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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Table 1. Main parameters to measure alcohol consumption.

Parameter	Measure of quantification	Beverage examples*
Volume (usually ABV: alcohol by volume)	Percentage of volume in the whole drink. Gets easily transformed into grams applying	4.5 % beer: 4.5 % of the total volume corresponds to ethanol 13% wine: 13% of the total volume corresponds to ethanol
Grams	Quantity of pure ethanol g = volume x 0.8 x ABV/1000	250 ml of 4.5% beer : 9 g 75 ml of 13% wine: 7.8 g 750 ml (1 bottle) of 13% wine: 78 g
Alcohol unit (mainly used in the UK)	10 ml of pure alcohol 8 grams of pure alcohol	250 ml of 4.5% beer : 1 unit 75 ml of 13% wine: 1 unit 750 ml (1 bottle) of 13% wine: 10 units
Standard drink (similar concept to alcohol unit, used mainly outside the UK)	Varies from different countries. **10 grams**: WHO, Australia, Austria, France, Hungary, Greece, Ireland, New Zealand, Poland, Spain, The Netherlands **11 grams**: Finland **12 grams** : Denmark, South Africa, Italy, Switzerland, Germany **14 grams**: United States, Canada, Portugal **20 grams**: Japan	250 ml of 4.5% beer: about 1 standard drink 75 ml of 13% wine: about 1 standard drink 750 ml (1 bottle) of 13% wine: 4 to 8 standard drinks in relation to different Countries

*Conversions are usually not exact, but become rounded for easiness of use.

ment can be seen as a way to engage GPs in a more active screening and advisory role for heavy drinking patients. An important aspect of medical management is to treat heavy drinking as any other medical disease, where clinicians provide education, support and pharmacotherapy. By delivering advice based on higher alcohol consumption thresholds, medical management tries to strengthen treatment rather than prevention; a paradigm where clinicians might feel more engaged.

The first large randomized control trial (RCT) testing this approach was the COMBINE study, which found it not only effective [34], but also cost-effective [35]. Medical management was superior to behavioral interventions alone. The combination of medical management with either naltrexone or acamprosate showed excellent results, with 6–7 patients needing treatment in order to achieve a good clinical outcome (similar to those seen in other chronic conditions such as chronic depression [36], or type 2 diabetes [37]). This fact supports the core concept of medical management to treat AUDs as any other medical disease, using the appropriate array of strategies available for professionals.

Although most of alcohol dependent (AD) patients do not receive specific alcohol-related treatment, most of them do attend health care facilities for other reasons [29]. Medical management is also a strategy to take advantage of this fact. As such, it advocates that alcohol patients should receive primary care based treatment for their problem. Just as primary care physicians treat mild and moderate cases of hypertension, they can also address AUDs by employing medications, brief interventions and referrals when needed. In fact, this approach is in line with actual trends trying to integrate substance abuse treatment into medical practice. It also tries to avoid the stigmatization of alcohol patients by preventing false dichotomization (alcoholic *vs.* non-alcoholic), adopting a more dimensional perspective.

Psychosocial interventions in AUDs

The most effective treatment for AUDs is the combination of psychosocial interventions and pharmacological therapy [38]. Most of the guidelines currently available advocate a psychosocial approach as the basis of treatment for all subjects. The following modalities of psychosocial interventions have proven efficacy in AD.

Motivational interviewing [39–41] is a client-centered, directive method for enhancing intrinsic motivation to change by exploring and resolving ambivalence (Table 2). Cognitive behavior therapy [42] is a structured goal-directed form of psychotherapy in which patients learn how their thought processes contribute to their behavior. Increased cognitive awareness is combined with techniques to help patients develop new and adaptive ways of behaving and alter their social environment, which in turn leads to changes in thought and emotion. Peer-support groups [43] are another form of psychosocial intervention with a long-standing tradition in AUDs. They usually emphasize working toward abstinence through group sharing and support. Contingency management [44,45] consists of offering incentives in order to encourage abstinence or discourage alcohol use. Family therapy [46] assumes that AUD affected individuals belong to a bigger system called "family", in which individuals communicate and interact constantly with one another, sometimes in an adaptive manner, sometimes disfunctionally. **Family therapy can be delivered with different specific forms and purposes, like helping the

family to cope with a patient who refuses treatment, teaching skills to all family members, pressurizing the subject to enter treatment or contingency management training to family members. Social behavior network therapy [47] integrates concepts of network therapy, marital therapy, community reinforcement and social skills training. Its main objective is to help the patient to build positive social support for a change in drinking.

