Management of alcohol misuse in patients with liver diseases

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ABSTRACT

Excessive alcohol use not only causes alcoholic liver disease (ALD) but also increases the risk of liver-related mortality in patients who already have other chronic liver diseases. Screening for alcohol misuse or alcohol use disorder (AUD) among patients with underlying liver disease is essential. This clinical review covers what is known about ALD, the impact of alcohol in patients with underlying liver diseases, current management of alcohol misuse and AUD, and the management of alcohol misuse and AUD specifically in patients with liver diseases. Several treatment options for alcohol misuse and AUD exist such as psychosocial intervention and behavioral and pharmacological therapies. The strategies used in the treatment of alcohol misuse and AUD are still applicable in those who consume alcohol and have underlying liver disease. However, certain medications still need to be carefully used due to potentially worsening already compromised liver function. Screening of ongoing alcohol use in subjects with liver disease is important, and prompt intervention is needed to prevent the associated morbidity and mortality from the detrimental effects of continued alcohol use on underlying liver disease. Considering alcoholism is a complex disease, probably a multidisciplinary approach combining psychotherapy and comprehensive medical care will be the most effective. Future research could focus on identifying additional treatment options for addressing the psychotherapy component since the self-determination and will to quit drinking alcohol can play such a crucial role in promoting abstinence.

INTRODUCTION

Alcohol is consumed worldwide and has been used for centuries.[1] When consumed in excess, it can lead to several adverse health outcomes with the impact on social and economic problems. A recent study[1] showed that 5.9% of all annual global deaths (~3.3 million in 2012) were attributed to consequences of alcohol consumption. Alcohol-related health disorders are generally determined by the quantity of alcohol consumed and the pattern of drinking.[1] In America, moderate drinking is defined as drinking up to one drink[2] per day for women and up to two drinks per day for men.[2] Drinking within this level does not increase the risk of alcohol-induced organ injury. Drinking becomes excessive when it causes or elevates the risk for alcohol-related problems or complicates the management of other health problems. According to the National Institute of Alcohol Abuse and Alcoholism (NIAAA), excessive drinking is defined as men who drink more than four standard drinks in a day (or >14 per week) and women who drink more than three drinks in a day (or >7 per week).[2] A standard drink contains roughly 14 g of pure alcohol, which is found in 12 ounces of regular beer, 5 ounces of wine, and 1.5 ounces of distilled spirits. The definition of chronic drinkers does not differentiate the pattern they employ. Binge drinking, which is defined as drinking five or more drinks for men (four or more drinks for women) within 2 hours,[3] can lead to health-related consequences.[4–6] Specifically, binge drinking has been shown to promote liver injury. Binge drinking can lead to repetitive liver injury, which leads to chronic liver damage.[7]

ALCOHOL AND LIVER DISEASE

Alcoholic liver disease

Alcoholic liver disease (ALD) represents a spectrum of clinical illness and pathological changes in people with acute and chronic alcohol consumption, ranging from simple fatty liver or steatosis, alcoholic hepatitis (AH), and alcohol-related cirrhosis.[8] Simple fatty liver, which is defined as the accumulation of fat (triglycerides, phospholipids, and cholesterol esters) in hepatocytes, is usually a self-limited condition that can resolve in those who remain abstinent for ~4–6 weeks.[9] However, alcoholic steatosis, which was once considered benign, is now recognized as a condition that may lead to advanced liver disease or cirrhosis.[10] In those who continue to drink, studies have shown that continued alcohol consumption (>40 g/day) can increase the risk of fibrosis or cirrhosis to 37%.[10] Furthermore, AH, which is defined as the infiltration of hepatocytes by inflammatory cytokines and cells causing hepatocellular injury, can develop.[8] Not only is AH a clinical entity with a rapid onset of jaundice and elevation in serum aspartate transaminase (AST) in people with excessive alcohol use, but it is also associated with high morbidity and mortality.[11] Patients with AH generally have been drinking

heavily for >5 years, and excessive alcohol use should have occurred for >6 months, with <60 days of abstinence before the onset of jaundice.[12] Approximately 15–20% of patients who drink alcohol excessively develop cirrhosis in their lifetime.[13]

