Hepatitis C Virus: A Changing Paradigm
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HCV and Alcohol

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Alcohol

The Centers for Disease Control ranks alcohol as the source for the third leading cause of preventable deaths in the US.

<table>
<thead>
<tr>
<th>Actual Cause</th>
<th>No. (%) in 1990</th>
<th>No. (%) in 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>100,000 (5)</td>
<td>150,000 (5.1)</td>
</tr>
<tr>
<td>Poor diet and physical inactivity</td>
<td>200,000 (10)</td>
<td>300,000 (10.6)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>100,000 (5)</td>
<td>80,000 (2.6)</td>
</tr>
<tr>
<td>Minor vehicle</td>
<td>25,000 (1)</td>
<td>30,000 (1.0)</td>
</tr>
<tr>
<td>Firearms</td>
<td>15,000 (0.8)</td>
<td>20,000 (0.7)</td>
</tr>
<tr>
<td>Suicide</td>
<td>10,000 (0.5)</td>
<td>12,000 (0.4)</td>
</tr>
<tr>
<td>Of drug use</td>
<td>5,000 (0.2)</td>
<td>5,000 (0.2)</td>
</tr>
<tr>
<td>Total</td>
<td>1,080,000 (50)</td>
<td>1,150,000 (48.5)</td>
</tr>
</tbody>
</table>

*Data are from Mokdad and Foege. The percentages are for all deaths.

Mokdad et al, JAMA 2004

Alcohol Dependence

* Approximately 10% of Americans will be affected by alcohol dependence (AD) sometime during their lives.
  
  Grant et al, Drug & Alcohol Dep 2004

* Alcohol dependence is a chronic, relapsing condition with a multifactorial etiology that includes genetic, neurobiological, psychological, and environmental components.

Koob & Volkow, Neuropsychopharmacology 2010
The Dionysos Study

What is light-to-moderate drinking? [1 drink = 14 g pure alcohol]

- Men: Up to 2 drinks per day
- Women: Up to 1 drink per day

When is "low-risk" drinking still too much?

- Taking medications that interact with alcohol
- Medical condition that can be made worse by drinking
e.g. liver disease (such as HCV), bipolar disorder, abnormal heart rhythm, and chronic pain.
- Underage
- Planning to drive a vehicle or operate machinery
- Pregnant or trying to become pregnant

Alcohol & HCV

• The prevalence of HCV is 3-fold to 30-fold higher in alcoholics compared with the general population
  Singal & Anand, J Clin Gastroenterol 2007

• Alcoholism is an independent risk factor for HCV
  Mendenhall et al., Gastroenterol Jpn. 1993
  Roman et al., Am. J Gastroenterol. 1996
Figure 1. HCV and ALD, either in combination or alone, represent the majority of liver diseases (data from the US Centers of Disease Control and Prevention 2007). HCV: Hepatitis C virus; ALD: Alcoholic liver disease; HBV: Hepatitis B virus.

Mueller et al., Word J Gastroenterol 2009

Figure 2. Natural course of ALD and HCV alone or in combination. Estimated risk and time interval for disease states are indicated (for more detail see original text).

Mueller et al., Word J Gastroenterol 2009

Figure 3. Natural course of ALD and HCV alone or in combination. Estimated risk and time interval for disease states are indicated (for more detail see original text).

Mueller et al., Word J Gastroenterol 2009
Alcohol Consumption Accelerates HCV-related Liver Disease

- Consumption of 50 g/d of alcohol increased the rate at which fibrosis progresses in HCV infected individuals.
  
  Payard et al., Lancet 1997

- Risk factor for developing cirrhosis of 9 in HCV+ patients who did not consume alcohol, compared to a significantly higher risk factor of 147 for those HCV+ patients that abused alcohol.
  
  Corran & Arico', Hepatology 1998

Moderate Alcohol Consumption and HCV

- Investigation of 78 HCV-infected patients with alcohol consumption <40g/d, who underwent two liver biopsies in a mean interval of 6.3 years. Progressive fibrosis with increased:
  - total alcohol consumption
  - daily alcohol consumption
  - frequency of drinking occasions

  Westin et al., J Viral Hepat 2002

- Prospective study with 260 HCV-infected patients showed that even moderate alcohol consumption, as low as 31-50 g/day in men and 21-50 g/day in women, may aggravate histological lesions.

  Hezode et al., Aliment Pharmacol Ther. 2006

HEPATITIS

Alcohol has no effect on hepatitis C virus replication: a meta-analysis

B S Anand, J Thamby
HCV and alcohol: synergism

- Increased production of reactive oxygen species (ROS)
- Iron accumulation
- Steatosis induction
- Modulation of the immune response and apoptosis
- Stimulation of HCV replication
- Direct DNA damage

As reviewed in: Singal & Anand, J Clin Gastroenterol 2007; Mueller et al., World J Gastroenterol 2009; McCartney & Beard, World J Gastroenterol 2010

Alcohol may represent a ‘barrier’ why patients do not receive HCV treatment

Alcohol (>30g/d) reduces the effectiveness of INF-alpha treatment (low likehood of achieving SVR).