Psychosocial interventions in patients suffering from AUDs and ALD

The limited pharmacological options for patients suffering from both AUD and ALD, and the fact that AUDs are successfully treated with psychosocial interventions, lead to the unequivocal conclusion that the backbone of AUD treatment in this population is psychosocial in essence. As part of this treatment, a proper psychosocial assessment is also crucial (Table 3). However, some differential aspects of this population should be noted. Firstly, they suffer from more frequent and more severe organic consequences related to AUDs. It is also possible that they have heavier drinking histories, and may display some differential psychological aspects due to suffering from life threatening conditions. These might include health-related concerns, more overall psychological distress or even some cognitive deficits related to their organic state, which might induce different responses to psychosocial treatments. It is also remarkable that all these features usually lead these patients to be excluded from trials investigating AUD treatment options. However, many studies now show that offering psychosocial interventions to these patients is a feasible, acceptable and efficacious strategy. For example, Georgiou *et al.* [48] offered 1 h of social behavior and network therapy to 20 orthotopic liver transplantation (OLT) candidates, integrated in the usual procedures of the transplantation unit. Patients' acceptance and participation were high, an observation that leads to the conclusion that psychosocial interventions could be a valid approach to support motivation in these patients. Further studies on psychosocial interventions reinforced the validity of this approach. For example, a study by Weinrieb *et al.* [49] found evidence that motivational enhancement therapy (MET), might reduce the frequency and quantity of alcohol consumption in pretransplant candidates with AUDs.

A recent systematic review, specifically focused on psychosocial interventions in AUD patients with chronic liver disease [50], found no robust evidence for any psychosocial intervention alone in maintaining abstinence. However, when integrating CBT, MET and comprehensive medical care, favorable and significant effects were observed both in inducing and maintaining abstinence [51]. One of the explanations for these results is that by integrating alcohol interventions with medical care, patients who would not accept a referral for alcoholism treatment might be engaged as they are usually willing to return for medical appointments. An improvement in their medical status could be another reason.

Several studies show that integration of medical care and addiction treatment leads to better drinking outcomes in AUD populations [52–54]. For example, in a study by Oslin *et al.*, 163 alcohol-dependent patients were randomly assigned for alcohol treatment in either a specialty center or in a primary care based facility. Those receiving integrated treatment showed greater engagement and greater reductions in heavy drinking [53]. O'Toole and colleagues assessed 120 patients receiving integrated substance abuse and acute medical care interventions. When compared to usual care patients, they showed higher rates of outpatient treatment initiation and retention [52]. Weisner *et al.* randomized 529 patients to either independent or integrated primary care and substance abuse treatment. Although many outcomes were not different between groups, the abstinence rate was higher in the integrated study arm [54].

In line with these findings, a recent study [55] in liver transplantation patients found that the integration of the addiction unit within the liver transplantation center reduced recidivism and mortality. Similar effects following integrated care have been observed in other special populations, such as those with hepatitis C and hazardous alcohol use [56].

Taken together, the data reviewed suggest that integrating medical care with addiction treatment at all stages of the disease might be crucial for increasing treatment acceptance and efficacy. However, the lack of prospective studies makes further research necessary in order to establish what benefits treatment integration brings and by what mechanisms are they achieved.

Pharmacological interventions in AUDs

Alcohol withdrawal syndrome

More than 50% of AUD patients experiences alcohol withdrawal syndrome (AWS) after the discontinuation or abrupt decrease in alcohol consumption (Table 4). Pharmacological treatment is necessary in moderate to severe forms of AWS [57]. Other than the normalization of fluids, electrolytes and glycemia imbalance, as well as vitamin administration (in particular thiamine), benzodiazepines (BZDs) are the gold standard for the treatment of AWS, as they are able to prevent AWS progression to severe forms including delirium tremens. Diazepam and

Table 2. Motivational Interviewing (MI) main characteristics.

	Definition	Components
Spirit	Foundational values of the practice of MI.	Partnership: collaboration with patients. Acceptance: patients objectives are the main guidance source. Compassion: active promotion of the other's welfare. Evocation: people have what they need to change, it has to be brought to the surface
Method	Central processes or phases that form the flow of MI. They are sequential but overlapping occurs.	Engaging: establishing a helpful connection and working relationship. Focusing: establishing the patient and professional's agenda. Evoking: eliciting patient's own motivations and abilities to change. Planning: developing commitment to change and formulating a specific plan of action.
Core interviewing skills	Fundamental communication skills to develop a consistent MI-practice.	Open-ended questions: questions that facilitate thinking before responding. Affirmation: to accentuate the positive, especially about patients themselves. Reflective listening: fundamental skill, based on focusing on persons' own narrative, aiming at discerning the true meaning of their discourse. Summaries: reflections that pull together several things said by the patient. Usually aiming at facilitating the continuation of change talk.

chlordiazepoxide are the most widely used drugs on the basis of their long half-lives, although there is no clear superiority among different BZDs [57].