The pathogenesis of ALD is complex and involves the dysfunction of metabolic regulators, endoplasmic reticulum stress response, transcription factors, and activation of inflammatory cytokines.[8] The main mechanism behind alcoholic fatty liver is inhibition of fatty liver β-oxidation by blocking transcription factors and enzymes involved in fat metabolism.[14] Alcohol consumption mainly inactivates peroxisome proliferator-activated receptor-α, which regulates transcription of genes for free fatty acid transportation and oxidation, and AMPK, which decreases the metabolism of fat in hepatocytes by promoting fatty acid oxidation.[11 15] There are several mechanisms behind AH and cirrhosis. Ethanol metabolism creates reactive species like acetaldehyde that can then cause hepatocellular injury. Acetaldehyde is hepatotoxic because it forms adducts with protein and DNA that then create glutathione, lipid peroxidation, and mitochondrial damage. The ultimate result of acetaldehyde is to essentially sensitize hepatocytes to oxidative damage.[16] Additionally, alcohol consumption can activate the innate and adaptive immune systems since alcohol increases gut permeability and, thus, translocation of bacteria-derived lipopolysaccharide from the gut to liver.[16 17]

Hepatitis C virus infection

In subjects with high alcohol intake, the coexistence of hepatitis C virus (HCV) contributes to an accelerated progression of hepatic inflammation to fibrosis, cirrhosis, and hepatocellular carcinoma.[18–20] A meta-analysis found that the pooled relative risk of cirrhosis in patients with HCV associated with heavy alcohol intake was 2.33 (95% CI 1.67 to 3.26).[18] There are several mechanisms underlying the synergistic liver injury. Excessive alcohol drinking consumption can lead to increased apoptosis in HCV-infected hepatocytes.[21] Alcohol can modulate HCV replication by the induction of miRNA-122,[19] and HCV and alcohol also cause a synergistic effect on the production of several cytokines such as TGF-β and TNF-α.[22] The exact relationship between alcohol and HCV in the liver remains to be completely elucidated. However, alcohol and HCV synergistically act to increase oxidative stress and increase viral replication. Alcohol and HCV can both increase the expression of cyclooxygenase 2, which is involved in free oxygen radical production. Additionally, both can also cause damage to hepatocellular mitochondria. Thus, the ultimate effects include not only causing damage within the liver through reactive oxygen species but also blocking cellular regeneration with mitochondrial damage.[23 24] The use of new antivirals for HCV treatment is promising with very high sustained virological response rate; however, data regarding treatment in patients with excessive alcohol use are limited.[25]

Hepatitis B virus infection

A few studies showed that hepatitis B virus (HBV) infection impairs survival of hospitalized patients with ALD and accelerates the development of hepatocellular carcinoma.[26 27] Alcohol has been shown to increase hepatitis B viral replication in transgenic mice.[28] A study from Nomura *et al* examined 1113 Japanese patients with chronic HBV who also consumed >60 g of alcohol per day. Results showed that levels of hepatitis B antigen tended to be higher and decreased slower as HBV patients aged, suggesting that alcohol may delay clearance of hepatitis B leading to increased risk for liver pathology.[29] So far, there is no evidence suggesting an effect of alcohol consumption on the efficacy of antiviral medications for HBV.[25] However, alcohol consumption may lead to an unnecessarily prolonged treatment, especially when the aminotransferase activity is used as one of the end points since elevation in its activity may not be due to HBV, but rather from excessive alcohol consumption.[25]

Hereditary hemochromatosis

Hereditary hemochromatosis (HH) is of relevance in the discussion of alcohol use disorder (AUD) since alcohol consumption in those with HH has been shown to increase iron overload and increase the risk of cirrhosis.[30] Excess hepatic iron seen in patients with HH generates reactive oxygen species that overcome the normal antioxidant defenses and cause peroxidation of lipid membranes resulting in cell damage and liver injury.[31] Because iron overload and alcohol can cause oxidative stress within cells, both create additive effects on hepatocellular damage and increase the risk of cirrhosis. A study from Fletcher *et al* evaluated subjects with hemochromatosis in order to evaluate the effects of excess alcohol use in cirrhosis development. Results showed that subjects who consumed >60 g of alcohol per day had a ninefold increased relative risk for developing cirrhosis.[32]

