# Alcohol Use Disorder

## First-line Pharmacotherapy

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DALHOUSIE UNIVERSITY
FACULTY OF MEDICINE
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*"Seek simplicity, and mistrust it."*
*Alfred North Whitehead*

# TABLE of CONTENTS

# ABBREVIATIONS

| | |
|---|---|
| AHRQ | Agency for Healthcare Research and Quality |
| AUD | Alcohol use disorder |
| AUDIT – c | AUDIT-consumption |
| AUDIT | Alcohol Use Disorder Identification Test |
| CADTH | Canada's Drug and Health Technology Agency |
| CAGE | Cut-down, Annoyed, Guilty, Eye-opener |
| CEP | Centre for Effective Practice |
| CI | Confidence interval |
| CrCl | Creatinine clearance |
| CV | Cardiovascular |
| DB | Double blind |
| DSM-V | Diagnostic and Statistical Manual of Mental disorders, 5$^{th}$ edition |
| HF | Heart failure |
| MA | Meta-analysis |
| MI | Myocardial infarction |
| NICE | National Institute for Health Care and Excellence |
| NMA | Network meta-analysis |
| NNT | Number needed to treat |
| OR | Odds ratio |
| QOE | Quality of evidence |
| RCT | Randomized controlled trial |
| RD | Risk difference |
| RR | Relative risk |
| SASK | Single alcohol question screen |
| SOE | Strength of evidence |
| SOR | Strength of recommendation |
| SRR | Standardized rate ratio |
| WHO | World Health Organization |

# INTRODUCTION

## Alcohol use in Canada

Alcohol is by far the most common drug used by Canadians; more than tobacco, cannabis, and other illicit drugs combined.[1] In 2021, 15.6% Canadians aged 12 years and older (or approximately 5.1 million people) reported engaging in heavy drinking on one occasion, at least once a month, in the previous year. [2]

In 2019, Statistics Canada asked Canadians about 5 harms they may have experienced in the past 12 months due to alcohol consumption.[2] "Types of harms included being unable to stop drinking once started, failing to do what was normally expected from you because of drinking, needing a first drink in the morning to get going after a heavy drinking session, being unable to remember what happened the night before, or having a feeling of guilt or remorse after drinking." [2] Of those who reported past-year alcohol use, 21% (4.8 million people) experienced at least one alcohol-related harm in the past year.[2]

## Health Harms of Alcohol

Alcohol use is associated with over 200 diseases and conditions including short-term health impacts (e.g. injury and alcohol poisoning) and long-term health impacts (e.g., alcoholic liver cirrhosis, fetal alcohol spectrum disorder, cardiovascular disease, and cancer).[1]

How much and how often an individual drinks are key factors that increase or decrease the risk for health impacts from alcohol.[1] There is a continuum of risk associated with increased alcohol consumption and Canada's Guidance on Alcohol and Health, published in 2023, provide direction on alcohol consumption and potential alcohol related risks. Canada's Guidance on Alcohol and Health | Canadian Centre on Substance Use and Addiction (ccsa.ca).[3]

In 2020, over 115,0000 hospitalizations and 650,000 emergency department visits across the country were due to conditions caused by alcohol.[4] In the same year, over 5,000 hospitalizations and 37,000 emergency department visits in Nova Scotia were due to conditions caused by alcohol.[4] Alcohol-related deaths have risen by 21% since the beginning of the pandemic, with 3,875 deaths attributable to drinking alcohol in Canada in 2021. From 2019 to 2021, the number of alcohol-related deaths among Canadians was higher in those aged 64 years and younger with an associated increased rate of 27% compared to an increased rate or 8% in those aged 65 years and older.[2]

## Alcohol Use Disorder (AUD)

The impact of alcohol is dependent on both the **volume consumed and the pattern of consumption** over time (e.g., drinking patterns). Alcohol use disorder (AUD) is characterized by compulsive heavy alcohol use **and** a loss of control over alcohol intake, so while AUD is associated with heavy drinking it is not defined by use alone.[5]

AUD is a psychiatric illness defined in the Diagnostic and Statistical Manual of Mental disorders, 5th edition (DSM-V) as alcohol use causing clinically significant impairment or distress.[6] It is characterized by impaired control over drinking, ongoing drinking despite knowledge of consequences, and neglect of responsibilities.[6]

## What is the Prevalence of AUD?

A 2012 Canadian Community Health survey by Statistics Canada reported 1 in 5 Canadians aged 15 years of age or older met the criteria for alcohol abuse or dependence, or AUD, in their lifetime.[7] A 2018 World Health Organization (WHO) Global status report on alcohol and health found that the 12-month prevalence estimate of AUD in the Canadian population age 15 years and older was 6.8%, and the prevalence estimate for alcohol dependence, or moderate to severe AUD, was 2.4%.[8]

## What is the Role of Primary Care in the Treatment of AUD?

Patients with AUD, or those who engage in high-risk drinking, are frequently in contact with the primary health care system. Primary care providers have an important role in screening, identifying, assessing, and treating AUD.[9,10,11] Patients generally trust and confide in their primary care providers, treatment interventions can be quickly implemented, and long-term follow-up can be provided.[9,11]

## What is the Role of Pharmacotherapy?

Pharmacotherapy can play a role in assisting individuals with AUD to *reduce or stop drinking*. Two Health Canada approved medications, acamprosate and naltrexone, are considered first line pharmacotherapies for the management of AUD.[10,11,12,13] Despite availability, several Canadian studies have found that pharmacotherapy is underutilized.[14,15]

## What is the Purpose of this Evidence Review?

1. Recognize the role of primary care providers in the screening, diagnosing, and treatment of AUD.
2. Identify and assess patients who may be at risk of alcohol-related harms.
3. Determine if pharmacotherapy is appropriate, and if so, select evidence-based options.

In preparing this document, we reviewed:

- Original publications of RCTs, meta-analyses (MAs) including Cochrane reviews, and network meta-analyses (NMAs).
- Reports from Canadian and international health technology assessment agencies including Canada's Drug and Health Technology Agency (CADTH), National Institute for Health Care and Excellence (NICE), and Agency for Healthcare Research and Quality (AHRQ).
- Canadian and American guidelines
- Review articles
- Choosing Wisely Canada
- Health Canada
- Statistics Canada
- World Health Organization (WHO)
- RxFiles Academic Detailing, Saskatchewan
- Centre for Effective Practice (CEP), Academic Detailing, Ontario

# KEY MESSAGES

- AUD is a chronic, relapsing medical condition.[5,16]

- Primary care providers have an important role in screening, identifying, assessing, and treating AUD.[10,11, 17,18]
  - Using a validated screening tool will help identify patients at risk.[9-11]
  - The DSM-V criteria is used to diagnose AUD as mild, moderate, or severe.[6,16]

- Pharmacotherapy can play a role in assisting individuals with moderate to severe AUD to reduce or stop drinking.[10,11]
  - Psychosocial interventions should also be offered and encouraged.[10,11]

- Naltrexone and acamprosate are first-line pharmacotherapy options for the treatment of moderate to severe AUD.[10,11]

- Factors to consider when selecting a medication include patient goals, dose, concurrent medical conditions/medications, and concurrent alcohol use.

- Abstinence and reducing heavy drinking are both considered important goals.[10,11,42,43]
  - There is a correlation with a reduction in heavy drinking and improved health outcomes; however, the magnitude of the reduction in the risk is uncertain due to limitations in the available evidence.[37-40]
  - Individuals with AUD are more likely to achieve self-identified treatment goals.[44,45]

- Abstinence:
  - Acamprosate is helpful in individuals with moderate to severe AUD who have a treatment goal of abstinence.[23, 25-31] The NNT to prevent a return to drinking is in the range of 9 to 12 (95% CIs 1-32).[23,25-28]
  - Naltrexone may also have a small effect in people who have abstinence as a treatment goal[25,28,29,31] (e.g. preventing a return to drinking, NNT 20; 95% CI 11-500[25]). However, not all MAs have found benefit with naltrexone for this treatment outcome.[24,27,30]

- Reduction in heavy drinking:
  - Naltrexone is helpful in individuals with moderate to severe AUD who have a treatment goal of reducing heavy drinking.[24-31] The NNT to prevent a return to heavy drinking is in the range of 9 to 12 (95% CIs 5-41).[24-28]
  - The best available evidence suggests that acamprosate is not effective in reducing heavy drinking.[23,25,26,28,29] Acamprosate is generally not recommended for people with this treatment goal.[10,11]

- Patients often go through many cycles of relapse and remission before achieving long term remission. Health care providers should address and normalize this possibility.[43]

- Treatment goals may change over time. Continued engagement and follow up is important.[42,43]

# SCREENING AND DIAGNOSING AUD

## Screening

- Despite high prevalence, alcohol problems often go undetected and untreated.[16]

- Several sources recommend universal alcohol screening in primary care.[10,11, 17,18]

- Universal screening:
  - Has been identified as an important public health strategy in the prevention of alcohol related adverse health outcomes.[10,11]
  - Provides opportunities for intervention which may otherwise be lost if providers rely on case identification alone.[11]

- The optimal time interval for screening is undefined. Expert opinion would suggest considering it annually, or for individuals who present with a medical or psychological problem which may be related to alcohol use.[9, 11,16, 19,20]

- Introducing screening questions in a non-judgmental manner is important to build rapport and foster trust in discussing personal alcohol use.