A number of non-BZD agents have been tested for the treatment of AWS and some have shown promising results, e.g., β-blockers, α2-agonists, neuroleptics and antiepileptics. Among them, GABAergic drugs as gabapentin [58], sodium oxybate [59–61], and baclofen [62] have shown an efficacy comparable to benzodiazepines in the treatment of AWS.

In AUD patients with advanced liver disease, symptoms of AWS and hepatic encephalopathy may overlap. Most of BZDs undergo an extensive metabolism in the liver with production of active metabolites [57]. Among BZDs, lorazepam or oxazepam may be preferred on the basis of their shorter half-life and absence of active metabolite products, although diazepam (at a reduced dose) together with its active metabolites can produce a smoother withdrawal [57].

Non-benzodiazepine GABAergic drugs, might be preferable for the treatment of AWS in patients with advanced liver disease, given their low rate of hepatic metabolism. Moreover, given the safety of baclofen in AUD patients with advanced liver disease [63], this drug could be preferable in ALD patients with AWS. However, RCT data are needed to validate the preliminary results on the use of these drugs in AWS.

Alcohol relapse prevention

Key point

The most effective treatment to prevent alcohol relapse is the combination of psychosocial interventions and pharmacological therapy.

Combined with psychosocial interventions, pharmacotherapies may promote abstinence, reduce alcohol intake and reduce lapse and relapse [64] (Table 5). Disulfiram, naltrexone, nalmefene and acamprosate represent the approved drugs in most of the world countries, even though the number of pharmacological agents being tested for the treatment of AUDs is constantly increasing [64].

Disulfiram was the first drug approved for the treatment of AUDs. The drug inhibits acetaldehyde dehydrogenase enzyme action. As a result, patients develop several distressing symptoms when disulfiram and alcohol are consumed together, including nausea, vomiting, flushing, hypotension, headache and diarrhea (termed "acetaldehyde syndrome"). The risk of acetaldehyde syndrome should act as a deterrent for alcohol consumption [65]. Results from RCTs of disulfiram are controversial. It should also be taken into account that the presence/absence of acetaldehyde syndrome after alcohol intake can invalidate the blind design. Data from open label studies indicate a possible efficacy of disulfiram in AUDs [66]. However, some possible serious adverse events, such as liver failure, neuropathy and psychosis do not support its use in patients affected by liver disease, peripheral neuropathy and psychosis [5,12,67].

Naltrexone is a μ and k-opioid receptor antagonist. Its effect is due to the reduction of alcohol-related dopamine release in the nucleus accumbens [68], with a reduction of reward sensation. Consequently, patients are less motivated to drink alcohol (so-called "extinction mechanism"). The most common side effects are headaches, nausea, dyspepsia, anorexia, anxiety and sedation. High levels of craving, a positive family history of alcoholism [12] and the presence of a specific polymorphism (Asn40Asp) in the μ-opioid receptor gene (*OPRM1*) [69] appear to predict a positive response to NTX.

Nalmefene, a μ and δ-opiod antagonist and k-opioid partial-agonist, is effective in reducing heavy drinking in AUD patients [70,71]. This drug has been recently approved in Europe for the treatment of AUDs 'as needed', and it is indicated in particular in patients in which the main objective is the reduction of alcohol intake, not total abstinence.

Acamprosate is a N-metil-D-aspartate glutamate receptor antagonist [72]. Meta-analytic data showed its efficacy in reducing alcohol

intake and maintaining alcohol abstinence, at least in mild to moderate forms of AUDs [73,74].

A recent meta-analysis has shown that the efficacy of acamprosate and naltrexone is comparable [75]. As such, the medication choice could be guided by patients' characteristics, including different typology of patients [76] and of craving [77]. However, more work is needed in order to better understand personalized treatment approaches for AUD patients.

In the last decades, a number of additional drugs have been tested. Some of these are currently approved for other indications and, in some cases, used as off-label treatment for AUDs in clinical practice (Table 5) [78].