NONALCOHOLIC FATTY LIVER DISEASE

The incidence of nonalcoholic fatty liver disease is increasing due to the epidemic of obesity and metabolic syndrome.[33] The Dionysos study showed that obese individuals who drank heavily (>100 kg of alcohol over a lifetime and >60 g of alcohol daily) had a significantly greater prevalence of hepatic steatosis.[34] An epidemiological study using a large population-based data set demonstrated a higher prevalence of abnormal alanine aminotransferase activity in overweight and obese individuals who consumed alcohol compared with overweight and obese individuals who did not.[35]

SCREENING FOR ALCOHOL MISUSE AND AUDS

There are several definitions describing the spectrum of excessive alcohol use and its consequences. Alcohol misuse means drinking more than the recommended limits of alcohol consumption. Those who misuse alcohol continue to complete daily tasks without consequences like the inability to work and socialize or destructive behaviors like drunk driving.[36] Alcohol abuse and dependence generally involve craving, compulsion, and continued use despite negative social and financial consequences.[37] However, alcohol dependence also includes physiological tolerance or withdrawal symptoms. In the Diagnostic and Statistical Manual of Mental Disorders (DSM-5),[38] alcohol abuse is combined with alcohol dependence into a single illness called AUD. Anyone meeting any 2 of the 11 criteria during the same 12-month (box 1) period would receive a diagnosis of AUD.

Box 1 Criteria for the diagnosis of alcohol use disorder[38]

In the past year, have you

- Had times when you ended up drinking more, or longer, than you intended?
- More than once wanted to cut down or stop drinking, or tried to, but couldn't?
- Spent a lot of time drinking? Or being sick or getting over other aftereffects?
- Wanted a drink so badly you couldn't think of anything else?
- Found that drinking—or being sick from drinking—often interfered with taking care of your home or family? Or caused job troubles? Or school problems?
- Continued to drink even though it was causing trouble with your family or friends?
- Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to drink?
- More than once gotten into situations while or after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?
- Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?
- Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?
- Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, restlessness, nausea, sweating, a racing heart, or a seizure? Or sensed things that were not there?

The severity of the AUD is defined as mild (presence of two to three symptoms), moderate (presence of four to five symptoms), or severe (presence of six or more symptoms). The 11 diagnostic criteria essentially cover the extent alcohol use have affected an individual's ability to complete daily tasks and obligations to school, work, and home in addition to the measures an individual takes to obtain alcohol despite the negative consequences.[39]

Screening questionnaires for patients with an AUD

Screening for the presence of an AUD requires obtaining a thorough history, often supplemented by the use of screening questionnaires. One of the common screening tools, the CAGE questionnaire, presents four questions (Have you ever felt you should **C**ut down on your drinking?, Have people **A**nnoyed you by criticizing your drinking?, Have you ever felt bad or **G**uilty about your drinking?, and Have you ever taken a drink first thing in the morning (**E**ye-opener) to steady your nerves or get rid of a hangover?). With two or more positive responses, CAGE has a reported sensitivity of 60–90% and specificity of 40–95% in the diagnosis of AUD.[37 40] Another commonly used screening tool is the Alcohol Use Disorder Identification Test (AUDIT), developed by the WHO. Each of 10-items is scored from 0 to 4 points (thus, the maximum score is 40). Six out of the 10 questions address the frequency of certain alcohol-related behaviors, like how often or how many drinks are consumed, if a patient is still able to complete daily life tasks despite drinking, if a patient is able to stop drinking once he or she starts, and if a drink in the morning after a night of heavy alcohol use is ever required. The scoring from 0 to 4 is based on the following responses with 0 points being 'never', 1 point is 'less than monthly', 2 points is 'monthly', 3 points is 'weekly', and 4 points is 'daily, or almost daily.' The remaining questions address issues related to drinking like if guilt is ever felt after heavy drinking, if a patient is able to remember the events of the night before after drinking, if the patient or somebody else has ever been injured, and if those close to the patient have ever expressed concern about drinking. Scoring varies based on patient responses, but still range from 0 to 4 points. A score of 8 or more in men, or 7 in women, indicates a strong likelihood of hazardous or harmful alcohol consumption.[36 41] The AUDIT has a sensitivity of 60–95% and specificity of 85–95% for alcohol abuse or dependence.[37 39 41 42] A shorter version, AUDIT-C (AUDIT-Consumption), comprises of three questions asking how often a patient has a drink containing alcohol in the past year, how many drinks are consumed on a typical day when drinking within the past year, and how often are six or more drinks consumed on one occasion in the past year.[43] The AUDIT-C is similarly scored from 0 to 4 points, with a score of 0 indicating none to minimal alcohol use and a score of 4 indicating frequent alcohol consumption. The totaled points are then assessed on a scale of 0–12 (scores of 0 reflect no alcohol use). A score of 4 or more in men, or 3 or more in women, is considered positive for alcohol misuse.[44] The higher the AUDIT-C score, the more likely it is that the patient's drinking is affecting his or her health and safety.[44 45] The Michigan Alcohol Screening Test (MAST), a 25-question test, is another reliable screening tool. MAST is scored based on 'yes/no' responses to questions that relate to the patient's self-appraisal of social, financial, and family issues related to heavy alcohol consumption. Scores from 0 to 3 indicate no underlying drinking problem, a score of 4 indicates an early or progressing drinking problem, and a score of 5 or more indicates alcoholism. However, one of the shortcomings of the MAST survey is that the questions address issues related to heavy drinking in the past rather than the current issues or problems a patient is currently facing.[42]

