ALCOHOL USE IN THE CLINIC

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OVERVIEW

Unhealthy alcohol use, the range of drinking that includes at-risk drinking and alcohol use disorder (1), is common and associated with a range of adverse health and social consequences. For example, data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC-III) indicate that 14% of adults have a current alcohol use disorder and 29% have had an alcohol use disorder over their lifetime, with rates highest among men and those of younger age (2). As such, unhealthy alcohol use is the third leading cause of preventable death and costs the United States over $220 billion each year (3). While patients with unhealthy alcohol use commonly interface with the medical system, including through primary care, they often do not receive indicated care for this condition. Less than 4% of individuals with a current alcohol use disorder received treatment for this from a health care provider (2). To improve individual and public health by preventing and mitigating the harms of unhealthy alcohol use, clinicians providing care in diverse medical settings (i.e., primary care, inpatient) should be well prepared to screen for unhealthy alcohol use and deliver effective treatments, including counseling and pharmacotherapy.

HEALTH BENEFITS AND HARMs

Which health conditions have definite links to alcohol use?

Unhealthy alcohol use leads to myriad medical, psychiatric and behavior-related complications and risks with increased risks typically occurring with higher levels of use (4, 5). Although methodological challenges and limitations in the literature create difficulty accurately assessing the impact of alcohol use on conditions commonly seen in primary care (6), systematic reviews have noted adverse impact on conditions such as hypertension (7), diabetes mellitus (8), osteoporosis (9), depression (10) and an association with breast cancer (11).
Heavy episodic drinking can lead to acute alcohol poisoning, a medical emergency that results from high blood alcohol levels that suppress the central nervous system and may cause loss of consciousness, low blood pressure and body temperature, coma, respiratory depression, and death.

Hypertension, stroke, cardiomyopathy, cirrhosis, chronic pancreatitis, brain atrophy, hypogonadism with osteoporosis and sexual dysfunction, gastroesophageal reflux, esophagitis, peptic ulcers, pancreatitis, seizures, and arrhythmias are among the diseases associated with excess alcohol use. Alcohol use, even at moderate levels, is carcinogenic and has been associated with increased risk of various types of cancer (including liver, mouth, throat, larynx, esophagus, and breast and colon) (11) and is an important reversible risk factor. Alcohol use is also independently associated with increased incidence of certain chronic diseases, including diabetes mellitus (8) and HIV (12), and further complicates their management given its negative impact on medication adherence (13).

Individuals with unhealthy alcohol use often have poor nutrition and are at risk for deficiencies in vitamin A, vitamin B complex, vitamin C, folic acid, carnitine, magnesium, selenium, zinc, essential fatty acids, and antioxidants.

A pregnant woman who drinks may harm the fetus, with complications including miscarriage, the fetal alcohol syndrome, or more subtle neurocognitive consequences.

In addition to physical complications, unhealthy alcohol use causes mental health and social consequences. Alcohol use disorders are associated with depression (10) and heavy drinking episodes are associated with motor vehicle accidents, falls, drowning, burns, firearm injuries, unsafe sex, intimate partner violence, child maltreatment, homicide, and suicide.

Does alcohol use have positive health effects?

Although unhealthy alcohol use is associated with increased risk of cardiovascular disease, moderate alcohol use is protective. The mechanisms underlying this association are likely multifactorial and may include development of favorable lipid profiles, inhibition of platelet activation, decreased fibrinogen levels and anti-inflammatory effects (14).

Based on a meta-analysis of seven studies, compared to lifetime abstainers, those with moderate alcohol use without heavy episodic drinking had a decreased risk of ischemic heart disease (pooled relative risk [RR] [95% CI]= 0.64 [0.53, 0.71] (14).

While these observational studies support protective effects of low levels of alcohol use on ischemic heart disease risk and similar associations have been seen for ischemic stroke (15), data from randomized controlled trials are lacking (14) and these studies may be impacted by unmeasured confounding (e.g. healthcare utilization). Given the overall effects of alcohol on health, these data should not translate into recommendations for initiation of low level alcohol use for cardioprotective effects as indicated by the American Heart Association (16).
Which groups are at particularly high risk for adverse health outcomes from alcohol use?

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) recognizes several groups as being particularly vulnerable to alcohol and its effects. This includes those who are younger (i.e. youth less than 21 years old and college-aged) and older (17). Individuals who are older than 65 years old, especially those with a chronic medical condition (i.e. diabetes mellitus, congestive heart failure), or taking specific medications that may interact with alcohol (see Box 1) and those with polypharmacy are particularly vulnerable to the harms associated with alcohol use due to impaired metabolism and alcohol-medication interactions.

Notably, based on an analysis of data from the National Health and Nutrition Examination Survey, patients with current alcohol use are commonly prescribed medications that may interact with alcohol (adjusted prevalence [95% CI]= 42% [40, 43%]) and this is especially true among older adults (adjusted prevalence [95% CI]=78% [76, 80]) (18).

Women are more vulnerable to harms associated with alcohol use given their increased sensitivity to alcohol and its harms and that any drinking during pregnancy may cause harm to the fetus. Minorities and underserved populations (e.g. those living in rural settings) often experience more harms associated with alcohol use (e.g. cirrhosis-related deaths).

In addition, regardless of age, patients with certain chronic medical conditions may be more sensitive to alcohol and its potential harms.

Clinical Bottom Line: Health Effects

Unhealthy alcohol use is associated with a range of adverse medical, psychiatric and behavior-related outcomes. Special caution with alcohol use is appropriate among young adults, older adults, women, minorities and underserved populations, as well as those with chronic medical conditions and prescribed medications.

