Harmful use of Alcohol
Alcohol Use Disorders and Alcoholic Liver Diseases

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Update on 2004 Background Paper, BP 6.14 Alcohol Use Disorders

Table of Contents

Abbreviations: ......................................................................................................................................... 5

Executive Summary ................................................................................................................................... 6

Burden of Disease ..................................................................................................................................... 6

Treatment Options ..................................................................................................................................... 7

1. Introduction ........................................................................................................................................... 8

1.1 Alcohol Consumption (ACo) and its relationship with Alcohol Use Disorders (AUD)......... 8

1.2 Alcohol Use Disorders (AUD) ............................................................................................................ 9

1.3 Alcoholic Liver Diseases (ALD) .......................................................................................................... 10

1.3.1 Alcoholic Fatty Liver ..................................................................................................................... 10

1.3.2 Alcoholic Hepatitis (AH) .............................................................................................................. 11

1.3.3 Alcoholic Cirrhosis (AC) ............................................................................................................. 11

1.4 Definition of AUD: Search for a consensus ....................................................................................... 11

1.4.1 ICD Criteria ................................................................................................................................... 11

1.4.2 The DSM Criteria ....................................................................................................................... 12

2. What is the size and nature of the disease burden that is caused by ACo, AUD, and ALD? .... 12

2.1 General Epidemiological trends for Europe and the World............................................................ 12

2.1.1 Unintentional injuries ............................................................................................................... 13

2.1.2 Intentional injuries .................................................................................................................... 13

2.2 Prevalence of Alcohol Use Disorders (AUD) .................................................................................. 13

2.3 Prevalence of Alcohol Liver Disease (ALD) .................................................................................... 16

2.4 The European Burden of ACo, AD and ALD .................................................................................. 16

2.5 Several Specific Epidemiologic Issues related to AUD and ALD ................................................... 20

2.5.1 Data collection challenges ....................................................................................................... 20

2.5.2 Alcohol and co-occurring chronic diseases ............................................................................. 20

2.5.3 Immunomodulatory effects of alcohol ...................................................................................... 23

2.5.4 Alcohol and its carcinogen effect ............................................................................................. 24

2.5.5 Alcohol and the elderly ............................................................................................................. 24

2.5.6 Alcohol and women .................................................................................................................. 24

2.5.7 Alcohol and genetics ................................................................................................................. 26

2.5.8 AUD diagnosis and biochemical markers ................................................................................ 26

3. What is the Control Strategy? ............................................................................................................. 27

3.1 Alcohol policy ..................................................................................................................................... 27

3.2 Remediation of Alcohol Use Disorders (AUD) .............................................................................. 29

3.2.1 Disulfiram (Antabuse): .............................................................................................................. 30

3.2.2 Oral naltrexone: .......................................................................................................................... 30

3.2.3 Extended-release naltrexone (monthly injection): ................................................................. 33

3.2.4 Acamprosate: ............................................................................................................................. 33

3.3 Alcoholic Liver Disease (ALD) ......................................................................................................... 34

3.3.1 Oxidative stress and hepatocyte membrane injury ..................................................................... 36

3.3.2 Extracorporeal Liver Support (ELS) ........................................................................................ 36

6.14-2
Update on 2004 Background Paper, BP 6.14 Alcohol Use Disorders

3.4 Alcoholic Cirrhosis (AC)........................................................................................................37
3.4.1 Antioxidants..................................................................................................................37
3.4.2 Propylthiouracil (PTU)................................................................................................37
3.4.3 Colchicine ....................................................................................................................38
3.4.4 Anabolic-androgenic steroids (AAS)............................................................................38
3.5 Transplantation ..................................................................................................................38

4.1 Economic burden ..............................................................................................................39
4.2 Feasibility and sustainability ..........................................................................................40

5. Why Does the Disease Burden Persist? ..............................................................................41

6. What can be learnt from past/current research into pharmaceutical interventions for this Condition? .........................................................................................................................42
6.1 Alcohol Use Disorders (AUD) .........................................................................................42
6.2 Alcohol Liver Disease (ALD) ..........................................................................................42

7. What is the Current “Pipeline” of Products that Are to Be Used for this Particular Condition? ..................................................................................................................................43
7.1 Alcohol Use Disorders (AUD) .........................................................................................43
7.1.1 Opioid antagonists ......................................................................................................43
7.1.2 Serotonergics ..............................................................................................................43
7.1.3 Dopaminergics ............................................................................................................44
7.1.4 GABA targeting ..........................................................................................................44
7.1.5 Other interventions .....................................................................................................44
7.2 Alcoholic Liver Disease (ALD) .......................................................................................45
7.3 “Spillovers” from the Hepatitis C pipeline and Other Fibrotic Conditions .................47

8. What is the Current Status of Institutions and Human Resources Available to Address the Disease? .......................................................................................................................................47
8.1 Public funding ..................................................................................................................47
8.1.1 European sources of funding for alcoholic liver diseases: selected countries ..........48
8.1.2 European Union .........................................................................................................48
8.1.3 United States sources of funding ...............................................................................49
8.2 Private sector funding ....................................................................................................51

9. Ways Forward from a Public Health Viewpoint with Regard to Public Funding ............53
9.1 Gaps between current research and potential research issues which could make a difference. .................................................................................................................................53
9.1.1 Basic research ...........................................................................................................53
9.1.2 Applied research .......................................................................................................53

10. What are the gaps between current research and potential research issues which could make a difference, affordable and could be carried out in a) five years b) in the long term? ..........................................................................................................................54
10.1 Systematic data recollection about morbidity ...............................................................54
10.2 Data comparability .......................................................................................................54
10.3 Alcohol pathogenesis ........................................................................................................... 55
10.4 Better understanding of young people’s drinking ............................................................... 55
10.5 Social harm ......................................................................................................................... 55
10.6 Alcohol policy .................................................................................................................... 55
10.7 Evidence-based treatment ................................................................................................. 55
10.8 Combination of pharmaceutical options ........................................................................... 56

11. For which of these gaps are there opportunities for pharmaceutical research (possible ways to go forward with regards to public funding?) ........................................... 56
   11.1 Alcohol pathogenesis ...................................................................................................... 56
   11.2 Public and private funding needs to be increased .......................................................... 56

12. Conclusion ............................................................................................................................ 57

References .................................................................................................................................. 57

APPENDIX .................................................................................................................................... 67
Update on 2004 Background Paper, BP 6.14 Alcohol Use Disorders

Abbreviations:

AAS: Anabolic-androgenic steroids
AC: Alcohol Cirrhosis
ACo: Alcohol Consumption
AD: Alcohol dependence
AH: Alcohol Hepatitis
ALD: Alcohol Liver Diseases
AUD: Alcohol Use Disorders
BAC: Blood Alcohol Concentration
DALYs: Disability Adjusted Life Years
DSM: Diagnostic and Statistical Manual of Mental Disorders
EMA: European Medicines Agency
EU: European Union
FDA: United States Food and Drug Administration
HIV: Human Immunodeficiency Virus
ICD: International Classification of Diseases
MHD: Mental Health Disorders
NIAAA: National Institute on Alcohol Abuse and Alcoholism
PTU: Propylthiouracil
ROS: Reactive Oxygen Species
SAMe: S-adenosyl-L-methionine
SSRI: Selective Serotonin Reuptake Inhibitor
TB: Pulmonary Tuberculosis
US: United States of America
WHO: World Health Organization
Executive Summary

Burden of Disease

- According to the World Health Organization (WHO), alcohol emerges as the third largest risk factor for premature mortality, disability and loss of health. Alcohol caused about 3.8 per cent of all deaths (2.5 million) and about 4.5 per cent of ‘disability adjusted life years’ lost (DALYs) (69.4 million).
- Worldwide, alcohol is the third leading cause of ill health, behind low birth weight and unsafe sex. Europe is the largest consumer of alcohol in the world and alcohol consumption appears as the third leading risk factor for disease and mortality.
- Even though alcohol is a causal factor in 60 types of diseases and injuries and a component cause in 200 others, and accounts for 20% to 50% of cirrhosis of the liver prevalence, it remains a low priority for public and health policy interventions.
- Alcohol Consumption (ACo) is responsible for increasing the risk of liver cirrhosis, certain cancers, raised blood pressure, stroke and congenital malformations. Furthermore, ACo increases the risk of many family, work and social problems.
- Excessive ACo (more than 14 standard drinks per week for men and seven standard drinks per week for women) is significantly associated with the burden of disease of infectious conditions, cancer, cardiovascular disease, and liver cirrhosis. Interestingly however, mild and moderate patterns of alcohol consumption also has beneficial effects on the burden of disease, mainly on diabetes and the ischemic disease subcategory of cardiovascular diseases. Yet the latter effects are by far outweighed by the detrimental consequences of excessive ACo.
- European countries estimates report that one in seven male deaths and one in 13 female deaths in the 15-64 age categories were caused by alcohol. That ratio translates into 95 000 men and over 25 000 women dying from alcohol-attributable causes in one year.
- Alcohol Use Disorders (AUD) constitutes a major part of neuropsychiatric disorders and markedly contributes to the global burden of disease. However, they only account for less than one-third of the overall impact of ACo. Alcohol dependence accounts for 71% of all alcohol-related deaths and for about 60% of social costs attributable to alcohol. Acute effects of ACo on the risk of both unintentional and intentional injury also account for a sizable effect on the global impact of burden of disease.
- Alcoholic liver disease (ALD) is the commonest cause of cirrhosis in the western world, and ALD is currently one of the ten most common causes of death. Liver fibrosis caused by alcohol abuse and its end stage, cirrhosis, presents enormous worldwide healthcare problems. Over 60% of patients with cirrhosis of the liver and superimposed alcoholic hepatitis have a life expectancy of only four years. Overall, stopping drinking has been shown to improve the survival of patients with all stages of ALD.

ALD comprises a spectrum of disease, including alcoholic fatty liver, AH, alcoholic fibrosis, cirrhosis, and hepatocellular cancer. Worldwide, the common causes of liver fibrosis and cirrhosis include alcohol, hepatitis B and hepatitis C.
Treatment Options

- Only 14.6 per cent of those with a lifetime history of alcohol abuse or dependence have received treatment. In Europe, only an estimated 8% of people with alcohol dependence receive treatment. Efforts to identify and properly care this population are warranted.
- Several policy options have been tested to decrease ACo. For example, drinking and driving reduction; education, communication, training and public awareness; alcohol market regulation; reduction of harm in drinking and surrounding environments; and interventions for individuals. The evidence is still weak to identify the true effectiveness of such interventions.
- Currently approved for treating AUD are disulfiram, naltrexone, and acamprosate. Other drugs are being investigated, used off-label (topiramate and ondansetron) or recently approved in Europe (nalmefene) for use in patients with alcohol dependence who want to reduce their alcohol consumption, either as a treatment goal or as a step towards abstinence. While some of them have shown promise in terms of efficacy (nalmefene, topiramate, and ondansetron), none has been found effective when used as a single treatment method without some sort of concurrent behavioral therapy.
- Coexisting diseases (especially mental disorders, but also noncommunicable diseases such as cardiovascular disease, cancer, diabetes or liver disorders) are highly prevalent among those subjects suffering from AUD. Latest evidence supports changing the current practice of treating both diseases (mental disorders and alcohol dependence) separately; to a new approach of incentivizing better coordination between clinics and centers to treat addictions.
- Overall, stopping drinking has been shown to improve the survival of patients with all stages of ALD. Thus, this condition can be prevented. However, progress in developing specific treatments for acute AH has been hampered by a poor understanding of disease pathogenesis. There are no FDA approved therapies for ALD.
- Many treatment modalities have been tried in patients with AH, however, few have been consistently shown to have a beneficial effect and, accordingly, none have achieved consensus status among practicing hepatologists. Thus, current therapy still focuses predominantly on supportive care.
- Current treatments for alcoholic cirrhosis are severely limited. One can attempt to have patients abstain from alcohol (where possible); eradicate existing viruses using interferon, ribavirin, and lamivudine (in cases involving viral hepatitis); and liver transplantation. The vast majority of patients with ALD in clinical practice have advanced fibrosis or cirrhosis. No adjunctive pharmacotherapies have been consistently shown to improve survival in more than one randomized controlled trial, although some have shown promise.
- There is little private-sector funding directed to AUD and ALD. Public sector funding may be insufficient as well, particularly when compared to the enormous economic and social burdens placed on the healthcare system by ALD.
1. Introduction

Around two billion people worldwide consume alcoholic beverages regularly and over 76 million people suffer from AUD. Many interacting issues are at work when dealing with alcohol abuse: the medical sequelae, alcohol intoxication, alcohol tolerance, alcohol dependence, and alcohol withdrawal. From a public health viewpoint, the diseases associated with alcohol abuse are preventable with abstention and such behavioral modifications should be considered as the primary intervention. The present review will offer an overview of the strategies to prevent Alcohol Consumption (ACo), pharmacological interventions for alcohol abuse and dependence (collectively termed AUD) and alcohol's hepatotoxic effects that result in ALD. This background paper update reviewed the latest evidence from 2002 through 2012, on the basis of an analysis of published systematic reviews and meta-analyses, which were identified through searches of The Cochrane Library, Medline, Web of Science, Google Scholar and National Institute on Alcohol Abuse and Alcoholism (NIAAA), with specific search terms for alcohol use disorders, alcoholic liver diseases and alcohol consumption. If relevant references within the timeframe described above were not found, older ones were considered. Reference sections of identified papers were cross-checked to identify other relevant studies contributing to this review.

1.1 Alcohol Consumption (ACo) and its relationship with Alcohol Use Disorders (AUD)

Evidence is overwhelming about the link between excessive use of alcohol and a wide range of harmful outcomes, including AUD; mortality and morbidity from chronic medical conditions, such as ALD and acute causes, such as vehicular accidents, intentional and unintentional injury; and a host of social and legal problems. WHO risk assessment framework illustrates the multidimensional association between ACo and health and social problems (Figure 6.14.1).

The conditions that lead to excessive ACo in some individuals and not in others are very complex. Alcoholism is a multigenic disorder involving interactions between genetic, psychosocial, environmental, and neurobiological factors. The pharmacological effects of ethanol that support alcohol reward and alcohol seeking behavior involve actions at multiple receptors and neurochemical systems occurring throughout the body. Neuropharmacologic studies in animals have provided evidence for specific neurochemical mechanisms in the brain that are involved in AD. There are many neurotransmitter systems that become deregulated during the development of alcohol dependence, including gamma (γ)-aminobutyric acid (GABA), opioid peptides, glutamate, serotonin and dopamine systems.
Figure 6.14.1. The relationship between alcohol consumption, intermediate variables and alcohol related outcomes.


1.2 Alcohol Use Disorders (AUD)

Prolonged excessive ACo promotes neuroadaptive changes in the brain’s reward and stress systems. It is theorized that AUD development is linked with the presence of a constant alcohol challenge to regulatory systems that attempt (but ultimately fail) to defend the normal equilibrium of various homeostatic set points. This mechanism is postulated to contribute to the transition from controlled alcohol use to uncontrollable drinking (Figure 6.14.2 offers a contextual framework to elucidate the vicious circle between dependence and relapse).

Briefly, alcohol has two major actions on the brain: increasing neuronal inhibition mediated through the inhibitory GABA and other receptors. Prolonged alcohol use down-regulates these receptors and decreases inhibitory neurotransmission. Prolonged alcohol use inhibits excitatory neurotransmission by inhibiting both N-methyl-d-aspartate (NMDA) and non-NMDA (e.g., α-amino-3-hydroxy-5-methisoxazole-4-propionic acid [AMPA]) receptors. Cessation or reduction of alcohol use initiates an imbalance between the decreased neuroinhibition and increased neuroexcitation. This causes the clinical manifestations of alcohol withdrawal: e.g., tremors, hallucinations, insomnia, anxiety or agitation, and possibly seizures. Alcohol also affects numerous other neurotransmitters (for additional details, go to Appendix 6.14.3 and 6.14.4). Although about 30% of all alcohol-dependent patients are admitted to general hospitals, usually to treat the alcohol-related physical diseases emphasized in this document, AUD themselves are often ignored or not diagnosed.
**1.3 Alcoholic Liver Diseases (ALD)**

The pathogenesis of ALD is multifactorial. Hepatocytes and parenchymal cells are the main targets of alcohol and its toxic metabolites, producing an excessive generation of molecules called free radicals, known as reactive oxygen species (ROS). ROS modify the signaling pathways regulating lipid or glucose metabolism, and can directly modulate proteins and DNA. Alcohol can also induce the permissiveness of the intestine cell wall, allowing larger amounts of endotoxins to pass into the blood. The body coordinated immune response by activation of immune cells residing in the liver (Kupffer cells), which affect the liver tissue by two mechanisms: a) become inflammatory cytokines, and their excessive amount have dire consequences, pushing the immune system response into overdrive, promoting the progression of liver disease b) Kupffer cells are the major source of ROS in the liver, leading to oxidative stress. The spectrum of ALD ranges from fatty liver (steatosis), present in most, if not all heavy drinkers, through steatohepatitis, fibrosis and ultimately cirrhosis. (Appendix 6.14.1 illustrates the systemic mechanism of alcohol-induced liver damage).