Biomarkers to identify AUD

The CAGE, AUDIT, and MAST have limitations, most apparent when individuals deny or minimize the magnitude of drinking behavior. Thus, biological confirmation through physical and laboratory examination is important to confirm the history when possible.[37] The physical examination can give many clues to alcohol abuse, but the findings are often nonspecific.[37] Several laboratory tests have been used to screen for alcohol use in clinical practice. Among them are elevated mean corpuscular volume (MCV), γ-glutaryl transferase (GGT), AST, alanine transaminase (ALT), and carbohydrate-deficient transferrin (CDT).[46] An increase in AST, ALT, and GGT is presumed

to be from alcohol-induced liver injury; however, the mechanisms that induce such escalations are not known. Alcohol is thought to alter lipid membrane, thus leading to an increase in MCV.[47] GGT is a glycoprotein found in hepatocytes and elevated levels are found to be an early indication of liver disease. However, other disease processes, like pancreatitis, can elevate GGT levels. Thus, GGT is not a sensitive biomarker and is found in ~30–50% of alcohol abusers.[48] AST is also found in the heart, muscle, kidney, brain, pancreas, and lung. However, ALT is found predominantly in the liver.[48] Thus, elevated ALT is more specific for hepatic-specific insults. These markers have low sensitivities and specificities to determine levels of alcohol drinking and to screen for excessive alcohol use.[43 49] CDT is a useful marker for excessive alcohol use.[50 51] Transferrin is a serum protein that functions as an iron carrier. It is a polypeptide with two N-linked polysaccharide chains, which are branched with sialic acid residues. Various forms of transferrin exist depending on the levels of sialylation with tetrasialotransferrin being the most common form. The product of alcohol metabolism, acetaldehyde, can inhibit hepatic sialyltransferase,[52] resulting in an increase in the proportion of transferrin with zero, one, or two sialic acid chains, known as *carbohydrate-deficient transferrin*.

Screening at-risk patients for developing an AUD

While assessing those who have AUD is essential, efforts should also be made to identify those who are at risk for developing an AUD. The subset of patients identified as drinking at levels considered 'risky' or 'hazardous', as aforementioned described as men who drink more than four standard drinks in a day (or >14 per week) and women who drink more than three drinks in a day (or >7 per week) may be at risk for developing AUD. The key principle to distinguish these patients from those who have AUD is that these at-risk patients are not dependent on alcohol. Thus, the goal is usually to moderate drinking rather than achieve abstinence (figure 1). For these patients, brief intervention (BI) can be conducted in general healthcare settings by health professionals who do not specialize in addiction treatment. BI consists of four or fewer sessions focusing on methods to reduce drinking by helping patients create a plan for change, giving feedback of personal risk with alcohol, and emphasizing the responsibility of the patient through an empathetic and optimistic counseling style.[53] The clinician's approach with BI varies depending on the severity of the patient's alcohol problem. BI has also been used to motivate patients with AUD to enter specialized treatment with the goal of abstinence (figure 2).[53]