Sodium oxybate (SMO) is a $GABA_B$ agonist; it is approved in US for the treatment of narcolepsy and in some EU countries for the treatment of AUD. The efficacy of SMO to promote total alcohol abstinence and to prevent relapse was showed in several clinical trials (for review see [79,80]), and confirmed in a recent Cochrane evaluation [81]. However, the potential risk of misuse in some patients limits its use in clinical practice in some countries [82], although this misuse seems to be a limited phenomenon that should not undermine its medical application [79].

Topiramate is currently approved for the treatment of seizures and migraine. It exerts its anti-alcohol effects mainly by facilitating γ-aminobutyric acid (GABA) transmission and reducing glutamatergic activity, thus reducing dopamine release in the limbic system [12]. The administration of topiramate in RCTs with a dose escalation design was effective in reducing daily alcohol intake and heavy drinking days, as well as increasing abstinence rates [83,84].

Ondansetron, a $5\text{-}HT_3$ receptor antagonist, is currently approved for the treatment of emesis. By affecting the 5-HT transporter activity, this drug leads to a dopaminergic downregulation, and, therefore, to a reduction in the reward related to alcohol intake [85]. Clinical studies hae shown promising results in reducing alcohol intake, mainly in patients with 'early onset' AUDs [86] and to those with the LL genotype of the *5-HTT* gene regulatory region [87,88].

Baclofen is a selective $GABA_B$ receptor agonist currently approved and used to control spasticity [89]. The activation of $GABA_B$ receptor may exert an inhibitory action on the dopamine neurons and suppress dopamine mediated alcohol-reinforced behaviors [90]. Both open label studies [91–94] and double blind studies [63,95] showed the efficacy of baclofen to promote alcohol abstinence and to reduce alcohol lapse and relapse. The utility of baclofen in the treatment of AUDs has been supported by case reports, case series, and observational and open label cohort studies in which baclofen was used in a dose higher than the dose initially tested [96–98]. At present two RCTs have tested the efficacy and safety of different doses of baclofen in AUDs. In the first study, patients were randomized to receive baclofen 30 mg daily (10 mg t.i.d.) or 60 mg daily (20 mg t.i.d.) or placebo. Both doses significantly reduced alcohol intake and increased abstinence rate. Moreover, the efficacy of baclofen at 60 mg daily was significantly higher showing a dose response. No differences in terms of safety were found between the three groups [99]. The second study evaluated the efficacy and safety of individually titrated high-dose baclofen (30–270 mg/day) with an escalation-dose protocol. The mean dose of baclofen was 180 mg/day. The drug was significantly more effective than placebo in increasing total alcohol abstinence, and no serious adverse events were reported [100]. However, the potential use of high doses of baclofen for AUDs remains very controversial both in terms of safety and efficacy. RCTs are needed before any definitive conclusions can be drawn.

Gabapentin, a drug structurally similar to GABA, is presently approved for the treatment of seizures and neuropathic pain [101]. Gabapentin, at a dose of 600 mg/day twice per day, was superior to placebo in reducing alcohol consumption in AUD patients with post-traumatic stress disorder who were resistant to selective serotonin re-uptake inhibitors, and in AUD patients with insomnia [102]. Gabapentin was shown to improve drinking outcomes when combined to naltrexone [103]. Moreover, a recent RCT showed a dose-dependent effect in achieving alcohol abstinence when comparing 900 mg *vs.* 1800 mg *vs.* placebo [104].

Finally, varenicline, a drug approved for the cessation of smoking addiction, showed promising results in reducing alcohol consumption in heavy drinking smokers [105,106]. In a recent RCT, the administration of varenicline showed a significant effect over placebo in reducing alcohol abuse outcomes with no significant adverse effects. The effect was similar both in smokers and non-smokers patients [107]. A subsequent analysis of data showed a greater effect of varenicline in those patients who reduced smoking and in those with a less severe AUD [108], although these data need further confirmation.

Preventing alcohol relapse in patients with AUDs and ALD. Patients affected by early stage ALD (hepatic steatosis, mild alcoholic hepatitis and fibrosis) can be treated with the above mentioned medications for AUD as long as liver function is monitored closely [64]. Currently, however, the use of most of these drugs is not supported in patients affected by advanced liver disease [5,78] even though alcohol abstinence is required. In particular, the liver metabolism

Key point

Among medications able to promote alcohol abstinence and to prevent alcohol lapse and relapse, recent studies suggest that baclofen is safe and effective in AUD patients with liver diseases.

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Table 3. Psychosocial assessment for ALD patients.