Chang et al., Aliment Pharmacol Ther 2005
Singal & Anand, J Clin Gastroenterol 2007

- Past alcohol use is not a predictor of poorer treatment outcomes
- Recent alcohol use was associated with increased treatment discontinuation and lower SVR
- However, when patients who discontinued treatment were excluded from analysis, the trend in favor of nondrinkers for SVR disappeared
Rate of alcohol relapse after liver transplantation

<table>
<thead>
<tr>
<th>Authors</th>
<th>Type of study</th>
<th>Patients (% of baseline)</th>
<th>Time (months)</th>
<th>Patients associated with relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redeker et al. [9]</td>
<td>retrospective</td>
<td>90</td>
<td>1-6</td>
<td></td>
</tr>
<tr>
<td>Douek et al. [10]</td>
<td>retrospective</td>
<td>63</td>
<td>57-72</td>
<td></td>
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<tr>
<td>Ledingham et al. [11]</td>
<td>prospective</td>
<td>59</td>
<td>48</td>
<td></td>
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<tr>
<td>Wynn et al. [12]</td>
<td>retrospective</td>
<td>93</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Tang et al. [13]</td>
<td>retrospective</td>
<td>50</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Hopkins et al. [14]</td>
<td>retrospective</td>
<td>57</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Hommerich et al. [15]</td>
<td>retrospective</td>
<td>68</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Hatzakis et al. [16]</td>
<td>retrospective</td>
<td>107</td>
<td>30+</td>
<td></td>
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<tr>
<td>Soria et al. [17]</td>
<td>prospective</td>
<td>51</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Percival et al. [18]</td>
<td>retrospective</td>
<td>67</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Gudinchet et al. [19]</td>
<td>prospective</td>
<td>61</td>
<td>42-53</td>
<td></td>
</tr>
<tr>
<td>Billings et al. [20]</td>
<td>retrospective</td>
<td>203</td>
<td>7-14</td>
<td></td>
</tr>
</tbody>
</table>

HCV, Alcohol and LT

- Extrahepatic sites of HCV replication may explain how the new transplant liver is infected by HCV in virtually all patients, with a 10- to 20-fold increase in levels of viraemia after liver transplantation.

- Progression to HCV-related cirrhosis is estimated to reach 20–30% at 5 year follow-up.

_ Gruener et al., J Antimicrob Chemother. 2004_

- Patients with both HCV and alcohol are more likely to die on the waiting list than those with ALD and HCV alone.

- However, after transplantation, non-risk adjusted graft and patient survival of patients with HCV + ALD are comparable to those of patients with HCV cirrhosis or ALD cirrhosis alone.

_Carbone & Neuberger, J Transplant 2010_

Alcohol & HCV

- Alcohol abstinence is the cornerstone of management for patients with alcohol liver disease, and this is particularly true if HCV coinfection coexist.

_Lieber, Alcohol Res Health 2003_


While alcohol may represent a barrier for treatment for HCV infection and HCV-related liver disease (e.g. pegIFN/RBV, LT), our goal is to break such a barrier.
Awareness of HCV status led to a slight reduction in alcohol drinking in a sample of ~400 HIV/HCV people.
Tsai et al., J Gen Intern Med 2007

A study with ~600 HCV-infected people showed that although 84% were aware of their increased risk of liver disease from alcohol, two-fifths still screened positive for problem alcohol use.
Campbell et al., Drug Alcohol Dep 2006

More work is needed….for example, NIH/NIAAA recommends consideration of pharmacotherapies for all alcoholic patients, a recommendation consistent with the increased knowledge on the neurobiology of alcoholism.

FDA-Approved Pharmacotherapies for Alcohol Dependence

**Disulfiram (Antabuse®)**
- Alddehyde dehydrogenase inhibitor
- When taken with alcohol leads to nausea, dizziness, headache, flushing
- Approved by FDA in 1954

**Naltrexone (ReVa®)**
- Opioid antagonist
- Blocks opioid receptors, thus blocking alcohol reward pathways
- Approved by FDA in 1984

**SR-Naltrexone (Vivitrol®)**
- Sustained-release naltrexone
- Approved by FDA in 2004

**Acamprosate (Campral®)**
- Glutamate receptor modulator
- Helps maintain complete abstinence during post-acute withdrawal
- Approved by FDA in 2004

Alcohol Pharmacotherapies and the Liver

• Alcohol pharmacotherapy trials usually exclude alcoholics with liver diseases.

• Disulfiram and Naltrexone cannot be used in patients with liver problems.

**Baclofen**

• Baclofen, a GABA<sub>δ</sub> receptor agonist, is mainly eliminated unmodified by the kidneys (10-15% liver metabolism).

• Several animal studies show baclofen reduces alcohol consumption and alcohol-seeking behaviors.

