Review

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# Treatment of alcohol use disorders in patients with alcoholic liver disease

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## Summary

Alcohol use disorders (AUDs) is one of the leading causes of disease and disability in almost all European countries. Among the alcohol-related diseases, alcoholic liver disease (ALD) is the most common. At present, alcohol is the most frequent cause of liver cirrhosis in the Western world. The cornerstone of treatment for ALD is achieving total alcohol abstinence and preventing relapse; medical and surgical treatments for ALD are limited when drinking continues.

This narrative review summarizes current treatments for AUDs with a particular emphasis to the treatment of AUDs in patients with ALD. Medical management, psychosocial and pharmacological interventions are analyzed, underlying limits and options in AUD patients. Finally, this review discusses the most appropriate setting for the management of AUD patients with advanced liver disease as well as the indications for liver transplantation in AUD patients.



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## Burden of disease

Alcohol consumption is one of the top five causes of disease and disability in almost all European countries [1] and the third leading cause of preventable deaths in the U.S [2]. It is estimated that alcohol is responsible for 5.9% of global mortality worldwide [3] and for 2.5 million deaths per year [4,5]. Alcohol consumption, (particularly harmful alcohol use related to alcohol use disorders [AUDs]), accounts for 5.5% of the global burden of disease and for 4.6% of disability-adjusted life year (DALY) [3]. Europe has the highest alcohol-attributable deaths and DALY in the world [3], although there is variation across countries. Alcohol-related mortality is influenced by socioeconomic factors (i.e., level of education, occupational class, income) and drinking habits (binge-drinking *vs.* daily drinking) [6]. Rates of alcohol-related mortality are generally higher in lower educational and occupational groups [6]. Among north-eastern European countries, the highest levels of social inequalities are observed in Finland and Denmark. In eastern Europe, Hungary, Lithuania and Estonia have high levels of alcohol-related mortality in lower socioeconomic groups [6]. Similarly, the United Kingdom has seen a dramatic increase of alcohol-attributable mortality by 400–500% since 1970 [7].

Hazardous drinking is generally associated to road accidents, traumas and violence [8], while chronic alcohol consumption is mainly associated to organ damage, in particular alcoholic liver disease (ALD) [9]. Alcohol is the most frequent cause of liver cirrhosis in the Western world [5] and the alcohol-attributable fraction of liver cirrhosis is up to 60% both in EU and North America [3]. In the last few decades, a dramatically increase of the mortality rates due to end-stage liver disease has been reported in some European countries, mostly related to the increased prevalence of alcohol consumption [7,10].

ALD represents the main alcohol-related medical complication [5,9,11]. It includes a spectrum of alcohol induced liver pathology, ranging from steatosis and alcoholic steatohepatitis (ASH) to progressive fibrosis, cirrhosis and hepatocellular carcinoma (HCC) [9]. Quantity, duration and pattern of drinking play a causal role on the phenotype of liver damage. Other than alcohol's direct toxicity, patterns of alcohol consumption (e.g., episodic, binge, continuous), duration and amount of alcohol intake [4,9], hepatitis virus infection, interaction with host factors (i.e., gut microbiota), gender, genetic, nutritional

factors and comorbidities are the main factors influencing the development and the progression of ALD [12–19].

## Alcohol use disorders: Alcohol abuse and alcohol dependence

Currently, AUD is the label employed for the categorization of pathological alcohol consumption. Alcohol dependence is now labeled severe AUD, while alcohol abuse would be classified as mild to moderate AUD. As a whole, AUDs affect nearly 10% of the general population both in the United States and Europe [11].

Despite this categorical approach, AUDs are better characterized from a dimensional perspective with a graded range of severities. Although there are forms of non-progressive, intermittent alcoholism [20], severe AUDs could be considered the end-stage of a disease progression. An AUD may start with normative drinking, progresses to risky and hazardous drinking, and then enters the final stage where a full blown addicted state ensues.

A solid body of evidence demonstrates that severe AUD is a chronic condition, usually with a relapse-remitting course [20]. Studies also suggest that it is a multifactorial disease, where complex genetic-environmental interactions occur. Both twin studies [21] and genome wide association studies show that genetic influences exert a moderate to high etiological influence [22].

The milder stages of AUDs also heavily induce the of burden of disease, both to patients and society. In fact, it is suggested that the individuals adding the biggest burden are those who drink heavily [23]. Therefore, individuals who are not yet dependent or addicted to alcohol, but drink problematically or beyond a safe level, should be targeted by health policies and health professionals. There are two main reasons for this approach: first, the individuals suffer or are at an imminent risk of suffering consequences related to their drinking (whether organic, including ALD, or psychological) and second, addressing and treating heavy drinking at an earlier stage might prevent the progression of the condition to a dependent state, and might, therefore, the organic consequences. Furthermore, it might do so in a more cost-efficient manner. These are the core concepts of screening and brief intervention, a strategy that has tried to change some of the paradigms of addiction treatment, where usually, only the most severely affected individuals receive treatment. Several systematic reviews and meta-analyses support the efficacy of screening and brief intervention [24–26], and a majority of guidelines advocate for the universal implementation of screening and brief intervention in primary care [27,28]. Although exact limits for categorizing normative, risky or harmful drinking might vary between countries and guidelines, knowing how alcohol quantities are measured is of special relevance (Table 1).

Systematic screening should allow primary care physicians to identify and offer treatment to mild and moderate forms of AUD, while at the same time identify more severe forms and refer them to specialized treatment. All these concepts together are known by the acronym SBIRT: screening, brief intervention and referral to treatment. However, the low proportion of alcohol-dependent subjects that receive treatment is a well-defined problem [29]. A recent European study showed that nine percent of primary health care patients present with an AUD, but just five percent are identified and only one percent receives treatment for this condition, a situation that has been labeled as the 'double treatment gap' [29].

Despite a huge treatment gap, the idea that AUDs should be tackled in medical settings, like any other chronic condition, was established many years ago [30], but faces clear difficulties in its implementation. The decision to refer patients to a specialized addiction clinic or to treat them directly is not always easy and clear. There is a tendency to advocate that alcohol dependence should be treated as any other medical condition that is usually effectively managed at the primary care level. This holds true for specialists like hepatologists who deal with ALD, one of the most common medical complications of AUDs.

The objectives of the present narrative review are to briefly summarize current treatments for both AUDs and ALD, and to review the evidence regarding the treatment of AUDs in patients with ALD. A search was conducted in PubMed, Scopus and Web of Knowledge, using the following terms: alcohol, alcohol abuse, alcohol dependence, AUDs, risky drinking, hazardous drinking, problematic drinking, ALD, hepatic cirrhosis, hepatic steatosis, alcoholic hepatitis, alcohol withdrawal syndrome, liver transplantation.

## Treatment

A cornerstone of the treatment of AUD patients with ALD is the achievement and maintenance of total alcohol abstinence. The efficacy of medical and surgical treatments for ALD is limited when drinking continues [12,31]. The persistence of alcohol consumption is the main risk factor for progression of liver damage and complications [31,32].

**Key point**

Total alcohol abstinence is mandatory in AUD patients with liver diseases.

### *Medical management of AUDs*

Evidence shows GPs can effectively treat heavy drinking with the SBIRT framework. However, evidence also shows the implementation of such a strategy is rather low [33]. Medical manage-

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