Type of assessment	What to assess
Psychiatry assessment	Absence of active psychiatric disorders with the potential to impact compliance. Special attention to psychotic and mood disorders. Absence of adjustment difficulties.
Addiction assessment	History of substance abuse (alcohol, tobacco, or illicit drug use). Need of structured rehabilitation and adequate social support to maintain abstinence.
Social support assessment	Adequate support from able caregivers especially in the perioperative period. Possibility of including education of the family and/or the patient's support network.
Cognitive assessment	Ability to comply with complex medical and behavioral regimens, frequent follow-up appointments and laboratory procedures. Insight into the nature of the transplantation procedure and post-transplantation care

and/or the possible liver toxicity of some of these medications have prevented their investigation in RCTs in patients with advanced liver disease (Table 5). Specifically, disulfiram could induce liver failure. Naltrexone could induce hepatocellular injury and it is contraindicated in patients with liver diseases as specified in a food and drug administration (FDA) "black box" [109]. No data are available on the use of naltrexone and nalmefene in AUD patients with liver disease. Acamprosate could be considered safe in this subset of patients given the absence of liver metabolism; however, the only available data are limited to a 1-day trial testing the administration of a single dose of acamprosate in Child-Pugh stage A and B cirrhotic patients [110]. Moreover, it is possible that long term administration of acamprosate could increase the risk of encephalopathy due to its antagonism of glutamate receptor [110]. Data from a single case-report show the safety of SMO administration in a patient with advanced ALD [61]. Topiramate could affect liver function [111] and/or could induce encephalopathy [112]. Liver toxicity has been reported in association with ondansetron, although a causal relationship it has not been established [78]. Finally, gabapentin and varenicline should be safe in this subset of patients given their minimal liver metabolism, but trials specifically enrolling AUD patients with advanced ALD are lacking [78]. For all these drugs, prospective trials specifically designed to investigate their efficacy and safety in AUD patients with comorbid ALD are urgently needed.

Among drugs tested for the treatment of AUDs to date, baclofen is the only one to have been formally tested in a RCT in AUD patients with advanced liver disease. Its efficacy in the treatment of AUDs, its pharmacological profile, and the absence of liver-related side effects in patients treated for neurologic disorders [113] or for AUDs [114] led to the rationale for designing a RCT, testing baclofen specifically in AUD patients with liver cirrhosis. Briefly, a total of 84 patients with AUDs and comorbid liver cirrhosis were randomized to receive baclofen 10 mg t.i.d., or placebo, for 12 weeks. At the end of the study, baclofen showed a significant efficacy in promoting total alcohol abstinence and in reducing alcohol lapse and relapse. The drug was very manageable, no serious side effects were reported, and no difference in side effects was found between baclofen and placebo. A significant decrease in AST, GGT and bilirubin was found in the baclofen group compared to placebo. Moreover, a significant improvement in liver function tests like serum albumin levels was found in the baclofen group compared to placebo. It is conceivable that improvement in liver function and damage was due to the significant reduction of alcohol intake in the group treated with baclofen. Additionally, these findings support the safety of the drug in this subset of patients [63]. The efficacy and safety of baclofen were also showed in a subgroup of these AUD patients with cirrhosis and hepatitis C virus (HCV) infection [115].

Subsequent open label trials supported baclofen efficacy and safety in AUD patients with liver disorders [116], including liver cirrhosis [117,118]. In view of its efficacy and safety, baclofen was included both in the European association for the study of the liver (EASL) [5] and the American association for the study of liver diseases (AASLD) [119] clinical practical guidelines for the management of ALD.

Another promising drug for patients affected by AUDs and ALD is metadoxine [120]. Metadoxine is able to accelerate the elimination of alcohol from blood and tissue during acute alcohol intoxication [121] and is also able to accelerate the recovery of functional structure of the liver [120]. In a retrospective preliminary study, Leggio and colleagues [122] showed its potential utility in AUD patients with ALD. Future prospective studies are needed to confirm these very preliminary findings.

Who should treat these patients? In which setting?

The optimal setting for the treatment of patients affected by AUD and ALD still needs to be defined [7,12,55,123]. At present it is regulated by local policies. In some centers ALD patients are managed by hepatologists who decide to treat them independently [48] or with the cooperation of

Table 4. Management of Alcohol Withdrawal Syndrome (AWS).