- There has not been consensus on the optimal method for screening although several validated tools exist (see Appendix II):
  - Alcohol Use Disorder Identification Test (AUDIT)
  - AUDIT-consumption (AUDIT-c)
  - **C**ut-down, **A**nnoyed, **G**uilty, **E**ye-opener (CAGE)
  - Single alcohol question screen (SASQ):
    - "*In the past year, how often have you consumed more than 4 drinks (for adult women)* ***or*** *5 drinks (for adult men) on any one occasion*?"
    - Any response greater than "never" or "zero times" would be a positive screen for high-risk drinking and would warrant follow up.

- The AUDIT screening tool has high sensitivity and specificity for the detection of AUD; however, it may be lengthy to administer.[9] Lack of familiarity with scoring this tool as well as time pressures during clinical encounters has been cited as a barrier to widespread use.[11]

- SASQ is an approach that has been specifically tailored for use in the primary care setting where time may be limited.[11]

- The CAGE screening tool is also known for its ease of use and detection of AUD in primary care.[10,11]

- Prescribers can choose to use any validated screening tool. The choice of screening tool should be based on:
  - Familiarity with how to use the test.
  - Being able to implement its use into routine clinical practice.

## Diagnosis

- AUD is a psychiatric illness defined in the DSM-V and characterized by impaired control over drinking, ongoing drinking despite knowledge of consequences, and neglect of responsibilities.[16]

- Patients who have a positive screening result should undergo a diagnostic evaluation using the DSM-V criteria to guide a structured interview.[16]

- Sample interview questions which reflect DSM-V criteria are listed below. Ask your patient: "In the past year have you:"[16]
  - Had times where 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 the aftereffects?
  - Experienced craving –wanted a drink so badly you found it hard to 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 troubles?
  - 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, irritability, anxiety, depression, restlessness, nausea, or sweating? Or sensed things that were not there?

**___/11** Severity of AUD is based on the number of criteria met.

| | **Severity of AUD is defined as** | |
|---|---|---|
| **Mild** | **Moderate** | **Severe** |
| **2-3** criteria | **4-5** criteria | **6** or more criteria |

# PHARMACOTHERAPY

- Pharmacotherapy can play a role in assisting individuals with moderate to severe AUD to reduce or stop drinking. This section focuses on pharmacotherapy in adults (> 18 years) with a diagnosis of AUD.

- The AUD pharmacotherapies discussed in this section do not address acute alcohol withdrawal symptoms and they have not been shown to prevent complications of withdrawal. See page 19 for information on withdrawal management.

## What medications are considered first line in the treatment of AUD?

- Naltrexone and acamprosate are both considered first line medications for AUD.[10,11]

- Naltrexone and acamprosate are commercially available medications that are Health Canada approved for the treatment of alcohol dependence.[21,22]
    - The DSM-V classification of AUD has replaced the DSM-IV classifications of alcohol dependence and alcohol abuse.[6]
        - Alcohol *dependence* is equivalent to *moderate to severe AUD*.
        - Alcohol *abuse* is equivalent to *mild AUD*.

- Naltrexone and acamprosate have distinct biological mechanisms in the management of AUD.
    - Acamprosate modulates the imbalance between glutamate-mediated excitation and GABA-mediated inhibition of neural activity.[21]
        - Acamprosate is thought to restore the normal balance between neuronal excitation and inhibition that becomes altered with chronic alcohol exposure. These effects are thought to reduce symptoms that are associated with post-acute withdrawal from alcohol including disturbances in sleep and mood.

    - Naltrexone is an opioid receptor antagonist that competitively blocks the opioid receptor.[22]
        - Naltrexone is thought to reduce the urge to drink, as well as interfere with the desire to continue drinking if alcohol is consumed.

- Both agents have been evaluated in several MAs and NMAs of RCTs.[23-31]
    - 5 MAs included double blind (DB) RCTs.[23-28]
    - 1 MA and 2 NMAs included both DB and open label RCTs.[29-31]
        - DB RCTs evaluating acamprosate have been classified as having low to medium risk of bias.
        - DB RCTs evaluating naltrexone have been classified as having a low to high risk of bias.

- MAs/NMAs have focused on outcomes related to consumption. Two MAs also considered the impact of these agents on health-related outcomes such as accidents, injuries, quality of life, function, or mortality.[25,26,28]

- Consumption outcomes evaluated in the available MA include:
  - The risk of return to any drinking.
  - The probability of achieving or maintaining abstinence.
  - The risk of return to heavy drinking.
    - The definition of heavy drinking in clinical trials is usually defined as
      - ≥ 4 drinks/day women
      - ≥ 5 drinks/day men

> In Canada, a standard drink is 17.05 mL or 13.45 grams of pure alcohol.[32]
> This is the equivalent to:
> - a bottle of beer (12 oz., 341 ml, 5% alcohol)
> - a bottle of cider (12 oz., 341 ml, 5% alcohol)
> - a glass of wine (5 oz., 142 ml, 12% alcohol)
> - a shot glass of spirits (1.5 oz., 43 ml, 40% alcohol)

- Both abstinence and reduced heavy drinking are considered important treatment goals.[10,11] See Academic Detailing Comment on page 12.

**Characteristics of Randomized Controlled Trials in Meta-analyses and Network Meta-analyses**

- Included participants:
  - With a diagnosis of **alcohol dependence or moderate to severe AUD.**
  - Mean age in the 40s.
- Most trials randomized patients **following detoxification or a short period of abstinence.**
- Excluded patients with co-morbid conditions.
- Had a treatment duration of 12 to 52 weeks (the majority 12 to 26 weeks)
- Conducted in an outpatient setting; however, very few were in a primary care environment.
- Participants also received psychosocial intervention or behavioral therapy, ranging from intensive to less intensive.
  - Intensive: e.g. integrated aspects of cognitive behavioral therapy, 12 step facilitation, motivation interviewing and support system involvement.
  - Less intensive: e.g. physician office visits that provide education about the disease, potential treatments, and advice for reducing drinking with or without support group attendance.

## *ACAMPROSATE*

- Acamprosate has been found to reduce the risk of **return to any drinking** when compared with placebo.[23,25-31] Four MAs estimated the NNT to be in the range of 9 to 12.[23,25-28]
  - NNT 9; 95% CI 6 to 15 (24 DB RCTs, N=6915, $I^2$=79%)[23]
  - NNT 9 (17 DB RCTs, N=4133, $I^2$=64%)[27]
  - NNT 12; 95% CI 8 to 26 (16 DB RCTs, N= 4847, $I^2$=80%, SOE: moderate)[25,26]
  - NNT 11; 95% CI 1 to 32 (20 DB RCTs, N=6380, $I^2$= 78%, SOE: moderate)[28]
    - The substantial heterogeneity, identified through the $I^2$ statistic, was reported to be due to different patient characteristics and study design.[23,25-28] For example, the severity of AUD, requirement of medically assisted withdrawal, length of therapy, and methods of patient recruitment differed across trials.

- A NMA of DB RCTs found that acamprosate is associated with an increased probability of **abstinence** compared to placebo up to 12 months in recently detoxified individuals (OR 1.86; 95% CI 1.49 - 2.33) (SOE: moderate).[30]

- The best available evidence suggests acamprosate is *not effective* in reducing the **return to heavy drinking**.
  - Direct comparisons in 4 MAs of DB RCTs have found that acamprosate does not significantly reduce the risk of return to heavy drinking compared to placebo.[23,25,26,28,29]
  - Indirect comparisons in 1 NMA that included both open label and DB RCTs found that acamprosate significantly reduces the rate of return to heavy drinking compared to placebo (RR 0.78; 95% CI 0.70 - 0.86).[31]

- There is insufficient direct evidence to determine whether treatment with acamprosate leads to improvements in health outcomes.[25,26,28]

### *NALTREXONE*

- MAs of DB RCTs have found that naltrexone reduces the risk of **return to heavy drinking** compared to placebo.[24-31] Four MAs estimated the NNT to be in the range of 9 to 12.[24-28]
  - NNT 9 (27 DB RCTs, N=4693, $I^2$=28%)[24]
  - NNT 11 (27 DB RCTs, N=3688, $I^2$=54%)[27]
  - NNT 12; 95% CI 8 to 26 (19 DB RCTs, N=2875, $I^2$=44%, SOE: moderate)[25,26]
  - NNT 11; 95% CI 5 to 41 (23 DB RCTs, N=3170, $I^2$=56%, SOE: moderate)[28]