PREVENTION AND SCREENING

When should clinicians screen for unhealthy alcohol use?

Given the negative consequences associated with unhealthy alcohol use, that it often goes unrecognized, and the availability of potentially effective treatments, NIAAA recommends routine screening, with a focus on particular clinical encounters and patients (see Box 2) (19). Similarly, the United States Preventive Services Task Force (USPSTF) and the Centers for Disease Control and Prevention (CDC) recommend routine screening of adults for unhealthy alcohol use with the provision of brief counseling for those with at-risk drinking (20, 21).

What are effective self-report-based methods to screen for unhealthy alcohol use in clinical settings?

The NIAAA recommends first asking patients: Do you sometimes drink beer, wine, or other alcoholic beverages? and then, among men who endorse alcohol use, asking How many times in the past year have you had 5 or more drinks in a day? and among women who
endorse alcohol use, asking How many times in the past year have you had 4 or more drinks in a day? (19). Alternatively, patients may be asked to complete a standardized instrument, such as the AUDIT or AUDIT-C (see Table 1), an approach which has been widely implemented in primary care settings (19, 22). While the USPSTF and CDC recommend a similar approach (20, 21), it is important to recognize that the operating characteristics of the AUDIT and AUDIT-C vary based on clinical setting and cut-offs used (19, 23). Further, implementation of these instruments is optimized in clinical settings when the instrument is used as intended (i.e. verbatim language) with standardized clinical reminders and processes in place (24). To streamline the screening process, there is a focus on the use of single-item screening questions (SISQ-alcohol), including the NIAAA item, How many times in the past year have you had x or more drinks in a day? (where x=5 for men, x=4 for women).

A recent study compared computer administered SISQ-alcohol to research assistant-administered standardized measures (e.g. timeline follow-back, short-inventory of problems (SIP) and MINI-Plus) to assess alcohol use and alcohol-related problems. Based on evaluation in 459 participants from two urban primary care clinics, the SISQ-alcohol had a sensitivity of 73.3 % (95 % CI 65.3-80.3) and specificity of 84.7 % (95 % CI 80.2-88.5), area under the curve (AUC) = 0.79 (95 % CI 0.75-0.83), for detecting unhealthy alcohol use, and sensitivity of 86.7 % (95 % CI 75.4-94.1) and specificity of 74.2 % (95 % CI 69.6-78.4), AUC = 0.80 (95 % CI 0.76-0.85), for alcohol use disorder (25).

SISQ-alcohol, thus, holds promise as a valid approach for detecting unhealthy alcohol use in primary care settings.

Patients with a negative screen, should be counseled regarding guidelines for continued low-risk drinking or abstinence as appropriate (e.g. cirrhosis, history of alcohol use disorder). Patients with a positive screen, should have further assessment of the frequency (i.e. On average, how many days a week do you have an alcoholic drink?) and quantity (i.e. On a typical drinking day, how many drinks do you have?) of their alcohol use as well as number of heavy drinking days, followed by careful assessment for an alcohol use disorder (19) and alcohol-related consequences.

While other instruments have been validated and widely implemented, such as the CAGE questionnaire and Michigan Alcohol Screening Test (MAST), these are more appropriate for screening for lifetime alcohol use disorders. Thus, they are less effective for detecting lower levels of drinking (i.e. at-risk drinking) that may also be associated with health-related concerns for routine screening and distinguishing current from prior alcohol use disorders.

Screening efforts should be conducted in a non-judgmental manner that optimizes patient comfort and helps them understand the relevance of alcohol use to their health and occurs in the context of inquiry about other health-related behaviors (e.g. exercise, nutrition, tobacco use) (4, 5). As patterns of alcohol use change over time, repeat screening is important but may be less necessary after a patient screens negative on multiple consecutive occasions, particularly among women and older adults (26).
Clinical Bottom Line: Prevention and Screening

Standardized processes, with use of validated instruments and approaches, should be incorporated into practices to facilitate routine screening for unhealthy alcohol use of all patients. Those who screen negative, should be counseled regarding maintaining lower-risk alcohol use or abstinence as appropriate. Those who screen positive, should be evaluated for alcohol use disorders and alcohol-related consequences and then provided appropriate treatment.

DIAGNOSIS

How should clinicians distinguish between lower-risk alcohol consumption, at-risk drinking, and alcohol use disorders?

While different definitions have been applied (19, 27), according to the NIAAA, alcohol use can be broadly classified into one of three categories. These categories are essential to determining risk for specific conditions and guiding appropriate preventative and treatment strategies for patients. Most common is so-called “moderate” or lower risk alcohol use without health consequences, the pattern of alcohol use associated with lower risk for alcohol-related consequences. According to the NIAAA, for men up to age 65, lower risk alcohol use is no more than 4 drinks on any single day and no more than 14 drinks per week. For women, who tend to have lower volumes of distribution, and men over age 65, lower risk alcohol use is no more than 3 drinks on any single day and no more than 7 drinks per week (19).

Hazardous or at-risk drinking, is the pattern of alcohol use associated with increased risk for alcohol-related consequences and occurs when the thresholds for lower risk alcohol use are exceeded (19) or when there is drinking in situations that increase risks at lower amounts (e.g. pregnancy). Heavy drinking is defined as more than 4 drinks on any day for men and more than 3 drinks on any day for women (28).

As defined by the World Health Organization and included in the International Classification of Diseases and Related Health Problems, 10th revision (ICD-10), harmful alcohol use refers to a pattern of drinking that is causing health consequences (27).