1.	Recognition of AWS symptoms	Autonomic hyperactivity, agitation, tremor, seizures, delirium – *in a patient with known or suspected AUD*
2.	Assessment of AWS severity	CIWA-Ar scale, AW scale
3.	Risk factors for severe AWS	PAWSS [141]: if score ≥4 high risk for severe AWS
	Patients with severe ALD should be considered at high risk for severe AWS	
4.	General treatment and supportive care	Normalization of fluids, electrolytes and glycemic imbalance Vitamins administration (parenteral thiamine 250 mg/day)
5.	Mild AWS. CIWA-Ar <8 or AW scale <6	Pharmacological treatment non strictly indicated Prescription of non-BDZ drugs to treat AWS and to start alcohol relapse prevention
	Moderate AWS. CIWA-Ar 8-15 or AW scale 6-9	Pharmacological treatment indicated Outpatient setting if low risk for severe AWS Combination of BZD and non-BZD drugs (BZD-sparing effect)
	Severe AWS. CIWA-Ar >15 or AW scale >9	Pharmacological treatment with IV BZD – *inpatient setting* ICU for refractory AWS (*treat with barbiturates and propofol*) Administration of haloperidol for hallucinations Administration of alpha2-agonists or beta-blockers for autonomic hyperactivity
Recommended BZD doses for the treatment of AWS		
	Fixed dose	diazepam 10 mg q.i.d. (day 1), 5 mg q.i.d. (2 days), then taper
	Approximate BZD equivalence (oral)	
	diazepam 10 mg = lorazepam 1 mg = chlordiazepoxide 30 mg = oxazepam 60 mg	
Non-BZD drugs to be preferred in those patients with advanced ALD		
	Drug	Doses
	Baclofen	10-20 mg t.i.d. tapering in 10 days
	Sodium oxybate	50-100 mg/kg/day titrated in 3-6 doses, tapering in 10 days
	Gabapentin	400 mg t.i.d. for 3 ays, 400 mg b.i.d. for 1 day, 400 mg for 1 day

AWS, Alcohol Withdrawal Syndrome; AUD, Alcohol Use Disorders; CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol revised; AW Scale, Alcohol Withdrawal Scale; PAWSS, Prediction of Alcohol Withdrawal Severity Scale; ALD, Alcoholic Liver Disease; BZD, Bendodiazepine; IV, intravenous; ICU, intensive care unit.

an external team of psychiatrists, social workers, and psychologists. In other centers, AUD patients are primary managed by psychiatrists together with hepatologists as consultants [124].

A multidisciplinary approach would be optimal for the management if these patients. This may take place in a medical setting by a team including different professional figures such as hepatologists, psychiatrists, addiction specialists, psychologists, social workers and surgeons, and working in the same center. This maximizes the potential to properly manage all aspects of AUDs. In particular, AUD patients should be screened for comorbid drug abuse including smoking addiction [78,123], psychiatric disorders and organic comorbidities (increased risk for cardiovascular disease, lung disease, neoplasms, etc.) [123,125].

Alternatively, AUD patients with any stage of ALD, should be mainly managed by a team of hepatologists with mandatory expertise in addiction medicine, and mental health professionals, which should be able to guarantee medical management, screening for comorbidities, and treatment for AUDs (including individual counseling and pharmacological therapy), referring patients to support programs (i.e., Alcoholics Anonymous) and to liver transplant center in those cases of advanced ALD. Recently this model showed its usefulness in AUD patients included in the waiting list for transplantation [55]. In particular, a team of internists – with expertise in alcoholism, hepatology, and addiction medicine – and psychologists (namely Alcohol Addiction Unit [AAU]) was integrated in to a liver transplantation team in 2002 in order to provide expert clinical support in the evaluation, management, and treatment of AUDs in patients both before and after liver transplantation. Patients treated by this group were compared to patients who were evaluated for their alcohol use before 2002, by consultant psychiatrists external to the transplantation team. A significantly lower prevalence of alcohol lapses and relapses, and a significantly lower mortality 10 years after liver transplantation were found among patients managed by the AAU integrated in the liver transplantation team [55].

Key point

Integration of AUD treatments in medical settings seems to increase its effectiveness in ALD patients (Fig. 1).

Liver Transplantation: The 6 month rule, relapse risk and moderate alcohol consumption

When liver function does not improve after an adequate abstinence or when the severity of disease does not allow waiting for improvement, liver transplantation (LT) represents the gold standard treatment for patients with advanced ALD [4]. At present ALD represents the second indication in US and Europe after HCV infection [126,127] and the survival rate of patients who receive LT for ALD is at least comparable or even higher than those patients in which LT is performed for other etiologies [126].

It is mandatory to reduce the risk of alcohol relapse after transplantation in order to reduce the probability of graft loss and the liver damage

Key point

When liver function does not improve after an adequate abstinence, liver transplantation represents the gold-standard option for AUD patients with advanced liver disease.