**1.3.1 Alcoholic Fatty Liver**

Alcoholic fatty liver is predominantly an asymptomatic condition that develops in response to a short duration (a few days) of alcohol abuse. Patients with fatty liver are asymptomatic so that they rarely present with liver related problems. Fatty liver is reversible with abstinence but it is a risk factor for progression to fibrosis and cirrhosis in those patients who continue drinking.
1.3.2  **Alcoholic Hepatitis (AH)**

Between 20-40% of persistent heavy drinkers will develop more serious liver disease. In some of these patients, they will get AH, while others will present with complications of portal hypertension, and other conditions. People with ALD can also be asymptomatic and may even have normal liver blood tests.\(^\text{11}\) The level of alcohol consumption necessary for the development of these advanced forms of ALD is probably 80 g of alcohol per day, the equivalent to six to eight drinks daily for several years.\(^\text{12}\)

1.3.3  **Alcoholic Cirrhosis (AC)**

Alcoholic cirrhosis may occur at any time before, during, after, or independent of a bout of AH. Liver fibrosis and cirrhosis (clinically distinct conditions but, unless specifically mentioned, they are used interchangeably in this report) represent a continuous disease spectrum characterized by an increase in total liver collagen and other matrix proteins which disrupt the architecture of the liver and impair liver function.\(^\text{13}\) Fibrosis results from sustained wound healing in the liver in response to chronic or iterative injury. The wound healing response is an integral part of the overall process of inflammation and repair: it is dynamic and has the potential to resolve without scarring\(^\text{12}\), however, hepatic fibrosis is a healing process gone awry in response to ongoing liver injury in ALD.\(^\text{14}\) As the liver becomes increasingly fibrotic, the number of functional hepatocytes decreases and the liver loses its capacity to remove toxic substances from the blood. At present, there are few interventions available to alter the underlying fibrotic process in many patients with liver disease, although data from clinical and laboratory based research show that cirrhosis may be reversible.\(^\text{15}\)

1.4  **Definition of AUD: Search for a consensus**

Consensus around diagnostic criteria for AUD becomes critical to signal which patterns of behaviour or physiological characteristics constitute symptoms to properly recognize the disorders. Diagnostic criteria allow clinicians to plan treatment and monitor treatment progress; make communication possible between clinicians and researchers; enable public health planners to ensure the availability of treatment facilities; help health care insurers to decide whether treatment will be reimbursed; and allow patients access to medical insurance coverage.

1.4.1  **ICD Criteria**

The World Health Organization (WHO) develops diagnostic criteria for the purpose of compiling worldwide statistics on all causes of death and illness, including those related to AUD. The International Classification of Diseases (ICD-10 codes) defines AUD in a way that is similar to the Diagnostic and Statistical Manual of Mental Disorders (DSM). The diagnosis focuses on an interrelated cluster of psychological symptoms, such as craving, physiological signs (such as tolerance and withdrawal) and behavioural indicators such as the use of alcohol to relieve withdrawal discomfort. However, in a departure from the DSM, rather than include the category "alcohol abuse," ICD-10 includes the concept of "harmful use." This category was created so that health problems related to alcohol and other drug use would not be underreported. Harmful use implies alcohol use that causes either physical or mental damage in the absence of dependence. Some differences between the two major diagnostic
criteria still exist, but they have been revised by consensus as to how AUDs are best characterized for clinical purposes.

1.4.2 The DSM Criteria

Researchers and clinicians in the United States (US) usually rely on the DSM diagnostic criteria, found in the DSM, currently in its Fourth Edition (DSM-IV). DSM-IV, like its predecessors, includes non-overlapping criteria for AUDs. However, in a departure from earlier editions, DSM-IV provides for the subtyping of dependence based on the presence or absence of tolerance and withdrawal. The criteria for abuse in DSM-IV were expanded to include drinking despite recurrent social, interpersonal, and legal problems as a result of alcohol use. In addition, DSM-IV highlights the fact that symptoms of certain disorders, such as anxiety or depression, may be related to an individual’s use of alcohol or other drugs. The 2013 update (published draft guidelines) no longer separate the categories of abuse and dependence. Therefore, both disorders are defined as single AUD. Research found that a single dimensional construct offered a simpler solution that better fit the research results.9

2. What is the size and nature of the disease burden that is caused by ACo, AUD, and ALD?

2.1 General Epidemiological trends for Europe and the World

Alcohol Consumption (ACo) has accompanied humans since the beginning of recorded history. The harmful use of alcohol significantly associates with more than 60 types of diseases and injuries, resulting in approximately 2.25 million deaths each year, after controlling for the beneficial impact of low risk alcohol use on morbidity and mortality in some diseases (e.g. diabetes, cardiovascular disease). Thus, approximately 4% of all deaths worldwide are attributable to alcohol.16 NIAAA estimated in 2007 that more than 17 million people in the United States have an AUD, with a cost to society of over US$ 180 billion annually.17

Even though accurate estimates for the incidence and prevalence of ALD are difficult to obtain, it is estimated that 20% to 50% of cirrhosis of the liver is attributable to ACo. The ICD-10 codes include more than 30 items with alcohol as part of the name or definition (necessary cause). Moreover, it has been identified as a component cause for over 200 ICD-10 disease codes.18

The impact of ACo is associated with two consumption domains: (a) the volume of alcohol consumed and (b) the pattern of drinking (Figure 1). In terms of volume, it is clear that most of the burden associated with alcohol is positively associated with regular heavier drinking patterns (commonly defined as drinking more than 40 grams of pure alcohol per day for men and 20 grams of pure alcohol per day for women).19 In addition, irregular patterns of drinking are strongly related with the burden of disease and injury (e.g. binge drinking, defined as drinking at least 60 grams of pure alcohol or five standard drinks in one sitting).20 In European settings, heavy episodic drinking patterns are more prevalent in poorer than in richer settings, and explain 25% of the differences in life expectancy between eastern and
western Europe.\textsuperscript{19,21} Rising levels of consumption are most pronounced in women and young people, with the latter more prone to heavy binge drinking.\textsuperscript{1}

2.1.1 Unintentional injuries

The relationship between alcohol and unintentional injuries has been established in published literature. It depends on the blood alcohol concentration (BAC) and shows an exponential dose-response relationship.\textsuperscript{22} Alcohol affects psychomotor abilities, with a threshold dose for negative effects generally found at BACs of approximately 0.04 to 0.05 per cent (about two to three drinks in an hour); accordingly, people with BACs at this level are more likely to injure themselves or others.\textsuperscript{20} Literature has also linked alcohol’s acute effects with the consumption pattern. People who drink less frequently are more likely to be injured or to injure others at a given BAC compared with regular drinkers, presumably because of less tolerance.\textsuperscript{23}

2.1.2 Intentional injuries

Alcohol consumption is linked to patterns of self-harm and aggression.\textsuperscript{21} For example, Borges and colleagues found a positive association between volume of ACo and suicide risk.\textsuperscript{24} There also is a clear link between ACo and aggression, including, but not limited to, homicides.\textsuperscript{25} Cultural factors may also have an effect to both differences in drinking patterns and aggression.\textsuperscript{6,21}

2.2 Prevalence of Alcohol Use Disorders (AUD)

With the exception of Islamic regions, alcohol is ubiquitous in the modern world (25). It seems possible that the role of alcohol as a major factor in the burden of disease will increase in the future. Even though a five year change in alcohol use (2001-2005) showed a relatively stable global ACo in most developed regions, developing regions such as Africa and South East Asia have reported consumption increase.\textsuperscript{16} Alcohol is linked to conditions also predicted to increase (e.g. accidents and injuries, cardiovascular disease).\textsuperscript{26} In terms of younger populations, there are some indications that relatively healthful patterns of drinking are deteriorating in young people, particularly in Europe.\textsuperscript{27} Globalization seems to lead to converging patterns of drinking around the world, and not necessarily to convergence to the most favorable patterns (i.e. regular light to moderate drinking with meals). It is arguable that the deterioration of the favorable pattern in young people in Europe has been linked to aggressive marketing focused to this age group. Drinking is being promoted as a lifestyle in association with recreation.\textsuperscript{27}

The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a large general-population survey conducted in 2001–2002, estimated the prevalence of alcohol abuse and dependence at 4.65 per cent and 3.81 per cent, respectively.\textsuperscript{16} Cohen and colleagues\textsuperscript{13} reported from the same survey that only 14.6 per cent of those with a lifetime history of alcohol abuse or dependence have received treatment. The results from this survey suggested a wide range of recovery from AD in the general population, from partial remission to full abstinence.\textsuperscript{12} Indeed, most prevalence studies have been carried out in North America,\textsuperscript{29}, so that the results may not be generalizable to other cultures. Rates of AUD also vary depending on the diagnostic criteria used. Community-based studies have estimated the prevalence of alcohol misuse or dependence as 2-4%, with much higher rates
of 17% (men) and 7% (women) when looser criteria such as excessive ACo are used. For hospital based studies, the same difficulties exist as the definitions for AUD are not clearly specified in many studies.

Notwithstanding the above, what is known is that the average volume of ACo and patterns of drinking are not related to each other. There is a marked variation between geographic regions (based on WHO sub-regions) on both dimensions. The average volume of drinking is highest in established market economies in Western Europe and the former Socialist economies in the Eastern part of Europe and in North America, and lowest in the Eastern Mediterranean region and parts of South-East Asia including India. Patterns are most detrimental to health in the former Socialist economies in the Eastern part of Europe, in Central and South America and parts of Africa (Figure 6.14.3). Overall, exposure to alcohol around the world varies considerably between regions, the overall exposure by volume is quite high and patterns are relatively detrimental. Global patterns of consumption are changing (Figure 6.14.3). Overall, developed countries have higher amounts of consumption compared to other countries and regions. However, low-income and middle-income countries (especially in South-East Asia and the western Pacific regions) have markedly increased their ACo over time, partially attributable to supply growth. In addition, the alcohol industry is particularly interested to increase their operations in the emerging economy countries (Brazil, India, China, and Russia). Low consumption is consistently reported in the regions of the world with large populations of Islamic faith, which have very high rates of abstention.

ACo has been recognized as the main risk factor for alcohol abuse. Ecologically, there is a very close association between a country’s total alcohol per head consumption and its prevalence of alcohol-related harm and AUD (21). A large portion of this consumption – 28.6% or 1.76 litres per person – was homemade and illegally produced alcohol or, in other words, unrecorded alcohol. The latter forms of alcohol production may be associated with an increased risk of harm because quality and safety standards for alcohol production are often lacking (30). In the EU, Just under half of this alcohol is consumed in the form of beer (44%), with the rest divided between wine (34%) and spirits (23%).

Excessive ACo can lead to AUD, which affects 12.5 per cent of people in the United States across their lifetime. Nearly 80 000 people die annually from the short- and long-term consequences of alcohol use in the United States.

In terms of alcohol-related mortality, almost one third of the alcohol-attributable deaths (29.6%) is related to unintentional injuries, with 21.6 per cent due to cancer and about 17 per cent due to liver cirrhosis. Cardiovascular diseases and intentional injuries are the next most important categories, accounting for 14 per cent and 12 per cent respectively (Figure 6.14.4). Worldwide, alcohol caused about 4 per cent of all deaths (2.5 million).

In terms of alcohol-related morbidity, about 4.5 per cent (men: 7.6 per cent; women:1.4 per cent) of ‘disability adjusted life years’ lost (DALYS) (69.4 million) is related to alcohol-attributable burden of disease. However, Present estimates of health effects probably underestimate the harm caused by alcohol, because the full range of social costs have not been properly quantified by research yet.
Update on 2004 Background Paper, BP 6.14 Alcohol Use Disorders

Figure 6.14.3: Total Adult (15+) per capita consumption, in liters of pure alcohol, 2005 a.

![Map showing per capita consumption of alcohol](http://www.who.int/substance_abuse/publications/global_alcohol_report/msbgsruprofiles.pdf)

*Best estimates of 2005 using average recorded alcohol consumption 2003–2005 (minus tourist consumption, see Appendix IV for details) and unrecorded alcohol consumption 2005.


Figure 6.14.4: Global distribution of all alcohol-attributable deaths by disease or injury, 2004

![Pie chart showing global alcohol-attributable deaths](http://www.who.int/substance_abuse/publications/global_alcohol_report/msbgsruprofiles.pdf)

- 14.0% Cardiovascular diseases and diabetes mellitus
- 16.6% Liver cirrhosis
- 29.6% Unintentional injuries
- 21.6% Cancer
- 6.0% Neuropsychiatric disorders
- 0.1% Prematurity and low birth weight

2.3 Prevalence of Alcohol Liver Disease (ALD)

ALD is the commonest cause of cirrhosis in the western world\textsuperscript{33}, and ALD is currently one of the ten most common causes of death.\textsuperscript{34} In addition, it remains the most common endpoint associated with ACo and accelerates the progression of other liver diseases such as hepatitis C virus (HCV), hepatocellular carcinoma, and hemochromatosis.\textsuperscript{35} ALD comprises a spectrum of disease, including alcoholic fatty liver, AH, AC, and hepatocellular cancer. In 2008, 0.95\% of all deaths registered in people aged ≥ 20 years in England and Wales were attributed to ALD.\textsuperscript{36} Patients with cirrhosis and superimposed AH have a four-year mortality of more than 60\%.\textsuperscript{37}

Worldwide, the common causes of liver fibrosis and cirrhosis include hepatitis B and hepatitis C and alcohol. Other causes include immune mediated damage, genetic abnormalities, and non-alcoholic hepatitis, which is associated with obesity and diabetes type 2. Changing patterns of ACo in the west and the increasing rates of obesity and diabetes mean that advances in preventing and treating viral liver infections may be offset by an increasing burden of fibrosis and cirrhosis related to alcohol and non-alcoholic abuse.\textsuperscript{38}

2.4 The European Burden of ACo, AD and ALD

The European Union is the heaviest drinking region in the world, as Figure 6.14.5 illustrates. Specifically, ACo is responsible for increasing the risk of liver cirrhosis, certain cancers, raised blood pressure, stroke and congenital malformations.\textsuperscript{30} Furthermore, ACo increases the risk of many family, work and social problems. For instance, in the European Region of the WHO, between 40 and 60 per cent of all deaths from intentional and unintentional injuries are estimated to be attributable to ACo.\textsuperscript{26} Moreover, in parts of Central and Eastern Europe alcohol abuse has been significantly associated with decreasing rates of male life expectancy.\textsuperscript{39}

Data from European countries from 2004 estimated that one in seven male deaths and one in 13 female deaths in the 15-64 age categories were caused by alcohol. That ratio translates into 95 000 men and over 25 000 women dying from alcohol-attributable causes.\textsuperscript{30} Middle-aged adults (mostly men) die from alcohol more frequently than any other age group. In terms of life-course, the longer the onset of consumption is delayed, the less likely AUD will emerge.\textsuperscript{30}

Rehm and colleagues\textsuperscript{19} clustered the European countries in four regions:

- EU10 (joined EU after 2004): Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia and Slovenia;
- EU 15 (old EU): Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden and the United Kingdom
- Baltic countries
- Russian federation
The alcohol-attributable mortality rate in EU10 was more than twofold increased, compared to EU15 for men, and 40 per cent increased for women. Baltic countries alcohol-attributable mortality was fourfold higher for men and three fold higher in women, compared to EU15 countries. The Russian federation showed an almost sevenfold increased mortality for men and fourfold for women, compared to EU15 countries.

In addition, socially disadvantaged people are more likely to experience more harm per gram of alcohol compared to more privileged sectors. The WHO’s 2004 Global Burden of Disease Study found that alcohol was the third most important risk factor, after smoking and raised blood pressure, for European ill-health and premature death. Partial estimates indicate that in 2004, over four million disability-adjusted life-years (DALYs) – years of life lost due to either premature mortality or to disability – were caused by ACo in the EU, corresponding to 15 per cent of all DALYs in men and 4 per cent of all DALYs in women (30). This level of alcohol-related death is highest in Europe and the Americas, where it ranges from 8 per cent to 18 per cent for males and 2 per cent to 4 per cent for females. In 2004, a total of 4 043 000 DALYS were estimated to be lost due to alcohol-attributable causes in the group aged 15-64 years in the EU (3 359 000 in men and 684 000 in women).

