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Management of Alcohol Dependence in Patients with Liver Disease

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Abstract

Alcohol dependence represents a chronic and relapsing disease affecting nearly 10% of the general population both in the United States and in Europe, with a widespread burden of morbidity and mortality. Alcohol dependence represents the most common cause of liver damage in the Western Countries. Although alcoholic liver disease is associated primarily with heavy drinking, continued alcohol consumption, even in low doses after the onset of liver disease, increases the risk of severe consequences, including mortality. Consequently the ideal treatment of patients affected by alcohol dependence and alcoholic liver disease should aim at achieving long-term total alcohol abstinence and preventing relapse.

The aim of the present review is to provide an update on the management of alcohol dependence in patients with alcoholic liver disease. Increasing evidences suggests the usefulness of psychosocial interventions and medications combined in order to reduce alcohol intake, promote abstinence and prevent relapse in alcohol dependent patients. Disulfiram, naltrexone and acamprosate have been approved for this indication; gamma-hydroxybutyric acid (GHB) is approved in Italy and Austria. However, these drugs have not been tested in patients with advanced liver disease. Amongst other emerging pharmacotherapies for alcoholism, topiramate, ondansetron, and baclofen seem the most promising ones. Both topiramate and ondansetron hold a safe profile in alcoholic patients; however, none of them has been tested in alcoholic patients with advanced liver disease. To date, baclofen represents the only anti-craving medication formally tested in a randomized clinical trial in alcoholic patients affected by liver cirrhosis, although additional confirmatory studies are warranted.

1. Introduction

Alcohol consumption, particularly heavy drinking, is an important risk factor for many health problems and represents a considerable contributor to the global burden of disease.[1]

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As highlighted by the World Health Organization (WHO), public health problems caused by harmful use of alcohol represent a substantial health, social and economic burden worldwide.[2] Harmful alcohol use seems a risk factor in more than 60 diseases and injuries resulting in approximately 2.5 million deaths per year worldwide.[3] Most of these diseases are related to alcohol use disorders (AUDs), which include alcohol abuse and dependence.

AUDs represent the most common cause of liver damage in the Western Countries,[4, 5] with a wide spectrum of diseases (e.g.: steatosis, steatohepatitis, fibrosis, cirrhosis), all of which may coexist in the same patient.[6] Although the incidence of alcoholic liver disease (ALD) is associated primarily with heavy drinking, continued alcohol consumption, even in low doses, after the onset of liver disease, increases the risk of severe consequences,[1] including mortality.[7] Therefore, there is a crucial need to develop effective treatments for alcohol dependence (AD) in patients with liver diseases, as discussed in the present review.

1.1 Data sources

A literature review using the PubMed database with the search terms “alcohol dependence”, “alcohol use disorder”, “alcoholism”, “liver disease”, “cirrhosis”, “alcoholic liver disease”, “treatment”, and “liver transplantation” was conducted up to September 2012. The literature search was limited to publications written in English language.

2. Alcohol dependence

AD represents a chronic and relapsing disease affecting nearly 10% of the general population both in the United States[8] and in Europe,[9] with a widespread burden of morbidity and mortality.[10,11] It is characterized by several clinical features related to alcohol, such as craving, loss of control, tolerance, and physical dependence.[12]

Alcohol craving plays a crucial role in AD [13] and is among the main determinants of alcohol relapse in alcoholic patients. The neurobiology of craving is complex, since several pathways are involved and the exact mechanisms are still not completely understood. These pathways include several neurotransmitters, such as gamma-aminobutyric acid (GABA), glutamate, opioids, dopamine (DA), serotonin, adenosine, neuropeptide Y, norepinephrine, acetylcholine and cannabinoids.[14] Furthermore, different subtypes of patients could have different and/or several mechanisms craving is based upon.[15,16] In particular, “*reward craving”* is characterized by a dopaminergic/opioidergic dysregulation (deficit of opioids/endorphins, hypersensitivity to the reinforcing effects of alcohol) or a characteristic personality trait defined by the search for “reward” (i.e. hedonism, etc.) and/or the ‘need for reward’. The associated symptoms include a spontaneous search for alcohol and the inability to abstain from binge drinking. The subject shows an early development of alcoholism (‘early onset’) and a positive family history of alcoholism.[16] *“Relief craving”* (desire to decrease tension) is characterized by a GABAergic/glutamatergic dysregulation (dysregulation of glutamate with neuronal overexcitability, hypersensitivity to the sedative effects of alcohol or a personality trait manifesting itself through reactivity to stress or a combination of both factors). The main characteristic of relief craving in these subjects, who are generally of the ‘late onset’ type of alcoholism, is mainly the ‘need for relief’; the related aspects are the presence of withdrawal symptoms and reactive drinking.[16] “O*bsessive*

craving" (a loss of control over intrusive thoughts about the intake of alcohol) is characterized by a serotoninergic dysregulation (deficit of serotonin) or a personality trait consisting of disinhibition or a combination of both factors. The main characteristic of obsessive craving is a loss of control, and associated symptoms consist of compulsive drinking and alcohol-related damage.[16] The growing knowledge of the neurobiological pathways involved in alcohol-seeking behaviours, lead to the identification of specific medications able to affect alcohol consumption (see next paragraphs).