- The effect of naltrexone on reducing the risk of **return to any drinking** is uncertain. Two MAs of DB RCTs found that naltrexone does not significantly reduce the risk of return to any drinking compared to placebo.[24,27] Alternatively, 3 MAs report that naltrexone has a small effect on reducing the risk of return to any drinking compared to placebo.[25,26,28,29]
  - Risk Difference -0.05 (95% CI -0.10 to -0.002); NNT 20, 95% CI 11-500 (16 DB RCTs with low risk of bias, N=2347, $I^2$=46%, SOE: moderate).[25,26]
  - Hedges g = 0.12, 95% CI 0.05 to 0.18 (36 placebo-controlled studies)[29]
  - Risk Ratio 0.93 (0.87-0.99); NNT 18, 95% CI 4-32 (20 DB RCTs, N=2719, $I^2$= 36% SOE: moderate)[28]

- The effect of naltrexone on helping to maintain **abstinence** is also uncertain due to conflicting results from 2 NMAs.
  - One NMA evaluated the efficacy of naltrexone in maintaining abstinence at 12 months in recently detoxified adults (17 DB RCTs). The NMA found naltrexone does not increase the odds of being abstinent at 12 months when compared to placebo (OR 1.36; 95% CI 0.97 to 1.91)[30]
  - Another NMA of shorter duration RCTs (DB and open label) found that naltrexone is associated with a higher rate of abstinence relative to placebo (Standardized Rate Ratio 1.15; 95% CI 1.01–1.32).[31]

- There is insufficient direct evidence to determine whether treatment with naltrexone leads to improvements in health outcomes.[25,26,28]

### *NALTREXONE VS. ACAMPROSATE*

- MAs of trials that have directly compared naltrexone and acamprosate have found no significant difference between the two medications for return to any drinking or return to heavy drinking ($I^2$=0%).[23-26,28]
    - However, only a few RCTs with small patient populations have directly compared naltrexone and acamprosate and contributed to this analysis.[33-36]

***Academic Detailing Comment: Does Drinking Less Reduce Harm?***

- Both abstinence and reduced heavy drinking are considered important treatment goals.[10,11]
- RCTs have not directly correlated a reduction in heavy drinking with improved health outcomes.[25,26,28]
    - However, secondary analyses of RCTs have found that individuals who achieve abstinence or low risk drinking have better physical and mental health outcomes compared to individuals who engage in heavy drinking.[37, 38]
- Additionally, several large observational cohort studies have found that reductions in alcohol consumption are associated with reductions in alcohol-attributable hospitalization and mortality.[39, 40]
- While there is a *correlation* with improved health outcomes and a reduction in heavy drinking, the magnitude of the reduction in the risk of health problems is uncertain due to limitations in the available evidence.

## When should medications for AUD be prescribed?

- Pharmacotherapy should be offered to *all primary care patients diagnosed with moderate or severe alcohol disorders*. This recommendation is included in several Canadian Clinical Practice Guidelines (QOE: Moderate; SOE: Strong).[10,11,41]
    - Guidelines also suggest that any patient who has stopped or reduced their drinking but continues to experience strong alcohol cravings or is at risk of relapse may be an appropriate candidate for pharmacotherapy, regardless of AUD severity (expert opinion).[10,11]
- Trials of pharmacotherapy for AUD most often included psychosocial interventions.[25,26]
    - Consider psychosocial interventions for individuals using pharmacotherapy. [11]
    - Pharmacotherapy should still be offered to individuals who are either unable, or unwilling, to participate in psychosocial treatment.[10,11]

# What to consider when selecting naltrexone or acamprosate?

## *PATIENT GOALS*

- Abstinence and reduced heavy drinking are **both** considered important treatment goals.
  - Abstinence avoids the negative consequences associated with alcohol. However, many individuals with AUD either do not want to have a treatment goal of abstinence, or are unable to achieve abstinence.[10,11,42,43]
  - Secondary RCT analyses have found that individuals with AUD are more likely to achieve self-identified treatment goals than goals that are set for them, whether this is a reduction in heavy drinking or abstinence.[44,45]
  - ***Local Clinical Expert Comment***: As health care providers, be mindful not to assume that the patient treatment goal is abstinence.

- Treatment goals may change over time and continued engagement is important.[42,43]
  - Listening to the individual's story and developing goals together may avoid the cycle of learned helplessness that can develop when individuals do not meet behavior change goals, which are set for them by health care providers.

- Patients often go through many cycles of relapse and remission before achieving long term remission. Health care providers should address and normalize this possibility early on.[43]

> ***Local Clinical Expert Comment: Questions to ask when establishing treatment goals.***
>
> 1. How does drinking cause problems in your life?
> 2. How does drinking help you?
> 3. In the short term where do you see your drinking?
> 4. In the long term where do you see your drinking? For example, in 5 years do you see yourself being able to drink in a controlled way or not drinking at all?
>
> When setting treatment goals, it is important to normalize the waxing and waning nature of the disorder for patients.

- **If abstinence is the patient treatment goal:**
  - Acamprosate is helpful in supporting abstinence in some individuals with moderate to severe AUD. [23, 25-31]
  - Naltrexone may have a small effect in people who have a treatment goal of abstinence[25,28,29,31]; however, not all MAs have found benefit with naltrexone for this treatment goal [24,27,30].

- **If a reduction in heavy drinking is the patient treatment goal:**
  - Naltrexone is helpful in supporting a reduction in heavy drinking in some individuals with moderate to severe AUD.[24-31]
  - The best available evidence suggests that acamprosate is not effective in reducing heavy drinking.[30] Acamprosate is generally not recommended for people with this treatment goal.

- Pregnant women and those with health conditions that are worsened by alcohol use (e.g., liver dysfunction, mood disorders, seizure disorders) should be encouraged to target abstinence. [10,11,43]

## *SPECIFIC POPULATIONS*

| CONDITION | CONSIDERATIONS |
|---|---|
| **Hepatic disease** | • Naltrexone has been associated with variable rates of serum enzyme elevations. No cases of hepatic failure have been reported.[22]<br>○ Evaluations assessing the hepatic safety of naltrexone have been at higher doses than those used for the treatment of AUD (> 50 mg/day).[22]<br>• Naltrexone is **contraindicated** in individuals with acute hepatitis or liver failure.[22]<br>• Liver function should be checked prior to initiation, or within several weeks of starting treatment, and monitored periodically while on treatment (e.g. every 3 - 6 months).[11,18]<br>○ Increased monitoring is advised if prescribed to patients with hepatic impairment.[11]<br>○ Use with caution if liver function tests more than 5x the upper limit of normal.[46]<br>• Choosing Wisely Canada recommends not waiting for liver enzyme results to initiate standard dose naltrexone.[47] There is little evidence of hepatotoxicity at standard doses (50 mg once daily) and delaying therapy may result in patients being lost to care.[47]<br>• Patients should be advised of the signs of acute hepatitis (i.e. fatigue, anorexia, nausea, and vomiting) and to stop treatment if symptoms appear.[22] |
| **Renal impairment** | • Acamprosate is **contraindicated** in individuals with severe renal impairment (CrCl < 30 mL/min).[21]<br>○ A dosage adjustment is **not required** in patients with mild renal impairment (CrCl 50-80mL/min). The recommended dose is 2 x 333 mg tablets administered TID.[21]<br>○ A dosage adjustment **is required** in patients with moderate renal impairment (CrCl 30-50mL/min). The recommended dose is 1 x 333 mg tablet administered TID. [21] |
| **Current opioid use or opioid use disorder** | • Naltrexone is **contraindicated** in patients who are currently or expected to be taking opioids (analgesia, opioid agonist treatment, or non-medical use) or are in acute opioid withdrawal.[22]<br>***Local Clinical Expert Opinion***: Naltrexone may be considered in individuals with a history of opioid use disorder who have been abstinent from opioids for 6 months or longer.<br>• Naltrexone can precipitate or exacerbate opioid withdrawal symptoms in individuals who are not free of exogenous opioids, so it should be initiated in an opioid free state (opioid-free for 7- 14 days).[22,48]<br>• Naltrexone is associated with a reduced tolerance to opioids. This may increase the risk of opioid overdose for patients who stop taking the medication and subsequently relapse to opioid use. Patients should be made aware of the potential risks.[22]<br>• Naltrexone blocks the effects of opioids used to treat acute pain.[22]<br>○ If opioids are required, the blocking activity of naltrexone may be overcome with higher opioid doses, but this increases the risk of respiratory depression. Patients who require opioids should be monitored closely in a hospital setting.[22]<br>○ Patients should be advised to inform other health care providers if they are taking naltrexone. |
| **Pregnancy** | • The safety and efficacy of naltrexone and acamprosate have not been fully established in pregnant individuals.[21,22] Specialist consultation, careful assessment of benefit and risks, fully informed patient consent, and regular monitoring and assessment is advised in these cases.[10,11] |
| **Breastfeeding** | • Acamprosate is **contraindicated** in individuals who are breastfeeding.[21]<br>• The safety of naltrexone in individuals who are breastfeeding is uncertain.[22] |

## *OTHER CONSIDERATIONS*

### *Dosing*

- For the treatment of AUD, the Health Canada approved dosing for naltrexone is 50 mg once daily and for acamprosate is 666 mg (2 x 333 mg tablets) administered three times daily.
  - The majority of RCTs have evaluated naltrexone and acamprosate at these standard doses.
  - MA evaluations of other doses of these medications have not found an association with improved outcomes for alcohol consumption (SOE: low).[25]

- Medications can be started at a lower dose and titrated up to reduce adverse effects.
  - Adverse effects for naltrexone as reported in a recent MA include dizziness, nausea, and vomiting (moderate strength of evidence).[28]
  - Adverse effects for acamprosate as reported in a recent MA include diarrhea (moderate strength of evidence).[28]

### *Concurrent alcohol use*

- It is safe to start naltrexone or acamprosate in patients who are using alcohol. However, the available evidence suggests these agents are likely more effective if started after a few days of abstinence or following completion of withdrawal management.