Figure 6.14.6 shows the burden of AUD among men and women within European regions. Men seem to be more consistently susceptible in all regions, compared to women. The burden for European women in this age group is much less but is generally in the range of the global values. Overall for both sexes, Central Eastern and Eastern Europe have the higher rates of lost DALYs due to alcohol-attributable causes.
In terms of cirrhosis (the most lethal consequence of AUD), its prevalence was estimated at 0.15 per cent or 400 000 both in Europe and the United States. However, the high rates of undiagnosed cirrhosis should caution about the accuracy of these estimates. Figure 6.14.7 shows the burden of liver cirrhosis as a per cent of the total DALY burden across various age group and regions. This burden peaks between the ages 45-59 at about 4-5% of all DALYs for men in Europe. The burden for European women in this age group is much less but is generally in the range of the global values. Over all age groups and both sexes, the EU10 countries have higher liver cirrhosis disease burdens than the EU15 countries, a situation reversed from that of alcohol abuse disorders.

The peak in distribution of disease burden for liver cirrhosis follows that for AUD by about 20 years. Although liver cirrhosis can be caused by infective agents (e.g. viral hepatitis), the time lag is not unreasonable under the hypothesis that the liver cirrhosis is in large part the result of the earlier alcohol abuse. Figures 6.14.7 reports frequency plots of the fraction of total DALYs attributed to each age group for the particular geographic area. European regions systematically report the highest burden of disease (with exception of EU 15 women), compared to world estimates. In addition, the timeframe between 15-29 and 45-59 years of age account for the largest amount of DALYs lost for all regions.

Table 6.14.1 summarizes alcohol-attributable burden of disease in Europe. It is worth noting the differences between alcohol-attributable mortality and alcohol-attributable burden of disease (morbidity). Mental disorders represent the largest amount of variability for morbidity (measured in DALYs), and the proportion is almost the same for men and women (46% and 44% respectively). AUD are less fatal compared to diseases such as cancer or...
cardiovascular diseases, however, it contributes more to alcohol attributable burden of disease.\(^{30}\)

Figure 6.14.7: Burden of Liver Cirrhosis as a per cent of the total DALY burden, 2002

![Liver Cirrhosis (Percent of All DALYs by age group)](image)

Source: Casswell S, Thamarangsi T. Alcohol and Global Health 3 Reducing harm from alcohol: call to action. development. 2009:9:10.\(^{32}\)


<table>
<thead>
<tr>
<th>Effects</th>
<th>Men</th>
<th>Women</th>
<th>Men (%)</th>
<th>Women (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detrimental effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>251,691</td>
<td>151,671</td>
<td>6.9</td>
<td>17.5</td>
</tr>
<tr>
<td>Cardiovascular diseases other than ischemic heart disease</td>
<td>128,338</td>
<td>25,969</td>
<td>3.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Mental and neurological disorders</td>
<td>1,891,310</td>
<td>382,584</td>
<td>48.3</td>
<td>44.2</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>512,560</td>
<td>212,676</td>
<td>14.0</td>
<td>24.6</td>
</tr>
<tr>
<td>Unintentional injury</td>
<td>834,059</td>
<td>50,936</td>
<td>17.4</td>
<td>5.9</td>
</tr>
<tr>
<td>Intentional injury</td>
<td>347,225</td>
<td>24,147</td>
<td>9.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Other detrimental</td>
<td>83,640</td>
<td>18,149</td>
<td>2.3</td>
<td>2.1</td>
</tr>
<tr>
<td>Total detrimental</td>
<td>3,849,521</td>
<td>866,131</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Beneficial effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>275,588</td>
<td>87,687</td>
<td>94.8</td>
<td>48.3</td>
</tr>
<tr>
<td>Other beneficial</td>
<td>15,049</td>
<td>94,054</td>
<td>5.2</td>
<td>51.7</td>
</tr>
<tr>
<td>Total beneficial</td>
<td>290,637</td>
<td>181,941</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

2.5 Several Specific Epidemiologic Issues related to AUD and ALD.

2.5.1 Data collection challenges

Disease frequency may be measured either by the pool of existing cases (prevalence) or by the occurrence of new cases (incidence). As the onset of many types of liver disease is insidious, there is often a long time interval (latent period) between disease occurrence and detection.\textsuperscript{42} Further, many patients with liver disease remain asymptomatic until their livers fail. Thus, it is very difficult, if not impossible, to accurately ascertain incidence rates of liver disease. While estimating prevalence may in general be more feasible than incidence rates, many epidemiologic investigations are conducted based on referral patients, which may not represent the true disease prevalence in entire populations.\textsuperscript{40} Population-based studies of liver disease are necessary for accurate information on the burden of disease and the contribution of specific etiologies of liver disease to this burden.

2.5.2 Alcohol and co-occurring chronic diseases

Table 6.14.2 summarizes chronic consequences of alcohol use and highlights the relationship between higher consumption and increased risk for both males and females, and protective effects for diseases such as diabetes mellitus and some CVDs (coronary heart disease, cerebrovascular disease, ischemic stroke, and haemorrhagic stroke) among those individuals with mild and moderate consumption patterns. With respect to treatment, persons exhibiting comorbid alcohol-related and medical or psychiatric disorders often fall through the cracks of the health care system because of administrative distinctions among addiction, medical, and mental health-related services.\textsuperscript{43,44}

Patients are often forced to choose between clinical settings, often resulting in neglect of one condition.

Alcoholism and other disorders might be related in a number of ways, including the following:
(a) Alcoholism and a second disorder can co-occur, either sequentially or simultaneously, by coincidence. For example, Jane-Llopis and colleagues found that 41 per cent of the individuals suffering from AUD who sought treatment had at least one current independent mood disorder, while more than 33\% had at least one current independent anxiety disorder\textsuperscript{45}; (b) A strong direct association has also been found between the magnitude of comorbidity and an increased severity of AUD\textsuperscript{46}; (c) Comorbid disorders might cause alcoholism; (d) Both alcoholism and the comorbid disorder may be caused, separately, by some third condition; (e) Alcohol use or alcohol withdrawal can produce symptoms that mimic those of an independent psychiatric disorder.

Alcohol abuse has been associated with increased odds of substance abuse and mental disorders. For example, Pickens and colleagues found that alcoholics were 7.1 times more likely to have a drug disorder and 2.3 times more likely to have a mental disorder than individuals in the general population.\textsuperscript{47} Another study found that a past history of AD was associated with a more than fourfold increased risk for a current or recent major depressive disorder.\textsuperscript{48}
### Table 6.14.2. Relative Risk for Major Chronic Disease Categories, by gender and Average Drinking Category

<table>
<thead>
<tr>
<th>Disease</th>
<th>ICD-9 code</th>
<th>ICD-10 code</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant neoplasms</td>
<td>140−208</td>
<td>C00−C07</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Mouth and oropharynx cancers</td>
<td>140−149</td>
<td>C00−C14</td>
<td>1.45</td>
<td>1.85</td>
</tr>
<tr>
<td>Esophagus cancer</td>
<td>150</td>
<td>C15</td>
<td>1.80</td>
<td>2.38</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>155</td>
<td>C22</td>
<td>1.45</td>
<td>3.03</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>174 (under 45 years)</td>
<td>C50</td>
<td>1.14</td>
<td>1.41</td>
</tr>
<tr>
<td></td>
<td>1.15 (45 years and over)</td>
<td></td>
<td>1.14</td>
<td>1.38</td>
</tr>
<tr>
<td>Other neoplasms</td>
<td>210−239</td>
<td>D00−D48</td>
<td>1.10</td>
<td>1.30</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>250</td>
<td>E10−E14</td>
<td>0.92</td>
<td>0.87</td>
</tr>
<tr>
<td>Neuropsychiatric conditions</td>
<td>290-319</td>
<td>F01-F99, G06-G09</td>
<td>1.00</td>
<td>0.97</td>
</tr>
<tr>
<td>Unipolar major depression</td>
<td>300.4</td>
<td>F34-F33</td>
<td>RR not available</td>
<td>AF could not be determined otherwise (Rehm et al., in press)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>345</td>
<td>G40-G41</td>
<td>1.34</td>
<td>2.22</td>
</tr>
<tr>
<td>Alcohol use disorders</td>
<td>291, 303, 306.0</td>
<td>F10</td>
<td>AF** 100%†</td>
<td>AF 100%</td>
</tr>
<tr>
<td>Cardiovascular diseases (CVD)</td>
<td>390-459</td>
<td>I00-I99</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Hypertensive disease</td>
<td>401-405</td>
<td>I10-I13</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>410-414</td>
<td>I20-I25</td>
<td>0.82</td>
<td>0.83</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>430-438</td>
<td>I50-I60</td>
<td>0.52</td>
<td>0.64</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>415-417, 423-424, 426-429, 440-441, 451-459</td>
<td>I00, I12-I16, I14-I17, I14-I151, I170-I199</td>
<td>0.59</td>
<td>0.65</td>
</tr>
<tr>
<td>Other CVD causes</td>
<td>500-579</td>
<td>K20-K92</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Cirrhosis of the liver</td>
<td>571</td>
<td>K70, K74</td>
<td>1.26</td>
<td>9.54†</td>
</tr>
</tbody>
</table>

**Note:** Relative risk estimates are shown to quantify the effect size of the risk relationships. For example, females in drinking category I have a relative risk of 1.14, compared to females with no alcohol intake. The relative risk of 1.14 corresponds to a 14% increase in relative risk. For females in drinking category III, the relative risk is 1.99, or almost double the risk of no alcohol intake. These estimates are age-adjusted and based on a life table for females as a reference. The same relationship can also be assessed with a relative risk of 1.99 for females and 2.02 for males. The differences in relative risks are also due to the confounding factors such as “other cardiovascular disease” or “other neoplasms.” The results for these categories should be regarded with caution.

**Category I:** for females, 0-1.95 g pure alcohol daily; for males, 0-3.99 g pure alcohol daily. **Category II:** for females, 2-3.99 g pure alcohol daily; for males, 4-5.98 g pure alcohol daily. **Category III:** for females, 4-9 g or more pure alcohol; for males, 6-9 g or more pure alcohol.

**AF** = attributable fraction—that is, the proportion of disease under consideration that is attributable to alcohol.

† For four diseases, a combined estimate was derived for drinking categories I and II.

By far, mood and anxiety disorders are the most common mental conditions associated with alcohol. Table 6.14.3 shows the high odds of co-occurrence of anxiety disorders (two to three times more likely) and mood disorders (almost two times more likely) than non-alcoholics to suffer from a comorbid disorder.

### Table 6.14.3. Prevalence of Comorbid Mood and Anxiety disorders in individuals with alcohol abuse and alcohol dependence. Focus on Major Depressive Disorder (MDD) and Posttraumatic Stress Disorder (PTSD).

<table>
<thead>
<tr>
<th>Comorbid Disorder</th>
<th>Alcohol Abuse 1-year rate (%)</th>
<th>Odds ratio</th>
<th>Alcohol Dependence 1-year rate (%)</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Mood Disorder</td>
<td>12.3</td>
<td>1.1</td>
<td>29.2</td>
<td>3.6</td>
</tr>
<tr>
<td>MDD</td>
<td>11.3</td>
<td>1.1</td>
<td>27.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Any Anxiety Disorder</td>
<td>29.1</td>
<td>1.7</td>
<td>36.9</td>
<td>2.8</td>
</tr>
<tr>
<td>PTSD</td>
<td>5.6</td>
<td>1.5</td>
<td>7.7</td>
<td>2.2</td>
</tr>
<tr>
<td>National Comorbidity Survey 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Mood Disorder</td>
<td>11.7</td>
<td>1.3</td>
<td>27.5</td>
<td>4.1</td>
</tr>
<tr>
<td>MDD</td>
<td>8.2</td>
<td>1.2</td>
<td>20.5</td>
<td>3.7</td>
</tr>
<tr>
<td>Any Anxiety Disorder</td>
<td>11.8</td>
<td>1.1</td>
<td>23.4</td>
<td>2.6</td>
</tr>
<tr>
<td>NESARC 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Mood Disorder</td>
<td>11.7</td>
<td>1.3</td>
<td>27.5</td>
<td>4.1</td>
</tr>
<tr>
<td>MDD</td>
<td>8.2</td>
<td>1.2</td>
<td>20.5</td>
<td>3.7</td>
</tr>
<tr>
<td>Any Anxiety Disorder</td>
<td>11.8</td>
<td>1.1</td>
<td>23.4</td>
<td>2.6</td>
</tr>
</tbody>
</table>


Even though a large amount of individuals with AUD also suffer from co-occurring Mental Health Disorders (MHD), usually both disorders are commonly treated separately. Historically, health services frequently treated co-occurring disorders as individual entities; however, such treatment is not well suited to the special needs of this group. Differences between both services in terms of clinician beliefs, training, behaviour, and ideology pose significant barriers to effectively treat co-occurring disorders. Regarding pharmacological options, AUD programs do not commonly rely on evidence-based recommended medication, slowing the adoption of pharmacotherapeutic interventions, whereas medication are commonplace in mental health programs. In addition, neither field seems to have the proper training to tackle both diseases (AUD providers often ignore or delay MHD treatment and clinicians may not feel equipped to treat with complex co-occurring disorders, preferring to refer them out to another agency for treatment). As a result, patients with co-occurring disorders receive suboptimal treatment.

Traditional 12-step programs have shown benefit for those patients with MHD, and tailored interventions for co-occurring disorders have been growing in number, delivering positive direct and indirect effects for patients with co-occurring disorders. Even though an
integrated care system (care for both/all disorders is provided by the same cross-trained clinicians, resulting in clinical integration of services) has delivered better outcomes to other chronic conditions, evidence is still weak for co-occurring AUD and MHD. Published literature found integrated care as predictor for improved post-treatment outcomes\(^5\), higher rates of abstinent individuals at six months, compared to those receiving usual independent medical care\(^4\), favourable outcomes compared with other type of services\(^3\), and enhanced training to clinicians about co-occurring patients was correlated with better mental health outcomes at 18 months, compared to those who received usual mental health services.\(^2\) Whatever the causes, patients with co-occurring AUD and MHD have not been served well by the traditional health services configuration. More research is needed comparing different interventions and combinations of interventions. Providers and decision makers are starting to realize the high prevalence of co-occurring disorders, in fact, the majority of patients with AUD most likely have a MHD.\(^4\) The United States Institute of Medicine has developed recommendations for implementing quality integrated care for individuals with co-occurring disorders (See Appendix 6.14.5).

The incidence of alcohol-related brain damage is approximately 10 per cent of adult dementias in the United States, whereas milder attention and memory deficits may improve gradually with abstinence. Alcoholics are far more likely to also have a diagnosis of antisocial personality disorder, drug abuse, mania, and schizophrenia as compared with non-alcoholics. Eating disorders are also associated with alcoholism. Between 33 and 83 per cent of bulimics may have a first-degree relative suffering from alcohol abuse or alcoholism. Studies indicate that approximately 10 to 30 per cent of alcoholics have panic disorder, and about 20 per cent of persons with anxiety disorders abuse alcohol. Among alcoholics entering treatment, about two-thirds have symptoms that resemble anxiety disorders. Alcoholics are 35 times more likely than non-alcoholics to also use cocaine. Similar odds ratios for other types of drugs are: sedatives, 17.0 times; opioids, 13.0 times; hallucinogens, 12.0; stimulants, 11.0; and marijuana and related drugs, 6.0. Surveys of both clinical and nonclinical populations indicate that at least 90 per cent of alcoholics are nicotine dependent. The progression of liver fibrosis and cirrhosis in patients with alcohol problems is enhanced by the presence of hepatitis B and hepatitis C virus markers.\(^3\)

2.5.3 Immunomodulatory effects of alcohol

There is an increased susceptibility to infections in alcohol related diseases.\(^2\),\(^3\) As a result, infection is one of the most common causes of death in patients with ALD, especially those with AH. Malnutrition, underlying liver cirrhosis and aggressive in-hospital medical procedures all contribute to the risk of infection.\(^1\) ALD and liver failure may even have a component of autoimmunity, in which the immune system turns on the body’s own tissues. A number of reviews provide an overview of current knowledge concerning alcohol’s effects on the human immune system.\(^4\),\(^5\) Several important infectious diseases that are highlighted in other sections of this report are also implicated in alcohol-related immunocompromised individuals. The incidence and severity of pulmonary tuberculosis (TB) is greater in alcoholics than in non-alcoholics.\(^6\) For example, data from United States in 2011 showed a 12.4 per cent of TB patients as alcohol abusers; the per centage ranges up to more than 66 per cent in some regions of the country.\(^7\) Significantly, long-term studies of drug and alcohol abusers who were followed for many years showed that these individuals had TB incidence rates from 15 to 200 times the rates for reference populations. In recent years, the incidence
of TB has been increased by the presence of human immunodeficiency virus (HIV) in drug and alcohol abusers.\textsuperscript{57} Alcohol abusers are more susceptible than non-abusers to septicemia, urinary tract infections, bacterial peritonitis lung abscess, empyema (an accumulation of pus in the chest), spontaneous bacterial peritonitis, diphtheria, cellulitis, and meningitis.\textsuperscript{58,59,60} It is clear that the increased incidence of infectious diseases in alcohol abusers represents a significant toll of individual suffering and of medical expense to society. The risk of untreatable infections in alcohol abusers will also increase as antimicrobial resistance increases. Most importantly however, is the association of ALD with hepatitis C. About 25% of all patients with ALD have also markers of HCV infection, even in the absence of risk factors such as intravenous drug abuse.\textsuperscript{35,61} Alcohol may favour the acquisition, replication, or persistence of the virus so ACo is clearly a risk factor for the progression of liver disease caused by HCV. Total lifetime ACo is a risk factor for the progression of liver disease caused by HCV.\textsuperscript{62}

\subsection*{2.5.4 Alcohol and its carcinogen effect}

Research from the International Agency for Research on Cancer (IARC) found causal links between alcohol and cancer of the oral cavity, pharynx, larynx, esophagus, liver, colon, rectum and female breast.\textsuperscript{30} Rehm and colleagues\textsuperscript{64} found an association between greater volumes of drinking and cancer risk increase.

