do not recommend disulfiram therapy unless the patient is concurrently enrolled in a psychosocial treatment program because the medicine alone is not sufficient to affect long-term abstinence.<sup>8</sup>

### CONCLUSION

Alcohol appears to accelerate progression both to cirrhosis and to HCC in HCV+ individuals. Increased morbidity and mortality appear to result from the additive and possibly synergistic action of alcohol and HCV on the liver. Not only is HCV-related liver disease worsened in the setting of alcohol abuse, but recent drinking renders antiviral therapy far less effective. Abstinence from alcohol, in our view therefore, is the most reasonable course in reducing major morbidity and mortality in HCV+, AD individuals. Because of this, reluctance to prescribe disulfiram because of mild aminotransferase abnormalities or a diagnosis of HCV infection may not be warranted. Carefully monitored disulfiram treatment may provide HCV+, AD patients a relatively safe, immediate, and efficacious treatment with far less risk to the liver than continued alcohol consumption. Stabilizing liver health may buy time to institute favorable prognostic factors that promote abstinence. Death from HCV+, AD liver failure removes this possibility. The difficult clinical decision to prescribe disulfiram to an HCV+ patient remains one of balancing the risks of the treatment against the risks of the combined effects of AD and HCV. In our view the burden of HCV+, AD related liver disease tips the balance towards disulfiram therapy if the patient has demonstrated compliance. This therapy must be carefully supervised clinically and monitored biochemically (hepatic enzymes) in order to decrease adverse events, at least until more specific data are available in this population.

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