2.1 Screening tools to detect alcohol abuse and dependence

Quantity-frequency questionnaires and retrospective diaries (time-line follow back [TLFB])[17] can be used to estimate individuals' drinking habits. A good alternative to quantity frequency questionnaires is the use of screening instruments to screen risky drinking, such as the Alcohol Use Disorders Inventory Test (AUDIT). Developed by the WHO in 1982, the AUDIT has proven to have good sensitivity and specificity in clinical settings across different countries. A total score of more than 8 indicates harmful drinking behavior, while a total score of more than 13 in women and 15 in men indicates likely AD.[18] In the United States, the National Institute of Alcohol Abuse and Alcoholism (NIAAA) recommends using the third question of the AUDIT ('*How often do you have six or more drinks in one occasion?*') as a single screening question, which should be followed by the whole AUDIT in case the answer is rated positive.[19]

Patients identified as having an AUD should be offered at minimum a motivational advice in the form of a brief intervention; a more prolonged, extended brief intervention may be necessary for some individuals. For many patients, these brief interventions are sufficient to induce lifestyle changes, but they should be reviewed regularly. Additional treatments are required for those patients with AD and those who do not respond to brief intervention (*see next paragraphs*).[20]

1.2 Biological markers of alcohol abuse

Biological markers can be used in clinical practice in the screening and monitoring of alcohol abuse. The most routinely used ones are gamma-glutamyltransferase (GGT), mean cellular volume (MCV), aspartate aminotransferase (AST), alanine aminotransferase (ALT), AST/ALT ratio (DeRitis ratio), and carbohydrate-deficient transferrin (CDT).

In a recent study, the sensitivity and specificity of these methods for excessive alcohol intake (>60 g ethanol/day) were, respectively, 37% and 92% for CDT, 53% and 76% for GGT, and 33% and 94% for MCV.[21] ALT and AST are less sensitive than GGT in detection of excessive alcohol consumption. When aminotransferases are elevated, if the AST/ALT ratio is greater than 2.0, 90% of cases are due to alcohol.[22] An increase of 40% or more in AST level and 20% or more in ALT value has been reported to be suggestive of relapse to drinking in alcohol-dependent men (sensitivity and specificity >90% for AST 80% for ALT). This was true even if the marker remained within the reference range.[21]

These biological markers are likely to lose their utility in patients affected by advanced liver disease. Newer CDT assays offer advantages, even though sensitivity and specificity rates remain poor.[23]

3. Alcoholic Liver Disease

In healthy individuals, a “non-harmful” daily intake of alcohol should be no more than two “drinks” for males and one “drink” for females. Data from the “Dionysos” study showed that consumption of more than about two drinks per day increases the risk of liver disease regardless of the gender.[24] ALD, one of the major medical complications of AUDs,[25] represents a wide spectrum of diseases including simple steatosis, alcoholic steatohepatitis (ASH), progressive fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). In particular, 80% of heavy drinkers develop steatosis, 10–35% alcoholic hepatitis, and approximately 10% cirrhosis.[6,25]

Steatosis is characterized by the presence of a single large triglyceride occlusion in the cytoplasm of the hepatocytes. Although liver function is usually normal, if alcohol abuse continues steatosis may progress eventually to cirrhosis.[25] It has been suggested that 15–20 years of alcohol abuse are necessary to develop alcoholic hepatitis, which usually results in cholestasis.[25]

The relationship between AUDs and liver impairment is known since the 1950s,[26] although the pathophysiology of ALD has been clarified, at least partially, only in the recent years. In fact, ALD is more complex than a simple ethanol-induced damage, being a multifactorial disease in which not only the amount of alcohol consumption, but also gender, genetic and nutritional factors have a role in the progression of the disease.[27]

First, liver damage is related to the toxicity of alcohol due to its metabolism via alcohol dehydrogenase. Alcohol dehydrogenase converts nicotinamide adenine dinucleotide to nicotinamide adenine dinucleotide-reduced form, which contributes to hyperuricemia, hypoglycemia, and hepatic steatosis by inhibiting lipid oxidation and promoting lipogenesis.[28] Another pathway of ethanol metabolism is the microsomal ethanol oxidizing system (MEOS). The activity of its main enzyme, cytochrome P4502E1 (CYP2E1), and its gene are increased by chronic consumption, resulting in metabolic tolerance to ethanol.[28] Twin studies suggest a genetic component to disease susceptibility,[29] and recent genome-wide association studies (GWAS) are identifying novel risk genes for ALD (e.g. polymorphisms of the CD14 genes and housekeeping gene variability) and the number of gene polymorphisms associated with ALD susceptibility is continuously growing.[30,31] In white people, associations between ALD risk and polymorphisms of the genes encoding the CYP have been shown.[25] The activity of the CYP2E1 is also associated with the generation of free radicals, with resulting lipid peroxidation and membrane damage as well as depletion of mitochondrial reduced glutathione and its ultimate precursor—methionine activated to S-adenosyl-L-methionine.[28] The involvement of free radical mechanisms in the pathogenesis of ALD is demonstrated by the detection of lipid peroxidation markers in the liver and the serum of alcoholic individuals, as well as by experiments in alcohol-fed rodents that show a relationship between alcohol-induced oxidative stress and the development of liver pathology.[32–34] In particular, oxidative stress promotes hepatocyte necrosis as well as a pro-apoptotic action via tumor necrosis factor-alpha. Furthermore, oxidative mechanisms can contribute to liver fibrosis by triggering the release of profibrotic cytokines and collagen gene expression in hepatic stellate cells.[34] From a clinical point of view, alcohol-related

