Dear primary care provider,

The following information is from the Canadian Alcohol Use Disorder Society's website: www.cauds.org.

About The Canadian Alcohol Use Disorder Society

The Canadian AUD Society, formed in Sept. 2020, is a national organization that aims to provide hope and improve quality of life by advancing proven and effective treatment for Alcohol Use Disorder. By positively transforming attitudes, beliefs and behaviours, it also advocates for a more compassionate perception of this disorder amongst care providers, patients and society as a whole.

Included in this Information Package

- An AUD Medications Table, Dr. Jeff Harries
- How I choose an AUD Pharmacotherapy, Dr. Jeff Harries
- Alcohol Use Disorder Clinical Pearls, Mayo Clinic

More Resources

For more information about treating AUD with proven and effective medications in conjunction with counselling and traditional supports, please visit our website www.cauds.org.

Sincerely,

Dr. Jeff Harries, MD, Penticton BC
And the CAUDS Team

As a nonprofit, we are not affiliated with or funded by pharmaceutical or related enterprise.

AUD Medications Table - August 2nd, 2020

Choice	When to Use	Clinical Scenario	Medications for AUD	Dose	Oral Frequency	Form	Cost	Coverage/Plan	Notes	Mechanism
First Line	Ideally Sober >7 days	Reduces craving when patient sober. If patient resumes drinking, it will not help them stop.	**Acamprosate**	333mg	333mg TID if wt < 60kg, or 666mg TID if wt > 60kg	Tab	$5/d unless covered under plan.	After MD/NP signs BC's Collaborative Prescribing Agreement once in their career all of their patients will be covered (once annual BC Pharmacare deductable reached). May be paid fully by Private Plans.	Do not use if decreased renal function.	Glutamate antagonist (reduces excitatory effect).
	Patient may start Medication even when still drinking.	Works for High Reward/Low Relief drinkers.Use for patient who is still drinking or has stopped and is likely to resume. Reduces chance of going back to heavy drinking if	**Naltrexone**	50mg	1/4 to 1 tab qAM or 1hr before first drink of day	Tab	$5/d unless covered under plan.	After MD/NP signs BC's Collaborative Prescribing Agreement once in their career all of their patients will be covered (once annual Pharmacare deductable reached). May be paid fully by Private Plans.	Do not use if patient using opiates as it will precipitate withdrawal symptoms. Not for anyone with liver failure, unless very closely followed. May be used with Ondansetron for people with EOAUD.	Mu-Opiod blocker reduces reward reinforcement and encourages extinction of urge. Supports functional improvement of executive decision network that may have been impaired/damaged by alcohol use.
Second Line		May be more likely to respond if also has hx or current use of significant cocaine/meth, and/or if has anger volatility, and/or if has PTSD, and/or BPD, and/or migraines	**Topiramate**	25mg	Daily, increase by 25mg/day each week x 3wks, then by 50mg/day each week to max of 300mg/day.	Tab	$40/mos	Yes/Plan G	If significant side effects occur patient is unlikely to benefit and this med should be stopped. In pregnancy, there is a 1/200 chance of causing cleft palate, use with caution in this group balancing risk of ongoing AUD and FAS vs cleft palate in child	Glutamate antagonist (reduces excitatory effect), GABA agonist (increases inhibitory effect), Kainate agonist that impacts Glutamate and GABA activity (excitatory reduction and inhibitory increase, respectively). Reduces craving, reduces irritability.
		If patient has hx of siezures coming off Etoh then this med may reduce chance of siezures. Hx of siezures may indicate med will work for reducing/stopping alcohol use	**Gabapentin**	300mg	1 tab TID, increase weekly up to 600mg TID	Tab	$28/mos	No	Do not use if hx of stimulant abuse.	Increases GABA which has an inhibitory effect, and decreases Glutamate which reduces excitation.
Special Clinical Scenarios		If patient has late stage liver disease and/or if drinking occurs to reduce anxiety or allow sleep.	**Baclofen**	10mg	Regular dosing is 10mg TID, may increase to 20mg TID as needed. For anxiety/insomnia use 10mg qhs and TID PRN.	Tab	$30/mos	No	Can use even if in acute liver failure	GABA-B agonist, this has an inhibitory effect.
		Early Onset AUD, (EOAUD): Dx <25yo, may have black-outs, anti-social personality traits, 1st degree relative with AUD/SUD, 4x more likely to have Opiate Use Disorder, 4x more likely to be incarcerated for violence, Hx of bad reaction to SSRI.	**Ondansetron**	4mcg/kg	BID (Please note this AUD dose (4mcg/kg BID) is much smaller than dose for nausea (4-8mg q8h).	Liquid 4mg/5ml (dispensing the liquid formulation of this med makes the med much cheaper than if compounded), Or use 4mg dissolving film and cut film into appropriate sized tiny pieces.	$45/mos	No, but CYMH may cover, depending on circumstances.	If drinking gets worse stop and use sertraline 50mg OD instead. May be used in addition to Naltrexone for people with EOAUD.	Serotonin transport function is impaired in EOAUD. Ondansetron, as a serotonin antagonist, can improve the function of the system that the alcohol damaged. Naltrexone can be used in addition to ondansetron and this works better than either alone.
		Use for patient with depression but AUD onset later than 25 yo and clinical scenario not of EOAUD.	**Sertraline**	50-100mg	Daily.	Capsule (yellow/white)	$30/mos	Yes/Plan G	Can help people with AUD who are depressed. If drinking gets worse stop and use ondansetron 4mcg/kg bid instead.	Serotonin transport function is impaired in AUD and Sertraline improves the functional deficit of serotonin that occurs. Naltrexone can be used in addition.
		If heavy cigarette consumption (>2ppd), using this med may help reduce alcohol intake.	**Varenicline**	Starter Pack (0.5mg od x 3d, then bid x 4d, then 1mg bid)	Daily		Starter Pack $75/Mos	Yes, for smoking.	Can help people with AUD reduce smoking and Alcohol intake.	Unknown