\subsection*{2.5.5 Alcohol and the elderly}

AUD in elderly people are common and associated with considerable morbidity. The ageing of populations’ worldwide means that the absolute number of older people with AUD is on the increase even though the prevalence of AUD in elderly people is generally lower than in younger people.\textsuperscript{65} Rates, however, may be underestimated because of under-detection and misdiagnosis. Age related changes in body composition means that equivalent amounts of alcohol produce higher blood alcohol concentrations in older people.\textsuperscript{66} Even so, elderly people have been shown to be at least as likely to benefit from treatment as younger people.\textsuperscript{67} AUD in elderly people may prove to be a silent epidemic, as media attention and public health initiatives related to AUD tend to focus almost exclusively on younger populations.\textsuperscript{68,69}

\subsection*{2.5.6 Alcohol and women}

There is marked regional variability in the extent of gender differences with regard to alcohol-related morbidity and mortality. Female alcohol- attributable mortality ranges from a negative value (more deaths prevented than caused) in established market economies of Western Europe, North America and the Western Pacific regions to more than 5% of all female deaths being attributable to alcohol in the former socialist countries of Eastern Europe around Russia.\textsuperscript{70} The differences among regions reflect the differences in the overall relationship between average volume of ACo and mortality generally. For DALY burdens, males have a far greater alcohol related DALY burden than females (Figure 6.14.6).

Meta-analysis of case control studies have found that women who drank three or more alcoholic beverages per day (or 40 grams of alcohol, with about 13 grams in a standard drink) had a 69 per cent higher risk of getting breast cancer compared with nondrinkers.\textsuperscript{71} In terms of consumption-risk, each additional 10 g of pure alcohol per day was associated with
an increase of 7% relative risk of breast cancer, whereas regular consumption of approximately 50 g of pure alcohol increases the relative risk of colorectal cancer by 10–20%, indicating that the association is stronger for female breast cancer.\textsuperscript{30} In addition, a range of one to six drinks per day results in a linear relationship between alcohol and breast cancer.

Controversy remains over the interpretation of these studies as the effect is modest in magnitude and is not restricted to one type of alcoholic beverage. The risk is most pronounced at high intakes of alcohol. Increased exposure to estrogens and androgens with ACo is one plausible—but unconfirmed—biological mechanism to explain alcohol’s effect on breast cancer risk.\textsuperscript{71,72}

For any given level of alcohol intake, women have an increased susceptibility to ALD\textsuperscript{71,73} (Table 6.14.4). However, the threshold of alcohol necessary for the development of advanced ALD varies substantially among individuals, and factors other than absolute ACo clearly have an important role in determining who will develop ALD and who will not. These observations highlight the role of genetic factors that may predispose specific persons to greater propensity toward alcohol-induced liver toxicity.

**Table 6.14.4. Relative Risk of Alcoholic Liver Disease at Different Levels of Alcohol Intake**

<table>
<thead>
<tr>
<th>Weekly units* of alcohol intake</th>
<th>Alcoholic cirrhosis</th>
<th>Alcoholic liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>&lt;1</td>
<td>3.7</td>
<td>1.09</td>
</tr>
<tr>
<td>1–6</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>7–13</td>
<td>0.9</td>
<td>4.1†</td>
</tr>
<tr>
<td>14–27</td>
<td>1.6</td>
<td>3.1†</td>
</tr>
<tr>
<td>28–41</td>
<td>7.0†</td>
<td>16.8†</td>
</tr>
<tr>
<td>42–69</td>
<td>13.0†</td>
<td>NR</td>
</tr>
<tr>
<td>≥70</td>
<td>18.1†</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Unit represents 10 to 12 g of alcohol (12 oz of beer, 4 oz of wine, 1 oz of spirits).
†Represents a statistically significant increased relative risk of having alcoholic liver disease. NR = not reported.
Reprinted with permission from McCullough.\textsuperscript{5}


The mechanisms for the differential impact of alcohol on heart disease and mortality and on neurological function in women and men are also still unclear. There remain possibilities at every level of alcohol processing: its metabolism by enzymes (lower concentrations of alcohol-metabolizing enzymes in women’s gastrointestinal tracts), lower content in body water compared with men of similar body weight, leading to higher blood alcohol concentrations\textsuperscript{74}, its absorption into the bloodstream, and its actions on the physiology of end
organs—that might explain mechanisms that could contribute to gender related differences in the health consequences of drinking.\textsuperscript{75} Adverse effects have been observed at levels of consumption that many would regard as low—between seven to 13 drinks per week.\textsuperscript{76} Even though definitive evidence about the pathophysiology of gender differences over ACo is still lacking, it’s important to recognize the higher health risk through ACo among women, compared to men (73).\textsuperscript{74}

### 2.5.7 Alcohol and genetics

Published evidence has identified genetic factors associated with AUD risk, and researchers have sought to identify the genes involved since the relationship was displayed. However, AUD complexity has slowed progress in identifying these genes. Thus, existing data suggest that each individual genetic element has only a small influence and that it will be necessary to identify the relevant gene networks to gain a greater understanding of the contribution of genetics to AUD.\textsuperscript{31}

The overall genetic contribution to AUD has been historically tested by comparing the concordance among identical (i.e. monozygotic) and fraternal (i.e. dizygotic) twins. As expected, studies have shown higher concordance rates among monozygotic twins, confirming the presence of a genetic component in the risk for AUD. Another approach involved within-family studies to estimate the overall similarity among family members sharing differing proportions of their genome (e.g., comparing sons with fathers or grandfathers). For example, Tsuang and colleagues found that sons of alcohol-dependent fathers tend to be more tolerant to alcohol and to have fewer hangovers, a fact which renders alcohol more pleasurable to them.\textsuperscript{77} Both approaches provided convergent evidence that genetic factors account for 50 to 60 per cent of the total variance in the risk for AUD.\textsuperscript{31}

Latest developments of techniques to study the human genome have resulted in widespread use of genome-wide association research for AUD. Genome-wide association studies now offer a host of emerging opportunities, as well as challenges, for discovering the genetic aetiology of AUD and for unveiling new treatment strategies. The key findings of these earlier studies show that variations (i.e. polymorphisms) in the DNA sequences of the genes encoding alcohol dehydrogenase 1B, aldehyde dehydrogenase 2, and other alcohol-metabolizing enzymes mediate the risk for alcoholism; furthermore, these polymorphisms also have an impact on the risk of alcohol-related cancers, such as oesophageal cancer. In addition, a gene encoding one of the receptors for GABA known as \textit{GABRA2} seems to have a role in the development of AUD.\textsuperscript{31} In summary, genetic variations in many of the genes encoding alcohol-metabolizing enzymes contribute to differences in alcohol intake and, thus, the risk for development of AUD. The frequency of these genetic variants differs dramatically across human populations of Asian, African, and European ancestry.

### 2.5.8 AUD diagnosis and biochemical markers

The major clinical assessment necessary for diagnosing ALD is determining whether the patient is abusing alcohol, but this is not always easy. Unfortunately, there is still no satisfactory laboratory marker with higher diagnostic sensitivity compared to the clinical history.\textsuperscript{78} Alcoholic patients and even their family members often minimize or conceal alcohol use. Because of the inherent difficulties in obtaining a reliable history of alcohol use, various biochemical markers have been evaluated for their ability to detect surreptitious
alcohol abuse. A comprehensive marker for AUD has not been identified although a series of successful markers exist for determining drinking status. Several biochemical and hematological tests, such as γ-glutamyltransferase (GGT) activity, aspartate aminotransferase (AST) activity, high-density lipoprotein cholesterol (HDL-C) content of serum, and erythrocyte mean corpuscular volume (MCV) are established markers of alcohol intake.\(^\text{78}\) Many conventional tests have only limited sensitivity when used singly.\(^\text{79}\)

Although hepatitis C virus (HCV) is a leading risk factor for liver fibrosis, there is no standard laboratory serum analyses, imaging tests or virologic assays that currently can distinguish those with hepatitis C, or any other condition, who are at risk for progressive fibrosis.\(^\text{42}\) Thus, increasing numbers of patients will require assessment of fibrosis, exposing them to the potential risks, inconvenience and cost of liver biopsy and its interpretation. If a non-invasive assay were developed that reliably excludes the possibility of significant fibrosis, then such patients may not require treatment with antiviral therapies, and, moreover, could be followed regularly to confirm lack of fibrosis progression. Increasing evidence that advanced fibrosis may be reversible, such that more frequent and refined analysis may render even severe disease amenable to therapy. The expectation that as antifibrotic therapies are developed, there will be a need for early and regular monitoring of response in order to establish effectiveness and optimize dosing.\(^\text{42}\)

3. **What is the Control Strategy?**

3.1 **Alcohol policy**

Five main policies has been generally described in the literature to tackle alcohol harm and abuse: (a) drinking and driving reduction; (b) education, communication, training and public awareness; (c) alcohol market regulation; (d) reduction of harm in drinking and surrounding environments; (e) interventions for individuals.\(^\text{7}\) Limited evidence describes the effectiveness among these approaches though. For example, drinking driving policies have proven to be highly effective (however, limited evidence did not find an impact from parallel interventions such as designated driver and safe drive programs\(^\text{7,80}\)), while education and public awareness have shown non-significant effects to effectively decrease ACo.

The regulation of the alcohol market has been identified as a highly effective policy to reduce alcohol abuse. Published literature by economists and others support that increases in monetary prices (e.g. raising taxes) could have long-term effectiveness for reducing alcohol abuse and its social, health, and economic consequences.\(^\text{81}\) Several reviews published between 2002\(^\text{82}\) and 2010\(^\text{83}\) confirm an inverse relationship between alcohol prices and the demand for ACo. Moreover, WHO models showed dramatic effects over country income and decreased mortality (2003 estimates reported that a 10 per cent tax raise in EU15 countries would prevent 9 000 deaths during the following year and approximately 13 billion additional euros excise duty would be gained).\(^\text{7}\) Such effective intervention however, has not received enough attention in some countries. For example, the United States have increased federal taxes rates on wine and beer only once since 1951, and twice on distilled spirits. Consequently, the real tax rates (inflation-adjusted values) have systematically declined over the years, as Figure 6.14.8 illustrates. In terms of the EU, taxation has been identified as a
constant feature of European countries; however, the variability of enforcement and the lack of standardized excise duties have proven to be two of the main challenges to tackle. In terms of strictness, if different policy areas are combined into a single scale, 2003 data showed variation from 5.5 (Greece) to 17.7 (Norway) out of a possible maximum of 20, with an average of 10.8.\textsuperscript{7}

**Figure 6.14.8. Average real United States Federal excise taxes (in dollars per barrel) on alcoholic beverages (1951-2009)**

In terms of large differences in tax rates between nearby countries, low-tax countries receive additional income as they become more attractive for shopping demands, resulting in lost revenue for high-tax governments. Moreover, some alcoholic drinks (e.g. wine) received 1.5 billion euros in subsidies through the common agricultural policy. In consequence, the public health perspective is still not a priority, compared to commercial and economic interests.\textsuperscript{7}

Advertisement monitoring (restricting volume and content) may be an effective tool to decrease alcohol harm. WHO models measuring the impact on advertisement ban found an estimated 202 000 years of disability and premature death avoided in the EU if such regulatory scheme would be enforced.\textsuperscript{7}
If a comprehensive EU wide package of preventive measures would be enforced (including effective policies such as random breath testing, taxation, restricted access, advertising ban and brief physician advice). Published literature in 2004 estimated that it would avoid 1.4 million years of disability and premature death a year.\textsuperscript{7}

Increased prices of alcoholic beverages have positive effects preventing a number of adverse consequences resulting from alcohol abuse. For example, Cook and colleagues found that increases in beer taxes and price significantly reduced fatal motor-vehicle crash rates.\textsuperscript{81} In addition, Sloan and colleagues reported that increases in alcohol prices were associated with a decline of homicide deaths. On the contrary, declining alcohol prices in England and Wales correlated with substantial increases in violence/related injury and trauma services.\textsuperscript{84} Other studies found a link between sexually transmitted diseases and alcohol price. For example, Canada’s higher taxes on beer and spirits significantly reduced the prevalence of gonorrhea and syphilis between 1981 and 2001 in Canada.\textsuperscript{81}

3.2 Remediation of Alcohol Use Disorders (AUD)

Remediation of AUD has been the primary control strategy but it remains a great challenge for many reasons. Currently, the following strategies are used to control the disease progression:

Behavioral treatment and pharmacological options are commonly used to deal with AUD. Psychotherapies (cognitive behavioral treatment, motivational enhancement therapy, community reinforcement, and 12-step facilitation) are by far the most common approaches to deal with AUD. However, their true effectiveness remains controversial. For example, Dawson and colleagues found three-quarters of people with AUD reduce or stop drinking without any kind of professional treatment or even interaction with a community support group\textsuperscript{9}, and project MATCH showed that psychotherapies offer very similar endpoints, even though their conceptual frameworks were quite different.\textsuperscript{9}

In terms of pharmaceutical options, the United States FDA and the European Medicines Agency (EMA) have approved four medications for AUD: Disulfiram (Antabuse®), oral naltrexone, extended release naltrexone (Vivitrol®), and acamprosate (Campral®). Off-label utilization of medicines originally approved to treat other maladies different than AUD are being studied. For example, Topiramate (a medication used to treat epilepsy and migraine), has demonstrated efficacy in two clinical trials of AD.\textsuperscript{85} Calcium channel blockers\textsuperscript{86}, dopaminergic agents\textsuperscript{86}, serotonin antagonists\textsuperscript{87}, serotonin uptake inhibitors\textsuperscript{87}, and GABA-altering drugs\textsuperscript{88} have also been used. The current medication options block the cascade of AUD in different stages of the disease, as Figure 6.14.9 illustrates.
3.2.1 **Disulfiram (Antabuse):**

An inhibitor of acetaldehyde dehydrogenase has been used for many years in the management of alcohol-dependent patients. It induces an adverse reaction to alcohol intake characterized by nausea. Supervised administration of the medicine by a significant other or health care provider is key to guarantee treatment effectiveness. So far, controlled clinical trials have yielded inconsistent results about its therapeutic benefit. However, the main reason of ambiguous results may relate to the fact that the psychological deterrent effect of the medication rather than its biological effect is useful, hence, it’s difficult to demonstrate that effect in a classical double blind, placebo-controlled trial. Although disulfiram is potentially useful in the early stages of AD, it’s not useful as a long-term therapy.

3.2.2 **Oral naltrexone:**

It has been approved by the FDA as an adjunct to psychosocial treatment for alcoholism. Naltrexone is an opiate antagonist that primarily blocks u-receptors at the standard dose of 50 mg daily by reducing the positive-reinforcing pleasurable effects of alcohol and to reduce craving. Efficacy studies shown a reduction of number of drinks consumed and heavy drinking days. A meta-analysis found evidence of modest efficacy over three months on preventing relapse to heavy drinking, medication discontinuation, and return to any drinking. First results seem to suggest that only high-compliant subjects will have beneficial effects, and hepatic toxicity may be a concern. Table 6.14.5 summarizes most of the clinical
placebo-controlled trials, including the ones that were the basis for the approval of the drug in the United States.