AUD treatment options

Once a patient is ready to engage in treatment, several models are available, comprising various combinations of education, support groups, skill development, and medical intervention.[37] Educational recovery groups may use lecture or interactive media, such as videos, to improve the understanding of addiction, process of recovery, and prevention of relapse. Support groups encourage participation to develop a network, including sponsors and accountability partners, most widely established in Alcoholics Anonymous.[37] Skill development groups may use cognitive

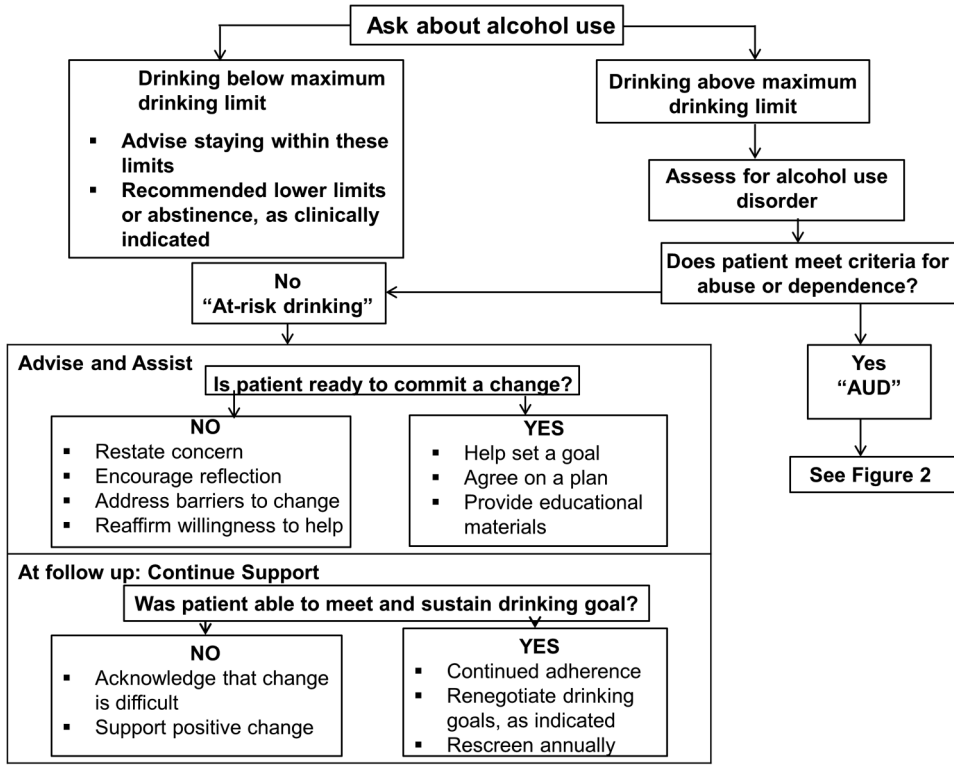

Figure 1 Brief intervention for patient with at risk drinking (modified from US Department of Health and Human Services[2]). AUD, alcohol use disorder.