- Overall, the evidence for naltrexone is predominantly from studies that have required patients to **abstain** for at least a few days prior to initiating medication, while the evidence for acamprosate is predominantly from studies that have required patients **undergo detoxification** before starting medication.[23,24,25,27,29]

- An AHRQ MA considered whether patients need to stop drinking before starting medications to benefit but the evaluation could not be completed due to few available studies.[25]

- A 2018 network MA found that naltrexone (14 studies, n = 850) and acamprosate (1 study, n = 518) do not improve total alcohol consumption in a predominantly non-abstinent population.[49]
  - The review included studies where patients had fewer than 5 days of abstinence (ranging from 0 to 4 days).[49] Studies with longer abstinence were excluded from the review. The quality of the RCT evidence was reported to be low. [49]

- Subgroup analyses of a MA considered the impact of longer and shorter periods of abstinence before starting medication.[29] The MA also evaluated detoxification and no detoxification before starting medication.[29]
  - A required abstinence before the trial was associated with greater abstinence and reductions in heavy drinking when naltrexone was compared to placebo (SOE: low). [29]
  - Abstinence and detoxification before the trial was associated with better abstinence outcomes when acamprosate was compared to placebo (SOE: low). [29]

**See the drug table in Appendix III for additional considerations for naltrexone and acamprosate.**

## Is there an advantage to combining naltrexone and acamprosate?

- There have been few evaluations of the efficacy and safety of combination therapy with acamprosate and naltrexone.
  - Available studies are limited by low power, imprecise measures of treatment effects, and other methodological limitations.

- Overall, evidence suggests that the combination of naltrexone and acamprosate is *not* more effective for improving alcohol related outcomes.[50]
  - One small RCT (N = 160) showed that combination therapy was significantly better than acamprosate alone, but not naltrexone alone, for the prevention of relapse into heavy drinking and the maintenance of abstinence.[36] Minor adverse effects (e.g. nausea, diarrhea) were observed to occur more frequently with combination therapy relative to the individual drugs.[36]
  - Another RCT (N=1,383) found that combining naltrexone and acamprosate is not more clinically effective than either drug alone.[33] Minor adverse events including nausea, vomiting, and decreased appetite were highest in the combination therapy group.[33]

- Clinical practice guidelines do not recommend the use of combination pharmacotherapy in AUD.[10,11,12,41]

- Based on the limitations in the available evidence, the clinical indications for use of combination therapy cannot be determined. More research is needed to determine the value, if any, of combination therapy with acamprosate and naltrexone.[10,11]

## How long should medications for AUD be prescribed?

- AUD is a chronic, relapsing condition and requires an ongoing and individually tailored approach to clinical management.

- There is a lack of evidence to guide the optimal duration of AUD pharmacotherapy. Most clinical trials have been short term (i.e. 12 to 26 weeks) with the longest trials evaluating the benefit of medication up to 52 weeks.

- Clinical practice guidelines recommend that AUD pharmacotherapy be prescribed for at least 6 months, at which point the benefit of treatment can be reassessed in collaboration with the patient.[10,11]

- ***Local Clinical Expert Opinion:***
  - Medications should be prescribed for a minimum of 3 months.
  - If the patient is achieving treatment goals, the medication may be continued to support recovery with ongoing monitoring for up to 2 years.
  - If the medication, as a tool is helping, individuals may choose to continue longer term.

## What is the role of disulfiram in the treatment of AUD?

- Disulfiram is another Health Canada approved medication for the treatment of AUD.

- Disulfiram is an aversion therapy that produces a toxic reaction when combined with alcohol.[51]
  - Disulfiram blocks the conversion of acetaldehyde to acetic acid.[51]
  - This results in a buildup of acetaldehyde during alcohol consumption which can produce a variety of adverse effects such as nausea, dizziness, flushing, sweating, palpitations, and hypotension.[51]
  - Effects can be severe and include respiratory depression, CV collapse, arrythmia, MI, acute HF, unconsciousness, convulsions, and in very rare cases can be fatal.[51]

- Several MAs and one NMA have evaluated the efficacy and safety of disulfiram.[25, 30,31,52,53]
  - Disulfiram study designs are varied, and most are low quality.
  - Results have been mixed.
    - Evaluations focused on DB RCTs have found no significant difference between disulfiram and placebo/control groups for return to any drinking, or percentage of drinking days (SOE: low).[25,28,53]
    - Evaluations of RCTs (predominantly open label trials) have found that disulfiram may be effective in reducing the risk of return to any drinking when taken with supervision (e.g. by partner, pharmacist, or AA sponsor) (low quality evidence).[31,52,53]

- Disulfiram is *not recommended in most patients with AUD.* It may be considered in structured and supervised situations such as ongoing addiction care where safety monitoring pathways are in place and adherence can be assessed regularly.[10,11]

- Disulfiram must not be administered to anyone without their full knowledge and consent. Patients and families must receive education on side effects and risks associated with the disulfiram alcohol reaction.[11]

- Disulfiram is no longer commercially available, although it can be compounded at a community pharmacy.

## What about alternate (off-label) options for the treatment of AUD?

### *Off-label Pharmacotherapies*

- Several off-label pharmacotherapies including topiramate and gabapentin have been evaluated for the treatment of AUD.
  - There is less evidence for these treatments as compared to naltrexone and acamprosate, and these medications are *not considered first line*.[10,11]
  - Further research is needed to determine who might benefit most from these medications and when to consider their use.[10,11]

- ***Local Clinical Expert Comment:***
  - Several off-label medications have a role in specialized addiction care.
  - The Addiction Medicine Consult Service (AMCS) can assist with the treatment of individuals with AUD. The AMCS can be accessed for advice if considering off-label pharmacotherapies (contact information available below).

### *Off-label Dosing (Targeted Therapy)*

- It has been suggested in clinical practice guidelines that naltrexone may also be administered on an as needed basis, in situations where an individual believes drinking is imminent or they are experiencing significant cravings.[11] This is often referred to as targeted therapy or the Sinclair method.

- Targeted therapy with naltrexone is currently not a Health Canada approved dosing regimen and the evidence of efficacy is uncertain.
  - As needed naltrexone therapy for AUD has not been well studied. The few small trials that have evaluated this dosing regimen are low quality with many methodological limitations.[54-57]
  - Results have been poorly reported, and results have been inconsistent across trials. Differences in patient populations, study settings, and intensity of concurrent behavioral therapies may explain this inconsistency. [54-57]

- ***Local Clinical Expert Opinion:***
  - Clinical experience suggests that targeted naltrexone therapy is safe and works well as a treatment option, particularly in individuals with *mild to moderate AUD or those who binge drink.*

## How to seek additional support

**Addiction Medicine Consult Services (AMCS):**

Provides rapid Addiction Medicine consultant advice to community physicians, pharmacists and nurse practitioners working in Mental Health and Addictions, Primary Care, Emergency Departments, Long term Care, and Acute Care in Nova Scotia.

AMCS provides verbal evidence-informed clinical advice and guidance to:
- Support clinicians so they can better diagnose and manage substance use disorders.
- Coach clinicians on medication management related to substance use.

AMCS is available Monday to Friday from 8:30 a.m. to 4:30 p.m.
Toll-free: 1-855-970-0234. *Voicemail only on evenings, weekends, and holidays.*

- In addition to coaching on medication management for substance use disorders, the AMCS can provide support and discuss a broad range of questions related to the delivery of addiction care in Nova Scotia.

- Examples of areas where AMCS may provide assistance:
  - System navigation, such as helping determine where a person may access the services most appropriate to the circumstance.
  - Finding a clinician expert, if needed
  - Discussing and/or assisting with diagnostic clarification
  - Discussing cases where a care provider may be struggling with managing patient rapport or relationships.
  - Helping to clarify and support individual treatment goals.

**Local clinical expert opinion: "When in doubt, call the AMCS."**

- A newer addition to services offered through NS Health Mental Health and Addictions is the establishment of recovery support centers. A recovery support center has been established in each zone of NSH, although the accessibility and opening hours may vary depending on the center. Further information on each zone recovery support center may be found at: https://mha.nshealth.ca/en/services/recovery-support-centre.