Several studies from Table 6.14.5 also measured relapse into heavy drinking in terms of patients percentage. Figure 6.14.10 illustrates those results.

**Figure 6.14.10. Relapse into heavy drinking placebo versus naltrexone (percentage of patients)**

### Table 6.14.5. Published placebo-controlled clinical trials of naltrexone 50 mg/day in alcohol dependence

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>No. patients</th>
<th>Duration (months)</th>
<th>Outcome Measure</th>
<th>Result&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krystal et al.&lt;sup&gt;92&lt;/sup&gt;</td>
<td>2001</td>
<td>US</td>
<td>627</td>
<td>3 or 12</td>
<td>TFR</td>
<td>No effect</td>
</tr>
<tr>
<td>Gastpar et al.&lt;sup&gt;93&lt;/sup&gt;</td>
<td>2002</td>
<td>Germany</td>
<td>342</td>
<td>3</td>
<td>TFR</td>
<td>No effect</td>
</tr>
<tr>
<td>Guardia et al.&lt;sup&gt;94&lt;/sup&gt;</td>
<td>2002</td>
<td>Spain</td>
<td>202</td>
<td>3</td>
<td>TFR</td>
<td>Increased</td>
</tr>
<tr>
<td>Kranzler et al.&lt;sup&gt;95&lt;/sup&gt;</td>
<td>2000</td>
<td>US</td>
<td>183</td>
<td>3</td>
<td>TFR</td>
<td>No effect</td>
</tr>
<tr>
<td>Chick et al.&lt;sup&gt;96&lt;/sup&gt;</td>
<td>2000</td>
<td>UK</td>
<td>169</td>
<td>3</td>
<td>TFR</td>
<td>No effect</td>
</tr>
<tr>
<td>Anton et al.&lt;sup&gt;97&lt;/sup&gt;</td>
<td>1999</td>
<td>US</td>
<td>131</td>
<td>3</td>
<td>TFR</td>
<td>Increased Decreased</td>
</tr>
<tr>
<td>Heinala et al.&lt;sup&gt;98&lt;/sup&gt;</td>
<td>2001</td>
<td>Finland</td>
<td>121</td>
<td>3</td>
<td>%RHD</td>
<td>Reduced (CS group) No effect (ST group)</td>
</tr>
<tr>
<td>Baldin et al.&lt;sup&gt;99&lt;/sup&gt;</td>
<td>2003</td>
<td>Sweden</td>
<td>118</td>
<td>6</td>
<td>%HDD</td>
<td>Reduced (CS group)</td>
</tr>
<tr>
<td>Monti et al.&lt;sup&gt;100&lt;/sup&gt;</td>
<td>1999</td>
<td>US</td>
<td>116</td>
<td>3</td>
<td>HDD DDD</td>
<td>(Decreased)&lt;sup&gt;c&lt;/sup&gt; (Decreased)&lt;sup&gt;c&lt;/sup&gt; No effect (ST group)</td>
</tr>
<tr>
<td>Morris et al.&lt;sup&gt;101&lt;/sup&gt;</td>
<td>2001</td>
<td>Australia</td>
<td>111</td>
<td>3</td>
<td>TFD TFR</td>
<td>No effect Increased</td>
</tr>
<tr>
<td>Latt et al.&lt;sup&gt;102&lt;/sup&gt;</td>
<td>2002</td>
<td>Australia</td>
<td>107</td>
<td>3</td>
<td>%RHD TFR</td>
<td>Decrease Increased</td>
</tr>
<tr>
<td>O'Malley et al.&lt;sup&gt;103&lt;/sup&gt;</td>
<td>1992</td>
<td>US</td>
<td>97</td>
<td>3</td>
<td>TFR</td>
<td>Increased (CS group) Increased (ST group)</td>
</tr>
<tr>
<td>Volpicelli et al.&lt;sup&gt;104&lt;/sup&gt;</td>
<td>1997</td>
<td>US</td>
<td>97</td>
<td>3</td>
<td>TFR</td>
<td>Increased in compliant patients</td>
</tr>
<tr>
<td>Volpicelli et al.&lt;sup&gt;105&lt;/sup&gt;</td>
<td>1992</td>
<td>US</td>
<td>70</td>
<td>3</td>
<td>TFR</td>
<td>Increased</td>
</tr>
<tr>
<td>Hersh et al.&lt;sup&gt;106&lt;/sup&gt;</td>
<td>1998&lt;sup&gt;d&lt;/sup&gt;</td>
<td>US</td>
<td>64</td>
<td>2</td>
<td>TFD</td>
<td>No effect</td>
</tr>
<tr>
<td>Oslin et al.&lt;sup&gt;107&lt;/sup&gt;</td>
<td>1997</td>
<td>US</td>
<td>44</td>
<td>3</td>
<td>%RHD</td>
<td>No change</td>
</tr>
<tr>
<td>Kranzler et al.&lt;sup&gt;108&lt;/sup&gt;</td>
<td>1998&lt;sup&gt;e&lt;/sup&gt;</td>
<td>US</td>
<td>20</td>
<td>2</td>
<td>%HDD</td>
<td>Reduced</td>
</tr>
</tbody>
</table>

<sup>a</sup> Studies are ranked by size.
<sup>b</sup> The results of the studies are only identified as ‘increased’ or ‘decreased’ when the inter-group difference was statistically significant at the level of 0.05.
<sup>c</sup> Positive results were only obtained in this study once the 40 noncompliant patients were excluded from the analysis.
<sup>d</sup> This study was performed in patients with concomitant alcohol and substance abuse.
<sup>e</sup> This study used an injectable sustained-release preparation of naltrexone.

CS = coping skills training; DDD = drinks per drinking day; HDD = heavy drinking days; ST = supportive therapy; TFD = time to first drink; TFR = time to first relapse; %DA = % days abstinent; %HDD = % heavy drinking days; %RHD = % patients relapsing to heavy drinking.

3.2.3 Extended-release naltrexone (monthly injection):
This therapy may decrease non-adherence compared to the oral version. Naltrexone was significantly more effective in reducing heavy drinking rate, compared to placebo (84). Naltrexone’s main side effects include nausea, headache and dizziness.

3.2.4 Acamprosate:
Acamprosate was approved in the United States in 2004, following extensive use in many European countries. The medicine has been used in Europe for almost 20 years and has consistently been found to be significantly better than placebo in reducing both drinking frequency and cumulative drinking days. Kranzler and Gage found that acamprosate improved rates of continuous abstinence, per cent days abstinence, and time to first drink. Kranzler and Gage found that acamprosate improved rates of continuous abstinence, per cent days abstinence, and time to first drink.109 A meta-analysis identified acamprosate as an effective and safe treatment strategy for supporting continuous abstinence after detoxification in alcohol dependent individuals.109 Acamprosate appears to normalize the balance between excitatory and inhibitory pathways altered by chronic alcohol consumption (Figure 6.14.1). However, the actual mechanism is still uncertain. However, published literature suggests that acamprosate depresses the elevated glutamatergic transmission and NMDA receptor activation that occur in AD and withdrawal.89 Side effects from the medication are most common on the gastrointestinal level. Table 6 summarizes high quality RCTs done in the last 20 years. The majority of these studies produced consistent results showing acamprosate treatment to be superior to placebo in maintaining abstinence.

Figure 6.14.11 illustrates results from comparing the effect of acamprosate versus placebo in terms of continuous abstinence. Most of the studies reported a significant effect of acamprosate over placebo; however, 31% of the studies did not find differences between groups in terms of the outcome of interest. In light of the extensive research into the neurochemical basis for alcohol addiction, it is curious that more approved interventions are not available. Perhaps this is because alcohol-seeking behaviour is complex and involves several neurotransmitter systems, which supports the switch to a range of medications instead of current monotherapies. However, research is still in early stages to empirically prove the adequacy of polytherapy protocols.
### Table 6.14.6: Published placebo-controlled clinical trials of acamprosate in alcohol dependence

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>No. patients</th>
<th>Duration Tt/F-U(^{(\text{mo})})</th>
<th>Outcome Measure</th>
<th>Result(^{c})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chick et al.(^{96})</td>
<td>2000</td>
<td>Britain</td>
<td>581</td>
<td>6/1.5</td>
<td>%A</td>
<td>No effect</td>
</tr>
<tr>
<td>Lhuinitre et al.(^{111})</td>
<td>1990</td>
<td>France</td>
<td>569</td>
<td>3/3</td>
<td>GGT</td>
<td>Decreased</td>
</tr>
<tr>
<td>Whitworth et al.(^{112})</td>
<td>1996</td>
<td>Austria</td>
<td>448</td>
<td>12/12</td>
<td>TFD</td>
<td>Increased</td>
</tr>
<tr>
<td>Tempesta et al.(^{113})</td>
<td>2000</td>
<td>Italy</td>
<td>330</td>
<td>6/3</td>
<td>%A</td>
<td>Increased</td>
</tr>
<tr>
<td>Gual et al.(^{114})</td>
<td>2001</td>
<td>Spain</td>
<td>288</td>
<td>6/none</td>
<td>CAD</td>
<td>Increased</td>
</tr>
<tr>
<td>Geerlings et al.(^{115})</td>
<td>1997</td>
<td>Germany</td>
<td>272</td>
<td>11/11</td>
<td>TFD</td>
<td>Increased</td>
</tr>
<tr>
<td>Poldrugo(^{116})</td>
<td>1997</td>
<td>Italy</td>
<td>246</td>
<td>6/6</td>
<td>CAD %A</td>
<td>Increased</td>
</tr>
<tr>
<td>Pelc et al.(^{117})</td>
<td>1997</td>
<td>Belgium/FR</td>
<td>188</td>
<td>3/none</td>
<td>CAD %A</td>
<td>Increased</td>
</tr>
<tr>
<td>Namkoong et al.(^{118})</td>
<td>2003</td>
<td>South Korea</td>
<td>142</td>
<td>2/none</td>
<td>TFD CAD</td>
<td>No effect</td>
</tr>
<tr>
<td>Roussaux et al.(^{119})</td>
<td>1996</td>
<td>Belgium</td>
<td>127</td>
<td>6/none</td>
<td>%A</td>
<td>No effect</td>
</tr>
</tbody>
</table>

- \(^{a}\) Studies are ranked by size.
- \(^{b}\) Duration of treatment (Tt)/duration of additional follow-up (F-U) beyond trial treatment period.
- \(^{c}\) The results of the studies are only identified as ‘increased’ or ‘decreased’ when the inter-group difference was statistically significant at the level of 0.05.
- \(^{d}\) Belgium, The Netherlands and Luxembourg.

CAD = cumulative abstinence duration; GGT = γ-glutamyltransferase levels; MCV = mean corpuscular volume; TFD = time to first drink; %A= % patients remaining abstinent at study end.


### 3.3 Alcoholic Liver Disease (ALD)

By the time of the study update, there are no FDA approved therapies for ALD, however, lifestyle changes, nutritional support, and off label therapies (such as pentoxifylline) may improve outcomes. In terms of policy options, increased prices of alcoholic beverages have been associated with lower rates of liver cirrhosis mortality.

Published evidence found that a 10 per cent increase in prices would lead to 8.3 to 12.8 per cent reductions in the cirrhosis mortality rate.\(^{120}\) Progress has been made to better understand the pathogenesis of the disease (described above), and the findings also provide possible mechanisms for developing therapeutics for ALD.\(^{10}\)

However, highly effective ALD treatment options remains to be developed. Historically, clinical trials have targeted different components of the pathogenesis of ALD (inflammation, increased metabolism, oxidative stress, and nutrition abnormalities). However, a 2006 systematic review of the available therapies found little if any substantial improvement to tackle the disease.\(^{121}\) (See Appendix 6.14.2 for additional details about ALD pathogenesis.)
Cessation or a marked reduction in alcohol intake has been shown to improve the survival of patients with all stages of ALD.\textsuperscript{122,123} Thus, measures to establish and maintain abstinence are a critical component of the management of patients with ALD. As an alternative, or preferably as an addition, to psychological therapies, some patients may derive benefit from pharmacological therapy. Some patients with AH can progress to cirrhosis even with abstinence\textsuperscript{123}, and patients with coexisting AH and cirrhosis have a worse long-term survival than patients with cirrhosis only.\textsuperscript{124} This suggests the need for longer-term treatment trials in patients with AH.

**Figure 6.14.11: Continuous abstinence (per cent) between acamprosate and placebo**

![Image of a bar chart showing continuous abstinence between acamprosate and placebo for various studies.]

**Source:** Modified from Pharmacotherapy of Alcohol Dependence: A Review of the Clin... : CNS Drugs [Internet]. Available at http://adisonline.com/cnsdrugs/Fulltext/2004/18080/Pharmacotherapy_of_Alcohol_Dependence__A_Review_of.2.aspx\textsuperscript{89}

Proportion of alcohol-dependent patients remaining continually abstinent in published randomised clinical trials of acamprosate 1998 mg/day in which this variable was measured. The proportion of patients remaining continually abstinent was a primary endpoint in the studies of Chick et al, Pailie et al., Tempesta et al., Barrias et al., Sass et al., Geerlings et al., Poldrugo, Pelc et al., Rousseaux et al., Besson et al., Pelc et al., Lhuintre et al. and Ladewig et al. Patient numbers for each study are shown in table II. NS= nonsignificant; *indicates p < 0.05 versus placebo.
In terms of corticosteroids, more than 12 RCTs and meta-analyses on this topic have not been enough to reach a consensus regarding its use.\textsuperscript{125,126} The rationale for steroid use is to decrease the immune and the proinflammatory cytokine response.\textsuperscript{10} Although several similarly designed, well-conducted studies showed that corticosteroids reduced mortality in patients with AH\textsuperscript{127}, a large study failed to show a survival benefit of corticosteroids in patients with moderate and severe AH.\textsuperscript{128} Thus, the efficacy of corticosteroids is controversial. Two potential side effects of steroids used in medium/high dose include poor wound healing and increased susceptibility to infection. This highlights the need for alternative therapies for AH.

### 3.3.1 Oxidative stress and hepatocyte membrane injury

There is some evidence implicating oxidative stress as a key mechanism in alcohol-mediated hepatotoxicity. Reactive oxygen containing species are the superoxide anion, hydrogen peroxide and hydroxyl and hydroxyethyl radicals, the latter arising during ethanol metabolism.\textsuperscript{129} Several recent trials using antioxidant supplementation in AH have shown no survival benefit. Specifically, to reduce hepatic oxygen consumption, investigators have examined the role of propylthiouracil in patients with AH. A 2011 meta-analysis combining the results of six randomized clinical trials demonstrated no significant effects of propylthiouracil versus placebo on all-cause mortality, liver related mortality, or complications of ALD. Occasional serious adverse effects such as leukopenia and generalized bullous eruption were reported.\textsuperscript{53} Another compound investigated because of its inflammatory properties is pentoxifyline. The first randomized controlled trial of pentoxifyline was reported in 2000 in AH and led to a 40% reduction in mortality compared to placebo.\textsuperscript{130} A 2009 meta-analysis of five trials found that pentoxifyline reduced mortality compared with control. However, the result was not supported by trial sequential analysis, which adjusts for multiple testing on accumulating data. Moreover, four of the five trials had high risk of bias, risking an overestimated intervention effect. The study concludes that pentoxifyline may have a positive effect on all-cause mortality and due to hepatorenal syndrome. No concussions could be reached about AH and ALD.\textsuperscript{131}

### 3.3.2 Extracorporeal Liver Support (ELS)

A further experimental therapy that may benefit patients with liver failure is ELS. Currently, two detoxification devices are available for clinical use: albumin dialysis (AD, MARS) and fractionated plasma separation (FPS, Prometheus). Albumin dialysis’ primary aim is to support impaired liver function while the liver recovers or the patient undergoes liver transplantation. Both procedures have the ability to remove water-solved and albumin-bound toxins, which contribute to the liver failure’s pathogenesis.\textsuperscript{132} Krisper and colleagues found that FPS achieved significantly higher clearance for all markers, compared to AD,MARS; and unconjugated bilirubin (strongly correlated to albumin-bound toxins) was influenced only by FPS. The previous study however, compared only the technical effectiveness of the two devices, warranting for additional research to be focus on clinical outcomes, treatment intensity, different patient groups, and treatment dose. Both techniques must still be considered experimental. Larger ongoing trials are needed to corroborate increased patient survival.\textsuperscript{132}
3.4 Alcoholic Cirrhosis (AC)

Current treatments for cirrhosis are severely limited. One can remove underlying injurious stimulus (where possible); eradicate existing viruses using interferon in viral hepatitis; and transplant the liver. Short-term viral eradication could lower risk of hepatic decompensating in up to 40 to 70 per cent of patients with HCV genotypes 1, 2 or 3.\textsuperscript{41} The high mortality of severe AH is coupled with the relatively young age of many of the patients and this makes it an important area for therapeutic trials. However, the vast majority of patients with ALD in clinical practice have advanced fibrosis or cirrhosis. Patients with AC must abstain, since continued AC leads to hepatitis, driving to hepatic fibrogenesis and decompensation.\textsuperscript{41} Unfortunately, as with AH, no adjunctive pharmacotherapies have been consistently shown to improve survival in more than one randomized controlled trial, although some have shown promise.\textsuperscript{130}

3.4.1 Antioxidants

Human trials have evaluated the pharmaceutical product silymarin, which is the active component of the herb milk-thistle and has potent antioxidant properties.\textsuperscript{124} Results are conflicting.

