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ALCOHOLIC LIVER DISEASE – A MINIREVEIW

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ABSTRACT

Alcoholic liver disease represents a spectrum of clinical illness and morphological changes that range from fatty liver to hepatic inflammation and necrosis (alcoholic hepatitis) to progressive fibrosis (alcoholic cirrhosis). The aim of the present review is to describe the current drug therapy, pathogenesis, clinical manifestation and risk factors of alcohol liver disease. We conducted a search of the Indian national library of Delhi (AIIMS) for articles published between 2000 and 2012 using the key phrases; epidemiology, alcohol liver disease, drug interaction, clinical manifestation, diagnosis, pharmacological and non pharmacological therapy. All relevant publications were retrieved and their bibliographies were scanned for additional sources. The process of selecting articles involved three stages : i) Title review ii) Abstract review and iii) article review, with specific rejection criteria for each of these stages. Generally studies were excluded if they i) were not written in English ii) were presented only in abstract form iii) literature review not focused on human or human cells. Our article suggests that, more research should be carried out in therapeutic management of alcoholic liver disease.

Keywords: Alcohol, Liver, Disease, Morality, epidemiology and Drugs.

INTRODUCTION

World Health Organization defines chronic alcoholics as " those excessive drinkers whose dependence upon alcohol has attained such a degree that it shows a noticeable mental disturbance or an interference with their body and mental health, interpersonal relations and their smooth social and economic functioning or shows prodromal developmental sign ". Arbitrarily an alcoholic was defined as an individual who consumed more than 80 gm of ethanol per day. Sustained excessive alcohol consumption is a brain-centered addictive behaviour disorder that crosses all boundaries of gender, race, age, economic strata and in many patients might lead to alcoholic liver disease (ALD) [1-3]. Alcoholic liver disease represents a spectrum of clinical illness and morphological changes that range from fatty liver to hepatic inflammation and necrosis (alcoholic hepatitis) to progressive fibrosis (alcoholic cirrhosis) [3].

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Furthermore, sustained excessive alcohol intake favours the progression of other liver diseases, such as virus-related chronic hepatitis, also increasing the risk of hepatocellular carcinoma [4].

EPIDEMIOLOGYs

In an assessment by the WHO in 2005, 4% of the burden of disease and 3.2% of all deaths globally were attributable to alcohol. Alcohol liver disease is the foremost health risk in developing countries and ranks third in developed countries [5]. Per capital alcohol consumption has declined in the US and Europe, except in some Northern European countries such as the UK and Finland [6]. Alcoholic liver cirrhosis mortality has trended downward but will continue to decline only if alcohol consumption continues to decline further [7]. The development of ALD is more rapid and occurs at a lower dose of alcohol in women than in men [8].The estimated increase in alcohol consumption between 1996 to 2007 in Canada and British Columbia (Figure 1) [11]. Deaths from alcohol liver disease between 2001 to 2009 (Figure 2) [10]. The National Institutes of Health estimates that in the United States in 2009, there were more than 31,000 deaths

from cirrhosis and that alcohol played a role in 48 percent of those deaths (age-adjusted death rate of 4.5 deaths per 100,000 population) [9].

Figure1. Estimated Increase In Alcohol Consumption Between 1996 To 2007 In Canada And British Columbia

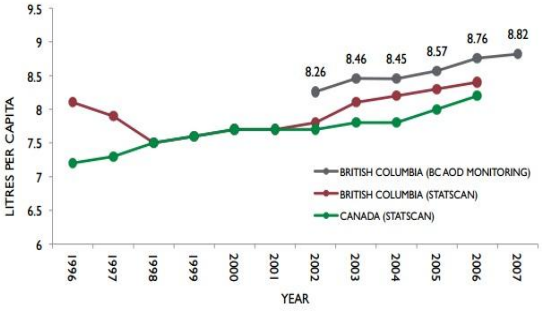
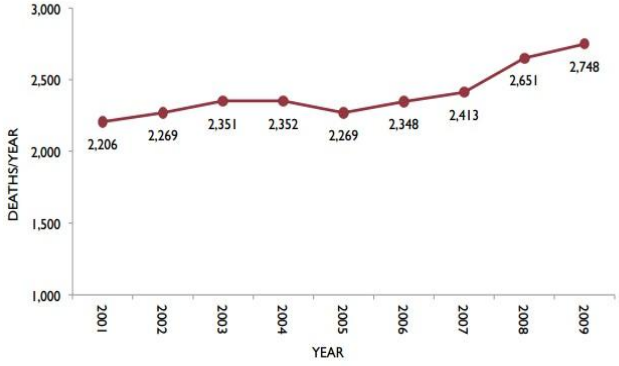


Figure-2. Deaths From Alcohol Liver Disease



RISK FACTORS FOR ALD

•Quantity of alcohol taken: Consumption of 60–80g per day (about 75–100 ml/day) for 20 years or more in men, or 20g/day (about 25 ml/day) for women significantly increases the risk of hepatitis and fibrosis by 7 to 47% [12,14].