damage can be present without any apparent symptoms or signs of liver disease. Otherwise, non-specific clinical features can include nausea, vomiting, or fatigue. When liver cirrhosis is present, typical signs and symptoms related to the cirrhotic status can include jaundice, ascites, encephalopathy, or upper gastrointestinal bleeding. The clinical course of alcoholic cirrhosis is influenced by the pattern of alcohol intake. Thus, periods of excessive alcohol intake can lead to superimposed ASH and the subsequent clinical exacerbations, while prolonged abstinence can compensate previously complicated cirrhosis. Given that alcohol intake is the trigger for both the induction of ALD and its progression to end-stage liver disease, the cornerstone of the treatment is to stop alcohol intake, regardless of the stage of the disease.

4. Treatment of alcohol dependence

The most common treatments for AD are psychosocial interventions (cognitive behavioural therapies, counselling, solution focused relapse prevention, and family/couples therapy), although evidence is robustly increasing on the use of medications, associated to behavioural interventions, to reduce alcohol intake, promote abstinence and prevent relapse.[35]

4.1 Psychosocial interventions

The “Matching alcoholism treatments to client heterogeneity” (MATCH) project [36] randomized more than 1700 subjects to receive a psychological treatment for AD for a period of 12 weeks; patients were then followed up for 1 year. The study compared the Twelve-step Facilitation (TSF) therapy,[37] the Motivational Enhancement Therapy (MET),[38] and the Cognitive-Behavioral Coping Skills Therapy (CBT).[39] All 3 interventions produced equally significant and sustained improvements in drinking outcomes, and there was little evidence that matching specific types of patients to a particular treatment improved the outcome.[40] The TSF therapy[37] is directed to achieve and maintain alcohol abstinence encouraging motivation to stop drinking. Treatment modalities are flexible and individualized on patient’s needs. The MET[38] is usually a brief treatment focused to increase patient’s motivation enhancing his energies to change. The goal is to analyze differences between the current and the desired psychological status. Highlighting these discrepancies should promote change, reinforcing patients’ self-efficacy. This technique attempts to increase patient’s awareness of the potential problems caused, consequences experienced, and risks faced as a result of patterns of alcohol consumption. The CBT[39,41] is a psychotherapeutic approach that highlights how to recognize situations at risk of relapse, and develop strategies to minimize this risk. Patients are encouraged to compile a diary of risky events that occur in daily life. Reactions to these episodes are analyzed during the sessions, in order to develop new and more efficient coping strategies. The CBT is more highly structured compared with MET, although an empathic approach is encouraged in both forms of treatment.

Brief Behavioral Compliance Enhancement Treatment (BBCET) is a manual-driven, low-intensity supportive program that has been shown to benefit the treatment of AD with a comparable efficacy to more complex cognitive-intensive behavioral therapies.[42] Moreover, BBCET represents an effective instrument to enhance patient’s compliance to medications.

Concerning psychotherapy, despite several hypotheses and attempts to treat AD patients, none of these approaches succeeded in finding subtypes of patients who would benefit more in a differential treatment approach. On such a basis, further studies for an individualized approach in the treatment of alcoholism (‘‘personalised medicine’’) seems to hold promise.[43]

Alcoholics Anonymous (A.A.) is the most widespread association of patients engaged in alcohol problems, and was initiated in USA in the 1930s. It is the best-known and the most frequently recommended intervention for alcohol-dependent patients, even though it only represents a co-adjuvant strategy and is not provided by health-care professionals. The organization is composed of alcohol dependent patients abstinent or with a current use of alcohol and its philosophy is based on self-help intervention. On the same time, since alcohol problems directly involve the patient’s family, other associations of family members have been funded all over the world. The philosophical foundation of the A.A. is the 12-step program, only one of which (Step 1) actually mentions alcohol; the other steps focus more on personal growth.[40] When compared with those who do not go to A.A., the individuals who participate in AA meetings typically have better drinking outcomes[44] and have been shown to have fewer health-related expenditures.[45] However, clinical trials aimed to objectively demonstrate the efficacy of such approach are lacking.