Evaluation of $\textit{S}$-$\textit{adenosyl-L-methionine}$ (SAMe) acts as both an antioxidant and maintains cell membrane fluidity. It has been evaluated in patients with alcoholic cirrhosis. Using death or liver transplantation as a combined end-point, there was a significant beneficial effect of SAMe treatment in patients with cirrhosis.\textsuperscript{133} SAMe participates in the synthesis of glutonate, the main cellular antioxidant, behaving as a methyl donor. Animal experiments have associated alcohol consumption with impaired methionate conservation, therefore, methionine supplementation has been proposed to treat ALD.\textsuperscript{134} However, a review of thirteen randomized clinical trials reported no beneficial effects of milk thistle for patients with ALD, highlighting the lack of high-quality evidence to support the intervention.\textsuperscript{135} Data from 1992 suggested that 11 to 12 per cent of European hospital-based specialists in gastroenterology/hepatology used sometimes SAMe for AH and cirrhosis.\textsuperscript{136} In addition, a review of nine randomized clinical trials could not find evidence supporting or refuting the use of SAMe for individuals suffering from ALD. The study however, warranted for long-term, high quality randomized trials to determine its efficacy.\textsuperscript{136}

3.4.2 Propylthiouracil (PTU)

This compound may improve the long-term survival of patients with AC. There has, however, been only one trial reported thus far. Fifteen per cent of European hospital-based specialists in gastroenterology/hepatology considered PTU to treat AH.\textsuperscript{137} However, evidence seem to suggest against its utilization for ALD problems. A systematic review from six clinical trials reported no significant effects of PTU versus placebo on all-cause mortality, liver related mortality, or complications of the liver disease among patients with ALD. Severe adverse events were also reported.\textsuperscript{53}


3.4.3 Colchicine

This anti-inflammatory drug has been evaluated in the treatment of patients with alcohol and non-alcohol-related cirrhosis because of its anti-fibrotic effects. To date, clinical results have been conflicting. However, latest meta-analysis reported that colchicine should not be used for alcoholic, viral, or cryptogenic liver fibrosis or liver cirrhosis (no significant effects of colchicine versus placebo/no intervention on 15 randomized clinical trials).\textsuperscript{134}

3.4.4 Anabolic-androgenic steroids (AAS)

Between 5 and 43 per cent of European hospital-based specialists in gastroenterology/hepatology (depending on the region) considered AAS as a valid therapy to treat ALD (135). The latest published evidence could not demonstrate however, any significant beneficial effect of anabolic-androgenic steroids on mortality, liver complications, and histology among ALD patients.\textsuperscript{137}

3.5 Transplantation

ALD is currently the second most common indication for liver transplantation in Europe and the United States. It accounts for approximately 17 to 25 per cent of all transplants performed in the United States and Europe.\textsuperscript{138} Figure 12 shows the increased rates of ALD from 1968 through 2008 as indication for liver transplantation in Europe. Transplantation is a highly successful treatment, particularly for end stage cirrhosis, with a 81 -84 per cent (one year survival rate) and 72 to 66 per cent (five year survival rate)\textsuperscript{139} if recipients remain alcohol-free in the post-transplant period.\textsuperscript{10} Without transplantation, five year survival is as low as 23 per cent.\textsuperscript{138} However, limited availability of organs, growing lists of patients needing a transplant, cost, issues of compatibility, and comorbid factors mean that not everyone is eligible for transplantation.

At present, most transplant centers require patients to have six months of abstinence and appropriate addiction treatment before they can undergo liver transplantation. Patients with active AH are not candidates for liver transplantation because of their lack of demonstrated abstinence and high perioperative mortality.

Data from 2007 in the United States reported that less than four per cent of patients with alcohol-induced cirrhosis were listed for liver transplantation, even though published evidence have found that ALD patients have similar, if not better survival than those who undergo transplantation because of non-alcohol-induced liver disease. Most studies suggest that alcohol relapse after transplantation occurs in 15% to 30% of patients.\textsuperscript{140}

Organ shortage is a major problem and the decision to be an organ donor remains voluntary in most European countries. A recent UK study demonstrated that, when compared to other patient groups, the general public, primary care physicians and even gastroenterologists, all place patients with ALD well down their list of patients most deserving a liver transplant.\textsuperscript{141} The perception that patients with ALD have played a significant role in their disease and the widely held belief that, ‘once a drinker always a drinker’ seems likely to be the most important factors contributing to this negative view of ALD patients. Transplantation for ALD remains a complex issue.
Overall, the best treatment outcomes from ALD are linked with two patient’s characteristics: a) lower cumulative doses of alcohol consumption b) long-term abstinence from alcohol.

Figure 6.14.12. Evolution in the indication for orthotopic liver transplantation in European Liver Transplant Registry (2008), alcoholic liver disease is the second common indication after viral cirrhosis.


4. What is known of the Economic Burden, Feasibility, and Sustainability of the Control Strategy?

4.1 Economic burden

Alcohol significantly affects the lives of many people in Europe through profits from alcohol production and trade as well as employment, salaries or other revenues to distillery and brewery workers, to wine farmers, to waiters and shopkeepers, and to producers of raw materials and other equipment to the alcohol industry and trade. For instance, it has been estimated that in 1990 the production and trade of alcoholic beverages provided directly or indirectly employment to nearly three million people or to about 2.0 per cent of the civilian employment in the 12 member states of the European Communities (EC). In 1992, the top six alcohol exporting countries were France, the United Kingdom, Italy, Germany, Spain and the Netherlands. ACo is also socially and culturally deeply embedded in the daily lives of most Europeans. However, published literature argue that social and economic burdens resulting from the effects of ACo on the individual, family, work and society outweighs commercial benefits. For example, 2003 data estimated the total tangible cost of alcohol to EU society to be 125 billion euros (equivalent to 1.3 per cent GDP), whereas the intangible cost (value place on pain, suffering, and lost life due to social and health harms caused by alcohol) were estimated to be between 150 and 760 billion euros. Even though these estimates seem large, different areas of human life could not be considered, suggesting that the true cost may be even higher. In terms of mortality and morbidity, EU data from 2004
estimated that over 7000 deaths and 200 000 DALYs were caused by harm to others attributable to ACo.\(^3\)

The precise estimation of the cost of alcohol abuse and its medical and social consequences remains the subject of methodological debate, as the many costs related to alcohol abuse and ALD cannot be measured directly. Indirect costs of liver disease, namely economic loss as a result of premature death, illness, and disability associated with liver disease, are substantial, as liver disease tends to affect people in their most productive phase of life. It has been calculated that the cost of alcoholism in Europe, in terms of lost production and cost of medical services, represents between 2 to 6 per cent of Gross National Product, depending on the country.\(^2\) In addition, the economic costs of alcohol-attributable crime in 2003 add up to 33 billion euros.\(^7\) In the United States, the total economic burden (direct and indirect costs) imposed by alcohol abuse as a proportion of total health care expenditure is a remarkable 16.6 per cent.\(^1,2\) In terms of ALD, lack of effective treatment to date further increases the disease burden with an estimated total cost reaching 3.8 billion US dollars per annum.\(^3\)

In terms of treatment options, the approved pharmacotherapy options suggest benefits based on cost-effectiveness analysis. For example, Schadlich and colleagues found that acamprosate therapy led to net savings and improved the patient’s state of health under the German healthcare system.\(^1\)

In terms of disulfiram, the medication is relatively inexpensive; however, recent guidelines suggest its administration under supervision of a healthcare professional, adding to the cost of the medication itself. In addition, all patients receiving disulfiram require routine laboratory monitoring adding the final cost of the treatment.\(^1\) In terms of naltrexone, even though the medication may cost more per dose than disulfiram, it is associated with less need for supervised administration because of less serious side effects; however, high compliance is needed to guarantee the treatment’s effectiveness. A longer-acting dosage form of the drug is currently under investigation to enhance compliance.\(^1\)

### 4.2 Feasibility and sustainability

Detoxification, with or without pharmacotherapy, is the first step of treatment. The major behavioral approaches currently used in alcoholism treatment include cognitive-behavioral therapy, motivational enhancement therapy, and Alcoholics Anonymous (AA) or related 12-step programs.\(^9\) Published literature has compared the effectiveness of these approaches. And most of the evidence did not detect significant differences among the three treatments in patient outcome, although certain treatment methodologies may be most appropriate for patients with certain characteristics.\(^9\) Historically, pharmacotherapy with aversive or anti-craving medications has been used as supplement to behavioral treatment approaches.

A wide spectrum of interventions was proven to be effective for decreasing ACo. For example, minimum drinking age, zero tolerance laws, decreasing the availability of alcoholic beverages are inversely related with alcohol abuse among youth and younger adults, by increasing the expected time and legal costs of alcohol use.\(^81\) Most countries in the world have at least one of these interventions operating; however, keeping them through time has proven to be difficult and costly. We need more research to better understand the cost effectiveness of such interventions.
The overall picture of alcohol as causing considerable global burden of disease will continue going forward, if the current levels and patterns of ACo remain stable. A definitive “cure” of AUD is not yet possible. Intensive basic and applied research into the genetic, metabolic, and behavioural mechanisms involved need to be better understood (Figure 1).

We also need to improve the quality of care of AUD, which remains low. McGlynn and colleagues found that across the United States, only 11 per cent of individuals suffering from AD had received guideline-recommended therapy. Prevention requires concerted effort with regard to diet, lifestyle, diagnosis, costs and access.

The economic role of the alcoholic drinks industry is considerable. For example, alcohol excise duties in the EU-15 countries amounted to 25 billion euros in 2001. In addition, the number of jobs supported is significant. Even though more research is required to measure the impact of decreasing ACo and job losses, current evidence suggest that declining consumption may not necessarily lead to job losses.

5. Why Does the Disease Burden Persist?

The burden persists for the following reasons:

1. The difficulty in changing large-scale alcohol consumption patterns: Cultural and historic trends of ACo can predict AUD; hence, the incidence and prevalence of AUD in certain regions of the world remain a complex problem to solve.

2. The lack of effective therapies: Pharmacotherapy remains at best a “supportive” option to treat AUD and ALD. The exact pathogenesis of both disorders continues to be a work in progress for scientists and may be a factor for the current low efficacy of the current medications options available.

3. The high rates of alcohol beverages availability: Overall volume of drinking plays a major role in the extent of alcohol problems, both at individual and at population levels. It may be possible to imagine a population with a net gain in health from drinking – a population with a low per capita consumption, with alcohol consumed frequently but only in small amounts – but no such national population has been identified in the real world. On the basis of patterns of consumption in real national populations, an increase in the volume of drinking will result in net losses in terms of years of life lost to death and disability.

4. The effectiveness of prevention interventions is low: By and large, targeted policy options have been more successful when dealing with vulnerable populations (e.g. young people). For example, universal interventions and multi-component prevention programs have shown to be effective among adolescents, however, such interventions aimed to different age groups (such as adults and the elderly) are much more difficult to implement and their short-term effects tend to disappear once the intervention ends. Some evidence suggests that family-based interventions may have small, but persistent and consistent medium and long-term prevention effects.
5. The globalization of the alcohol industry: Producers have an immense power to influence policies at the country level in order to protect their commercial interests, which are frequently in conflict with public health priorities. On the other hand, civil society is not organized enough to act as counterweight to the industry. Civil society has lessons to learn from advocacy groups such as activists against tobacco, and become a stronger public health voice.

6. Physicians and individuals do not consider AUD as a medical condition, hence, a medical treatment is not perceived as a priority. Attitudes changes about the disease are necessary to increase the utilization of current therapies. In addition, the involvement of physicians in the management of AUD is critical to increase the pharmacologic treatment.91

6. What can be learnt from past/current research into pharmaceutical interventions for this Condition?

6.1 Alcohol Use Disorders (AUD)

Advances in neurobiology support the development of medications to treat alcoholism by modifying the activity of specific chemical messengers (i.e. neurotransmitters) in the brain. These include opioid antagonists, specific glutamate antagonists, selective serotonin reuptake inhibitors and dopamine antagonists, 5-HT3 receptor antagonists.89

The practical effectiveness of these compounds and any pharmacological intervention may be compromised by poor patient compliance and other factors. It is important to investigate whether use of specific medications in combination can further enhance their effectiveness. For example, a 2007 RCT examined the effects of combining naltrexone and fluoxetine for those subjects suffering from AD and major depression (results not published). Additional research is needed to determine how medications interact with different psychosocial factors and treatments. For example, a 2007 RCT funded by NIH examined the effects of combining naltrexone and fluoxetine for those subjects suffering from AD and major depression (results are not available yet).

However, many of these compounds, in addition to reducing alcohol intake, may suppress appetite or have other undesirable effects. Thus, the development of suitable medications with greater selectivity toward excessive alcohol intake remains a major goal. Understanding the neurobiological basis and their corresponding effects of these interventions in human alcoholics, perhaps with new imaging technologies, remains an option to explore further.

6.2 Alcohol Liver Disease (ALD)

The high mortality of AH and cirrhosis, highlights the need for better therapy and our increased understanding of the precise mechanisms of ethanol-induced liver injury and there are now several promising therapeutic modalities in this area. In contrast, little progress has been made towards the development of specific pharmacotherapy for advanced fibrosis and cirrhosis. Potential reasons for the lack of progress in cirrhosis thus far include: (a) a lack of a
clear understanding of disease pathogenesis; (b) problems with compliance in long-term treatment trials; and (c) the confounding effect of drinking behavior during the duration of the trial (d) treatment may not be cost effective, compared to other therapies aimed to prevent AH and cirrhosis. As a result, at present the management of patients with advanced fibrotic ALD is directed primarily at preventing and treating the complications of portal hypertension, liver failure and hepatocellular carcinoma and deciding if and when to consider patients for orthotopic liver transplantation.\textsuperscript{41} Alcohol hepatitis is characterized by death and injury of hepatocytes so that it seems rational to develop therapies to stimulate proliferation of hepatocyte mass. This concept has been examined in patients with AH by treating them with insulin and glucagon, which is thought to stimulate liver regeneration.\textsuperscript{146} However, the results have been discouraging, and cases of severe hypoglycemia have dimmed enthusiasm for this approach. In advanced liver disease such as cirrhosis, the liver is unable to regenerate itself enough. Researchers are looking at various means, including use of adult bone, blood or liver stem cells and growth control proteins (e.g. cyclins, cyclin-dependent kinases) to stimulate growth.\textsuperscript{146}

7. **What is the Current “Pipeline” of Products that Are to Be Used for this Particular Condition?**

7.1 **Alcohol Use Disorders (AUD)**

Current available options to treat AUD have modest effects, making it necessary to identify newer treatment options for AD. The following drug classes have been classified as third phase drugs\textsuperscript{91}, showing some efficacy to treat the disease.