- Recovery support centers can assist with triaging the appropriate setting for alcohol withdrawal management. They may also provide ongoing early recovery support through intensive group work.

## WITHDRAWAL MANAGEMENT

- All individuals with recent, regular, and heavy alcohol use should be assessed for the risk of developing complications from alcohol withdrawal.[58]

- It is estimated that up to 80% of individuals with AUD can undergo medically supervised withdrawal management on an outpatient basis.[10,11]

- Risk levels can be assessed using the Prediction of Alcohol Withdrawal Severity Scale (PAWSS).[10,58,59]
  - PAWSS is a clinician administered screening tool that has been validated for assessing the risk of developing severe alcohol withdrawal symptoms in the medically ill patient ≥ 18 years of age (see Appendix IV)
    - Do not use in individuals with an active or uncontrolled seizure disorder.

- Outpatient withdrawal management can be considered for individuals who have a PAWSS score less than 4, provided they:[10,11]
  - Have no other concurrent conditions that would require inpatient management.
  - Can attend daily medical visits for the first 3-5 days, and alternating days thereafter (remote follow-up options are acceptable alternatives).
  - Can take oral medications.
  - Have a reliable family member or community-based contact who can monitor symptoms during acute withdrawal period (3-5 days) and support adherence to medications.

- A PAWSS score of four or higher is considered high risk for moderate to severe alcohol withdrawal syndrome. Inpatient management of withdrawal is recommended.[10,11,59]

- Inpatient management is also recommended if there are barriers to community withdrawal management, or for individuals who are:[10, 59]
  - Unable to stop drinking.
  - Pregnant
  - Using multiple substances
  - Have had severe withdrawal symptoms in the past (seizures or delirium tremens)
  - Medically compromised (e.g. have severe or uncontrolled comorbid medical conditions, acute confusion or cognitive impairment, or co-occurring serious psychiatric symptoms).
  - Experiencing or at risk for experiencing severe withdrawal symptoms.

### *Alcohol Withdrawal Monitoring Scales:*

- The PAWSS can only be used to *predict the risk of severe complications of withdrawal*. Withdrawal symptoms should be regularly monitored to assess withdrawal symptoms and to inform ongoing care.[10,58,59]

- There are various scales available for *monitoring the severity of alcohol withdrawal symptoms*.[10,58,59]
  - The Clinical Institute Withdrawal Assessment for Alcohol Revised (CIWA-Ar) is a clinician administered scale (see Appendix IV).
    - CIWA-Ar can be used to monitor the progress of the alcohol withdrawal process at initial presentation and when patients return for follow-up appointments.
  - The Short Alcohol Withdrawal Scale (SAWS) is a patient-administered scale used to monitor the severity of withdrawal symptoms (see Appendix IV).

### *Alcohol Withdrawal Symptoms:*

- Up to 50% of individuals with long-term AUD will experience some degree of withdrawal when alcohol is stopped.[10,11]

- Symptoms of alcohol withdrawal typically begin within 6-24 hours after the last intake of alcohol and peak at 24-48 hours, with resolution within 5-7 days.[59]

**Stages of Alcohol Withdrawal Syndrome[59]**

| *Onset after last drink or decrease in intake* | *Symptoms* |
|---|---|
| **6-12 hours** | Minor withdrawal symptoms – sweating, tremor, anxiety, agitation, insomnia, headaches, nausea/vomiting. Usually lasts for 24-48 hours but can persist for several days to weeks |
| **12-24 hours** | Alcoholic hallucinosis – usually visual but can also be auditory. Usually resolves within 48 hours. |
| **24-48 hours** | Withdrawal seizures – generalized tonic-clonic. Life threatening may occur as early as 2 hours after last drink. Rarely progresses to status epilepticus. |
| **48-72 hours** | Delerium tremens – sweating, agitations, hallucinations, disorientation, tachycardia, hypertension, fever. Life threatening symptoms, peak at 3-5 days. |

- Patients with history of sustained alcohol consumption are also at risk for developing Wernicke's encephalopathy and Korsakoff's psychosis due to malnutrition and a resultant deficiency in thiamine.[58,59]
    - Wernicke's encephalopathy is an acute neurological condition characterized by ophthalmoplegia, ataxia, and confusion.[58,59]
    - Korsakoff's psychosis consists of memory loss, learning deficits, and confabulation and is thought to be the consequence of one or more episodes of WE.[58,59]

### *Pharmacotherapy for Management of Alcohol Withdrawal*

- The goals of treatment are to minimize/or prevent the symptoms of alcohol withdrawal. Monitor for the emergence of severe withdrawal and continued alcohol use.[10]

- Canadian guidelines recommend the use of non-benzodiazepine medications (i.e. carbamazepine, gabapentin) for outpatient management of **mild to moderate** withdrawal symptoms in individuals at **low risk of severe complications** (PAWSS <4). (QOE: low to moderate; Strong recommendation).[10]
    - Note: Non-benzodiazepine medications have not been found to prevent seizures or delirium tremens and should not be used in individuals at risk of these complications.[60,61]

**Sample Dosing Protocols Non-Benzodiazepines:**

| *Drug* | *Protocol* | *Comments* |
|---|---|---|
| **Gabapentin*** [19] | 1200mg daily (÷ BID or TID) tapered over 4 to 6 days.<br><br>**Loading Dose:** 1200mg ÷ BID or TID<br>**Days 1 to 3**: 600-1200mg ÷ BID or TID<br>**Days 4 to 7**: taper to 300-600mg ÷ BID or TID | Caution: potential for non-medical use, diversion, and dependence, CNS depression; renal impairment |
| **Carbamazepine IR** [10,11] | **Day 1:** 200 mg QID<br>**Day 2:** 200 mg TID<br>**Day 3:** 200 mg BID<br>**Day 4-5:** 200 mg OD | Caution: drug interactions |

IR = immediate release tablets, * *For patients who are also taking an opioid, prescribe a naloxone kit when prescribing gabapentin.*

- Benzodiazepines have been found to be effective in preventing severe withdrawal symptoms including seizures.[62]

- Benzodiazepines should be used with caution in outpatient use and requires close monitoring.
    - Important considerations:[10]
        - The combined use of benzodiazepines and alcohol can cause respiratory depression and death, the importance of abstaining from alcohol must be emphasized to patients and families or caregivers.
        - Prescribe a short, tapered prescription (5–7 days), daily dispensing from a pharmacy, and frequent clinical visits to closely monitor side effects, symptoms, and alcohol use, and to make dose adjustments as needed. ***Benzodiazepines should not be prescribed to patients beyond the acute withdrawal period.***
        - Fixed dosing is recommended for the outpatient setting. Dosing should be individually tailored, with adjustments made following daily check-ins.
        - Enlisting family members or caregivers to assess symptom severity and dispense medication is recommended (if appropriate and with the patient's consent).

**Sample Dosing Protocols Benzodiazepines:**

| *Drug* | *Protocol* | *Comments* |
|---|---|---|
| **Diazepam**[10] (Long acting) | **Day 1:** 5-10 mg QID<br>**Day 2:** 5-10 mg TID<br>**Day 3:** 5-10 mg BID<br>**Day 4:** 5-10 mg HS | Caution: potential for non-medical use, diversion, and dependence; CNS depression; renal/liver impairment |
| **Lorazepam**[10] (Intermediate acting) | **Day 1-2:** 1-2 mg q4h<br>**Day 3-4:** 0.5-1 mg q4h | Caution: potential for non-medical use, diversion, and dependence; CNS depression; renal/liver impairment<br><br>*Intermediate acting benzodiazepines should be used in older adults, individuals susceptible to oversedation, or individuals with compromised liver function*. |

***** *For patients who are also taking an opioid, prescribe a naloxone kit when prescribing a benzodiazepine.*

## *Nutritional Supplements:*

- Guidelines recommend oral thiamine (100-200mg) and encourage vitamin supplementation for folic acid (1mg) and vitamin B6 (2mg) before and during withdrawal management. [10,11]
    - Note: Thiamine is not well absorbed when taken orally. The ideal dose and duration are uncertain.[63]