•Pattern of drinking: Drinking outside of meal times increases upto 2.7 times the risk of alcoholic liver disease.

•Gender: Females are twice as susceptible to alcohol-related liver disease and may develop alcoholic liver disease with shorter durations and doses of chronic consumption. The lesser amount of alcohol dehydrogenase secreted in the gut, higher proportion of body fat in women and changes in fat absorption due to which menstrual cycle may explain this phenomenon.

•Hepatitis C infection: A concomitant Hepatitis C infection significantly accelerates the process of liver injury.

•Genetic factors: Genetic factors predispose both to alcoholism and to alcoholic liver disease. Monozygotic twins are more likely to be alcoholics and to develop liver cirrhosis than dizygotic twins. Polymorphisms in the enzymes involved in the metabolism of alcohol, such as alcohol dehydrogenase (ADH), aldehyde dehydrogenase (ALDH), CYP4502E1, mitochondrial dysfunction and cytokine polymorphism may partly explain this genetic component. However, no specific polymorphisms have currently been firmly linked to alcoholic liver disease.

•Diet: Malnutrition, particularly Vitamin A and E deficiencies can worsen alcohol-induced liver damage by preventing regeneration of hepatocytes. This is particularly a concern as alcoholics are usually malnourished because of a poor diet, anorexia and encephalopathy [13].

SPECTRUM OF LIVER DISEASE

Alcoholic liver Diseases can be of three types:

1. Alcoholic fatty liver (Steatosis) - 80%
2. Alcoholic hepatitis - 10-35%
3. Alcoholic cirrhosis - 10%

ALCOHOLIC FATTY LIVER (STEATOSIS)

Fatty liver is the first stage of alcoholic liver disease. Steatosis is invariable if consumption exceeds 80 gm of alcohol per day.

Alcohol is metabolized by ADH into acetaldehyde, then further metabolized by ALDH into acetic acid, which is finally oxidized into carbon dioxide (CO_2) and water (H_2O) [15]. This process generates NADH and increases the NADPH/NADP+ ratio. A higher NADH concentration induces fatty acid synthesis while a decreased NAD level results in decreased fatty acid oxidation [14]. Subsequently, the higher levels of fatty acids signal the liver cells to compound it to glycerol to form triglycerides. These triglycerides accumulate, resulting in fatty liver.

ALCOHOLIC HEPATITIS

Alcoholic hepatitis is characterized by the inflammation of hepatocytes between 10% and 35% of heavy drinkers develop alcoholic hepatitis. While development of hepatitis is not directly related to the dose of alcohol, some people seem more prone to this reaction than others. This is called alcoholic steato necrosis and the inflammations appears to predispose to liver fibrosis. Inflammatory cytokines (tumour necrosis factor- alpha (TNF- α), interleukins (IL6 and IL8) are thought to be essential in the initiation and perpetuation of liver injury by inducing apoptosis and necrosis. One possible mechanism for the increased activity of TNF-α is the increased intestinal permeability due to liver disease. This facilitates the absorption of the gut-produced endotoxin into the portal circulation. The Kupffer cells of the liver then phagocytes endotoxin, stimulating the release of TNF-α. TNF-α then triggers apoptotic pathways through the activation of caspases, resulting in cell death [13].

ALCOHOLIC CIRRHOSIS

Alcoholic cirrhosis is only one of many consequences resulting from chronic alcohol ingestion. It is most severe form of alcoholic liver injury. Alcoholic cirrhosis, historically referred to as Laennec's cirrhosis, it is

most common type of cirrhosis encountered in North America and many parts of Western Europe and South America. It is characterized by diffuse fine scarring, fairly uniform loss of liver cells and small regenerative nodules (micronodular cirrhosis).

Gradually alcoholic cirrhosis may progress to macronodular cirrhosis with time, with continued alcohol intake and destruction of hepatocytes. Fibroblast appears at the site of injury and collagen deposition occurs pericellular, in the space of disse and around central veins. This leads to formation of nodules. With continuing hepatocyte destruction and collagen deposition, the liver shrinks in size, acquires a nodular appearance and becomes hard as ”end stage” cirrhosis develops. Survival for patients with end stage cirrhosis is one year in 60-70% and five years in 35 to 50% cases.