By Dr. Jeff Harries. For further details see UpToDate, American Psychiatric Association AUD Practice Guidlines 2018, Canadian Psychiatric Assoc AUD Training Overview June 2015, and BCCSU 2019 AUD Guidelines **(in red outline).**

How I Choose an AUD Pharmacotherapy

Step		Clinical Considerations	Patient Response	Naltrexone	Acamprosate	Topiramate	Gabapentin	Ondansetron	Baclofen	Varenicline	References
				First Line		Second Line		Other			
One	Why drink?	**Reward** - (Life more exciting, enjoyable, more fun, better times, more confident and relaxed)									1
		or is it a Combination of Reward and Relief?									
		Relief - (To reduce irritability, to help forget problems at work or home, troubles with friends & family, poor sleep)									
Two	Early Onset AUD	AUD established by age 25									2
		May have Blackouts and/or Anti-Social Personality Traits									3
		4x more likely to be arrested for violent crime or have an Opiate Use Disorder.									4
		May have history of taking Sertraline (Zoloft) for depression and it increased anxiety or the urge to drink.									5
Three	Topiramate?	May have PTSD									6
		May have History of significant use of Cocaine or Meth									7
		May have Anger problem									8
		May have Headaches									9
		May have Borderline Personality Disorder									10
		May have Obesity/Eating Disorder									11
Four	Other Issues	Goal of reduced intake or abstinence									12
		Goal of abstinence only									12
		Use if Naltrexone and/or Acamprosate unnsuccessful or contraindicated									12
		History of Seizures									13
		Anxiety and/or sleep problems									14
		Chronic or Neuropathic Pain									15
		Gambling Disorder									16
		Smoking (if heavy use like 2ppd or more use Varenicline)									17
		Acute/Chronic Liver Failure									18
		Patient wants to "detox" at home in spite of being advised of risks of acute withdrawal.									12
		If patient on opiates including Suboxone or Methadone (do not use Naltrexone).									12

Medications

Notes: Remember, choose the med most likely to work and trial it. If the first choice med is not helping to reduce symptoms or Etoh use, despite dose adjustments as appropriate, then discontinue and trial the second most likely med to work. Don't stop trialing until success occurs. Counselling should also be pursued along with pharmacotherapy in keeping with patient's wishes. BCCSU AUD Guideline compatible info outlined **in red borders.**

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MAYO CLINIC

REVIEW

Evidenced-Based Pharmacotherapies for Alcohol Use Disorder: Clinical Pearls

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Abstract

Pathologic alcohol use affects more than 2 billion people and accounts for nearly 6% of all deaths worldwide. There are three medications approved for the treatment of alcohol use disorder by the US Food and Drug Administration (FDA): disulfiram, naltrexone (oral and long-acting injectable), and acamprosate. Of growing interest is the use of anticonvulsants for the treatment of alcohol use disorder, although currently none are FDA approved for this indication. Baclofen, a γ-aminobutyric acid B receptor agonist used for spasticity and pain, received temporary approval for alcohol use disorder in France. Despite effective pharmacotherapies, less than 9% of patients who undergo any form of alcohol use disorder treatment receive pharmacotherapies. Current evidence does not support the use of pharmacogenetic testing for treatment individualization. The objective of this review is to provide knowledge on practice parameters for evidenced-based pharmacologic treatment approaches in patients with alcohol use disorder.