7.1.1 **Opioid antagonists**

An oral form of the antagonist nalmefene (an injectable, marketed as Revex\textsuperscript{®}) for reversing the effects of opioid anaesthetics) has been shown to increase abstinence in a preliminary placebo-controlled, double-blind study of 105 alcoholics.\textsuperscript{89} Nalmefene is also less likely than naltrexone to produce the adverse side effect of liver damage. Consequently, large-scale clinical trials of nalmefene in alcoholic populations would be important but we found none in the USA database of RCT. Further animal and human studies are needed. Nalmefene has a longer half-life (about eight to twelve hours) and possesses a greater protein binding ability than naltrexone. The dose and optimal duration of therapy for nalmefene have not yet been established. Hence, implantable long-term delivery systems are under investigation.\textsuperscript{91}

7.1.2 **Serotonergics**

*Selective serotonin reuptake inhibitors (SSRIs):* Serotonin 5-HT1A receptors may be associated with ACo and the development of tolerance, 5-HT2 receptors have been found to contribute to reward, and 5-HT3 receptors are linked to the development of reinforcement. Results of clinical trials using SSRIs have been mixed as most double-blind, placebo-controlled studies using SSRIs have not reduced drinking or any other measures of AD. However, there is good evidence that fluoxetine may reduce heavy drinking in depressed alcoholics.\textsuperscript{147} Sertraline may be efficacious among individuals with late-onset alcoholism.
However, results have been disappointing for early-onset alcoholism. Sertraline also enhances naltrexone efficacy for those individuals with MDD.\textsuperscript{148} Ondansetron, an antiemetic, may be a treatment for the same biologically predisposed subtype (type B) that does not respond to SSRIs. Ondansetron, which has functionally opposite effects to SSRIs, blocks serotonin. While further evidence is needed, early studies suggest ondansetron could provide important adjunctive treatment for a particular alcoholic subgroup. Ondansetron has been administered with naltrexone in early-onset alcoholic patients. In an eight-week, double-blind, placebo-controlled trial, the combination was found to significantly reduce drinks per day and per drinking day and had a positive effect on the percentage of days abstinent compared to placebo.\textsuperscript{149}

### 7.1.3 Dopaminergics

Atypical antipsychotics (aripiprazole, olanzapine, quetiapine) have all demonstrated various degrees of usefulness in reducing ACo or increasing abstinence.\textsuperscript{85} For example, Guardia and colleagues found that alcohol-dependent patients showed good adherence and compliance to olanzapine, but no differences in relapse rate or other drinking variables when comparing olanzapine with placebo-treated patients. Moreover, the study did not find differences over drinking variables.\textsuperscript{150} Aripiprazole did not show an overall advantage over placebo over primary outcomes. Overall, antipsychotics `adverse effects may not warrant its utilization for treating AD.

### 7.1.4 GABA targeting

Medications with effects over the glutamate system show promise as treatments for alcohol withdrawal. For example, topirimate may have beneficial effects by facilitating functioning of the neurotransmitter GABA. Johnson and colleagues demonstrate efficacy of the medicine in very heavy drinking alcohol dependent patients.\textsuperscript{151} Individuals also reduced cigarette smoking, which may offer additional benefits to alcohol-dependent smokers. Cognitive dysfunction, abnormal sensations and anorexia has been identified as side effects.\textsuperscript{85} Baclofen, a GABA receptor agonist, reduced symptoms of alcohol withdrawal over alcohol-dependent individuals.\textsuperscript{152} Gabapentin has shown moderate efficacy in early treatment among individuals with high alcohol-withdrawal symptoms\textsuperscript{153}, or individuals with comorbid insomnia.\textsuperscript{154}

### 7.1.5 Other interventions

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) launched in 2007 the Clinical Investigations Group (NCIG), an effort to accelerate the development and approval of newer pharmaceutical treatment to address AUD. NCIG is currently working on three trials. Quetiapine, a drug used in treating psychiatric disorders, was examined in 224 very heavy-drinking alcohol-dependent individuals. Results from this study have been analyzed and submitted for publication. Data from a trial of levetiracetam XR (Keppra XR®), an anti-seizure drug, are currently being analyzed, and subjects are being recruited for a trial evaluating varenicline (Chantix®), a smoking cessation medication. In addition, NCIG staff are in the process of choosing compound(s) for a fourth trial.\textsuperscript{155}

Table 6.14.7 summarizes the information described above about the experimental “pipeline” for AUD.
7.2 Alcoholic Liver Disease (ALD)

There are a large number of potential interventions that might be used to modulate the course of fibrosis in ALD, particularly in the latter states of hepatitis and cirrhosis (See Chapter 3.2).

There seems to be a mismatch between the potential targets for ALD (particularly in its latter stages as evidence by Table 6.14.8) and the actual number of compounds tested in the regulatory system (Table 6.14.6) as inferred from information on clinical trials.

Clinical trial information probably provides a reasonably up to date and reliable source in this regard. We reviewed information on 2004 USA clinical trials on the NIH website devoted to clinical trials using the search term “alcoholic liver disease”, “liver fibrosis”, or “cirrhosis”. We found are no industry-sponsored clinical trials for interventions designed to eliminate AD in this database. We also repeated the search using another clinical trials database, which includes some UK trials (www.controlled-trials.com) and found similar results. We note the presence of a new EU clinical trials database (https://eudract.ema.europa.eu/eudract-web/index.faces) which came into force on 1 May 2004 wherein all clinical trials on medicinal products for human use that takes place in the 25 EU states must be registered. However, the information submitted will be confidential and only national and EU regulatory authorities as well as the EC will be able to find out what trials are going on.
Table 6.14.8: Possible therapeutic interventions in liver fibrosis in progressive or established fibrosis based on laboratory/academic research and animal models.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Possible Therapeutic intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td>• Removal of injurious agent&lt;br&gt;• Interleukin-10 — anti-inflammatory effect&lt;br&gt;• Tumour necrosis factor inhibitors — anti-inflammatory effect&lt;br&gt;• Antioxidants — suppress fibrotic response to oxidative damage</td>
</tr>
<tr>
<td>Stellate cell activation</td>
<td>• Interferon gamma (or interferon alpha) — inhibits activation of hepatic stellate cells&lt;br&gt;• Hepatocyte growth factor — inhibits activation of hepatic stellate cells&lt;br&gt;• Peroxisome proliferator-activated receptor ligand — reduces activation of hepatic stellate cells</td>
</tr>
<tr>
<td>Perpetuation of stellate cell activation</td>
<td>• Transforming growth factor -1 antagonists — reduce matrix synthesis and enhance matrix degradation&lt;br&gt;• Platelet derived growth factor antagonists — reduce proliferation of hepatic stellate cells&lt;br&gt;• Nitric oxide — inhibits proliferation of hepatic stellate cells&lt;br&gt;• Angiotensin-converting-enzyme inhibitors — inhibit proliferation of hepatic stellate cells</td>
</tr>
<tr>
<td>Inhibitors of Stellate cell secretion of collagen rich matrix</td>
<td>• Angiotensin converting enzyme inhibitors — reduce fibrosis&lt;br&gt;• Polyhydroxylase inhibitors — reduce experimental fibrosis&lt;br&gt;• Interferon gamma — reduces fibrosis&lt;br&gt;• Endothelin receptor antagonists — reduce fibrosis and portal hypertension&lt;br&gt;• To enhance or initiate resolution of fibrosis</td>
</tr>
<tr>
<td>Stellate cell apoptosis</td>
<td>• Gilotoxin — causes apoptosis of hepatic stellate cells&lt;br&gt;• Nerve growth factor — causes apoptosis of hepatic stellate cells</td>
</tr>
<tr>
<td>Degradation of collagen rich matrix</td>
<td>• Metalloproteinases — enhance activity of metalloproteinases&lt;br&gt;• Tissue inhibitor of matrix (TIMP) antagonists — enhance activity of metalloproteinases&lt;br&gt;• Transforming growth factor-1 antagonists — downregulate TIMPs and increases activity of metalloproteinases&lt;br&gt;• Relaxin — downregulates TIMPs and increases activity of metalloproteinases</td>
</tr>
</tbody>
</table>

Treatment will remain a challenging task, however, and thus far no drugs are approved as liver antifibrotic agents in humans. Therapies will need to be well tolerated over decades, with good targeting to liver and few adverse effects on other tissues. The liver offers a unique advantage as a target for orally administrated agents, since those with efficient liver “extraction” will have, in principle, agents targeted directly to the liver since systemic distribution will be minimized. Combination therapies may prove synergistic rather than
additive, but agents must first be tested individually to establish safety and ‘proof-of-principle’.

It is uncertain whether antifibrotic therapies will require intermittent or continuous administration.\textsuperscript{146,156} Testing of antifibrotic agents in clinical trials presents unique challenges, since efficacy cannot be simply assessed by a serum test such as viral load, and, moreover, a clinical benefit may only be apparent after a prolonged period of treatment. In contrast, for example, trials of antiviral medications for HCV, can obtain evidence of efficacy within weeks or months by a simple blood test assessing viral load. Additionally, there are no established serum markers that can substitute for obtaining tissue, obligating investigators to perform percutaneous liver biopsies at the onset and completion of therapy, which limits attractiveness to patients. More research is needed to identify biomarkers capable to assess liver fibrosis.

7.3 “Spillovers” from the Hepatitis C pipeline and Other Fibrotic Conditions

Possibly for these reasons, the contrast between the “liver fibrosis” pipeline and the drug pipeline directed to liver diseases resulting from chronic hepatitis infections is telling. The medical need and the potential market for a liver-specific anti-fibrotic agent will be large and this appears to be driven in large part by the market for hepatitis, not ALD.

Most of the impetus for developing useful anti-fibrotic therapies for ALD could, in principle, be developed as “spillover” from research into chronic hepatitis C. Liver fibrosis is a paradigm for wound healing in other tissues in the body such as the lung and kidney as it involves analogous cells and cell mediators. Thus, there is a large “research gap” between academic research into fibrotic conditions and translation into clinical, and even pre-clinical research into anti-fibrotic interventions to treat alcoholic liver disease.

8. What is the Current Status of Institutions and Human Resources Available to Address the Disease?

8.1 Public funding

The level of research into the epidemiology, aetiology and treatment of ALD is not consistent with the burden of alcoholism in both the EU and the US. Much of the research currently undertaken deals with addictions and its psychosocial nature, which although very relevant, often neglects the latter stages of AUD and ALD in terms of treatment options. Overall, there is an imbalance between the severity and magnitude of AUD and ALD and the amount of money spent on research.
8.1.1 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 ALD and fibrosis is being funded by the Wellcome Trust.

There are several UK clinical trials devoted to various fibrotic conditions, none of them are for liver fibrosis. 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.

The UK counterpart of the National Institutes of Health, the Medical Research Council (MRC) is sponsoring a clinical trial on use of steroids to treat pulmonary fibrosis. We note the MRC has a research collaboration with the Japanese company Teijin to find novel drug targets for kidney and lung fibrosis, although this has been operative for several years without an apparent “hit” and liver fibrosis in apparently not specifically included in the research.

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 US dollars.

8.1.2 European Union

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. The European council later renewed the program for 2008-2013 period. 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 trac alcohol policies and their implementation. For example, several initiatives show promise. In 2009, the “Alcohol Measures for Public Health Research Alliance” (AMPHORA) was funded to involve researchers and institutions from 14 European countries, and counterparts from all 27 Member States and provide with new scientific evidence for public health measures to reduce alcohol-related harm, through addressing social and cultural determinants, marketing and advertising, taxes and pricing, availability and access, early diagnosis and treatment of disease, interventions in drinking environments and safer untaxed alcohol products (ftp://ftp.cordis.europa.eu/pub/fp7/docs/web-ph-booklet_en.pdf).
8.1.3 United States sources of funding

Public financing

The resources come from federal and state sources. Both public payer programs paid for more than 77% of all substance abuse treatment (including alcohol) in 2003, even though public payers funded only 45% of general health expenditure.\textsuperscript{157} Medicare, a jointly funded program by federal and state resources, which covered 14% of non-elderly Americans in 2007\textsuperscript{158}, vary greatly in terms of eligibility and requirements across states. For example, Tompkins and colleagues found that six states did not offer treatment benefits for substance abuse problems\textsuperscript{157} and a different study found that 74% of 31 states with Medicaid managed-care plans covered outpatient treatment services.\textsuperscript{159} Interestingly, programs funded primarily by public resources tend to offer a more comprehensive service compared to programs primarily funded by private resources.\textsuperscript{160} In terms of research resources, the NIAAA is the lead United States governmental agency at the NIH for alcohol use and abuse. The NIAAA receives about 400 million US dollars each year. The NIAAA is supporting over a dozen clinical protocols with regard to alcohol abuse and its sequelae (Table 6.14.9).

Its extramural programs include one with Germany (which 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 (Figure 6.14.13).

The 2004 NIAAA appropriation is about 4% of the estimated ALD economic burden in the United States (9 billion US dollars in 1998) but a trivial fraction of the direct and indirect economic costs from alcohol abuse. In contrast, the appropriated funding for diabetes research by the federal agency responsible for this (NIDDK) is about 1.5% of the annual United States diabetes economic burden, and that for cancer research (NCI) is about 2.5% of the average annual direct and indirect cost of cancer. Unlike ALD, however, both cancer and diabetes are much better represented in the development pipeline and do not suffer from apparent neglect by the private sector.
### Table 6.14.9: Clinical trials related to alcoholic liver disease, liver fibrosis, alcoholic hepatitis, cirrhosis, fibrosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Sponsor</th>
<th>Phase</th>
<th>Treatment</th>
<th>NOTES</th>
<th>Trial Sites*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney fibrosis</td>
<td>NIDDK</td>
<td>II</td>
<td>Pirfenidone</td>
<td>Patients with glomerulosclerosis</td>
<td>1 state (25)</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>NHLBI</td>
<td>II and III</td>
<td>Oral bosentan</td>
<td></td>
<td>International</td>
</tr>
<tr>
<td>Lung scleroderma</td>
<td>NHLBI</td>
<td>III</td>
<td>Cyclophosphamide de azathioprine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood hepatic cirrhosis</td>
<td>NCRR c</td>
<td>I</td>
<td>Colchicine</td>
<td></td>
<td>1 state (15)</td>
</tr>
<tr>
<td>Systemic Sclerosis</td>
<td>Genzyme/ Cambridge Antibody Technologies</td>
<td>I and II</td>
<td>Anti TGF beta 1 monoclonal antibody</td>
<td></td>
<td>4 states</td>
</tr>
<tr>
<td>Nonalcoholic Steatohepatitis (NASH)</td>
<td>NIDDK</td>
<td>II</td>
<td>metformin</td>
<td>NASH associated with diabetes</td>
<td>1 state (30)</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>NCRR and NIDDK</td>
<td>III</td>
<td>Methotrexate/ursoadiol vs, methotrexate/colchicine</td>
<td></td>
<td>2 states (405)d</td>
</tr>
<tr>
<td>Liver Fibrosis</td>
<td>InterMune</td>
<td>II</td>
<td>Interferon gamma 1b</td>
<td>In HCV patients only</td>
<td>(500)</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>NIDDK</td>
<td>III</td>
<td>Ursodiol/methotrexate vs. methotrexate</td>
<td></td>
<td>11 states</td>
</tr>
<tr>
<td>Primary biliary fibrosis</td>
<td>NIDDK</td>
<td>I</td>
<td>budesonide</td>
<td></td>
<td>(50)</td>
</tr>
<tr>
<td>NASH</td>
<td>NIDDK</td>
<td>II</td>
<td>Pioglitazone</td>
<td></td>
<td>(60)d</td>
</tr>
<tr>
<td>OTHERS</td>
<td>InterMune</td>
<td>III</td>
<td>Interferon gamma</td>
<td></td>
<td>North America and EU (600)</td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
<td>InterMune</td>
<td>II</td>
<td>Pirfenidone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney disease in diabetics</td>
<td>InterMune</td>
<td>I and II</td>
<td>Pirfenidone</td>
<td></td>
<td>(120)</td>
</tr>
</tbody>
</table>

*a. Proposed or actual enrolment (in parenthesis).*
*b. National Health, Lung, and Blood Institute*
*c. National Center for Research Resources*
*d. Several different phase I, II or III trials combined*
8.2 Private sector funding

The pharmaceutical industry worldwide has moved slowly in alcoholism treatment, and resources spent on alcohol-related therapies are quite low, compared to other diseases. Some factors were identified elsewhere that may reduce the interest of the industry to invest more research on the disease; such factors were investment and marketing risk, and health liability.91

With regard to the United States, the dollar amount spent on AUD treatment has been declining since 1986, when private insurance contributed 2.8 billion, or almost 30 per cent of all expenditures, as Figure 6.14.14 shows. From 1986 to 2003, private expenditure decreased by 20%. However, these estimates may underestimate actual expenditure, since they only account for AUD if they are counted as a primary diagnosis.157
Figure 6.14. Distribution of funding of Alcohol and other Substance Disorders by payer for 1986 and 2003.


Out-of-Pocket Financing

Data from 2003 reported an increase of out-of-pocket expenditure by 0.5 billion US dollars, compared to 1986 figures (1.7 billion to 1.3 billion respectively) to treat alcohol-related diseases. However, the annual increase is lower than inflation, suggesting that individual’s contribution actually declined. Two main elements may explain the decrease: the increasing use of Medicaid (which requires lower copayments compared to private schemes) and increased use of public funded treatment (low or no cost sharing).