# CLINICAL RESOURCES FOR AUD

| Clinical Service/Resource | Contact Information |
|---|---|
| **Addiction Medicine Consult Service (AMCS)**<br><br>Provides verbal evidence-informed clinical advice and guidance to healthcare providers. | https://mha.nshealth.ca/en/clients-and-providers/resources-providers/addictions-medicine-consult-service<br>• Phone: 1-855-970-0234. M-F 8:30am -4:30pm. Voicemail only - evenings, weekends, holidays. |
| **Atlantic Mentorship Network (AMN)**<br><br>Healthcare provider educational support for managing patients with pain and addiction. | https://www.atlanticmentorship.com/<br>• Phone: 1-902-430-5022<br>• Email: Atlantic.MentorshipNetwork@nshealth.ca |
| **Recovery Support Centre**<br><br>Provides education, recovery and harm reduction support, along with 1:1 support and group treatment for people struggling with substance use concerns. | https://mha.nshealth.ca/en/services/recovery-support-centre<br>• Access service as per NSH zone programs |
| **Mental Health and Addictions (NS Health)**<br><br>Intake service: Patient support for accessing services. | https://mha.nshealth.ca/en<br>• **Crisis Line** (24/7): Phone 1-888-429-8167<br>• **Intake Service** (M-F 8:30am-4:30pm; T & Th until 8pm): Phone 1-855-922-1122 |
| **988 Crisis Helpline**<br><br>Provides urgent, live, trauma-informed support 24 hours a day, 7 days a week. | https://988.ca/<br>• Phone or text: 988 |
| **Access Wellness Nova Scotia**<br><br>Single session 1-to-1 counselling, online, phone, in person (select locations). | https://go.lifeworks.com/access-wellness-nova-scotia-en<br>• Phone: 1-833-691-2282 (7 days a week, 8:30am – 11:00pm) |
| **Help with Drinking**<br><br>Information & resources for both the public and healthcare providers (linked with BC Centre on Substance Use). | https://helpwithdrinking.ca/ |
| **Self Management and Recovery Training (SMART)**<br><br>Online peer support for recovery. | https://smartrecovery.org/ |
| **Alcoholics Anonymous**<br>Peer support groups.<br><br>**Al-Anon**<br>Support for people concerned about someone's drinking. | https://www.aa.org/<br><br>https://al-anon.org/ |
| **Outpatient Withdrawal Management, Patient and Family Guide (NS Health)** | https://www.nshealth.ca/sites/default/files/documents/pamphlets/2312.pdf |

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# APPENDICES

## APPENDIX 1: GLOSSARY OF EVIDENCE BASED MEDICINE TERMS

**Number Needed to Treat (NNT)** [1]
The number of subjects who need to be treated for one subject to have a favorable outcome. **Note:** It is the inverse of absolute risk reduction (1 ÷ absolute risk reduction). Thus, if the results of a study indicate that the probability of death in a control group is 25% and the probability of death in a treatment group is 10% the number needed to treat would be 1.0 ÷ (0.25 - 0.10) = 6.7, therefore 7 subjects.

**Risk Difference (RD) (synonym: Absolute Risk Reduction)** [1]
The value of the difference between the probability that an event will occur in the group exposed to a given factor and the probability that this event will occur in the group not exposed to this factor.
**Note:** For example, if the results of a trial were that the probability of death was 25% in the control group and 10% in the experimental group, the absolute risk reduction would be 0.25 – 0.10 = 0.15.

**Relative Risk (RR) (synonym Risk Ratio)** [1]
The ratio (quotient) of the risk that an event will occur among the subjects exposed to a given factor and the risk that this event will occur among the subjects not exposed to this factor. **Note:** A relative risk (RR) of 1 indicates that the risk is equal in the groups compared, and RR > 1 indicates that the factor increases the risk, and an RR < 1 indicates that the factor decreases the risk.

**Standardized Rate Ratio (SRR)**[2]
Rate ratios are closely related to risk ratios but compare the incidence rates, person-time rates, or mortality rates of two groups. Consider as an example a prospective cohort study that was used to investigate the effects of hormone replacement therapy (HRT) on coronary artery disease in post-menopausal women. The investigators calculated the incidence rate of coronary artery disease in post-menopausal women who had been taking HRT and compared it to the incidence rate in post-menopausal women who had not taken HRT. The findings are summarized in this table:

| Post-menopausal Hormone Use | # with Coronary Artery Disease | Person-Years of Disease-free Follow-up |
|---|---|---|
| Yes | 30 | 54,308.7 |
| No | 60 | 51,477.5 |

- The rate in those using hormones was 30 / 54,308.7 = 55.2 per 100,000 person-years
- The rate in those NOT using hormones was 60 / 51,477.5 = 116.6 per 100,000 person-years.

So, the rate ratio was 0.47. Interpretation: Women who used postmenopausal hormones had 0.47 **times the *rate*** of coronary artery disease compared to women who did not use postmenopausal hormones. (Rate ratios are often interpreted as if they were risk ratios, e.g., post-menopausal women using HRT had 0.47 times the risk of CAD compared to women not using HRT, but it is more precise to refer to the ratio of rates rather than risk.) **A standardized rate ratio** is calculated when the numerator and denominator rates are standardized to the same (standard) population distribution.

**Odds Ratio (OR)** [1]
The odds ratio is a measure of the effect of treatment that compares the probability of suffering an event in the treatment group with the probability of suffering it in the control group. For example, if the results of a trial indicate that the probability of death in the control group is 25% and the probability of death in the treatment group is 10%, the odds ratio would be 0.10 ÷ (1.0 – 0.10) ÷ (0.25 ÷ (1.0 – 0.25) = 0.33.

**Effect Size** [1]

1. A generic term for the estimate of effect for a study. How much one group differs from another.
2. A dimensionless measure of effect that is typically used for continuous data when different scales (e.g. for measuring pain) are used to measure an outcome and is usually defined as the difference in means between the intervention and control groups divided by the standard deviation of the control or both groups.

**Hedges g statistic**

The Hedges g statistic is a measure of effect size. A Hedges g value in the range of 0.2 are considered small, values in the range of 0.5 are considered medium, and values of 0.8 are considered large.

**95% Confidence Interval (95% CI)** [1]

A 95% confidence interval indicates that there is a 95% probability that the confidence interval calculated from a particular study includes the true value of the parameter. If the interval includes a null value (a difference in means of 0, and odds ratio or a relative risk of 1, or a correlation coefficient of 0, for example), the null hypotheses cannot be rejected. A narrow confidence interval around a point estimate indicates a more precise estimate than a wide confidence interval.

**Meta-analysis** [3]

Meta-analysis is the statistical combination of results from two or more separate studies. Potential advantages of meta-analyses include an improvement in precision, the ability to answer questions not posed by individual studies, and the opportunity to settle controversies arising from conflicting claims. However, they also have the potential to mislead, particularly if specific study designs, within-study biases, variation across studies, and reporting biases are not carefully considered.

**Network Meta-analysis** [4]

A network meta-analysis is a technique for comparing three or more interventions simultaneously in a single analysis by combining both direct and indirect evidence across a network of studies. A network meta-analysis produces estimates of the relative effects between any pair of interventions in the network, and usually yields more precise estimates than a single direct or indirect estimate. It also allows estimation of the ranking and hierarchy of interventions. However, they also have the potential to mislead, particularly if specific study designs, within-study biases, variation across studies, and reporting biases are not carefully considered.

**Heterogeneity** [1,5]

Studies brought together in a systematic review will differ. Any kind of variability among studies in a systematic review may be termed heterogeneity. The presence of heterogeneity affects the extent to which generalizable conclusions can be formed. It is important to identify heterogeneity in case there is sufficient information to explain it. **Note**: A distinction is sometimes made between "statistical heterogeneity" (differences in the reported effects), "methodological heterogeneity" (differences in study design) and "clinical heterogeneity" (differences between studies in key characteristics of the participants, interventions, or outcome measures). Statistical tests of heterogeneity are used to assess whether the observed variability in study results (effect sizes) is greater than that expected to occur by chance. However, these tests have low statistical power.

**$I^2$** [5]

A statistic for quantifying inconsistency (heterogeneity) in a meta-analysis. A rough guide to interpretation is as follows:

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity*.
- 50% to 90%: may represent substantial heterogeneity*.
- 75% to 100%: considerable heterogeneity*.

*The importance of the observed value of $I^2$ depends on the magnitude and direction of effects, and the strength of evidence for heterogeneity (e.g. P value from the chi-squared test, or a confidence interval for $I^2$).

**Strength of Evidence (SOE)** [6]

The Agency for Healthcare Research and Quality (AHRQ), a health technology assessment group, have developed guidelines to evaluate the overall strength of evidence considered in their systematic reviews and meta-analyses. The AHRQ approach evaluates 4 key domains for the evidence: risk of bias, consistency, directness, and precision. This information is used to classify the overall SOE as high, moderate, low, or insufficient.

| SOE | Definition |
|---|---|
| High | High confidence that the evidence reflects the true effect. Further research is very unlikely to change confidence in the estimate of effect. |
| Moderate | Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate. |
| Low | Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. |
| Insufficient | Evidence either is unavailable or does not permit a conclusion. |

**Quality of Evidence (QOE) using GRADE System** [7]

The GRADE system categorizes quality of evidence and strength of recommendations for use in clinical practice guidelines. The GRADE system classifies the quality of evidence in one of four levels—high, moderate, low, and very low. Evidence based on randomized controlled trials begins as high-quality evidence, but our confidence in the evidence may be decreased for several reasons, including:

- Study limitations
- Inconsistency of results
- Indirectness of evidence
- Imprecision
- Reporting bias.