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In 2017, the *Pain in the Nation* report highlighted that deaths from alcohol, drugs, and suicide had reached the highest levels ever recorded and combined were the fifth highest cause of death in the United States.[1] The 12-month prevalence of alcohol use disorder (AUD) as defined by the Diagnostic and Statistical Manual of Mental Disorders 5th edition in the United States is estimated to be 12.9% with a lifetime prevalence reaching as high as 29.1%.[2] AUDs are associated with substantial morbidity and mortality.[3] Despite the availability of effective psychosocial and pharmacologic options, alcohol and other substance use disorders are widely under-treated. In fact, fewer than 10% of individuals with AUD receive treatment.[2,4] The purpose of this review is to delineate currently available US Food and Drug Administration (FDA)–approved pharmacotherapy options as well as less studied pharmacotherapy options without FDA approval for AUD treatment and provide strategies for optimizing medication selection.

APPROACHING AUD AS A CHRONIC DISEASE

AUD is a preventable and treatable condition. Similar to other chronic multifactorial diseases, the pathophysiology of AUD is approximately 50% heritable and 50% secondary to environmental factors.[5] The reward pathway for alcohol that is believed to facilitate early use is mediated by dopamine release and opioid peptide neuron activity in the ventral tegmental area and the nucleus accumbens, resulting in a euphoric state. There is also evidence to support alcohol induced γ-aminobutyric acid (GABA) release and glutamate suppression in the central nucleus of the amygdala produce a calming sensation.[6] These systems create a tremendous initial positive reinforcement of use. With time, prolonged exposure to alcohol causes a number of neurochemical changes to take place, resulting in sensitization, tolerance, withdrawal, and dependence which can cause a subsequent additional negative reinforcement of use.[7] Prolonged alcohol exposure has also

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ARTICLE HIGHLIGHTS

- Patients 18 years of age or older should be screened for alcohol use disorder (AUD) and receive brief interventions when they present for health maintenance exams.
- AUD, and more broadly addiction, is a chronic relapsing illness which is treatable.
- Treatment should include psychosocial and pharmacologic interventions.
- FDA-approved medications for AUD include disulfiram, naltrexone, and acamprosate.
- Off-label medications for AUD may be used depending upon patient preference or comorbidities and include gabapentin, topiramate, baclofen, and ondansetron.

been associated with decreased volume in the prefrontal cortex and orbitofrontal cortex which have central roles in impulsivity and decision-making.[7] Just as treatment of other chronic conditions reduces health care spending by preventing hospitalizations, every dollar spent on substance use disorder treatment saves $4 in health care and $7 in criminal justice costs.[8] Furthermore, treatment of AUD is effective, with relapse rates comparable to those for asthma, type 1 diabetes, and hypertension.[9]

SCREENING RECOMMENDATIONS

In 2018, the United States Preventive Services Task Force (USPSTF) updated screening recommendations to endorse screening for unhealthy alcohol use (UAU) in primary care settings for all adults 18 years of age and older, including pregnant women, and providing brief behavioral counseling for those with UAU. UAU is defined by the National Institute on Alcohol Abuse and Alcoholism as exceeding 4 drinks per day or 14 drinks per week for healthy adult men aged 21 to 64 years; or, 3 drinks per day or 7 drinks per week for adult women of any age and men 65 years or older.[10] While anything less than this amount is not considered UAU, moderate alcohol use for healthy adults can be defined as up to 1 drink per day for women and up to 2 drinks per day for men.[10] A standard drink contains approximately 14 g of alcohol and is defined as 12.0 oz of beer (5% alcohol), 5.0 oz of wine (12% alcohol), or 1.5 oz of liquor (40% alcohol).[10] In contrast to its recommendation for adult patients, the USPSTF did not find sufficient evidence to recommend UAU screening or brief behavioral counseling interventions for adolescents.[11] However, the American Academy of Pediatrics still recommends screening youth for UAU, making routine alcohol screening a reasonable practice for adolescents among most family practice providers.[12]