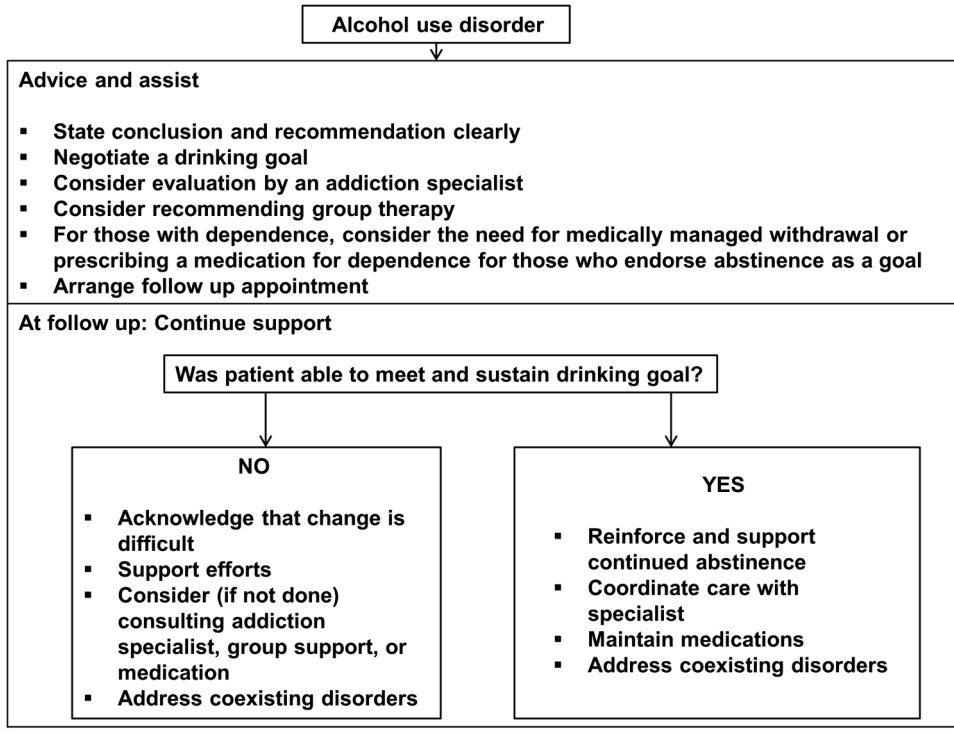

Figure 2 Brief intervention for patient with alcohol use disorder (modified from US Department of Health and Human Services[2]).

behavioral therapy (CBT) or dialectic behavioral therapy to reverse maladaptive thoughts and beliefs that support substance use, and also offer other problem-solving and stress management techniques. Notably, motivational enhancement therapy (MET) has been a counseling approach found to be effective in patients with alcohol and drug abuse. MET consists of an initial assessment session followed by two to four individualized treatment sessions led by a therapist. The core of MET effectiveness lies in utilizing motivational interviews to challenge patients with self-reflection and encourage a genuine motivation to create a plan for change. MET has been found to be successful in helping those with alcohol abuse not only reduce the amount of drinking but also improve participation in treatment.[54]

Several randomized control studies have demonstrated promising results with the efficacy of psychosocial intervention on achieving and maintaining abstinence. In one study, male veterans with alcohol-induced cirrhosis or hepatitis were current drinkers who were randomly assigned to receive integrated outpatient treatment (IOT), which combined motivational enhancement therapy (MET) and CBT[55 56] with primary medical care, or referral to standard alcoholism and medical treatment for 2 years. Results showed that 74% of patients in the IOT group were abstinent, compared with 47% in the controls. Additionally, the mean number of visits over 2 years for the IOT group was 42.2, compared with 17.4 for the control group ($p<0.001$). Interestingly, patients were more likely to accept treatment when integrated into primary medical care. In another study, the efficacy of MET on alcohol use in patients with HCV versus controls was evaluated over 3 months and showed that participants in the MET group had 35% days abstinent at 3 months, which increased to 73% at 6 months, compared to 35% and 59%, respectively, for the control group. An explanation for these results could be that a compassionate and understanding relationship established between patient and physician in addition to involving family and friends as additional support contributed to higher compliance rates. Gentle encouragement and a welcoming environment that promote self-reflection with MET likely led to patients feeling at ease and, thus, more willing to accept treatment.

However, not all psychosocial interventions have shown to yield favorable results. A study from Kuchipudi *et al* randomly assigned 114 active drinkers with pancreatitis, gastric ulcer, or alcoholic liver disease, who were all newly admitted patients, into a control group that provided medical care or a motivational intervention (MI) group that provided therapy that discussed the patient's relationship with alcohol, offered compassionate support, in addition to regular medical care. Despite receiving additional MI, no important difference in reported abstinence at 10–16 weeks after the hospital discharge was observed.[57] The role of psychosocial intervention on maintaining abstinence in patients with alcoholic cirrhosis awaiting orthotopic liver transplantation has been evaluated. Weinrieb *et al*[58] randomized 91 patients to MET delivered by an addiction therapist (n=46) during 6 months versus standard intensive outpatient therapy (controls, n=45). A total of 69 subjects completed 24 weeks of observation (n=35 in the MET group) and 25 (n=13 in the MET group) were assessed at 96 weeks.[58] Twenty-three subjects drank after randomization before transplant, but those in the MET group consumed significantly fewer drinks per drinking day than those in the control group.[58] However, because of the

limited number of study subjects, the authors suggested that further studies to validate the findings or to identify better methods to identify and intervene with patients at risk of pretransplant and post-transplant drinking should be explored.