Observational studies start with a "low quality" rating. Grading upwards may be warranted if the magnitude of the treatment effect is very large, if there is evidence of a dose-response relation or if all plausible biases would decrease the magnitude of an apparent treatment effect.

Quality of evidence definitions:

1. High quality – Further research is very unlikely to change confidence in the estimate of effect.
2. Moderate quality – Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
3. Low quality – Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
4. Very low quality – any estimate of effect is very uncertain.

**Strength of Recommendation (SOR) using the GRADE system** [7]

The GRADE system categorizes quality of evidence and strength of recommendations for use in clinical practice guidelines. GRADE offers two types of recommendations: strong and weak. When the desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not, guideline panels offer strong recommendations. When there is uncertainty due to low quality of evidence or evidence suggests the desirable and undesirable effects are closely balanced the guideline panel offers a weak recommendation.

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# APPENDIX II: VALIDATED SCREENING TOOLS FOR AUD

## The Alcohol Use Disorders Identification Test (Audit)[1,2]

Read questions as written. Record answers carefully. Begin the AUDIT by saying "Now I am going to ask you some questions about your use of alcoholic beverages during this past year." Explain what is meant by "alcoholic beverages" by using local examples of beer, wine, vodka, etc. Code answers in terms of "standard drinks". Place the correct answer number in the box at the right.

**1. How often do you have a drink containing alcohol?**
(0) Never [Skip to Qs 9-10]
(1) Monthly or less
(2) 2 to 4 times a month
(3) 2 to 3 times a week
(4) 4 or more times a week

**2. How many drinks containing alcohol do you have on a typical day when you are drinking?**
(0) 1 or 2
(1) 3 or 4
(2) 5 or 6
(3) 7, 8, or 9
(4) 10 or more

**3. How often do you have six or more drinks on one occasion?**
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

Skip to Questions 9 and 10 if Total Score for Questions 2 and 3 = 0

**4. How often during the last year have you found that you were not able to stop drinking once you had started?**
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

**5. How often during the last year have you failed to do what was normally expected from you because of drinking?**
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

**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?**
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

**7. How often during the last year have you had a feeling of guilt or remorse after drinking?**
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

**8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?**
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

**9. Have you or someone else been injured as a result of your drinking?**
(0) No
(2) Yes, but not in the last year
(4) Yes, during the last year

**10. Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?**
(0) No
(2) Yes, but not in the last year
(4) Yes, during the last year

**Interpretation:** Scores of 8 or higher indicate hazardous or harmful use. Proceed to diagnosis and assessment for AUD.

Total score:

The 10-item AUDIT takes approximately 3 minutes. Using a cut-point of 8, the AUDIT has an estimated sensitivity of 97% and specificity of 78% for the identification of hazardous alcohol use in general primary care populations.[1]

## Single Alcohol Screening Question (SASQ) [1,3]

"In the past year, how often have you consumed more than 4 drinks (for adult women) or 5 drinks (for adult men) on any one occasion?"

Studies have found that the sensitivity of single question screening ranges from 60-90% versus reference standards (e.g., AUDIT), and systematic reviews have concluded that this is a valid option in clinical settings where time and patient interactions are limited.[1]

## The AUDIT-C Consumption (AUDIT-C) Tool [1,4]

| | |
|---|---|
| **1. How often do you have a drink containing alcohol?**<br>(0) Never<br>(1) Monthly or less<br>(2) 2 to 4 times a month<br>(3) 2 to 3 times a week<br>(4) 4 or more times a week | |
| **2. How many units of alcohol do you drink on a typical day when you are drinking?**<br>(0) 1 or 2<br>(1) 3 or 4<br>(2) 5 or 6<br>(3) 7, 8, or 9<br>(4) 10 or more | |
| **3. How often do you have six or more drinks on one occasion?**<br>(0) Never<br>(1) Less than monthly<br>(2) Monthly<br>(3) Weekly<br>(4) Daily or almost daily | |
| **Interpretation:** In men, a score of 4 or more is considered positive for hazardous drinking.<br>In women, a score of 3 or more is considered positive for hazardous drinking.<br>If score is positive, proceed to diagnosis and assessment for AUD. | Total score: |

The AUDIT-Consumption (AUDIT-C) tool consists of three questions about alcohol consumption and uses sex-specific cut-points: for adult male patients, a score of 4 or higher indicates hazardous or harmful drinking, while in adult female patients, a score of 3 or higher indicates hazardous or harmful drinking. The AUDIT-C has a sensitivity of 86% and specificity of 78% for the identification of hazardous alcohol use in general primary care populations using sex-specific cut points (women — 3, men — 4).[1]

## The Cut-down, Annoyed, Guilty, Eye Opener (CAGE) Tool [1,5]

Consists of four yes/no questions

| | |
|---|---|
| **1** | Have you ever felt you ought to Cut down on your drinking? |
| **2** | Have people Annoyed you by criticizing your drinking? |
| **3** | Have you ever felt bad or Guilty about your drinking? |
| **4** | Have you ever had a drink in the morning (Eye-opener) to steady your nerves or get rid of a hangover? |

Using a cut-point of 2 or more "yes" responses, the CAGE has an estimated sensitivity of 84% and specificity of 85% for the detection of AUD and alcohol-related harms.[1]

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## Appendix III: Drug Table Naltrexone and Acamprosate for AUD

| | Naltrexone | Acamprosate |
|---|---|---|
| **Mechanism of action** | • Known opioid-receptor antagonist.<br>• Reduces the urge to drink, as well as interfere with the desire to continue drinking if alcohol is consumed.<br>• Not associated with tolerance or dependence. | • Possible glutamate receptor antagonist.<br>• Restores balance between neuronal excitation and inhibition that becomes altered by chronic alcohol exposure; reduces symptoms associated with post-withdrawal (i.e., sleep and mood disturbances).<br>• Not associated with tolerance or dependence. |
| **Dose** | • Standard daily dose: 50 mg (1 x 50 mg tablet) orally daily<br>• Dose titration: 25 mg for first few days to help with GI tolerability.<br>*NOTE: If patients are physically dependent on opioids this medication will precipitate withdrawal.* | • Standard daily dose: 666 mg (2 x 333 mg tablets) orally TID<br>• Dose titration: 333 mg TID for first few days to help with GI tolerability.<br>• Dose adjustments for renal impairment:<br>  • Moderate (CrCL 30-50 mL/min): 333 mg TID is recommended.<br>  • Severe (CrCL 30 mL/min or less): *Contraindicated.* |
| **Place in Therapy** | • Most effective to help reduce heavy drinking.<br>• Small, uncertain effects to support abstinence (return to any drinking). | • Most effective to support abstinence (return to any drinking).<br>• Generally, not recommended to help reduce heavy drinking. |
| | Studied in conjunction with psychosocial interventions; should be offered/encouraged as combination therapy.<br>Current evidence does not suggest added benefit when naltrexone and acamprosate are combined. | |
| **Treatment Initiation** | • Safe to start while patients are using alcohol but may be more effective if started following a few days of abstinence.<br>• Start in patients who are *opioid free* (7-14 days) because naltrexone can precipitate or exacerbate opioid withdrawal symptoms.<br>***Local Clinical Expert Opinion***: Naltrexone may be considered in individuals with a history of opioid use disorder who have been abstinent from opioids for 6 months or longer.<br>• Naltrexone is associated with a reduced tolerance to opioids. Patients should be made aware of the potential risk. | • Safe to start while patients are using alcohol but may be more effective if started following completion of withdrawal management. |
| **Treatment Duration** | A specific treatment duration has not been well established. Guidelines recommend at least 6 months then reassess. ***Clinical Practice Guidelines***<br>***Local Clinical Expert Opinion:***<br>• Medications should be prescribed for a minimum of 3 months.<br>• If the patient is achieving treatment goals, the medication may be continued to support recovery with ongoing monitoring for up to 2 years.<br>• If the medication, as a tool is helping, individuals may choose to continue longer term. | |

| | Naltrexone | Acamprosate |
|---|---|---|
| **Common Adverse effects** | • Nausea, vomiting, abdominal pain, anxiety, insomnia, nervousness, fatigue, joint and muscle pain, and headache. | • Diarrhea, nausea, vomiting, abdominal pain. |
| | Adverse reactions usually occur early during drug therapy and are transient. Dose titration minimizes side effects. | |
| **Drug interactions** | • Opioids<br>• Caution with other potentially hepatotoxic medications | • None reported |
| **Contraindications** | • History of sensitivity to naltrexone<br>• Any current opioid use (analgesia, opioid agonist treatment, or non-medical use) or acute opioid withdrawal<br>• Acute Hepatitis or Liver Failure | • History of sensitivity to acamprosate<br>• Severe renal impairment (CrCL of 30mL/min or less)<br>• Breastfeeding* |
| **Precautions** | • Renal impairment: Use with caution as naltrexone and its primary metabolite is excreted through the urine.<br>• Breastfeeding*<br>• Pregnancy*<br>• Hepatotoxicity: Naltrexone has been associated with variable rates of serum enzyme elevations. No cases of hepatic failure have been reported. Advise patients of signs of acute hepatitis (i.e., fatigue, anorexia, nausea, vomiting) and to stop treatment if they appear. | • Moderate renal impairment (see "dose" section for dosage adjustments)<br>• Pregnancy* |
| **Lab Monitoring** | • Liver function should be checked prior to initiation, or within several weeks of starting treatment, and monitored periodically (e.g., every 3 - 6 months). ***Clinical Practice Guidelines***<br>○ Choosing Wisely Canada recommends not waiting for liver enzyme results to initiate naltrexone. There is little evidence of hepatotoxicity at standard doses (50 mg once daily) and delaying therapy may result in patients being lost to care.**<br>○ Increased monitoring is advised in hepatic impairment. | • Renal function tests (urea/electrolytes/serum creatinine) |
| **Cost/30 days*** ** | $84 (50 mg daily) ***generics available*** | $163 (666 mg TID) |
| **Nova Scotia Pharmacare Status** | Full benefit | Full benefit |