Although many screening tools for AUD are available, the USPSTF determined the Alcohol Use Disorders Identification Test – Concise (AUDIT-C) or Single Alcohol Screening Questionnaire (3- and 1- item screening tools, respectively), have the greatest accuracy for assessing UAU in adults 18 years of age and older.[13] If positive, a more comprehensive screening tool such as the full 10-item AUDIT should be used and this should be followed by a comprehensive evaluation.[14] The American Academy of Pediatrics does not endorse a specific screening tool for adolescents; however, there are several that have been validated in this patient population.[12] There are additional screening tools designed specifically for older adults and pregnant patients as well. Table 1 compares the various screening tools.[12-20]

ASSESSMENT

Although beyond the scope of this article, a thorough assessment of a patient's alcohol use is helpful in developing goals for therapy and an appropriate treatment plan. AUD assessment should elucidate the patient's diagnosis and examine the patient's history, current experiences, and readiness for change. Examples of assessment tools include: Alcohol Problems Questionnaire, Clinical Institute Withdrawal Assessment of Alcohol Scale, Leeds Dependence Questionnaire, and the Severity of Alcohol Dependence Questionnaire.[21] Motivational interviewing may elicit patient symptoms and concerns and enhance the patient's

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TABLE 1. Screening Tools for Alcohol Use Disorder[a]

Tool	Description	Validated population
Initial Screening Recommended by USPSTF		
AUDIT-C[b]	Three questions on frequency of alcohol use, amount consumed, and number of occasions of heavy drinking[14]	Adults Sensitivity: 0.73-0.97 in females and 0.82-1.00 in males Specificity: 0.28-0.91 in females and 0.34-0.89 in males[14]
SASQ	One question: "How many times in the past year have you had 5 [for men] or 4 [for women and all adults older than 65 years] or more drinks in a day?"[14]	Adults Sensitivity: 0.73-0.88 Specificity: 0.74-1.00
Additional tools		
CAGE[c]	Cut Down, Annoyed, Guilty, Eye-opener[13]	Adults and adolescents older than 17 y old Sensitivity: 0.77 Specificity: 0.79[12]
AUDIT[b]	10-question evaluation including the AUDIT-C as well as 7 additional questions evaluating signs of alcohol dependence and common problems associated with alcohol use[14]	Adults and adolescents Sensitivity: 0.38-0.73 Specificity: 0.89-0.97
TWEAK	Tolerance, Worried, Eye-opener, Amnesia, (K) cut down[15]	Pregnant women
T-ACE	Tolerance, Annoyed, Cut down, Eye-opener[16]	Pregnant women
4P'S	Parents, Partner, Past, Present Pregnancy[17]	Pregnant women
NET	Normal drinker, Eye-opener, Tolerance[18]	Pregnant women
CRAFFT	Car, Relax, Alone, Forget, Family, Friends, Trouble[19]	Pediatrics
CARET	Comorbidity Alcohol Risk Evaluation Tool[20]	Older adults

[a]USPSTF = US Preventive Task Force.
[b]US AUDIT-C and US AUDIT are versions of this tool using US standards for alcohol consumption.
[c]Limited to alcohol dependence and not full spectrum of alcohol use disorder.

likelihood of curtailing/ceasing alcohol use and seeking treatment interventions.

TREATMENT OF AUD

Although the focus of this article is pharmacotherapy for the treatment of AUD, the importance of psychosocial interventions and treatment of underlying psychiatric comorbidities as part of the treatment plan should not be overlooked. Psychosocial interventions, including brief interventions, motivational enhancement therapy, cognitive behavioral therapy, other behavioral approaches, family therapies, and 12-step facilitation have all been shown to be effective components of AUD treatment and may reduce alcohol consumption and improve abstinence rates.[22,23] Studies have also shown that treating comorbid psychiatric conditions, such as attention deficit hyperactive disorder and depression, with medication decreases heavy drinking and prolongs time to relapse.[22]

Pharmacotherapy

Goals of therapy in AUD may include abstinence or decreased heavy drinking through reduced alcohol consumption.[10] Biomarkers can aid with screening, detection of early relapse, and monitoring medications. Table 2 describes relevant biomarkers and other measures used in AUD. There are three medications that are currently FDA-approved for the treatment of moderate to severe AUD: disulfiram, naltrexone, and acamprosate. Nalmefene is not currently available in the United States, but it is approved for AUD treatment in Europe. There are other medications that are used

off-label for AUD including gabapentin, topiramate, baclofen, and ondansetron. Studies examining the use of off-label pharmacotherapy are understandably less robust and often with smaller sample sizes. These medications are discussed in detail below and summarized in Table 3.