PATHOGENESIS

There are a number of hypothesis regarding the pathogenesis of alcoholic liver injury. Ethanol metabolism usually takes place in the mitochondria. Ethanol is oxidised to acetaldehyde by alcohol dehydrogenase, which in turn is oxidized to acetate by acetaldehyde dehydrogenase. These oxidation reactions are associated with the formation of NADH and NAD and alter the redox state of the cell. This has harmful effects on lipid and carbohydrate metabolism - for example, steatosis. In habitual drinkers, a microsomal mixed function oxidase, the microsomal ethanol oxidizing system, is increased by enzyme induction and is also responsible for production of acetaldehyde. Acetaldehyde is increased in zone 3 (also the maximal site of action of alcohol dehydrogenase). This is also the site of the terminal veins making this zone the most hypoxic and therefore highly susceptible to hypoxic injury. Oxygen derived free radicals may cause direct hepatocyte injury by lipid peroxidation. Acetaldehyde binds covalently to proteins forming adducts that are antigenic. Humans and animals exposed to long term alcohol excess develop persistent circulating antibodies that recognise acetaldehyde protein adducts [17].

Acetaldehyde modified self proteins may serve as neoantigens, initiating harmful humoral and/or cellular immune responses, which leads to tissue injury [18]. The expression of the pro-inflammatory cytokines, TNF-α, transforming growth factor-beta (TGF-β), (IL)-1 and IL-6 are increased in alcoholic liver injury, while the anti-inflammatory cytokine, IL-4 is decreased [19]. These cytokines stimulate stellate cells which produce collagen leading to liver fibrosis. A study suggests that it is TNF-α that is the main candidate accounting for toxicity as addition of an equivalent amount of IL-6 seen in ALD did not produce injury in a normal rat liver whereas equivalent amounts of TNF-β did produce injury [20]. Removal of toxic reactive oxygen species is achieved via three major antioxidant enzymes: Catalase, superoxide dismutase and glutathione peroxidase. The generation of high concentrations of free radicals during the metabolism of alcohol may exceed the capacity of the antioxidant defence mechanisms and contribute to the development of alcohol induced liver injury [21]. This results in oxidative liver damage.

CLINICAL FEATURES

Alcoholic fatty liver disease does not usually cause any noticeable symptoms unless the build-up of fatty acids in your liver is severe.

- Weakness
- Loss of appetite
- Nausea
- Abdominal pain

Alcoholic hepatitis

- Yellowing of the eyes and skin (jaundice)
- Abdominal pain or tenderness
- The appearance of ‘spider-like’ red blood vessels in your skin
- Loss of appetite
- Nausea
- High temperature, usually around 38°C (101°F)
- Fatigue

Cirrhosis

Early stage symptoms include:

- Tiredness and weakness
- Loss of appetite
- Weight loss
- Feeling sick
- Very itchy skin
- Blotchy red palms
- Insomnia

Later symptoms include

- Jaundice
- Hair loss
- Build-up of fluid in the legs, ankles and feet (oedema) or in the abdomen, making you look heavily pregnant (ascites)
- Dark urine and black, tarry or very pale stools
- A tendency to bleed and bruise more easily, such as frequent nosebleeds and bleeding gums
- Vomiting blood
- Muscle cramps
- Right shoulder pain
- Dizziness and fatigue
- Breathlessness
- Rapid heartbeat
- Fever and shivering attacks (because you are more prone to infections)
- Memory loss and confusion
- Changes in your personality (caused by toxins in the bloodstream affecting your brain)
- Staggering when walking
- Increased sensitivity to alcohol and drugs (because the liver cannot process them)

DIAGNOSIS

Alcoholic liver disease is often first suspected when tests for other medical conditions show that the liver has been damaged.

Blood tests:

Used to assess the liver are known as liver function tests. They can detect enzymes in your blood that are normally only present if your liver has been damaged. Blood tests can also detect if you have low levels of certain substances, such as a protein called serum albumin, which is made by the liver. Low levels of serum albumin suggest that your liver is not functioning properly.

Imaging tests:

An ultrasound scan, computerized scan or a magnetic resonance imaging (MRI) scan may be carried out on your liver. The scans can produce detailed images of your liver and highlight any scarring. Some scans may also measure the stiffness of the liver, which is a good indication of whether your liver is scarred.

Liver biopsy: A fine needle is inserted into to the body (usually between your ribs). A small sample of liver cells is taken and sent to a laboratory to be examined under a microscope. The biopsy is usually carried out under local anesthetic, as a day case or with an overnight stay in hospital. The outcome of the biopsy will confirm a diagnosis of cirrhosis and may provide more information about the cause.