*This document is not intended to be all-inclusive. Please refer to the Health Canada Product Monographs and the Academic Detailing document "Alcohol Use Disorder: First-Line Pharmacotherapy 2024"*
*TID = three times daily; CrCL = creatinine clearance; *Safety and efficacy have not been well established in these patient populations ** https://choosingwiselycanada.org/recommendation/addiction-medicine/*
*** Pricing is approximate from www.mckesson.ca. **Clinical Practice Guidelines**: British Columbia Centre on Substance Use (BCCSU), 2019, available at: https://www.bccsu.ca/clinical-care-guidance/.*

# Appendix IV: Alcohol Withdrawal Management Scales

## Prediction of Alcohol Withdrawal Scale (PAWSS) [1,2]

| | |
|---|---|
| **PART A: THRESHOLD CRITERIA — Yes or No, no point** | |
| Have you consumed any amount of alcohol (i.e., been drinking) **within the last 30 days**?<br>**OR** Did the patient have a positive (+) blood alcohol level (BAL) on admission? | |
| If the answer to either is YES, proceed to next questions. | |
| **PART B: BASED ON PATIENT INTERVIEW — 1 point each** | |
| 1 | Have you been recently **intoxicated/drunk**, within the last 30 days? |
| 2 | Have you **ever** undergone alcohol use disorder rehabilitation treatment or treatment for alcoholism?<br>(i.e., in-patient or out-patient treatment programs or AA attendance) |
| 3 | Have you **ever** experienced any previous episodes of alcohol withdrawal, regardless of severity? |
| 4 | Have you **ever** experienced blackouts? |
| 5 | Have you **ever** experienced alcohol withdrawal seizures? |
| 6 | Have you **ever** experienced delirium tremens or DTs? |
| 7 | Have you combined alcohol with other "downers" like benzodiazepines or barbiturates, **during the last 90 days**? |
| 8 | Have you combined alcohol with any other substance of abuse, **during the last 90 days**? |
| **PART C: BASED ON CLINICAL EVIDENCE — 1 point each** | |
| 9 | Was the patient's blood alcohol level (BAL) greater than 200mg/dL? (SI units 43.5 mmol/L)*<br>**OR** *Have you consumed any alcohol in the past 24 hours? |
| 10 | Is there any evidence of increased autonomic activity?<br>e.g., heart rate >120 bpm, tremor, agitation, sweating, nausea |

*Due to the common absence of a BAL the committee has added this modification. Please see next page.

**Interpretation**

Maximum score = 10. This instrument is intended as a SCREENING TOOL. The greater the number of positive findings, the higher the risk for the development of alcohol withdrawal syndrome (AWS).

**A score of ≥4 suggests HIGH RISK for moderate to severe (complicated) AWS; prophylaxis and/or inpatient treatment are indicated.**

# Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-AR) [1,3]

Patient _____ Date _____ Time _____
(24 hour clock, midnight = 00:00)

Pulse or heart rate, taken for one minute _____ Blood Pressure _____

**Nausea and Vomiting**

Ask *"Do you feel sick to your stomach? Have you vomited?"* Observation.

0 no nausea and no vomiting
1 mild nausea with no vomiting
2
3
4 intermittent nausea with dry heaves
5
6
7 constant nausea, frequent dry heaves and vomiting

**Tactile Disturbances**

Ask *"Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?"* Observation.

0 none
1 very mild itching, pins and needles, burning or numbness
2 mild itching, pins and needles, burning or numbness
3 moderate itching, pins and needles, burning or numbness
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

**Tremor**

Arms extended and fingers spread apart. Observation.

0 no tremor
1 not visible, but can be felt fingertip to fingertip
2
3
4 moderate, with patient's arms extended
5
6
7 severe, even with arms not extended

**Auditory Disturbances**

Ask *"Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?"* Observation.

0 not present
1 very mild harshness or ability to frighten
2 mild harshness or ability to frighten
3 moderate harshness or ability to frighten
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

**Paroxysmal Sweats**

Observation.

0 no sweat visible
1 barely perceptible sweating, palms moist
2
3
4 beads of sweat obvious on forehead
5
6
7 drenching sweats

**Visual Disturbances**

Ask *"Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?"* Observation.

0 not present
1 very mild sensitivity
2 mild sensitivity
3 moderate sensitivity
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

Continue to next page

| | |
|---|---|
| **Anxiety**<br>Ask *"Do you feel nervous?"*<br>Observation.<br>0 no anxiety, at ease<br>1 mild anxious<br>2<br>3<br>4 moderately anxious, or guarded, so anxiety is inferred<br>5<br>6<br>7 equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions | **Headache, Fullness in Head**<br>Ask *"Does your head feel different? Does it feel like there is a band around your head?"* Do not rate for dizziness or lightheadedness. Otherwise, rate severity.<br>0 not present<br>1 very mild<br>2 mild<br>3 moderate<br>4 moderately severe<br>5 severe<br>6 very severe<br>7 extremely severe |
| **Agitation**<br>Observation.<br>0 normal activity<br>1 somewhat more than normal activity<br>2<br>3<br>4 moderately fidgety and restless<br>5<br>6<br>7 paces back and forth during most of the interview, or constantly thrashes about | **Orientation and Clouding of Sensorium**<br>Ask *"What day is this? Where are you? Who am I?"*<br>0 oriented and can do serial additions<br>1 cannot do serial additions or is uncertain about date<br>2 disoriented for date by no more than 2 calendar days<br>3 disoriented for date by more than 2 calendar days<br>4 disoriented for place/or person |
| The CIWA-Ar is not copyrighted and may be reproduced freely.<br>This assessment for monitoring withdrawal symptoms requires approximately 5 minutes to administer.<br>The maximum score is 67 (see instrument). Patients scoring less than 10 do not usually need additional medication for withdrawal. | Total CIWA-Ar Score _____<br>Rater's Initials _____<br>Maximum Possible Score 67 |

### Interpretation

| Score | Severity |
|---|---|
| 0-9 | Very mild withdrawal |
| 10-15 | Mild withdrawal |
| 16-20 | Moderate withdrawal |
| >20 | Severe withdrawal |

Due to the need for a clinical interview, the CIWA-Ar is not appropriate where there is a language barrier or if the patient is cognitively impaired, delirious, or displaying a decreased level of consciousness.[1]

# Short Alcohol Withdrawal Scale (SAWS) [1,4]

| Please put a tick in the boxes to show how you have been feeling for all of the following conditions **in the last 24 hours**. | | | | |
|---|---|---|---|---|
| | NONE<br>0 points per check | MILD<br>1 point per check | MODERATE<br>2 points per check | SEVERE<br>3 points per check |
| Anxious | | | | |
| Sleep disturbance | | | | |
| Problems with memory | | | | |
| Nausea | | | | |
| Restless | | | | |
| Tremor (shakes) | | | | |
| Feeling confused | | | | |
| Sweating | | | | |
| Miserable | | | | |
| Heart pounding | | | | |

## Interpretation

| Score | Severity |
|---|---|
| < 12 | Mild withdrawal |
| ≥ 12 | Moderate to severe withdrawal |

1. British Columbia Centre on Substance Use (BCCSU), B.C. Ministry of Health and B.C. Ministry of Mental Health and Addictions. Provincial Guideline for the Clinical Management of High-Risk Drinking and Alcohol Use Disorder. 2019. Vancouver, B.C.: BCCSU. Accessed at: https://www.bccsu.ca/clinical-care-guidance/ in February 2023.
2. Maldonado JR, Sher Y, Ashouri JF, et al. The "Prediction of Alcohol Withdrawal Severity Scale" (PAWSS): systematic literature review and pilot study of a new scale for the prediction of complicated alcohol withdrawal syndrome. *Alcohol*. 2014;48(4):375-390.
3. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *Br J Addict*. 1989;84(11):1353-1357.
4. Gossop M, Keaney F, Stewart D, Marshall EJ, Strang J. A Short Alcohol Withdrawal Scale (SAWS): development and psychometric properties. *Addict Biol*. 2002;7(1):37-43.