Alcohol use disorder, as defined by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), is present if an individual meets at least 2 of the 11 criteria (Box 3) (29). Determining severity is important as those patients with a moderate or severe alcohol use disorder (meeting 3 or more criteria) may benefit from more intensive treatment. This reflects a change from the DSM-IV, which included separate diagnoses for alcohol abuse and alcohol dependence.

Unhealthy alcohol use refers to individuals who are not abstainers or lower risk drinkers and includes those with hazardous/at-risk drinking, harmful drinking or alcohol use disorder (1).

Based on screening and assessment as above, a patient’s level of alcohol use may be appropriately categorized (see Table 1). Patients are classified as having an alcohol use disorder if they have met at least two criteria for an alcohol use disorder in the past 12
months. Otherwise, these patients are considered to have at-risk drinking. Classifying alcohol use accurately is important as it directly guides treatment options.

As appropriate, prior treatment history, family history of substance use disorders and mental illness, and alcohol-related consequences should be assessed.

What is the role of the physical examination and laboratory testing in the evaluation of patients with unhealthy alcohol use?

In conjunction with self-reported data collected in the history, the physical exam and laboratory testing may be helpful in identifying and evaluating patients with unhealthy alcohol use. For example, patients with evidence of worsening hypertension or tachycardia may be manifesting withdrawal. Signs and symptoms consistent with liver, cardiac or neurocognitive disease, may signal consequences of alcohol use (see Box 4).

To date, there are no widely available biomarkers that reliably measure alcohol use and predict the impact of alcohol use on health. Increased mean corpuscular volume (MCV) of red blood cells; elevated \( \gamma \)-glutamyltransferase (GGT); and increased aspartate (AST) to alanine (ALT) aminotransferase ratio may signal unhealthy alcohol use but this is with varying sensitivity and specificity (30). Markers related to ethanol metabolism, such as phosphatidylethanolol (PEth) and carbohydrate deficient transferrin (CDT), are under investigation (31).

Which other conditions should clinicians be alert for in patients with unhealthy alcohol use?

Substance use disorders, especially tobacco use disorders, and mental illness commonly co-occur in patients with unhealthy alcohol use.

An analysis of NESARC-III data (n=36,309) demonstrated that patients with any alcohol use disorder had an 80% increased risk of a major depressive disorder (adjusted odds ratio [AOR] [95% CI] =1.8 [1.6 – 2.0])(2). This risk was greatest among those with a severe alcohol use disorder (AOR [95% CI]= 2.9 [2.5 – 3.5]). The odds of mental illness increased with severity of alcohol use disorder across multiple diagnoses, including other mood disorders, anxiety disorders, post-traumatic stress disorder and personality disorders.

Similarly, chronic pain and unhealthy alcohol use often co-occur. Patients should be carefully evaluated for these underlying conditions as their presence can impact treatment decisions and response to treatment. As sexual risk behaviors are common in the setting of unhealthy alcohol use, patients should be evaluated accordingly.

Clinical Bottom Line: Diagnosis

Diagnosis relies on a comprehensive evaluation, including history, physical exam and supporting laboratory data. The diagnosis relies on patient self-reported information. While there is no single laboratory test that reliably measures alcohol use and its impact, various markers can be used to detect alcohol use and measure its impact on health. Given their increased prevalence among patients with unhealthy alcohol use, efforts to screen for and
address comorbid conditions (i.e. substance use, mental illness, and chronic pain) and sexual risk behavior among patients with unhealthy alcohol use should be part of routine care.

**TREATMENT**

Treatment approaches are guided based on the patients’ level of alcohol use and diagnostic category. Brief interventions advising less or no use are appropriate for those with at-risk alcohol use; for those with disorders, advice should include engaging in more intensive treatment. More comprehensive treatment approaches, including management of withdrawal symptoms, and behavioral interventions with pharmacotherapy, may be indicated for those with an alcohol use disorder.

**What is appropriate language to use when treating patients with unhealthy alcohol use?**

Regardless of the patients’ level of alcohol use, caution should be used to avoid imprecise and stigmatizing language. For instance, “problem drinking” has various definitions making its use, problematic. In contrast, a term such as alcohol “abuse” refers to a specific DSM diagnosis, but is often used in a generic sense to refer to unhealthy alcohol use or alcohol use disorder. To avoid stigma and help focus on the medical aspects of unhealthy alcohol use and facilitate appropriate treatment the following practices have been advocated: 1) use of people-first language (i.e. a person with an alcohol use disorder); 2) focus on the medical aspects of the condition and its treatment; and 3) avoidance of use of slangs and idioms (32). Thus, terms such as alcoholic and alcohol abuser should be avoided (32, 33). When considering and discussing unhealthy alcohol use, it can be helpful to make the comparison to another chronic medical condition, such as diabetes mellitus, where the cause is also based on a combination of genetic and behavioral factors and treatment requires a comprehensive approach (32, 34).