Endoscopy: An endoscope is a thin, long, flexible tube with a light and a video camera at one end. In an endoscopy it is passed down your oesophagus and into your stomach. Images of oesophagus and stomach will be transmitted to an external screen. The doctor will be looking for varices, which are a sign of cirrhosis.

Pharmacological & Non-Pharmacological Treatment

Successful treatment for alcoholic liver disease often depends on whether someone is willing to stop drinking alcohol, and make changes to their lifestyle.

Nutritional therapy

Many patients with ALD are malnourished and disease severity correlates with the degree of malnutrition. While visceral proteins (albumin, pre albumin and retinol binding protein) are the most common laboratory tests used to assess a patients nutritional status, these results can be confounded by the underlying liver disease or super imposed infections. Evaluated clinical findings such as muscle wasting, edema, loss of subcutaneous fat are helpful in identifying protein energy malnutrition. Nutritional assessments of alcoholic patients can reveal adequate calorie intake [22]. The most common vitamin deficiency are folate, Vitamin B-6, Vitamin A and Thiamine. Mineral deficiency include selenium, zinc, copper and magnesium [23].

Nutritional Recommendations for ALD Patients

- Evaluate for clinical signs of malnutrition in all ALD patients
- Daily caloric intake: 35-40 kcal/kg
- Daily protein intake: 1.2-1.5 g/kg
- Evening snack of 700 cal and 26 g protein
- Avoid unsaturated fats
- Zinc sulfate 220 mg daily
- Magnesium oxide 400 mg daily

Medication for treating symptoms

Despite the prevalence and morbidity of ALD, there is no US Food and Drug Administration–approved therapy for any form of ALD. In patients who show disease progression despite alcohol cessation and efforts to improve nutritional status, off-label drug therapy or complementary and alternative therapy may be considered.

Pentoxifylline is a nonselective phosphodiesterase inhibitor that has been shown in clinical trials to improve mortality in alcoholic hepatitis, primarily through the prevention of hepato renal syndrome [24]. Trials with pentoxifylline in patients with moderate ALD have not been performed. Because it has a very good safety profile, it may be used in patients with moderate ALD if they can tolerate the common side effect of nausea.

Silybum marianum (milk thistle) has anti-inflammatory and antioxidative properties resulting in anti-fibrotic and immune modulating effects [25]. It is safe to use in patients with liver disease and is widely used in Europe. But its efficacy has not been established in ALD.

S-adenosyl methionine (SAMe) is a major methylating agent that has important epigenetic and anti-inflammatory effects. In animal studies, SAMe is depleted in the early stages of ALD, leading to early fatty liver infiltration and mitochondrial damage. This damage can be reversed with SAMe supplementation [26]. SAMe is available at health food stores.

Probiotics are live microorganisms that, when consumed in adequate amounts, confer a health benefit to the host. There are many mechanisms by which probiotics enhance intestinal health and influence the gut-liver axis, including modulation of the intestinal microflora, modification of intestinal barrier functions and immune modulation. Probiotics have been shown to have beneficial effects in multiple studies in experimental ALD, and their effects are now being evaluated in a multicenter trial in ALD that is sponsored by the National Institutes of Health [27].

Medications and Complementary Therapy for ALD Patients

- Pentoxifylline 400 mg 3 times daily (Prescription)
- Silybum marianum (milk thistle) 200 mg 2-3 times daily (Complementary)
- SAMe 400 mg 3-4 times daily (Complementary)
- Probiotics as directed (Complementary)

Alcohol-related drug interactions

Many drugs interact with alcohol resulting in undesirable outcomes. There are two types of alcohol-drug interactions: pharmacokinetic and pharmacodynamic. Pharmacokinetic interactions occur when alcohol alters the metabolism or excretion of the drug or vice versa. Pharmacodynamic interactions refer to the additive effects of alcohol and certain drugs, particularly in the central nervous system (CNS) (e.g., sedation) without affecting the pharmacokinetics of the drug.