4.2 Pharmacotherapy for the treatment of alcohol dependence

Despite progress in pharmacological treatments of AD, pharmacotherapy is still underutilised in clinical practice.[46] A few drugs are approved for AD, such as disulfiram, naltrexone and acamprosate, although the exact panel of approved drugs may vary across countries. Other drugs have been proposed and tested in this population of patients, based on the growing knowledge of the neurobiology of AD [table 1].

4.2.1 Disulfiram—Disulfiram, an inhibitor of acetaldehyde dehydrogenase, was the first drug available for alcoholism treatment. It produces and increases acetaldehyde concentration after drinking alcohol, resulting in hypotension, flushing, nausea and vomiting. This adversative effect should reinforce the individual’s desire to stop drinking by providing a psychological disincentive.[46] Results from over 50 years of disulfiram prescription in clinical settings as a pharmacotherapy for AD are contrasting. While a large 3-arm study showed no statistical difference in total abstinence between the examined groups (disulfiram 250mg vs. disulfiram 1 mg vs. multivitamin),[47] other studies showed that patients who receive disulfiram report more total days of abstinence from alcohol as well as lower levels of GGT, which is the objective marker of alcohol consumption, when compared to placebo groups.[48,49]

While most reactions to drinking alcohol when taking disulfiram are temporary, at worse, disulfiram can induce hepatotoxicity and liver failure.[50] Additionally, 28% of the reported cases of disulfiram-induced hepatotoxicity resulted in death.[51] This is of special concern considering that AD patients may already be present with a wide spectrum of ALD.

4.2.2 Naltrexone—Naltrexone, an opioid receptor antagonist increases DA release in the mesolimbic system.[52] Naltrexone’s use in alcohol-dependent patients is based on the role

of the opioid system in the compulsive desire for alcohol.[16] After the approval for AD treatment in 1994,[53,54] there have been conflicting results;[54] however, several meta-analytic studies support the efficacy of naltrexone, in particular to reduce heavy drinking, though with small effect sizes.[55–57]

The COMBINE study tested the efficacy of two medications (i.e., naltrexone and acamprosate), behavioral interventions (Medical Management [MM] and Cognitive Behavioral Intervention [CBI]), and their combinations in AD patients in a 16 week multi-site study. While all groups showed a substantial reduction in drinking, participants who received naltrexone with MM, CBI or both, showed a significant improvement in the drinking outcomes, with respect to the other groups (acamprosate and MM alone). However, at one year follow-up the results were similar between all groups, and no longer significant.[58] High levels of craving, a positive family history of alcoholism[41] and the presence of a specific polymorphism (Asn40Asp) in the mu opioid receptor gene,[59,60] have been shown being predictors of a positive response to naltrexone.

The naltrexone long-acting formulation (administered monthly by I.M. injection) seems to improve clinical outcomes, by enhancing patient adherence.[41,61]

Naltrexone carries a risk of hepatotoxicity, especially in patients with significant liver problems.[62] Interestingly, long-acting formulation of naltrexone may produce less hepatotoxicity than oral naltrexone, because the injected drug does not undergo first pass metabolism in the liver. However, FDA approval of both oral and I.M. naltrexone for AD includes a black-box warning about the risk of liver damage.

4.2.3 Acamprosate—Acamprosate has a mechanism of action that is only partially known. A glutamatergic antagonist and GABA agonist, it is thought to normalize the glutamatergic excitation that occurs during alcohol withdrawal.[63] European large clinical trials resulted in strong effect sizes for improving drinking outcomes.[64–66] Successively, meta-analyses confirmed the efficacy of acamprosate in improving rates of abstinence and increasing time to first drink.[67] However, other trials in the US and Europe have failed to find similar effects calling for further studies that take into account patients' typologies and severity of alcoholism.[68–70] In particular, differences in the US and European trials could be attributed to differences in study design and population. A recent Cochrane review of 24 randomized clinical trials (n = 6915) showed that acamprosate, compared to placebo, significantly reduced the "risk of any drinking" and increased the cumulative abstinence duration (CAD). On the other hand, no significant effect of acamprosate was found in reducing heavy drinking. The Cochrane review concluded that acamprosate is safe and effective in promoting continuous abstinence after detoxification in AD patients.[71]

4.2.4 Gamma-Hydroxybutyric Acid—Gamma-Hydroxybutyric Acid (GHB) is an endogenous compound with neuromodulatory functions. It has an alcohol-mimetic effect on the central nervous system.[72,73] The mechanisms of action of GHB are not completely known: in particular, it is a GABA receptor agonist; however, a selective endogenous GHB receptor has been cloned.[74] This substance interferes with the mesolimbic-cortical system modulating the activity of DA, serotonin, acetylcholine, opioids and GABA.[75,76] GHB

seems to be useful to decreases alcohol craving by reproducing rewarding effects and is effective to reduce alcohol intake, to promote alcohol abstinence and to prevent relapse.[77–81] In the past decades, however, the risk of abuse for GHB has been reported, thus limiting its potential clinical use. As such, while GHB is approved for alcoholism in some European Countries (e.g. Austria and Italy). on the other hand GHB is classified as a controlled substance in many other countries.[77] . Therefore, at present the scarcity of RCTs and the addictive potential of this compound limits its use in clinical practice.[82] Future large multicentric randomized controlled studies are warrant to establish the efficacy and safety of GHB in the treatment of AUD patients.