FDA-Approved Pharmacotherapy

Naltrexone. Naltrexone was first approved in 1994 and has been shown to decrease relapse to heavy drinking and total alcohol consumption.[24] The FDA approved extended-release injectable naltrexone (Vivitrol) to treat people with alcohol dependence in 2006. In October 2010, it received the additional indication for treatment of opioid use disorder.

Naltrexone works as a nonselective antagonist of μ, κ, and δ-opioid receptors.[23] Endogenous opioids are released following alcohol consumption, contributing to positive reinforcement effects that may promote continued drinking in the alcohol-dependent individual.[25] Potentially, by blocking this activity, naltrexone reduces the rewarding effects of alcohol and results in reduction in alcohol consumption.[23] A Cochrane review, which used 50 randomized controlled trials (RCT) studying 7793 patients, showed the number needed to treat (NNT) to reduce heavy drinking to be 12 (relative risk [RR], 0.83) and decreased the daily drinking NNT of 25. Another systematic review showed abstinence with an NNT of 20 (risk difference [RD], -0.05) and a decreased the heavy drinking NNT of 12 (RD, -0.09).[26,27]

The target population for naltrexone is men and women who wish to reduce heavy drinking or pursue abstinence, do not have significant hepatic insufficiency, and who are not taking opioids. Efficacy may favor males.[28] Naltrexone trials showed reduced alcohol cravings and reduced relapse to heavy drinking compared to placebo.[29,30] Whereas some trials suggest naltrexone may be more effective in reducing heavy drinking than maintaining abstinence, a meta-analysis has shown naltrexone does reduce risk of relapse to any amount of drinking.[26,31] Although not shown to be as efficacious, naltrexone can also aid in complete abstinence from alcohol.[28] Similar efficacy between long-acting intramuscular (IM) naltrexone and oral naltrexone has been observed in small proof-of-concept studies, although no large-scale head-to-head comparisons have been performed.[32] Because naltrexone is especially effective in decreasing heavy drinking, it could be considered in highly motivated patients to be taken as needed in settings where they wish to consume alcohol but wish to avoid heavy drinking, although this has been less studied in humans.[33]

Naltrexone is dosed 50 mg by mouth once daily or 380 mg via IM injection once monthly. Liver function tests (LFTs) should be monitored regularly; although no standard monitoring frequency is defined in product labeling, baseline, 1-month and annual LFTs should be checked at minimum as there is a black box warning for hepatotoxicity with both the oral and IM form. Naltrexone is partially contraindicated if LFTs are three to four times the upper limit of normal. Adverse effects include somnolence, nausea, vomiting, decreased appetite, abdominal pain, insomnia, and dizziness. These side effects can be mitigated by taking naltrexone with food and building up the dose.[27] Additionally, naltrexone blocks the analgesic effect of opioids and can precipitate withdrawal from opioids in those who are opioid dependent.[34] Because of this effect, especially in the emergency situations, one method to alert health care providers of naltrexone use would be carrying a card stating the patient uses naltrexone rendering opioid analgesics ineffective. Providers could consider challenging patients with a small dose of naloxone before initiating naltrexone in anyone suspected of using opioid analgesics to avoid precipitated withdrawal, although this may not be necessary in the setting of a thorough history and adequate patient education. Likewise, this medication should be stopped 48 to 72 hours before surgery.[24] In contrast to disulfiram, naltrexone can be taken while a patient continues to consume alcohol.

Naltrexone should not be taken with opioids, and it is also FDA approved to promote

TABLE 2. Monitoring Parameters for Alcohol Use Disorder

Parameter	Use	Reference value
Aspartate aminotransferase/ alanine transaminase	Indicates liver damage due to alcohol	<2:1 ratio
Gamma-glutamyltranspeptidase	Indicates heavy alcohol use in the past several weeks	9-48 U/L
Carbohydrate deficient transferring	Indicates heavy alcohol use in the past several weeks	<60 mg/L
Ethanol glucuronide	Detected in urine for 22-31 hours after drinking	Undetectable
Hemoglobin/hematocrit	Screening for anemia	Men: 13.5-17.5 g/dL Women: 12.0-15.5 g/dL
B12 level	Screening for B12 deficiency	200-900 ng/mL
Folate level	Screening for folate deficiency	2-20 ng/mL
Thiamine level	Screening for thiamine deficiency	70-180 nmol/L

abstinence in opioid use disorder, making it an attractive option for patients with comorbid alcohol and opioid use disorders. For opioid use disorder treatment, studies have revealed greater length of retention and more negative urine drug screens with the IM form compared with the daily oral formulation.[35,36] A complete review of naltrexone for opioid use disorder is beyond the scope of this manuscript.