In a recent systemic review (comprising of five randomized and eight non-randomized/observational studies), the authors found that integrated combination of psychotherapy with CBT, MET, and comprehensive medical care increased alcohol abstinence.[56] So far, no psychosocial intervention was fully successful in maintaining abstinence in subjects with liver diseases, but an integrated therapy with CBT and medical care appears to reduce recidivism.

Pharmacological therapies

Three oral medications (naltrexone (NTX), acamprosate (ACP), and disulfiram) and one injectable medication (extended-release NTX) are currently FDA-approved for treating alcohol dependence.[2 37] All approved drugs have been shown to be effective adjuncts to the treatment of alcohol dependence.[2] Each drug has a different mechanism of action, but all have been shown to help in avoiding relapse to heavy drinking, and in achieving and maintaining abstinence.[2]

Naltrexone

NTX is available in oral (50–100 mg, once daily dosing) and injectable form (380 mg, once monthly intramuscular injection). It is an μ-opioid receptor (OPRM1, opioid receptor, mu 1) antagonist targeting the endogenous opioid peptides, thus blocking the brain's reinforcing reward from alcohol consumption.[2] NTX has also been shown to block decrease craving in those who are alcohol-dependent.[59] Thus, NTX can be useful for reducing alcohol consumption since it can block the pleasure from alcohol in order to reduce the amount of alcohol consumed and also block craving and help in maintaining abstinence. A meta-analysis from Bouza *et al*[60] examining clinical trials of NTX for the treatment of AUD showed that compared to placebos, short-term treatment (≤12 weeks) with NTX reduced relapse rates, but was not associated with a significant modification in the abstinence rate. Because NTX is an opioid antagonist, NTX displaces opioid medications from active binding sites, which can cause withdrawal. Thus, contraindications for the use of this medication include concurrent use of opioids or while a patient is in acute opioid withdrawal, or anticipating a need for opioid analgesics.[2] Caution should be used in patients with severe liver or renal disease, but no dosage adjustment is recommended.[37] Before prescribing NTX, a patient should be opioid-free for a minimum of 7–10 days, and monitoring of hepatic panel is recommended.[2] One of the notable features of NTX for treating AUD is that it has minimal side effects and has no abuse potential.

Acamprosate

ACP acts through γ-aminobutyric acid (GABA) and glutamate neurotransmitter systems[2] reducing symptoms of protracted abstinence and increasing the proportion of dependent drinkers who maintain abstinence for several weeks to months.[2] Evidence supporting the use of ACP for the treatment of AUD has been mixed. The Combining Medications and Behavioral Interventions (COMBINE) study found that ACP was not more effective than placebo for reducing drinking. However, several reviews have found that ACP increases abstinence rates and duration compared to placebo.[60 61] ACP is available in an oral form with the recommended dose at 666 mg three times daily (1998 mg/day). Dose adjustment is required in those with renal impairment (creatinine clearance between 30 and 50 mL/min) to 333 mg three times daily[2] and is contraindicated in subjects with severe renal disease (clearance <30 mL/min).[37] ACP is started 5 days after drinking cessation, but still can safely be used even with alcohol. ACP has several advantages over other medications used to treat AUD. Unlike oral or injectable NTX, ACP can be safely used in patients with liver disease since it is not metabolized in the liver. Additionally, since it does not displace opioids from their binding sites, it can be safely used in patients receiving opioids without precipitating withdrawal.[62] ACP has a good safety profile with mild side effects and no overdose risk. However, there is a pharmacokinetic interaction where ACP can increase levels of NTX in the blood.[63]