4.2.5 Topiramate—Topiramate is an anticonvulsant that increases GABAA-facilitated neuronal activity and antagonizes AMPA and kainate glutamate receptors with a consequent reduction of DA release in the nucleus accumbens. Moreover, topiramate modulates ionotropic channels, inhibiting L-type calcium channels, limiting the activity of voltage-dependent sodium channels and facilitating potassium conductance, all of which contribute to ability of topiramate to reduce the hyperactivity and resulting anxiety of withdrawal. Another mechanism of action for topiramate is weak inhibition of the carbonic anhydrase isoenzymes, CA-II and CA-IV, in the brain and in the kidney.[83]

In a 12-week RCT with AD patients (n = 150), topiramate, combined with BBCET significantly decreased the number of drinks consumed per day and increased the number of their abstinent days. Topiramate was also effective in reducing certain components of alcohol craving, i.e. obsessive thoughts about alcohol, automaticity of drinking, and interference due to drinking.[84]

A large multi-site RCT (n=371) administered up to 300mg/day of topiramate compared to placebo for 14 weeks.[85] In addition to topiramate (or matched placebo), all participants received a weekly manual-guided compliance intervention, Brief Behavioral Cognitive Enhancement Therapy (BBCET) provided by healthcare professionals, and used to facilitate medication adherence. This study demonstrated that topiramate was effective, as compared to placebo, in reducing alcohol drinking outcomes (e.g. heavy drinking days) through the course of the study.[86] Additionally, this trial showed a statistically significant effect of topiramate for improved physical health, reduced alcohol craving, and increased psychosocial well-being. Moreover, topiramate was more effectivethan placebo in decreasing all liver function test values, including GGT. This decrease was probably due to the reduction of heavy drinking. [86,87] Though topiramate is not approved for AD, it may represent an effective pharmacotherapy option for AD, even if optimal dose has still to be determined.[46]

4.2.6 Baclofen—Baclofen is a GABAB receptor agonist, currently used to control spasticity.[88] Preclinical studies have shown its efficacy in decreasing alcohol intake, in preventing the acquisition of alcohol drinking behavior, in suppressing the motivation to consume alcohol and in suppressing the alcohol deprivation effect in alcohol-preferring rats.[89–91] In alcohol-dependent patients, both open-label[92] and double-blind[93,94] studies have shown that baclofen (10 mg t.i.d) is effective in reducing alcohol intake, in promoting alcohol abstinence and preventing relapse. Baclofen was effective to increase CAD and to

reduce alcohol craving in the main obsessive and compulsive components. Furthermore, the drug was able to significantly reduce state anxiety.[92–94] A recent US trial, on the other hand, failed to demonstrate an effect of baclofen in treating alcohol-dependent patients.[95] However the investigators noted a high placebo response which could have impacted the sensitivity of the trial to detect a baclofen effect. Furthermore, the relative low severity of AD in the enrolled sample has been suggested as another possible feature that may have contributed to the these findings.[96] Finally, it has been noted that testing baclofen at a dose of 20 mg t.i.d. might be useful[97] and a recent study suggesteda dose–response effect for baclofen in the treatment of AD.[98] Baclofen has proved to be easily manageable, having a good tolerability and low side effects, without any risk of abuse.[92–95] Clinical experience with baclofen dates back about 4 decades, as a safe drug to control spasticity. In the alcohol studies, administration of baclofen in AD patients did not produce any serious or severe side effect, thus the medication was clinically manageable.[97] In addition, although baclofen may have significant sedative effects, alcoholics have an increased tolerance to these effects.[97]

4.2.7 Ondansetron—The Serotonin (5-HT) system plays a key role in regulating the severity of alcohol drinking.[99] Ondansetron, a 5-HT3 receptor antagonist, is thought to work by affecting the function of the 5-HT transporter (5-HTT) resulting in down-regulation of the dopaminergic neurons decreasing the reward from alcohol.[100]