Reviewed in: Maccioni & Colombo, 2009
**Baclofen in open-label clinical studies**

**Ability of Baclofen in Reducing Alcohol Craving and Intake: II—Preliminary Clinical Evidence**

Giovanni Addolorato, Fabio Carpo, Ennamadori Capurso, Giancarlo Colombi, Gian Luigi Gessa, and Giovanni Gasbarrini

**Baclofen for Alcohol Dependence: A Preliminary Open-Label Study**

Bettina A. Flitney, James C. Carroll, Mayhew M. Cody, William Panza, Kathy Brown, Michael Debono, Karin Croisy, Mary Moneta, and Amy Truitt

**Baclofen in a double-blind randomized controlled study**

**Baclofen, Alcohol Drinking and stress-related hormones**

- Two additional 12-week open-label studies with baclofen confirmed these results, also showing a reduction in some stress-related hormones (e.g., aldosterone, cortisol).


Leggio et al. Alcohol 2008

- Baclofen, as compared to placebo, reduces GH levels in a human lab setting where baclofen also reduces alcohol self-administration and affects the biphasic effects of alcohol.

Leggio et al. in preparation
Baclofen showed its safety and efficacy in achieving and maintaining alcohol abstinence in a subset of alcohol-dependent patients with high severity as reflected by the presence of liver cirrhosis.

**Trial Flow-chart and Results (primary outcomes)**

| CAD: 30.8 ± 5.5  |  p = 0.0002 |
| CAD: 62.8 ± 5.4  |  p = 0.001 |

*CAD: Cumulative Abstinence Duration*
Pilot study at Loma Linda University Medical Center
• Baclofen used for 5-8 months in 14 patients with alcoholic hepatitis. No side effects were reported
• 13/14 patients completely stopped drinking/craving alcohol and one patient reported a significant reduction in alcohol consumption.
• There was a significant reduction in total bilirubin (p=.0057) and AST (p=.0438) and there was a trend for reduced ALT (p=.083).

Avanesyan & Runyon. AASLD 2010

Pilot study at Royal Alexandria Hospital Paisley, Glasgow, UK
• Baclofen used 'off label' in > 50 patients
• Patients reduce/stop drinking/craving, and the dose required is lower in those patients with alcohol liver disease.

Differences between European and US baclofen-treated alcoholics

**Table 2:** Drinking and Psychometric Characteristics of US and European Trials

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>US Trial (n)</th>
<th>European Trial (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>13 (6-2-1)</td>
<td>12 (6-2-1)</td>
</tr>
<tr>
<td>Race</td>
<td>13 (6-2-1)</td>
<td>12 (6-2-1)</td>
</tr>
<tr>
<td>Marital Status</td>
<td>13 (6-2-1)</td>
<td>12 (6-2-1)</td>
</tr>
<tr>
<td>Education</td>
<td>13 (6-2-1)</td>
<td>12 (6-2-1)</td>
</tr>
<tr>
<td>Employment</td>
<td>13 (6-2-1)</td>
<td>12 (6-2-1)</td>
</tr>
<tr>
<td>Smoking History</td>
<td>13 (6-2-1)</td>
<td>12 (6-2-1)</td>
</tr>
<tr>
<td>Number of drinks</td>
<td>13 (6-2-1)</td>
<td>12 (6-2-1)</td>
</tr>
<tr>
<td>Average intake</td>
<td>13 (6-2-1)</td>
<td>12 (6-2-1)</td>
</tr>
</tbody>
</table>
| Total alcohol abstinence evaluated according to the Child-Pugh classification

**Table 3: Total alcohol abstinence by Child-Pugh classification

<table>
<thead>
<tr>
<th>Child-Pugh</th>
<th>Total Alcohol Abstinence (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>14 (75)</td>
<td>3 (25)</td>
<td>0.2381</td>
</tr>
<tr>
<td>B</td>
<td>5 (25)</td>
<td>2 (25)</td>
<td>0.3</td>
</tr>
<tr>
<td>C</td>
<td>6 (38)</td>
<td>5 (38)</td>
<td>0.2381</td>
</tr>
<tr>
<td>Total</td>
<td>13 (78)</td>
<td>10 (62)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*Point and interval odds ratio estimates and relative p values were calculated using exact logistic regression.

Baclofen in alcoholics with HCV infection
(subgroup analysis of previous RCT)

- Baseline characteristics between HCV-infected patients vs. HCV patients: significantly higher AST and ALT in HCV-infected patients.
- In this subgroup, baclofen confirmed a significant effect, as compared to placebo, in promoting alcohol abstinence ($p = 0.01$)

Leggio et al. in preparation

Final Remarks

- HCV and alcoholism frequently coexist and act synergistically in causing more severe liver injury than that seen with either disease alone.
- Although, this synergism clearly occurs at alcohol intake of $>30$ g/d, there is no safe limit for alcohol consumption.
- Alcohol may represent a barrier for HCV-infected patients to have access to HCV treatments.
- Considering the increased availability of alcohol interventions, integrated medical care approaches are urged for patients with alcohol problems and HCV infection.

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  - Alcohol Beverage Medical Research Foundation (ABMRF)
  - Brown University Center for Alcohol & Addiction Studies
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