**What should clinicians do if they identify patients with hazardous or at-risk alcohol use?**

The goal for patients with hazardous or at-risk alcohol use is that they decrease their alcohol use to moderate levels to prevent alcohol-related harms. Brief interventions, which are designed to be 5 to 20 minutes in duration and effective when delivered by physicians and non-physicians alike, are feasible and effective in primary care settings (35). Brief interventions are designed to elicit the patient’s perception of their alcohol use and its associated risks and then include: 1) clear advice with a specific recommendation regarding alcohol use; 2) personalized and normative feedback regarding the impact of alcohol on the patient’s health and their alcohol use relative to norms; 3) empathy with acknowledgement of the patient’s ability and responsibility in making a change; 4) among patients who express interest in change, provision of a menu of options for facilitating change; 5) review and discussion of situations that are likely to trigger excessive alcohol use; 6) establishment of a drinking agreement and arrangement of follow-up (1, 19). Among individuals who are not ready to make a change in their alcohol use, it is most appropriate to provide specific advice about recommended alcohol use and then inquire about their reasons for both drinking and avoiding alcohol use (i.e. pros and cons of alcohol use) and ask what it would take to raise importance of patient’s alcohol use to motivate change (i.e. increase readiness to change on 1-10 scale), with a plan for follow-up evaluation (1).
A systematic review evaluated the efficacy of behavioral counseling interventions (the majority of which were brief) conducted in primary care targeting those with at-risk drinking (n=23). The authors found that compared to controls, those receiving the counseling intervention decreased their alcohol consumption by 3.6 drinks per week from baseline; 12% fewer adults endorsed heavy drinking episodes, and 11% more adults reported drinking less than the recommended limits over 12 months (35).

Notably, brief, multi-contact interventions were most effective (19). Electronic brief interventions have been studied but to date have not been shown to be routinely effective (36).

**How should care of patients with an alcohol use disorder be prioritized?**

Patients with alcohol use disorder seen in primary care settings may present with a ranging set of treatment needs, including management of withdrawal symptoms as well as prevention to relapse. Care should be prioritized to promote patient safety and stabilization first. While reduction in alcohol consumption is the initial goal for patients with alcohol use disorder, few are able to maintain controlled drinking and so abstinence is typically the goal of therapy.

**How should alcohol withdrawal be addressed in the primary care setting?**

Among patients with an alcohol use disorder, alcohol withdrawal may manifest with a range of signs and symptoms, including abnormal vital signs (i.e. elevated heart rate, blood pressure, temperature), autonomic hyperactivity, gastrointestinal symptoms, and central nervous system effects (see Box 5) (4, 37). Some patients can safely be managed in the outpatient setting with close follow-up, while patients at greater risk for harm (e.g. severe withdrawal with delirium tremens, seizures, concomitant drug use, elderly, etc.) or unlikely to follow-up should be referred to an inpatient setting (see Box 6) (38).

Standardized instruments may be used to assess the degree of withdrawal and guide treatment. Most commonly used is the Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar) (39), which includes 10 items that are summed to create a score. A score less than 8 indicates mild withdrawal, a score 8 to 15 indicates moderate withdrawal, and scores greater than 15 indicates severe withdrawal. These scores can be used to guide changes in clinical status and medication management.

Multiple dosing strategies and medication regimens have been previously evaluated for the treatment of alcohol withdrawal symptoms and seizure prevention (4, 40). The use of benzodiazepines dosed according to symptoms (i.e. symptom-triggered) is the safest and most effective established strategy and preferred over alternatives, such as anticonvulsants (41-43). Typically, long-acting benzodiazepines (e.g. chlordiazepoxide and diazepam) are preferred while short-acting benzodiazepines should be considered in older adults and those with liver disease. Additional medications may be used as needed for symptom management, such as alpha-2-agonists and beta-blockers for autonomic hyperactivity and neuroleptics for hallucinations (44). Other agents, such as topiramate, gabapentin and baclofen, remain under investigation for use for managing alcohol withdrawal (44).
Since withdrawal can begin as early as 5 to 8 hours but up to 72 hours after the last drink (40), patients should be monitored closely during this time for alcohol withdrawal and then bridged to treatment for relapse prevention.

**What is the role of psychotherapeutic interventions for patients with an alcohol use disorder?**

For patients with an alcohol use disorder, as well as those with at-risk alcohol use unable to meet treatment goals, psychotherapeutic interventions are a mainstay of treatment. Cognitive behavioral therapy, motivational enhancement therapy, and 12-step facilitation are commonly used approaches in treatment programs (38) with similar efficacy (45).

**Cognitive behavioral therapy** has two main components. First, through functional analysis, patients are guided to identify the thoughts, feelings and circumstances that occur before and after alcohol use. The goal is to help the patient develop new insights into why they consume alcohol, identifying coping difficulties, and determine triggers for relapse. Then, through skills-based training, patients develop new behaviors and techniques for coping with these triggers.

**Motivational enhancement therapy**, grounded in stages of change theory, helps patients increase their internal motivation to change their alcohol use.

**Twelve-step facilitation** involves a manual-driven approach to facilitate recovery with the underlying premise that alcohol use disorders are secondary to a medical and spiritual disease. Twelve-step facilitation is more than a simple referral to Alcoholics Anonymous (AA), but rather a formal process of facilitating a patient’s engagement in AA.

Other psychotherapeutic interventions, such as community reinforcement and behavioral couples therapy, are also supported by the literature (46).

Mutual-Help groups, including Alcoholics Anonymous, represent an additional treatment option for patients with alcohol use disorder. Alcoholics Anonymous (AA) is the most well-known of these groups focused on alcohol, yet other groups exist. There are conflicting data regarding the impact of AA (46).

A recent analysis, however, using instrumental variables models to analyze data from six randomized clinical trials found that for most individuals, AA attendance was associated with increasing days of abstinence at 3- and 15-month follow-up (47).

Given that AA is free, widely accessible, and that the only requirement is that the individual have a desire to stop drinking, patients should be routinely referred and encouraged to attend at least one meeting. Strategies that may improve engagement include increased provider familiarity with local groups, stocking AA literature and following up on a patients experience after a referral (48).
When should clinicians consider pharmacotherapy for relapse prevention for patients with an alcohol use disorder?