A randomized, placebo-controlled study provided preliminary evidence on the role of ondansetron in reducing alcohol drinking.[101] Subsequently, in another clinical trial, ondansetron was more effective than placebo in increasing total days abstinent and percentage of days abstinent.[102] Furthermore, when compared to placebo, ondansetron (4 mcg/kg b.i.d.) resulted in a significant reduction in alcohol craving, in early-onset alcoholism (EOA) but not in late-onset alcoholism (LOA) [EOA is defined as the initial onset of alcoholism at the age of 25 years or younger compared to LOA in which initial alcoholism after the age of 25].[103] More recently, in a large study ondansetron was administered to AD patients after dividing them by genotype in the 5’ regulatory region of the 5-HTT gene: LL, LS, or SS. In addition to standardized cognitive behavioral therapy, participants were randomized to receive either 4 mcg/kg b.i.d. or placebo. Individuals with the LL genotype who were receiving ondansetron significantly reduced their drinks per day and increased their days of abstinence compared to LL individuals on placebo. Also, among participants receiving ondansetron, those with the LL significantly reduced their drinking compared to the LS and SS individuals.[104] These findings are consistent with a pilot human laboratory study,[104] where drinking was evaluated under well-controlled conditions (i.e. alcohol self-administration in a human laboratory setting). Specifically Kenna and colleagues[105] reported that AD individuals taking 0.25mg twice a day of ondansetron with the LL genotype reported a significant reduction in drinking. By contrast, the researchers found no reduction in drinking with ondansetron in individuals with the LS or SS genotype.[105] In summary, ondansetron seems effective only in specific subtypes of patients (EOA, LL genotype) at a very low dose (4 mcg/kg). At this dose, ondansetron’s side-effect profile was not dissimilar from placebo, even when considering the incidence of QT

prolongation (more frequent at higher doses). As such, this drug represents an interesting approach for the personalized treatment of AD.

5. Treatment of Alcohol Dependence in Patients with ALD

Medical and surgical treatments for ALD have limited success if drinking continues and the persistence of alcohol intake is a risk factor for decompensated cirrhosis and its complications.[4] Therefore, the most effective treatment for AD patients affected by ALD is to achieve total alcohol abstinence and prevent relapse. Medical recommendations, brief motivational interventions and/or psychosocial approach, although essential treatment components, may not be sufficient to achieve and maintain alcohol abstinence in all AD individuals and the addition of effective anticraving medications could be very useful in these patients. However, notwithstanding that relapse prevention represents the main objectives in treatment of AD patients with ALD, such individuals are usually excluded from pharmacological treatments because of concerns that these medications might worsen liver disease.

Patients affected by early-stage ALD (hepatic steatosis, mild alcoholic hepatitis and fibrosis) can be treated with anticraving medications, although caution is recommended, in particular by monitoring liver function tests.[106] On the contrary, in patients affected by advanced ALD with a severe impairment in liver function, pharmacological options are limited. Among approved drugs, disulfiram should be avoided in this population because of possible hepatotoxicity.[107] Naltrexone has not been extensively tested in patients with ALD, given the reports of drug related hepatic injury,[108] and its use in this population is not recommended. However, in a recent observational study conducted in a sample of 114 HIV-infected patients (89% with a coexisting diagnosis of AD, 57% with coexisting Hepatitis C Virus (HCV) infection and 32% with coexisting diagnosis of opioid dependence), the administration of naltrexone for the treatment of alcohol and/or opioid dependence was only rarely (2/114) associated with a coincident liver enzymes elevation, that reversed after naltrexone discontinuation.[109]

Acamprosate has a good safety profile[110] and the absence of liver metabolism and of pharmacokinetic interactions with alcohol could represent an advantage in the treatment of AD patients affected by liver disease. Findings of a preliminary study suggested that acamprosate administered for 1 day was well tolerated in patients with Child-Pugh class A and B cirrhosis.[111] However, no trials with repeated administrations of acamprosate in AD patients with cirrhosis have been conducted.

In summary, as reported by the recent European Association for the Study of the Liver (EASL) Clinical Practice Guideline, disulfiram, naltrexone and acamprosate cannot be recommended at present in these patients because of the potential side-effects (Recommendation B1).[6]

Topiramate is not extensively metabolized (78% excreted unmodified) and it has a renal excretion.[112] Only 22% of the drug goes through hepatic hydroxylation, hydrolysis, and glucuronidation.[113] To the best of our knowledge, there are no reports of topiramate-

induced liver toxicity, at least in alcoholic patients. Given topiramate's effect in reducing alcohol intake, this medication could represent a useful drug for the treatment of AD in patients with ALD; however no studies have evaluated its safety profile in this specific cluster of patients.

Given the primary renal metabolism and the very low liver metabolism (about 15%)[114] to date, baclofen represents the only anticraving medication formally tested in a RCT in alcoholic patients affected by advanced liver disease.[115] All patients enrolled in the study had a diagnosis of both AD and cirrhosis. Eighty-four patients were randomized to receive baclofen (10 mg t.i.d.) or placebo for 12 consecutive weeks. At each visit, routine psychological support counselling was provided. Attendance at support groups (e.g., AA) was encouraged. Results of this trial showed a significantly higher number of patients who achieved and maintained abstinence throughout the experimental period in the baclofen group compared to the placebo group. CAD was approximately 2-fold higher in baclofen- than placebo-treated patients. Moreover, a significant effect of baclofen compared to placebo was found in reducing craving measured by the Obsessive Compulsive Drinking Scale (OCDS). Finally, treatment with baclofen significantly reduced several liver parameters (ALT, GGT, bilirubin, and international normalized ratio) and significantly increased albumin values. No serious systemic or single organ event leading to drug cessation was reported, and no patient discontinued the drug. In summary, the results of this study showed that the oral administration of baclofen was significantly more effective than placebo in inducing and maintaining alcohol abstinence and in increasing CAD in alcohol-dependent patients with liver cirrhosis who were seeking treatment. This study confirmed the efficacy of baclofen in reducing alcohol intake and craving, promoting alcohol abstinence; furthermore, this study highlighted the safety of this medication.[115]