Table.1 Alcohol-related drug interactions

Drug/Drug Class	Effect(s) and Proposed Mechanism(s) [28-33]	Recommendations/ Comments
Analgesics (non opioids)		
Aspirin, NSAIDs (e.g., ibuprofen, etc)	Increased risk of GI hemorrhage.	Warn patients of the increased risk for GI bleeding when aspirin or NSAIDs are taken with alcohol, especially if taken on an empty stomach.
Acetaminophen (*Tylenol*, *Paracetamol*, etc)	Chronic alcoholics are more susceptible to acetaminophen induced hepatotoxicity.	Warn patients who chronically consume several alcoholic drinks a day or more to avoid taking large or prolonged doses of acetaminophen. (Do not exceed 4 g/24 hr).
Analgesics (Opioids)		
Alfentanil	Chronic alcohol consumption may increase the risk of pharmacodynamics tolerance to alfentanil.	Consider higher doses of alfentanil in patients who regularly consume alcohol.
Long-Acting Morphine (Kadian [34], Avinza [35])	Increased morphine release rate and absorption, which may lead to potentially fatal doses.	Tell patients to avoid alcohol and alcohol-containing drugs (*NyQuil*, etc).
Meperidine (*Demerol*)	Excessive CNS depression and impaired psychomotor performance.	Tell patients to limit alcohol intake to avoid excessive CNS depression.
Antidepressants		
Tricyclic Antidepressants (e.g., amitriptyline, etc)	Excessive CNS depression and impaired psychomotor performance.	Warn patients taking tricyclic antidepressants of enhanced CNS depression, especially within the first week of treatment and with the more sedating tricyclics such as amitriptyline and doxepin.
Antidiabetics		
Sulfonylureas	Acute alcohol use increases the risk of severe hypoglycemia.	Monitor for hypoglycemia if the combination is used.
Insulin	Enhanced glucose-lowering action of insulin.	Tell patients to limit alcohol consumption and avoid drinking on an empty stomach.
Metformin[36,37] (*Glucophage*, etc)	Theoretically, an increased risk for lactic acidosis.	Tell patients to limit alcohol consumption.
Antihypertensives		
Verapamil (*Calan*, etc)	Increases alcohol concentrations and prolongs intoxication.	Warn patients of the potential for enhanced effects of alcohol when combined with verapamil.
Anti-infectives		
Metronidazole (*Flagyl*)	Metronidazole inhibits aldehyde dehydrogenase, which leads to accumulation of acetaldehyde, a metabolite of alcohol.	Tell patients to avoid alcohol or alcohol-containing drugs while taking metronidazole and for at least 1 day after stopping the drug.
Isoniazid	Increased risk of hepatotoxicity in	Tell patients to limit or avoid

	the presence of chronic alcohol consumption on a daily basis.	alcohol.
Other Agents		
Phenytoin (*Dilantin*, etc)	Chronic alcohol abuse may reduce serum phenytoin concentrations.	Monitor for a decreased anticonvulsant effect in heavy drinkers.
Warfarin (*Coumadin*, etc)	Enhanced anticoagulant effects with acute alcohol intoxication.	Warn patients of increased risk of falls when under the influence of alcohol, which may result in bleeding injuries.
Nitroglycerin	Hypotension.	Tell patients to limit alcohol intake.
Immunosuppressive		
Methotrexate (*Rheumatrex*)	Increased risk of methotrexate induced liver injury.	The manufacturer advises against initiating methotrexate in patients who drink alcohol excessively [38].

DRUG INDUCED ALD

Chronic alcohol ~ Drug interactions

In addition to tolerance to ethanol, alcoholics also tend to display tolerance to various other drugs. The tolerance of the alcoholic to these drugs has been generally attributed to central nervous system adaptation [39] but in addition, metabolic adaptation must be considered. Indeed, it has been shown that the rate of drug clearance from the blood is enhanced in alcoholics [40,41]. Controlled studies showed, however, that administration of pure ethanol with non-deficient diets either to rats or man (under metabolic ward conditions) resulted in a striking increase in the rate of blood clearance of meprobamate and pentobarbital [42] and propranolol [43]. Similarly, increases in the metabolism of antipyrine [44], tolbutamide [39, 44], warfarin [40], propranolol [45], diazepam [46] and rifampicin [47] were found. Furthermore, the capacity of liver slices from animals fed ethanol to metabolize meprobamate was increased [37] which clearly showed that ethanol consumption affects drug metabolism in the liver itself, independent of changes in drug excretion or distribution or hepatic blood flow.

The Current Status of Institutions and Human Resources Available to Address the Disease

Public Funding

Overall, there is an imbalance between the severity and magnitude of alcoholic liver diseases and the amount of money spent on research.

European Sources of Funding for Alcoholic Liver Diseases: Selected Countries

United Kingdom

The UK Medical Council on Alcohol has a large clinical trial on psycho-social interventions. Basic research on alcoholic liver disease and fibrosis is being funded by the Welcome Trust.