Pharmacotherapy for relapse prevention should be considered for all patients with an alcohol use disorder (49), particularly those with moderate to severe disorder. There are currently three Food and Drug Administration (FDA)-approved medications that should be considered for treatment in patients with alcohol use disorders: disulfiram, acamprosate and naltrexone. Outcomes with these medications are typically best when provided in conjunction with a minimum of brief psychosocial counseling (50). For acamprosate and naltrexone, a brief period of abstinence prior to initiation is not mandatory, but is associated with improved outcomes.

**Disulfiram**, approved by the FDA in 1951, was the first FDA approved medication for alcohol use disorder. It irreversibly inhibits the activity of acetaldehyde dehydrogenase, leading to build up of acetaldehyde after ethanol ingestion. This medication is appropriate when the initial goal is abstinence and as a deterrent to alcohol use given the aversive side effects, including nausea, flushing, and palpitations associated with alcohol use.

Although models with selected patient populations have demonstrated efficacy, results from a meta-analysis of four studies failed to show significant benefit with disulfiram for preventing relapse or related outcomes (49).

Thus, other treatment options should be considered first and disulfiram should be reserved only for highly motivated patients and, ideally, when there is support to monitor medication adherence.

**Acamprosate**, FDA approved in 2004, is believed to work through the N-methyl-d-aspartate (NMDA) receptor to restore GABA and glutamate balance. The main challenges with this medication are that it is dosed three times daily and commonly leads to diarrhea and vomiting. In addition, as it is metabolized by the renal system, dose adjustment is necessary in the setting of renal insufficiency. On the other hand, it is safe for use in patients with hepatic dysfunction where naltrexone may be contraindicated.

Results from a meta-analysis pooling data from 16 studies found that to prevent one person from returning to any drinking, the number needed to treat (NNT) to achieve abstinence with acamprosate was 12 (95% CI = 8 – 26) (49). In contrast, based on data from 7 studies, acamprosate was not associated with decreasing the likelihood of return to heavy drinking.

**Naltrexone** was initially FDA approved as a once daily oral medication in 1994 and then as a long-acting injectable medication in 2006. As an opioid-receptor antagonist, it works to decrease the reward pathways associated with alcohol use and decreases cravings. The main concerns with naltrexone are potential for worsening depression and suicidal ideation compared to placebo ([http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021897s005s010lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021897s005s010lbl.pdf)). While patients and their families should be advised accordingly, trial data and clinical experience indicate that this is relatively uncommon. There is also concern for hepatotoxicity, particularly with the oral formulation which carries a warning for this risk, and periodic liver function test monitoring is appropriate though such
toxicity is rarely seen at doses used to treat alcohol use disorder. In fact, on average liver enzymes usually decrease in treated cohorts. Given its mechanism of action, use of opioids is contraindicated with naltrexone; patients need to be counseled prior to treatment initiation of this risk, as well options for pain management should the need arise.

The NNT to prevent one person from returning to any drinking (n=16 studies) and heavy drinking (n=19 studies) with oral naltrexone was 20 (95% CI= 11 to 500) and 12 (95% CI=8 to 26) respectively (49).

Injectable naltrexone provides a good treatment option for those individuals willing to receive a monthly injection as it can improve medication adherence. As naltrexone is also FDA approved for the treatment of opioid use disorders, it represents a potential option for patients with concurrent alcohol and opioid use disorders.

Studies investigating the efficacy of other medications, such as baclofen, gabapentin, ondansetron, topiramate and varenicline, are underway with promising results (51).

Despite their demonstrated effectiveness and availability, research consistently demonstrates that patients are under-prescribed medications to treat alcohol use disorders and prevent relapse.

For example, one study found that among 101,026 patients with an alcohol use disorder receiving care through the Veterans’ Health Administration, only 3% of patients received any form of naltrexone, 7% of whom received long-acting naltrexone (52).

These data, coupled with a mixed-methods evaluation of factors impacting implementation, support the need for increased provider awareness of the safety and effectiveness of these medications and skill to prescribe them (53). Ongoing trainings, such as those available through the Substance Abuse and Mental Health Services Administration (http://www.samhsa.gov/medication-assisted-treatment and http://store.samhsa.gov/shin/content/SMA15-4907/SMA15-4907.pdf) are useful resources for practicing clinicians seeking to improve their knowledge and confidence for prescribing these medications.

**When should clinicians consider antidepressants or anxiolytics in the treatment of patients with unhealthy alcohol use?**

Alcohol use disorders commonly co-occur with other substance use disorders, and mental illness, including mood disorders, anxiety disorders, and personality disorders (2). Antidepressants are not effective standalone treatments for alcohol use disorders. These medications can, however, be effective for depressive symptoms among patients with unhealthy alcohol use, especially those with at-risk drinking (10, 54). Benzodiazepines are considered standard treatment for the management of the acute phase of alcohol withdrawal but are not useful effective treatment for alcohol use disorder and pose the risk of creating an additional substance use disorder. Given mixed results regarding how to most effectively prioritize treatment, it is appropriate to provide treatment for the alcohol use disorder and the co-occurring mental illness simultaneously with close monitoring for medication side effects and utilization of multi-modal approaches (e.g., counseling) when possible (55).
**Are there medications of particular concern in the setting of unhealthy alcohol use?**

Box 1 provides a medications with potential interactions with alcohol. A more detailed list of over the counter and prescription medications that may interact with alcohol is available at: [http://pubs.niaaa.nih.gov/publications/Medicine/medicine.htm](http://pubs.niaaa.nih.gov/publications/Medicine/medicine.htm). Clinicians should note that these include medications commonly prescribed to treat lipid disorders (e.g. statins), insomnia and non-steroidal anti-inflammatories, acetaminophen even at recommended doses, and anticoagulants.