It is important, however, to keep in mind that data on the role of baclofen to treat AD in cirrhotic patients come from only one RCT. Although further studies are needed to confirm these findings, the research done so far suggests that baclofen can be useful in patients with advanced ALD, as reported by the recent EASL Clinical Practice Guideline (Recommendation B2).[6] Questions on optimal dosing and duration of the treatment still remain open.[116]

At present there is no medication able to improve alcohol-related liver damage independently from a reduction in drinking. Therefore, finding an effective medication for AD that is not only safe for the liver, but also effective to treat ALD, represents an exciting breakthrough.[117] Metadoxine is a drug approved in several European countries for acute alcohol intoxication (AAI), based on its ability to facilitate the elimination of alcohol from blood and tissues.[118,119] Metadoxine increases the activity of acetaldehyde dehydrogenase and prevents the decrease in alcohol dehydrogenase activity shown in chronic ethanol fed rats.[120,121] In Europe, metadoxine is also indicated as a supportive treatment for patients with ALD. In humans, studies comparing metadoxine to either vitamins[122,123] or placebo[124–127] showed the ability of this drug to reduce indices of liver cell necrosis and cholestasis. In addition to the utility of metadoxine for AAI and ALD, preliminary evidence suggests that metadoxine may reduce alcohol drinking and promote alcohol abstinence, thus representing a potential novel pharmacotherapy for AD. A 30-day double-blind placebo-

controlled study enrolling a group of 60 AD patients, showed an effect of metadoxine, as compared with placebo, in reducing the score of the Munich Alcoholism Test (MALT), psychological symptoms (i.e., anxiety, depression, and insomnia), and the need for treatment with benzodiazepines and/or neuroleptics.[128] Furthermore, in an open-label study by Guerrini and colleagues,[129] 160 AD patients treated with metadoxine plus psychological intervention demonstrated a significant improvement in the rate of complete abstinence, compared with those who only received psychological intervention. Moreover, in a recent retrospective study, Leggio and colleagues evaluated the medical records of 94 AD patients who received metadoxine 500 mg t.i.d (mean dose 1277 mg/day) for a period of 8.9 days (range 2–42 days) for concomitant ALD. The short-term treatment with metadoxine resulted in a reduction in alcohol drinking and promotion of alcohol abstinence, and an improvement in some of the biomarkers suggesting alcohol-related liver damage. These studies provides preliminary evidence that metadoxine might represent a novel pharmacotherapy to treat both AD and ALD, thus suggesting the need for a double blind placebo-controlled randomized clinical trial in order to test this hypothesis (to both reduce alcohol use and improve hepatic function in AD individuals).[117]

6. Management of Alcohol Dependence before and after liver transplantation

When liver function does not improve with alcohol abstinence, patients affected by advanced ALD must be evaluated for orthotopic liver transplantation (OLT),[6] that represents the gold standard treatment for end-stage liver disease. Survival rates after OLT for alcoholic cirrhosis are similar to—or even better than—that for other end-stage liver diseases.[25,130] However, several ethical concerns are still present due to the limited availability of organs and the risk of alcohol recidivism after OLT.[25,130] Alcohol recidivism is defined as any alcohol intake before and/or after OLT, since total alcohol abstinence is required in these patients.[6] At present, in order to reduce the risk of alcohol recidivism after OLT, a period of total alcohol abstinence before OLT is generally required (usually 6 months).[131] Notwithstanding the knowledge of being affected by a life-threatening condition, AD patients even when affected by liver cirrhosis often show clandestine alcohol abuse when awaiting a liver transplant.[132] To prevent this situation, the treatment of AD in order to achieve and maintain alcohol abstinence before and after OLT should be a priority. Different treatment strategies for managing cirrhotic AD patients have been tested, but contrasting data emerged, with a highly variable rate of recidivism after OLT with a percentage ranging from 10 to 95%.[133,134] This is probably due to the different definition and classification of alcohol consumption (e.g. recidivism, lapse and relapse) after OLT among studies.[135]