The National Health Service has a Phase II clinical trial directed to use of Combivir® for treating primary biliary cirrhosis, the UK Cancer Research Center has a trial on use of pentoxiphylline and alpha-tocopherol to treat radiation-induced fibrosis [48].

The Foundation for Liver Research (based in the Royal Free & Union College, London) is supporting development of the above identified liver dialysis (MARS) technology at a level of about $4 million USD.

European Union (EU)

Within the EU for 2004, the following areas of work have been identified as "priority areas": health determinants: tobacco; alcohol; drugs; nutrition and physical activity; sexual and reproductive health; mental health; injury prevention; environmental health determinants; socioeconomic determinants of health; health promotion in particular settings; training in public health; disease prevention, in particular cardiovascular diseases, cancer and diabetes. The financial envelope of the public health program for the period 2003-2008 is € 312 million. The budget available for 2004 is about € 61 million. Thus, it appears that the EU has made alcohol research a priority in terms of Public Health but how this is to be implemented, and whether pharmacological interventions are part of this priority is far less clear.

The Health and Consumer Protection Directorate of the EC has funded several alcohol-related projects funded under its Health Promotion Program- all directed to psychosocial interventions. Other initiatives are of interest in this regard as well. The WHO supports an Alcohol Control Databank (European Alcohol Information System). The database is designed primarily to tract alcohol policies and their implementation.

United States Sources of Fundings

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is the lead U.S. governmental agency at the NIH for alcohol use and abuse. The NIAAA received about $400 million USD last year. The NIAAA is supporting over a dozen clinical protocols with regard to alcohol abuse and its sequelae. Its extramural programs include one with Germany (who is contributing €9 million for three years) on a project dealing with addiction research, but not therapeutic interventions. In comparison to the total appropriations package for other NIH research centers, the individual share to the NIAAA is small. The

2004 NIAAA appropriation is about 4% of the estimated ALD economic burden in the United States ($9 billion USD in 1998) but a trivial fraction of the direct and indirect economic costs from alcohol abuse.

Private Sector Funding

With regard to the U.S., in the short term at least there appears to be a shortage of U.S. private research funding specifically directed to alcoholic liver diseases.

Maxim Pharmaceuticals is a small biotechnology company that is developing histamine dihydrochloride (Ceplene (TM)) to prevent alcohol-induced damage in rodents. Maxim and the National Cancer Institute are, however, engaged in trials for histamine dihydrochloride to treat metastatic kidney cancer and liver cancer.

Inter Mune- This company in clinical trials with a formulation of interferon gamma-1b for Hepatitis C virus (HCV) patients with liver fibrosis but not in alcoholic patients with liver fibrosis. Its compound pirfenidone (5-methyl-1-phenyl-2 (1H) pyridine) has received Orphan Drug approval for pulmonary fibrosis. Biomedicines Pharmaceuticals- This company in-licenses technology and has licensed omega –interferon from Boehringers Ingelheim to test in hepatitis and fibrosis/cirrhosis. Cambridge Antibody Technologies- This large traded company has an anti-TNF alpha monoclonal antibody in U.S. clinical trials.

Fibro Gen- This is a privately held company with monoclonal antibody used to treat pulmonary fibrosis which blocks a fibrotic protein (connective tissue growth factor). It is unclear if this antibody has proceeded beyond Phase I trials.

PREVENTION

The most effective way to prevent alcoholic liver disease is to stop drinking alcohol, or stick to the recommended daily limits and have at least two alcohol-free days a week.

The recommended limits of alcohol consumption are:

- Men - upto 21 units of alcohol a week (3-4 units a day)
- Women - upto 14 units of alcohol a week (2-3 units a day)
- A unit of alcohol is equal to about half a pint of normal strength lager, a small glass of wine or a pub measure (25ml) of spirits. Use the drinking self-assessment tool to work out whether person is drinking too much.

Alcohol misuse

- There are different types of alcohol misuse, depending on how much alcohol you drink. To help you find out how harmful your drinking is, read our page on defining a drink problem. This may help you to look for treatment for alcohol misuse and prevent alcoholic liver disease from progressing to a further stage.

CONCLUSION

This review highlights the importance of preventing ALD and particularly alcoholic hepatitis (AH) and cirrhosis. This can be done through a variety of public policy measures, including regulatory, financial and educational approaches. This is a long-term approach. Due to the strong cultural affinity for alcohol in our country, dealing with the sequelae of alcohol abuse will continue to be a significant challenge. The burden of disease is substantial, the health service costs are increasing and the therapeutic options are lacking. Liver transplantation, a very expensive treatment option, has disappointing long term outcomes. There is a need for basic and applied research on all aspects of this problem. Moreover, blaming the ALD patient for behaviour which induced their disease will not change the reality that these patients consume substantial health service resources and need more effective treatments.