Review

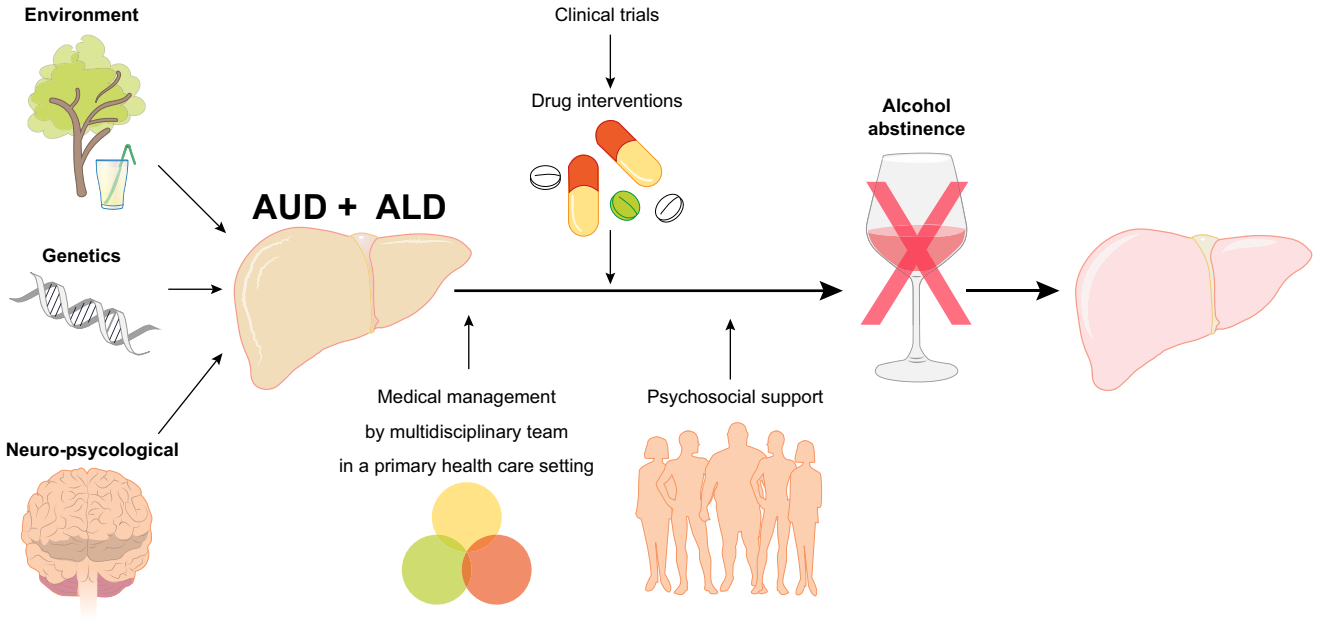

Fig. 1. Environment (including alcohol availability) associated to genetic predisposition to alcohol addiction and to neuro-psychological impairment (i.e. mood and affective disorders and/or craving onset) increase the risk of Alcohol Use Disorders (AUD) development. AUD is the most frequent cause of liver diseases in the Western world. The most effective management strategy for AUD patients with liver diseases is to achieve total alcohol abstinence. The combination of psychosocial interventions and pharmacological therapy represent the most effective treatment to achieve abstinence and to prevent relapse. Alcohol abstinence leads to an improvement of liver function and/or to a reduction of liver disease progression.

related to alcohol relapse [55,128]. Moreover, in an era of organ shortage, the risks of alcohol relapse could induce unwillingness of surgeons to transplant AUD patients, other than the incorrect and moralistic perception that AUDs are a "self-inflicted disease" and thus not deserving of such a restricted and expensive procedure [129].

To reduce the risk of relapse, an abstinence period of 6 months before LT – the so-called "6-months rule"- is usually required [55]. This rule, although largely questioned and deemed as arbitrary [128] should be adopted mainly because a recovery of liver function after a prolonged alcohol abstinence could avoid unnecessary OLT. Moreover, although some evidences indicate that 6-month alcohol abstinence could minimize the risk of relapse, this criterion should be not adopted in patients where the severity of the disease does not allow a 6-month waiting time [5,130]. The last guidelines of the International LT Society [131] clearly report that the role of the "6-month rule" is questionable and not evidence-based. Decisions on LT candidacy should not be made solely on length of sobriety criterion (Recommendation IA) and when medical urgency does not allow a 6 month waiting time, the LT evaluation may proceed in selected patients (Recommendation IC) [131].