6.1 Psychological treatment

Researchers have tried to apply alcoholism interventions to liver transplant patients.[132] However, as observed by Wagner and colleagues[136] and by Weinrieb and colleagues,[137] alcoholic patients listed for OLT show lower motivation for alcoholism treatment with respect to nontransplant patients, denying a need for further intervention. Weinrieb and colleagues compared MET with naltrexone and placebo in a three-arm pilot study with 60 alcoholic patients. The study, however, was not completed for several reasons, such as

infirmity, intensive medical management, and denial for alcoholism treatment. In particular, several patients refused to be treated with naltrexone, mainly for its potential hepatotoxicity.[138] In a pilot study, Georgiou and colleagues evaluated three 1-hour outpatient sessions of Social Behavior and Network Therapy (SBNT), which employed techniques of MET in 20 alcoholic liver transplant recipients.[139] Patients reported that the sessions were less judgmental and more constructive than what they had experienced in the community, an observation that leads to the conclusion that psychosocial interventions could be a valid approach to support motivation in these patients. Moreover, Weinrieb and colleagues evaluated the impact of MET vs. standard treatment (counselling or support groups) in 91 alcoholic patients awaiting for OLT. After completing baseline measures, subjects were randomized to receive either seven individual sessions of MET with case management, each lasting 50 minutes, or standard treatment. Even though 25% of both groups continued drinking during the period of observation, a modest effect of the motivational treatment was shown in limiting the quantity and frequency of pretransplant alcohol consumption among liver transplant candidates.[140]

Bjornsson and colleagues[134] evaluated, in a retrospective design, the impact of the management of alcoholic patients by addiction psychiatrists, social workers and tutors in the period before OLT (structured management), and reported a 22% prevalence of alcohol recidivism in the group treated with structured management vs. 48% in the group treated by standard treatment.[140] Erim and colleagues evaluated the impact of psycho-educational therapy in this cluster of patients, showing low rates of alcohol recidivism. However alcohol abstinence was only evaluated using breath alcohol concentration (BAC) determinations.[141]

Recently our group conducted a retrospective analysis of 92 cirrhotic alcoholic patients who underwent OLT between 1995 and 2010. Clinical evaluation and management of alcohol use was provided by consultant psychiatrists external to the Liver Transplantation Center, to those patients transplanted before 2002, and by a clinical staff of an Alcohol Addiction Unit (AAU) within the Liver Transplantation Centre to those transplanted after 2002. The aim was to evaluate differences in recidivism between patients groups. Patients followed-up at the AAU received a multimodal treatment, in particular clinical and medical management, including counselling; some patients received pharmacological treatment with baclofen. Counselling sessions were provided by the same trained professional staff in individual sessions of up to 30 minutes and focused on craving evaluation, and identification of risk factors for possible relapse. Patients followed at AAU within Liver Transplantation Centre showed a significantly lower prevalence of alcohol recidivism and mortality. Furthermore, an analysis of those patients followed at AAU relieved no differences in the rate of alcohol recidivism in patients transplanted with either 6 months or <6 months of alcohol abstinence before OLT. These data suggests that the presence of an AAU within a Liver Transplant Centre could represent a useful strategy to manage alcoholic patients with end-stage ALD listed for OLT to reduce the risk of alcohol recidivism and of mortality after transplantation [Addolorato et al, under review].

7. Conclusions

AD represents the most common cause of ALD. The most effective strategy to revert ethanol-induced liver damage is to achieve and maintain the total alcohol abstinence. The combination of psychosocial intervention and pharmacological therapies represents an effective treatment approach in these patients. However, in those patients affected by advanced liver disease, the risk of hepatotoxicity limits pharmacological options. Nonetheless, some medications hold promise as possible treatments for alcoholism in patients with liver diseases. Acamprosate could be used in patients with mild or moderate hepatic impairment (Child A and B cirrhosis).[142] Topiramate has not been formally tested in patients with liver diseases, but a large trial indicated a safe hepatic profile.[86] Baclofen has shown to be effective and safe in patients with liver cirrhosis,[113] including those with HCV infection comorbidity.[143] Metadoxine could be even used as a unique treatment for both alcoholism and ALD.[117] However, future studies are needed to further investigate the role of these medications in patients with ALD. Finally, OLT remains the gold standard treatment when liver function does not improve with alcohol abstinence.

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Table 1

Drugs approved or under investigation for the treatment of alcohol dependence, mechanisms of action, most common side effects, and possible liver toxicity.

Drug	Mechanism of action	Most common Side effects	Liver toxicity
Disulfiram	ADH inhibition	hypotension, flushing, nausea and vomiting.	hepatotoxicity and liver failure
Naltrexone	opioid receptor antagonist	Nausea	hepatotoxicity, in particular in patients with significant liver problems
Acamprosate	Glutamatergic antagonist and GABA agonist	Diarrhea	Contraindicated in Child C Cirrhosis
Gamma Hydroxybutyric Acid (GHB)	Alcohol mimetic with an endogenous receptor, GABA-B receptor agonist	anterograde amnesia, risk of abuse (GHB is a controlled substance in many countries)	Not reported
Topiramate	GABAA receptor agonist (non-BDZ site) glutamate receptors antagonist	Dizziness, sedation, Anorexia, metabolic acidosis, hyperammoniemia	Not reported
Baclofen	GABAB receptor agonist	sedation weakness	Not reported
Ondansetron	5-HT3 receptor antagonist	QT prolongation	Not reported
Metadoxine	increases the activity of acetaldehyde dehydrogenase	Reversible peripheral neuropathy	Not reported

ADH: acetaldehyde dehydrogenase; BDZ: benzodiazepine, 5-HT3: serotonin

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