The patient protection and Affordable Care Act (ACA), signed in 2010, may have positive effects for those individuals suffering from AUD, in terms of access to treatment. The National Association of State Alcohol and Drug Abuse Directors (NASADAD) studied ACA effects on those states that enacted it before the federal regulation (Maine, Massachusetts and Vermont). People living in all three states had increased access to AUD treatment and states achieved cost savings.
9. Ways Forward from a Public Health Viewpoint with Regard to Public Funding

9.1 Gaps between current research and potential research issues which could make a difference.

9.1.1 Basic research

The burden of alcohol-related mortality and morbidity is due to alcohol-related injuries, malignant cancers, cardiovascular disease and ALD. We need to investigate further proper treatment protocols capable of dealing with co-occurring diseases and AUD. The paucity of such interventions is evident. Little information is available on the utility of combinations of different pharmacological agents to treat AUD. Indeed, the “true” effectiveness of each treatment needs to be established better to run such studies. Unfortunately, this is not the case for most potential drug treatments.

In terms of ALD, stopping drinking has been shown to improve the survival of patients with all stages of ALD. Many kinds of treatment have been tried in patients with AH but few are consistently beneficial. Current treatments for AC are severely limited. For those subjects that could not significantly decrease their ACo and developed ALD, effective antifibrotic treatments are needed urgently. There is need for:

- New therapeutic interventions for liver fibrosis
- New biochemical markers and diagnostics for the variety of alcoholic liver diseases

Alcoholic hepatitis leads to death and injury of liver cells so research has been directed to stimulating proliferation of hepatocytes. Results have been discouraging. Researchers are looking at various means, including use of adult bone, blood or liver stem cells and growth control proteins (e.g. cyclins, cyclin-dependent kinases) to stimulate growth. There is need for:

- More basic research into liver regeneration using stem cells
- More basic research into the co-morbidities of alcoholic liver disease (TB, infections, HCV) and effect of alcohol use on treatment efficacy.

Even though both transplantation and antifibrotic treatment should be investigated more, our attention should be focused to prevent ALD consequences.

9.1.2 Applied research

Pharmacologic treatment alone will not likely be enough to manage AUD. No medication to date has been proven effective in clinical trials without some form of concomitant behavioral therapy. The combination of both approaches needs to be investigated more, improving the odds of achieving meaningful sobriety or decreasing the consequences of continued alcohol abuse.

The distinction between the “alcoholic liver fibrosis” pipeline and the pipeline directed to liver diseases resulting from chronic hepatitis infections is telling. The medical need and the potential market for a liver-specific anti-fibrotic agent will be large and this appears to be driven in large part by the market for hepatitis, not ALD. Most of the impetus for developing
useful anti-fibrotic therapies for ALD could, in principle, be developed as “spillover” from research into chronic hepatitis C. Nearly 200 million people worldwide are affected by HCV but, just as in alcohol-derived liver disease, there are no approved therapeutic interventions to delay or reverse liver fibrosis associated with HCV. There is a need for:

- Closing the gap between the targets for anti-fibrotic therapies and the actual number of anti-fibrotic interventions. Public funding should be directed to translating this basic research into the clinic and to improve the inefficiencies in going from animal models to humans.
- Encouraging information “spillover” from research on hepatitis-induced liver fibrosis, lung and biliary fibrosis to research on alcohol-induced liver fibrosis.
- Public funds to support clinical trials specifically on ALD

10. What are the gaps between current research and potential research issues which could make a difference, affordable and could be carried out in a) five years b) in the long term?

10.1 Systematic data recollection about morbidity

Previous research has explored extensively alcohol-related mortality, however, the paucity of alcohol-related morbidity research is surprising, as 1.5 per cent of all deaths were attributable to alcohol, but 6 per cent of all life years lost to disability were attributable to alcohol. In addition, even developed countries do not gather as much disability data in comparison to mortality data. The latter is easier to quantify and must be collected by law. Developed and developing countries should enhance data recollection allowing refined analysis between alcohol use and disability or quality of life. If such a disability registration existed, investigators could explore which are the main factors that explain the association between alcohol and morbidity. Fewer studies examine alcohol-related morbidity alone or a combination of morbidity and mortality. Rehm and colleagues grouped morbidity and mortality together examined the impact of alcohol on coronary heart disease; in this study, which used data from the National Health and Nutrition Examination Epidemiologic Follow–Up Study, based on a large representative survey of the United States general population, the data did not distinguish between people newly diagnosed with CHD and people who had died of the disorder. Overall, information about alcohol-related morbidity alone is limited because studies identifying morbidity as the endpoint demand substantial resources to assess individual outcomes in an objective and standardized way.

10.2 Data comparability

The robustness and comparability of data is still weak. Even developed countries in the European region do not have standardized definitions to better compare trends and patterns (e.g. cut-off levels for episodic heavy drinking and binge drinking). The problem is also valid for economic evaluations, which do not use a standardized methodology yet. In addition, the amount of repeated and comparative surveys need to be increased, specifically about heavy drinking, drunkenness, context of drinking, unrecorded consumption (smuggling) and AD.
In addition, externalities surrounding alcohol abuse need to be accounted for (similar to passive smoking). For example, the effect of alcohol on the drinker’s peers and family, effects on the victims of violence and traffic injury, and the indirect costs to society. The impact of these issues should be relevant in debates about the public and political acceptability of effective alcohol policy.\textsuperscript{32}

10.3  Alcohol pathogenesis

In terms of the pathogenesis of the disease, the latest findings about gut increased permeability to alcohol (consequence from chronic ACo), which promotes an increase of endotoxin levels in the bloodstream, becomes a promising field to measure its epidemiologic and epigenetic effects. For example, recent NIAAA funded research revealed that alcohol induced alterations in microRNA expression in the cell lining of the gut may cause a reduction of protein levels, leading to increased intestinal permeability, indirectly inducing liver damage.\textsuperscript{10} These findings should help develop targeted pharmaceutical agents to abolish the protein decay. Another promising field for research is related with the source of fibrosis. The latter has been traditionally linked to stellate cells, including hepatocytes themselves. However, additional mediating factors may contribute to the process. For example, transforming growth factor (TGF)-\(\beta\) induces early fibrosis. Inhibition of the TGF-\(\beta\) pathway, in turn, has been found to prevent liver injury.\textsuperscript{162}

10.4  Better understanding of young people’s drinking

Historically, adolescents have been the major focus point for research regarding alcohol consumption patterns, however, strong evidence recognizes young adults (18-25 age group) as the heaviest drinking group age.\textsuperscript{7,69} More research is needed to better understand their motivation, risk factors, and how ACo affects this population segment.

10.5  Social harm

More research is needed to effectively measure all aspects of social harm related to alcohol. Currently, analysis within the family, at the workplace, criminal behavior, sexual behavior and less serious but more common harms are scarce. Validity and reliability of current survey measures need to be revised, and wider conceptual frameworks need to be developed in order to properly measure harm to others from a person’s drinking.\textsuperscript{7}

10.6  Alcohol policy

Systematic investigation is needed to measure the effects of policy changes. For example, the impact of policy changes regarding prices and taxation on alcoholic beverages between countries and regions over time.

10.7  Evidence-based treatment

Approximately only 10 per cent of United States treatment programs have access to medications and evidence-based behavioral treatment. The remaining 90 per cent still relies on a model developed 50 years ago, when scientific understanding of AUD was rudimentary.\textsuperscript{9} The principal weakness of current treatment options is related with the assumption that a relatively brief period of counseling will dramatically affect the prognosis...
Update on 2004 Background Paper, BP 6.14 Alcohol Use Disorders

of a severe chronic illness. Such approach has no scientific basis and is not used for other chronic diseases. More research is needed to understand why the shift from older therapies to newer ones has not occurred yet.

More evidence is needed to determine the effectiveness of many of the interventions to reduce harmful alcohol consumption such as targeted policy option to reduce drinking in adults that are sustainable over time. Also health service research is needed to identify organizational models to effectively coordinate between treatment for AUD and other non-communicable diseases and to scale these up.

10.8 Combination of pharmaceutical options

More RTCs are needed to identify potential combinations of pharmaceutical options capable of offering higher rates of efficacy than individual treatments. For example, one study evaluated the combination of acamprosate and disulfiram. However, the disulfiram arm was not randomized. The results suggested that concomitant administration of disulfiram improves the effectiveness of acamprosate on absolute abstinence and on relapse prevention.

11. For which of these gaps are there opportunities for pharmaceutical research (possible ways to go forward with regards to public funding?)

11.1 Alcohol pathogenesis

Latest findings described about AUD pathogenesis, offer clear pathways to explore the development of specific substances blocking the alcohol cascade in non-traditional segments. In addition, more research and highly effective compounds are needed to have substantial impact on the main stages of AUD: acute drinking, chronic drinking, and relapse.

In terms of ALD, no safe and effective treatments are currently available. In addition, liver anti-fibrotic therapies are on the world market due in large part of the inability of most drugs to inhibit excessive fibrosis in the liver without simultaneously affecting the production of beneficial and needed fibrotic mechanisms in other parts of the body. Novel therapies to inhibit and reverse fibrosis remain the ultimate goal to treat liver cirrhosis.

11.2 Public and private funding needs to be increased

Commonly, developed economies devote a share of resources to investigate and promote interventions for reducing alcohol abuse and harm. However, that’s not the case for the most part of developing economies. Governments all around the world need to recognize the enormous burden of disease related to alcohol and increasingly explore which context-based variables are driving ACo. Private funding to accelerate the development of newer treatment options should be promoted, with special emphasis to efficacious treatment to deal with relapse.

6.14-56
12. Conclusion

Alcohol, a longstanding public health problem, remains a challenge for health services around the world. An impressive amount of knowledge in neuroscience, genomics, pharmacology, psychology, social sciences, and mathematics has been developed in the last 20 years to help people change their alcohol-related behaviour. Even though several medications options are available to treat AUD or ALD, none could be categorized as ‘highly efficacious’; hence, preventing both maladies still offers the best possible outcomes. The scientific community is working on numerous and novel approaches to improving efficacy, quality, effectiveness, accessibility and cost-effectiveness of treatment. However, treatment needs to better combine the full menu of evidence-based options and evaluate more rigorously the current most common interventions, such as the 12-step program. Therefore, organization and delivery of alcohol services need to be reformed to offer longitudinal and integrated care, improving the communication and collaboration between primary care settings and supportive groups.

Due to the strong cultural affinity for alcohol in Europe, 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 effective therapeutic options are still lacking. Because the biological basis of AD appears to be multifactorial, the future of AUD and ALD may be combination therapy, using pharmacological options acting on different neuronal pathways, such as acamprosate and naltrexone. Additionally, psychotherapy should be used in association with pharmacotherapy due to high rates of comorbidity affecting these patients. 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

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Appendices


Figure: Neurocircuitry schematic illustrating the combination of neuroadaptations in the brain circuitry for the three stages of the addiction cycle that drive drug-seeking behavior in the addicted state. Note the activation of the ventral striatum/dorsal striatum in the binge intoxication stage. During the withdrawal/negative effect stage, the dopamine systems are compromised and brain stress systems such as CRF are activated to reset further the salience of drugs and drug-related stimuli in the context of an aversive dysphoric state. During the preoccupation/anticipation stage, contextual cues via the hippocampus and stimuli cues via the basolateral amygdala converge with frontal cortex activity to drive drug seeking. Other components in the frontal cortex are compromised, producing deficits in executive function.

## Table Neurotransmitter Systems in the Brain Involved in Different Stages of the Addiction Cycle and Existing and Potential Pharmacotherapies Targeting Them in the Treatment of Alcohol Dependence

<table>
<thead>
<tr>
<th>Neurotransmitter System</th>
<th>Existing and Potential Pharmacotherapies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopamine system</strong></td>
<td>Dopamine receptor partial agonists</td>
</tr>
<tr>
<td></td>
<td>- $D_2$ receptor partial agonists</td>
</tr>
<tr>
<td></td>
<td>- Dopamine receptor antagonists</td>
</tr>
<tr>
<td></td>
<td>- $D_3$ receptor antagonists</td>
</tr>
<tr>
<td><strong>$\gamma$-Aminobutyric acid (GABA) system</strong></td>
<td>GABA receptor modulators</td>
</tr>
<tr>
<td></td>
<td>- $GABA_B$ receptor modulator (gabapentin)</td>
</tr>
<tr>
<td><strong>Brain stress system</strong></td>
<td>CRF-related targets</td>
</tr>
<tr>
<td></td>
<td>- CRF receptor antagonists</td>
</tr>
<tr>
<td></td>
<td>Non-CRF-related targets</td>
</tr>
<tr>
<td></td>
<td>- Norepinephine receptor antagonists</td>
</tr>
<tr>
<td></td>
<td>- Dynorphin/µ-opioid receptor antagonists</td>
</tr>
<tr>
<td></td>
<td>- Neuropeptide Y receptor agonists</td>
</tr>
<tr>
<td></td>
<td>- Substance P receptor antagonists</td>
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<tr>
<td><strong>Glutamate system</strong></td>
<td>Glutamate receptor agonists and agonists</td>
</tr>
<tr>
<td></td>
<td>- $N$-methyl-$D$-aspartate (NMDA) receptor partial agonists (ocamprosate)</td>
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<tr>
<td></td>
<td>- $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonists (topiramate)</td>
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<tr>
<td></td>
<td>- metabotropic glutamate receptor 5 (mGluR5) antagonists</td>
</tr>
<tr>
<td></td>
<td>- mGluR2 and mGluR3 agonists</td>
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### Table 6.14.5

<table>
<thead>
<tr>
<th>Recommendations for Implementing Quality Integrated Care for Individuals With Co-Occurring Disorders (CODs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Coordination of care and integrated treatment by leadership and all key stakeholders. Development of a shared vision among systems of care (Minkoff, 1991; 1997, 2001; Mueser et al., 2003).</td>
</tr>
<tr>
<td>- A &quot;no wrong door&quot; policy. Whenever individuals enter a service system, they will find access to care, including &quot;entitlement of comparability and formal determination of infant to treat or refer.&quot;</td>
</tr>
<tr>
<td>- Clear and agreed upon definitions of coordination of care, formally documented between providers and in purchaser agreements. This will help ensure coordination and accountability for outcomes.</td>
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<tr>
<td>- Assertive outreach and patient engagement and retention activities, key to improving outcomes for COD patients.</td>
</tr>
<tr>
<td>- Development and adoption of standardized performance indicators across organizations and systems.</td>
</tr>
<tr>
<td>- Comprehensive assessment practices across systems of care (e.g., alcohol and other drug treatment programs, mental health departments, primary care, chronic disease programs, and emergency departments). The IOM specifically recommends (1) screening for alcohol misuse by all adults, including pregnant women (U.S. Preventive Services Task Force); (2) screening for a co-occurring mental or substance-use problem at initial presentation with either condition; and (3) screening of entrants into child welfare and juvenile justice systems, because of the high prevalence of CODs among children (IOM, 2006). Assessments onsite when possible, by referral when necessary.</td>
</tr>
<tr>
<td>- Interdisciplinary training of staff, to enhance clinical capacity and fluency with diagnostic and treatment placement criteria, and therapeutic techniques, regardless of type of program.</td>
</tr>
<tr>
<td>- Comprehensive services across programs and across disorders (e.g., individual and group therapy, family therapy, vocational counseling, assistance with housing and income programs, case management, etc.).</td>
</tr>
<tr>
<td>- All types of disorders treated as &quot;primary.&quot; No program, patient, type of disorder, or approach to treatment is considered more important than others.</td>
</tr>
<tr>
<td>- Motivational enhancement activities, which studies show are among the most effective components of care (Cleary et al., 2008).</td>
</tr>
<tr>
<td>- Availability of long-term services and continuity of care across programs and time. Patients may benefit from a disease management/chronic care rather than an episodic treatment approach.</td>
</tr>
<tr>
<td>- &quot;Reduction of negative consequences&quot; or harm-reduction philosophy (Mueser et al., 2003). Improvement in mental health symptoms and functioning should be emphasized as important interim goals.</td>
</tr>
<tr>
<td>- Comparable administrative infrastructures, including information technology systems and instruments, electronic medical records, and assessment tools.</td>
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<tr>
<td>- Sharing of patient information, including patient records when possible, and encouragement of patients to consent to releasing information. Programs should require clear guidelines and safeguards around the use, disclosure, and protection of confidential health information.</td>
</tr>
<tr>
<td>- Flexible funding across systems to reduce barriers posed by distinct financing mechanisms.</td>
</tr>
<tr>
<td>- Co-location of services and clinicians whenever possible (Friedmann et al., 2000a; Hallett et al., 1995; Sterling and Weiser, 2005).</td>
</tr>
<tr>
<td>- Clinical integration of services whenever possible (i.e., dual services provided by the same clinicians, or clinicians in the same programs).</td>
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<tr>
<td>- Program and organizational linkages with other systems involved with the patient (e.g., criminal justice and welfare systems, schools, and employee assistance programs).</td>
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</tbody>
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