In the last few years LT has been showed to improve survival in patients affected by severe alcoholic hepatitis not responding to medical management [9,130,132]. Death usually occurs within 2 months in these patients, and so early LT is attractive, although this indication remains controversial and is still under clinical evaluation [9]. At this point in time, it could be suggested as a treatment for a very selected population of AUD patients. Future studies should clarify patients' selection and graft survivals [131].

The rate of alcohol intake after LT is highly variable, with a percentage ranging from 10 to 95% [55,124,133]. This is partly due to the lack of consensus on the definition and classification of alcohol consumption (e.g., recidivism, lapse, and relapse). In particular, several reports used the term 'recidivism', without specifying if it refers to a lapse, relapse or both. For this reason, the term "recidivism" should be avoided or, if it is used, it should specify the percentage of lapse and relapse within patients showing recidivism after LT [55,134]. The term recidivism should also be avoided as it is a legal term defined as 'relapse to criminal behavior', it is not a term used historically in the addiction field of medicine, and it could unintentionally perpetuate a long-outdated moral and legal perception of addiction.

Returning to occasional or moderate drinking could be tolerated in transplanted patients because it may not affect long term survival [135–137]. However, alcohol consumption in AUD patients, even if at low dose, could induce the increase of craving [77]. Craving alcohol could trigger loss of control, thus switching from mild alcohol consumption to heavy alcohol con-

Table 5. Pharmacological treatment of AUD.

Drug	Dosage	Mechanism	Metabolism	Excretion	ALD patients
FDA approved for AUD					
Disulfiram	250-500 mg q.d.	Acetaldehyde dehydrogenase inhibitor	Hepatic	Hepatic	No
Naltrexone	50 mg q.d. (oral) 380 mg monthly i.m.	μ and k-opioid receptor antagonis	Hepatic	Renal	No
Nalmefene	18 mg as needed	μ and δ-opiod receptor antagonist k-opioid receptor partial-agonist	Hepatic	Renal	No data
Acamprosate	666 mg t.i.d.	N-metil-D-aspartate receptor antagonist	Minimal	Renal	Limited data, probably yes
Not FDA approved for AUD					
Sodium oxybate	50 mg/kg/day	GABAB receptor agonist	Hepatic	Hepatic	Limited data, probably yes
Topiramate	300 mg q.d.	Facilitates GABAA transmission reduces glutamatergic activity	Hepatic	Renal	No data, probably yes
Ondansetron	1-16 μg/kg b.i.d.	5-HT3 receptor antagonist	Hepatic	Renal	No data, probably yes
Baclofen	10-20 mg t.i.d.	GABAB receptor agonist	Minimal	Renal	Yes
Gabapentin	900-1800 mg t.i.d.	GABA transmission modulator	Minimal	Renal	No data, probably yes
Varenicline	2 mg q.d.	Nicotinic acetylcholine receptor partial agonist	Minimal	Renal	No data, probably yes
Metadoxine	500 mg t.i.d.	Acetaldehyde dehydrogenase activity enhancer	Oxidative	Metabolic	Yes

sumption. Since heavy drinking negatively affects survival of these patients [15], total alcohol abstinence should be promoted both before and after LT [5].

Conclusions

AUDs represent the most common cause of ALD in the Western world [1–3,31]. The achievement and maintenance of total alcohol abstinence remains the cornerstone of treatment. The combination of psychosocial interventions, pharmacological therapy and medical management seems to be the most effective management strategy for AUD patients with ALD (Fig. 1). This observation has important implications, both at the patient and policy levels. In fact, important efforts have been made to promote the integration of addiction treatments in medical settings [138]. However, the trend toward this integration is still facing some challenges, such as rigid regulatory policies, the paucity of addiction education among physicians, the lack of parity in insurance coverage for addictions [139] and a high degree of stigma [140].

The concepts of integration should be seen under the general concept that there should not be a distinction between AUDs and other medical diseases. Therefore, the goal is to offer to these patients the same treatment strategies that patients with other medical problems usually receive.

Finally, most AUD patients affected by advanced ALD are currently excluded from clinical trials investigating alcohol medications, given the concern that these medications might worsen liver disease. At present only baclofen has been tested in these patients in a formal RCT. However, for some of these drugs (i.e., naltrexone), the possible side effects on the liver are only hypothesized and no RCTs have been performed in this subset of patients. Because of the paucity of alcohol medications available for these patients, new and safe pharmacological options are needed. Further rigorous prospective researches are expected and warranted.

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