REFERENCES

1. Lelbach WK. Cirrhosis in the alcoholic and its relation to the volume of alcohol abuse. *Ann N Y Acad Sci,* 252, 1975, 85-105.
2. Becker U, Deis A, Sorensen TI *et al.,* Prediction of risk of liver disease by alcohol intake, sex and age: a prospective population study. *Hepatology,* 23, 1996, 1025-1029.
3. Tome S, Luckey MR. Review article: current management of alcoholic liver disease. *Aliment Pharmacol Ther,* 19, 2004, 707-14.
4. Bellentani S, Tribelli C, Saccoccio G, et al. Prevalence of chronic liver disease in the general population of northern Italy: The Dionysos study. *Hepatology,* 20, 1994, 1442-1449.
5. World Health Organization. Public health problems caused by harmful use of alcohol: report by the Secretariat. Fifty-eighth World Health Assembly, Provisional agenda item 13.14. Geneva, Switzerland: WHO 2005.
6. Sand J, Valikoski A, Nordback I. Alcohol consumption in the country and hospitalizations for acute alcohol pancreatitis and liver cirrhosis during a 20-year period. *Alcohol,* 44, 2009, 321-325.
7. Saunders JB, Latt N. Epidemiology of alcoholic liver disease. *Baillieres Clin Gastroenterol,* 7, 1993, 555-579.
8. Loft S, Olesen KL, Dossing M. Increased susceptibility to liver disease in relation to alcohol consumption in women. *Scand J Gastroenterol,* 22, 1987, 1251-1256.