Use of prescription opioids and benzodiazepines, both taken as prescribed and/or non-medically, are of great concern when mixed with alcohol.

Alcohol contributes to approximately one fifth of prescription opioid-related and one-fourth of benzodiazepine-related emergency department visits, respectively (56). Further, alcohol is involved in one-fifth of deaths related to prescription opioids or benzodiazepines (56).

Opioids and benzodiazepines should be prescribed judiciously (57) and patients counseled accordingly.

In addition, given the potential risk for harms associated with polypharmacy (i.e. receipt of five or more long-term medications), those patients with unhealthy alcohol use and polypharmacy deserve particularly close monitoring and careful assessment of their medications to avoid potential harms (e.g. falls, medication non-adherence, etc.).

**What additional care should be considered for patients with unhealthy alcohol use to promote health?**

Patients with current alcohol use disorder have an increased prevalence of comorbid conditions that warrant screening and treatment. These include other substance use and mental health disorders including tobacco use disorder, drug use disorders, anxiety disorders, mood disorders, and personality disorders (2). In addition, there is an increased prevalence of insomnia, anemia, osteoporosis, and liver disease. In addition to standard vaccinations as recommended for healthy adults (e.g. influenza), vaccination against hepatitis B and hepatitis C virus should be considered among those with established liver disease (http://www.cdc.gov/vaccines/schedules/downloads/adult/adult-pocket-size.pdf). Pneumococcal polysaccharide (PPSV 23) and zoster vaccination are recommended for those with an alcohol use disorder. Patients with longstanding alcohol use disorder can also experience specific cognitive and neurologic deficits including peripheral neuropathy, Wernicke’s encephalopathy, and Korsakoff syndrome. Due to the increased risk of sexually transmitted infections, including HIV, associated with unhealthy alcohol use (12), patients should be appropriately screened, counseled and offered prevention and treatment as indicated (58).

**What type of follow-up care should clinicians provide for patients with unhealthy alcohol use and when is specialty referral appropriate?**

Patients with unhealthy alcohol use should be seen regularly for ongoing monitoring of their alcohol use and treatment effects, as well as for any associated medical, psychiatric and behavioral-related adverse effects. Referral to specialty care is appropriate for patients with
Clinical Bottom Line: Treatment

For patients with at-risk drinking, brief interventions can be effective for enhancing motivation and decreasing alcohol use. For patients with an alcohol use disorder, treatment hinges on ensuring patient safety and stabilization. Benzodiazepines are the mainstay of treatment for decreasing alcohol withdrawal symptoms and risk of seizures; hospitalization is indicated for patients with moderate to severe withdrawal and high risk for complications. For relapse prevention, psychotherapeutic interventions (i.e. cognitive behavioral therapy, motivational enhancement therapy and/or 12-step facilitation) in conjunction with pharmacotherapy (naltrexone or acamprosate) and self-help groups is recommended. Comprehensive care for all patients with unhealthy alcohol use should include optimizing medication regimens. Referral to specialty services, including Addiction Specialists, should be considered for patients failing to respond to treatment, with evidence of an alcohol use disorder and/or with significant comorbidity.

PRACTICE IMPROVEMENT

What factors do U.S. stakeholders use to evaluate the quality of care for patients with unhealthy alcohol use?

The 2014 Centers for Medicare and Medicaid Services (CMS) Electronic Health Records Incentive Program includes the National Committee for Quality Assurance measure for initiation and engagement of alcohol and other drug dependence treatment. Specifically, the measure indicates that the following should be measured: 1) percentage of patients who initiated treatment within 14 days of a diagnosis of alcohol or drug dependence and 2) percentage of patients who initiated treatment and who had two or more additional services with and an alcohol or other drug dependence diagnosis within 30 days of the initial visit. The Health Resources and Services Administration HIV/AIDS Bureau’s contains a similar metric and indicates that all new patients with an HIV diagnosis should be screened for alcohol use. Similarly, there is quality measure supported by CMS, the National Quality Forum and the American Medical Association - Physician Consortium for Performance Improvement indicating that patients with hepatitis C virus should receive counseling regarding their alcohol use. These are consistent with the USPSTF recommendation, which indicates that adults aged 18 years or older should be screened for unhealthy alcohol use and provide individuals identified to have hazardous/at-risk drinking, with brief behavioral counseling to reduce their hazardous/at-risk drinking (20). Given the evidence (35), this is a grade B recommendation. The Veterans Health Administration’s comprehensive clinical guidelines state that all patients seen in general medical and mental health settings should be screened for unhealthy alcohol use (59). Those who meet criteria for unhealthy alcohol use should be delivered a brief counseling intervention with consideration of referral to specialty
addiction programs at the initial visit or follow-up. These guidelines also provide algorithms for treatment, including the role of pharmacotherapy.

**What clinical practice changes are occurring as a result of the Affordable Care Act?**

With the passing of the Affordable Care Act, treatment of alcohol use disorders is considered an essential health benefit and insurance coverage for such services is required. As such, there have been important initiatives to improve access to and delivery of treatment of unhealthy alcohol use and other substance use through routine clinical settings. In addition, efforts to determine how to best measure and improve upon quality of screening and treatment delivery for unhealthy alcohol use are actively underway (60). Given the significant individual and public health impact of unhealthy alcohol use, such initiatives are welcomed and warranted.