Disulfiram

Disulfiram inhibits acetaldehyde dehydrogenase, a key enzyme in alcohol metabolism, resulting in the accumulation of acetaldehyde causing unpleasant reaction such as nausea, flushing, and palpitation.[2] Thus, unlike other medications used to treat AUD, disulfiram has no effects on brain opiate, GABA, or glutamate receptors. The disulfiram–alcohol reaction begins ~10–30 min after alcohol is ingested, and the intensity of the reaction depends on the amounts of disulfiram and alcohol consumed together. Because life-threatening reactions like seizures or death can occur, disulfiram dosages must be titrated carefully. It is available in an oral form (dosing 250 mg once daily, with the range between 125 and 500 mg).[2] Disulfiram is contraindicated in patients with the concomitant use of alcohol or metronidazole, with coronary artery disease, severe myocardial disease, or hypersensitivity to rubber (thiuram) derivatives. It can be used with caution in patients with chronic liver diseases, provided a hepatic panel is obtained at baseline followed by frequent monitoring while on the medicaton.[2] The efficacy of disulfiram is limited when patients take it at their own discretion because compliance is generally poor, but it is more effective when provided in a monitored fashion, such as in a clinic setting.[2] So far, there is no evidence supporting the combination of any of the medications to treat patients with AUD.[2] A large US trial (COMBINE study) found no benefit to combining ACP and NTX.[64]

Disulfiram works best in patients who are committed to maintaining abstinence due to the side effects that can be experienced if a patient decides to relapse.[61] Thus, using incentives, keeping a close physician–patient relationship to ensure adherence, and providing regular reminders are options to help ensure patients remain diligent to treatment. Since the risk for relapse to alcohol dependence is very high in the first 6–12 months after initiating abstinence,[2] a minimum initial period of 3 months of pharmacotherapy is recommended.[2] However, it is not uncommon to continue treatment for a year or longer if the patient responds to medication and the risk assessment for relapse

is high. After discontinuation of treatment, patients may need to be closely followed as relapse may still occur.[2]

Other pharmacological treatments

Several medications, such as topiramate (GABA agonist and glutamate antagonist),[65] baclofen ($GABA_B$ receptor agonist),[66–68] and ondansetron (5-hydroxytryptamine 3 receptor antagonist, 5-HT3)[69] are among medications that have also shown benefits for the treatment of alcohol dependence. Topiraamte decreases the extracellular release of dopamine in the midbrain. Because dopamine mediates the rewarding effects of alcohol, the efficacy of topiramate lies in its ability to block neurotransmitter signaling and thus facilitate alcohol abstinence. Baclofen is a GABA receptor agonist. GABA receptors in the ventral tegmental area have been shown to control the activity of mesolimbic dopamine neurons. Thus, because baclofen can decrease levels of dopamine associated with alcohol use, it is used as a means to treat the pleasure received from alcohol use. In a randomized controlled study, 30 of 42 subjects with cirrhosis (71%) in the baclofen group achieved and maintained abstinence compared with 12 of 42 (29%) assigned to placebo. Cumulative abstinence duration was about twofold higher in patients allocated baclofen than in those assigned to placebo (63±5 vs 31±6 days; p=0·001). No hepatic side effects were recorded. Leggio *et al*[70] demonstrated that in patients with HCV cirrhosis, baclofen not only demonstrated alcohol abstinence but also an improvement in liver function tests, albumin and international normalized ratio (INR).[70] Ondansetron is a serotonin 5-HT3 receptor antagonist commonly used to treat nausea, but also has been shown to have some efficacy in treating AUD. Of note, ondansetron has not been shown to treat all patients with alcohol dependence. Rather, ondansetron has been shown to be most effective in patients with early-onset subtype of alcohol independence.[71] NIAAA is actively engaged in supporting the development and testing of new pharmaceuticals for the treatment of AUD.

The strategies used in the treatment of alcohol misuse and AUD are still applicable in those who consume alcohol and have underlying liver disease, despite additional challenges. For instance, while effective in managing AUD, NTX needs to be judiciously used in those with underlying liver disease.[2 37]

CONCLUSION

Screening of ongoing alcohol use in subjects with liver disease is important, and prompt intervention is needed to prevent the associated morbidity and mortality from the detrimental effects of continued alcohol use on underlying liver disease. Considering alcoholism is a complex disease, probably a multidisciplinary approach combining psychotherapy and comprehensive medical care will be the most effective. Future research could focus on identifying additional treatment options for addressing the psychotherapy component since the self-determination and will to quit drinking alcohol can play such a crucial role in promoting abstinence. Additionally, further investigation could be dedicated to understand how to better incorporate compassionate interventions with medical care for the treatment of AUD. While there is no clear and best solution on how to best treat alcoholism and its effects on liver disease, efforts should still be made to provide preventative education on a very potentially avoidable cause of morbidity and mortality in patients with chronic liver disease.

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