9. http://pubs.niaaa.nih.gov/publications/Surveillance93/Cirr09.htm (Accessed on November 28, 2012).
10. http://www5.statcan.gc.ca/cansim/a26?lang=eng&retrLang=eng&id=1020552&paSer=&pattern=&stBy Val=1&p1=1&p2=37&tabMode=dataTable&csid
11. Kendall PRW. Public Health Approach to Alcohol Policy: An Updated Report from the Provincial Health Officer. 2008.
12. O'Shea RS, Dasarathy S, McCullough AJ. Alcoholic liver disease: AASLD Practice Guidelines. *Hepatology,* 51, 2010, 307–328.
13. Menon KV, Gores GJ, Shah VH. Pathogenesis, diagnosis, and treatment of alcoholic liver disease. *Mayo Clin. Proc,* 76, 2001, 1021–1029.
14. Mandayam S, Jamal MM, Morgan TR. Epidemiology of alcoholic liver disease. *Semin. Liver Dis,* 24, 2004, 217–232.
15. Inaba, Darry, Cohen, William B. Uppers, downers, all rounders: physical and mental effects of psychoactive drugs, 5th ed, Ashland, Or: CNS Publications.
16. Koskinas J, Kenna JG, Bird GL *et al.,* Immunoglobulin a antibody to a 200kilo Dalton cytosolic acetaldehyde adduct in alcoholic hepatitis. *Gastroenterology,* 103, 1992, 1060–1070.
17. Xu D, Thiele GM, Beckenhauer JL *et al.,* Detection of circulating antibodies to malondialdehyde-acetaldehyde adducts in ethanol-fed rats. *Gastroenterology,* 115, 1998, 686–692.
18. Fang C, Lindros KO, Badger TM, et al.Zonated expression of cytokines in rat liver: effect of chronic ethanol and the cytochrome P4502E1 inhibitor, chlormethiazole. *Hepatology,* 27, 1998, 1304–1310.
19. Neuman MG, Shear NH, Bellentani S *et al.,* Role of cytokines in ethanol-induced cytotoxicity in vitro in hep G2 cells. *Gastroenterology,* 115, 1998, 157–166.
20. Polavarapu R, Spitz DR, Sim JE *et al.,* Increased lipid peroxidation and impaired antioxidant enzyme function is associated with pathological liver injury in experimental alcoholic liver disease in rats fed diets high in corn oil and fish oil. *Hepatology,* 27, 1998, 1317–1323.
21. Fattaccioli V, Andraud E, Gentil M *et al.,* Effects of ethanol administration on rat liver protease activities: relationship with oxidative stress. *Hepatology,* 29, 1999, 14–20.
22. Mendenhall CL, Moritz TE, Roselle GA, Morgan TR, Nemchausky BA, Tamburro CH *et al.,* A study of oral nutritional support with oxandrolone in malnourished patients with alcoholic hepatitis: results of a Department of Veterans Affairs cooperative study. *Hepatology,* 17, 1993, 564-576.
23. Halsted CH. Nutrition and alcoholic liver disease. *Semin Liver Dis,* 24, 2004, 289-304
24. .Lucey MR. Management of alcoholic liver disease. *Clin Liver Dis,* 13, 2009, 267-275.
25. Lieber CS, Leo MA, Cao Q, Ren C, DeCarli LM. Silymarin retards the progression of alcohol-induced hepatic fibrosis in baboons. *J Clin Gastroenterol,* 37, 2003, 336-339.
26. Anstee QM, Day CP. S-adenosyl methionine (SAMe) therapy in liver disease: a review of current evidence and clinical utility. *J Hepatol,* 57, 2012, 1097-1109.
27. Kirpich IA, McClain CJ. Probiotics in the treatment of the liver diseases. *J Am Coll Nutr,* 31, 2012, 14-23.
28. Hansten PD, Horn JR. *Drug interactions analysis and managemen*t. St. Louis, MO: Facts and Comparisons Publishing Group. 2007.
29. Tatro DS. *Drug interaction facts*. St. Louis, MO: Facts and Comparisons Publishing Group. 2007.
30. Gordis E. Alcohol-medication interactions. National Institute on Alcohol Abuse and Alcoholism. No. 27 PH 355 January 1995. http://pubs.niaaa. nih. gov/publications /aa27.html.(Accessed December 2, 2007).
31. Alcohol-drug interactions. UHS health Promotion Office. University of Rochester. http://www.rochester.edu/uhs/healthtopics/Alcohol/interactions.html (Accessed December 2, 2007).
32. Weathermon R, Crabb DW. Alcohol and medication interactions. *Alcohol Res Health,* 23, 999, 40-54
33. Kalant H, Khanna JM, Marshman J. Effect of chronic intake of ethanol on pentobar- bital metabolism. *J Pharmacol Exp Ther,* 5, 1970, 318-324.
34. Personal communication, medical information department. Alpharma Pharmaceutical Piscataway NJ, 08854, 2007.
35. Product information for Avinza. King Pharmaceutical. Bristol, TN 37620, 2006.
36. Product information for Glucophage, Glucophage XR. Bristol-Myers Squibb. Princeton NJ, 08543. 2000.
37. Schaffalitzky de Muckadell OB, Mortensen H, Lyngsoe J. Metabolic effects of glucocorticoid and alcohol administration in phenformin- and metformin-treated obese diabetics. *Acta Med Scand,* 206, 1979, 269-273.
38. Product information for Rheumatrex. Stada Pharmaceuticals, Inc. Cranbury, NJ 08512, 2003.
39. Kater RMJ, Tobon F, Iber FL. Increased rate of tolbutamide metabolism in alcoholic patients. *J Am Med Assoc,* 207, 1969, 363-365.
40. Kater RMH, Roggin G, Tobon F, Zieve P, Iber FL. Increased rate of clearance of drugs from the circulation of alcoholics. *AM J Med Sci*, 258, 1969, 35-39.
41. Misra PS, Lefevre A, Ishii H, Rubin E, Lieber CS. Increase of ethanol meprobamate and pentobarbital metabolism after chronic ethanol administration in man and in rats. *AM J Med,* 51, 1971, 346-351.

42. Sotaniemi EA, Anttila M, Rautio A, Stengard J, Saukko P, Jarvensivu P. Propranolol metabolism after a drinking party. *Clin Pharmacol Ther*, 29, 1981, 705-710.
43. Vessell ES, Page JG, Passananti GT. Genetic environmental factors affecting ethanol metabolism in man. *Clin Pharmacol Ther*, 12, 1971, 192- 201.
44. Carulli N, Manenti I, Gallo M, Salvioli GF. Alcohol-drugs interaction in man: Alcohol and tolbutamide. *Eur J Clin Invest*, 1, 1971, 421-424.
45. Pritchard JF, Schneck DW. Effects of ethanol and phenobarbital on the metabolism of propanolol by 9000 g rat liver supernatant. *Bio chem. Harmacol*, 26, 1977, 2453-2454.
46. Sellman R, Kanto J, Raijola E, Pekkarinen A. Human and animal study on elimination from plasma and metabolism of diazepam after chronic alcohol intake. *Acta Pharmacol Toxicol*, 36, 1975, 33-38.
47. Grassi GG, Grassi C. Ethanol-antibiotics interactions at hepatic level. *J Clin Pharmacol Biopharmacol*, 11, 1975, 216-225.
48. NIH clinical trials website, at http://www.clinicaltrials.gov)