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**REFERENCES**


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## Box 1

### Examples of common alcohol-prescription medication interactions by class among individuals with current alcohol use (18)

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular Agents</strong></td>
<td>Angiotensin converting enzyme inhibitors</td>
</tr>
<tr>
<td></td>
<td>Beta-blockers</td>
</tr>
<tr>
<td></td>
<td>Diuretics</td>
</tr>
<tr>
<td><strong>Central Nervous System Agents</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anticonvulsants</td>
</tr>
<tr>
<td></td>
<td>Anxiolytic/sedative/hypnotics</td>
</tr>
<tr>
<td></td>
<td>Opioids</td>
</tr>
<tr>
<td><strong>Coagulation modifiers</strong></td>
<td>Anticoagulants</td>
</tr>
<tr>
<td><strong>Metabolic Agents</strong></td>
<td>Antidiabetic</td>
</tr>
<tr>
<td></td>
<td>Antihyperlipidemic</td>
</tr>
<tr>
<td><strong>Psychotherapeutic Agents</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antidepressant</td>
</tr>
<tr>
<td><strong>Respiratory Agent</strong></td>
<td>Antihistamines</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Antibiotics</td>
</tr>
<tr>
<td></td>
<td>Nonsteroidal anti-inflammatory agents</td>
</tr>
</tbody>
</table>
Box 2

National Institute on Alcohol Abuse and Alcoholism Recommended Screening Opportunities

- Routine examination
- Before prescribing a medication with potential interactions with alcohol
- In the Emergency Department or urgent care center
- When seeing patient who either are or have the following:
  - Pregnant, planning conception
  - Risk factors for unhealthy alcohol use (e.g. smoke tobacco; young adults)
  - Potentially alcohol-related health problems (e.g. arrhythmia, cirrhosis, trauma)
  - Chronic condition resistance to usual treatment (e.g. pain, depression, diabetes mellitus, hypertension)
**Box 3**

**DSM-5 Criteria for Alcohol Use Disorder**

1. Alcohol taken in larger amounts or for longer than intended
2. Persistent desire or unsuccessful efforts to cut down or control alcohol use
3. Great deal of time spent obtaining, using, or recovering from alcohol use
4. Craving or strong desire to use alcohol
5. Failure to fulfill major obligations due to alcohol use
6. Continued use despite problems caused or exacerbated by alcohol use
7. Important activities given up or reduced because of alcohol use
8. Recurrent alcohol use in physically hazardous situations
9. Continued use despite knowledge of physical or psychological problems that are caused or exacerbated by alcohol
10. Tolerance
11. Withdrawal

*Mild*: 2-4 symptoms; *Moderate*: 4-5 symptoms; *Severe*: 6+ symptoms
Box 4

Findings that May Indicate Unhealthy Alcohol Use

- Hypertension
- Jaundice
- Spider angiomata
- Cardiomyopathy
- Atrial fibrillation
- Gynecomastia
- Hepatosplenomegaly
- Ascites
- Testicular atrophy
- Palmar erythema, plethoric facies
- Peripheral neuropathy
- Cognitive abnormalities
Box 5

**Signs and Symptoms of Alcohol Withdrawal (adapted from reference 39)**

Minor Symptoms: Diaphoresis, nystagmus, tachycardia, hyperreflexia, hypertension, nausea or vomiting, low-grade fever, diarrhea, mild agitation

Hallucinations (auditory, visual, tactile): May occur while intoxicated; sensorium otherwise clear unless progression to delirium tremens

Withdrawal seizures: Grand mal-peak occurrence 12 to 48 hours after last drink; cluster may occur over 3 to 6 hours, although last seizure occurs more than 6 hours after first in 15% of cases

Delirium tremens: Agitated confusional state with tremulousness, hallucinations, and striking autonomic overactivity; fever in 82% of cases, often associated with comorbid illness
### Box 6

**Indications for Referral for Inpatient Detoxification**

**Reasons to Refer Immediately for Inpatient Detoxification**

1. Patient in moderate to severe withdrawal
2. Patient with prior seizure history or delirium tremens
3. Patient unable to cooperate with daily follow-up
4. Patient has comorbid psychiatric or medical complications requiring hospitalization
5. Patient is unable to take medication by mouth
6. Patient unsuccessful with outpatient detoxification
7. Pregnancy

**Reasons to Strongly Consider Inpatient Detoxification**

1. Coexisting benzodiazepine use
2. High risk for severe alcohol withdrawal, including older age, heavy drinking for over extended period of time, drinking more than 100g ethanol daily, random blood alcohol level greater than 200mg/dL, signs and symptoms of alcohol withdrawal when not drinking
Table 1
Recommended Screening Instruments (adapted from reference 5)

NIAAA Single Question Screening Item

**Question:** How many times in the past year have you had x or more drinks in a day?
(where x is 5 for men, 4 for women and one standard drink is equivalent to 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of 80-proof spirits)

**Scoring:** One or more episodes is considered a positive screen

<table>
<thead>
<tr>
<th>AUDIT</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How often do you have a drink containing alcohol?</td>
<td>Never</td>
<td>Monthly or less</td>
<td>2-4 times a month</td>
<td>2-3 times a week</td>
<td>4 or more times a week</td>
</tr>
<tr>
<td>2. How many drinks containing alcohol do you have on a typical day when you are drinking?</td>
<td>1-2</td>
<td>3-4</td>
<td>5-6</td>
<td>7-9</td>
<td>10 or more</td>
</tr>
<tr>
<td>3. How often do you have 5 or more drinks on one occasion?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>4. How often during the last year have you found that you were not able to stop drinking once you started?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>5. How often during the last year have you failed to do what was normally expected of you because of drinking?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>7. How often during the last year have you had a feeling of guilt or remorse after drinking?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>8. How often during the last year have you been unable to remember what happened the night before because of your drinking?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>9. Have you or someone else been injured because of your drinking?</td>
<td>No</td>
<td>Yes, but not in the last year</td>
<td>Yes, during the last year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?</td>
<td>No</td>
<td>Yes, but not in the last year</td>
<td>Yes, during the last year</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Scoring:** Points for each of the ten items are added together. Total score of ≥8 for men up to age 60 or ≥4 for women, adolescents and men over age 60 are considered positive. Cutoffs may vary depending on purpose and population of interest.

<table>
<thead>
<tr>
<th>AUDIT-C</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How often did you have a drink containing alcohol in the past year?</td>
<td>Never</td>
<td>Monthly or less</td>
<td>2-4 times a month</td>
<td>2-3 times a week</td>
<td>4 or more times a week</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Questions</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. How many drinks did you have on a typical day when you were drinking in the past year?</td>
<td>0</td>
</tr>
<tr>
<td>None or 1-2</td>
<td>1</td>
</tr>
<tr>
<td>3-4</td>
<td>2</td>
</tr>
<tr>
<td>5-6</td>
<td>3</td>
</tr>
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<td>7-9</td>
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</tr>
<tr>
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</tr>
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</tr>
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<td>Never</td>
<td></td>
</tr>
<tr>
<td>Less than monthly</td>
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<tr>
<td>Monthly</td>
<td></td>
</tr>
<tr>
<td>Weekly</td>
<td></td>
</tr>
<tr>
<td>Daily or almost daily</td>
<td></td>
</tr>
</tbody>
</table>

**Scoring**: Points for each of the three items are added together. Total score of ≥ 6 for men and ≥ 4 for women is considered positive. Cutoffs may vary depending on purpose and population of interest.
## Table 2
Pharmacotherapy for Patients with an Alcohol Use Disorder

<table>
<thead>
<tr>
<th>Medication (Typical Dosage)</th>
<th>Indication</th>
<th>Mechanism</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepines</strong>&lt;br&gt;-Symptom-triggered: chlordiazepoxide, 50-100mg; diazepam, 10-20mg; or lorazepam, 2-4mg every 1-2 hours until symptoms subside.&lt;br&gt;-Fixed-dose: chlordiazepoxide, 50mg; diazepam, 10mg; or lorazepam, 2mg every 6 hours on day 1, then one half dose every 6 hours on days 2 and 3</td>
<td>Treatment or prophylaxis for alcohol withdrawal syndrome</td>
<td>Enhance GABA * inhibition of neuronal excitability</td>
<td>Oversedation, paradoxical hyperactivity, depression. Addictive potential.</td>
<td>Caution in the presence of respiratory or hepatic impairment.</td>
</tr>
<tr>
<td><strong>Naltrexone</strong>&lt;br&gt;-Oral 50-100mg daily&lt;br&gt;-Injectable 380mg monthly</td>
<td>Relapse prevention</td>
<td>Opioid antagonist that may reduce the subjective reward associated with alcohol use</td>
<td>Nausea, indigestion, headache, fatigue, Depressive symptoms. Rarely medication-associated hepatitis. Potential for precipitated opioid withdrawal if opioids present.</td>
<td>Contraindicated in the presence of opioid use. Avoid if decompensated cirrhosis; use with caution with hepatitis, compensated cirrhosis.</td>
</tr>
<tr>
<td><strong>Acamprosate</strong>, (666mg 3 times daily)</td>
<td>Relapse prevention</td>
<td>May antagonize glutamate-mediated neuronal hyperexcitability and reduce prolonged (but not acute) withdrawal symptoms</td>
<td>Diarrhea, nausea/vomiting, myalgias, rash, dizziness, palpitations. Rarely associated with renal impairment.</td>
<td>Reduced dosage with renal insufficiency. May be used with naltrexone. Medication adherence may be challenging.</td>
</tr>
<tr>
<td><strong>Disulfiram</strong> (250-500mg daily)</td>
<td>Prevention of drinking and relapse prevention</td>
<td>Aldehyde dehydrogenase inhibition results in acetaldehyde accumulation with alcohol use, leading to unpleasant symptoms (i.e., alcohol-disulfiram reaction)</td>
<td>Drowsiness, rash. Rarely medication-associated severe hepatotoxicity, optic neuritis, peripheral neuropathy.</td>
<td>Potential for many medication-medication interactions. Patient must be abstinent at least 12 hours prior to medication administration. Avoid in patients with hepatic impairment or cardiovascular disease. Most appropriate for patients with strong motivation to be abstinent and with support to promote medication adherence.</td>
</tr>
</tbody>
</table>
GABA=γ-aminobutyric acid.

Naltrexone, disulfiram, and acamprosate are all U.S. Food and Drug Administration pregnancy category C (animal studies indicate potential fetal risk or have not been conducted and no or insufficient human studies have been done; drugs in this category should be used with pregnant or lactating women only when potential benefits justify potential risk to the fetus or infant). Benzodiazepines are category X (contraindicated in pregnancy) or D (positive evidence of risk).