Clinical Pearls. Naltrexone is a first-line therapy for many patients, especially those who desire reduced cravings or reduced consumption of alcohol even if complete abstinence is not the goal. There is some evidence to support the use of naltrexone to promote low-risk drinking or abstinence using a targeted approach in environments which pose increased risk of use or heavy drinking.[37,38] Typical dosing regimens include starting at 25 mg for 7 days then increasing to 50 mg daily and taking with food as it may cause some gastrointestinal distress. Avoid naltrexone for those with severe liver disease or those on chronic opioid pain medication. Because of its opioid antagonistic effect, naltrexone should be stopped 48 to 72 hours before surgery. Perioperative management can be difficult for those using long-acting naltrexone for this reason.

Acamprosate. Acamprosate was approved by the FDA in 2004 with demonstrated primary effectiveness for maintaining abstinence from alcohol. Acamprosate has an agonistic effect at $GABA_A$ receptors and weak antagonistic effects at N-methyl-D-aspartate receptors and metabotropic glutamate receptor 5.[39,40] Compared with naltrexone and disulfiram, the molecular mechanism of acamprosate in AUD is not well defined.[41]

The target population for this medication would include patients who want continued sobriety after a period of abstinence and who do not have severe renal impairment. Better outcomes have been noted in those with an increased length of sobriety before treatment initiation.[42,43] A systematic review using 27 studies and 7519 patients showed an NNT of 12 for return to any drinking (RD, -0.09) and another Cochrane review of 24 trials including 6915 patients showed an NNT of 9 for reducing risk of any drinking (RR, 0.86).[26,44]

Data from a meta-analysis of naltrexone and acamprosate studies have shown acamprosate to primarily support abstinence versus naltrexone, which seems to primarily support reduction in heavy drinking as shown in Table 4.[26] In a meta-analysis of head-to-head comparisons, neither acamprosate nor naltrexone showed superiority to the other medication in terms of return to heavy drinking (moderate strength evidence), percentage of drinking days (low-strength evidence), or return to any drinking (moderate-strength evidence).[45] Acamprosate has been shown to be especially effective

TABLE 3. Comparison of Medications for Alcohol Use Disorder[a]

Medication	Precautions	Additional indications	Approximate monthly cost[b]
FDA-approved pharmacotherapy			
Acamprosate	Renal impairment		$270/180 tablets
	Hypercalcemia		
Naltrexone	Liver disease	Opioid use disorder	$108/30 tablets
	Active opioid use	Binge-eating disorder (in combination with bupropion)[c]	$1,366/IM injection
Disulfiram	Liver disease	Stimulant abuse[c]	$104/30 tablets
	Active alcohol use		
	Psychosis		
	Cardiovascular disease		
Non-FDA–approved pharmacotherapy			
Nalmefene	Active opioid use		Not available in the United States
	Liver disease		
	Renal impairment		
Gabapentin	Renal impairment	Peripheral neuropathy	$150/90 tablets
	Potential for abuse	Seizure disorder	
		Restless leg syndrome	
		Anxiety[c]	
		Cannabis use disorder[c]	
		Alcohol withdrawal[c]	
Topiramate	Liver disease	Migraine prophylaxis	$151/60 tablets
	Renal impairment	Seizure disorder	
	Pregnancy (may cause fetal harm)	Binge-eating disorder[c]	
Baclofen	Renal impairment	Muscle spasm	$96/90 tablets
Ondansetron	QTc prolongation	Nausea	$204/50-mL bottle (solution required for appropriate dose)
	Serotonin syndrome		

[a]FDA = US Food and Drug Administration; IM = intramuscular.

[c]Denotes off-label use.

[b]Cost derived from average cash prices, excluding insurance coverage, as available on goodrx.com as of February 21, 2019.

in those with negative emotional state–based craving (relief drinkers) and has also been shown to reverse alcohol-related changes in sleep architecture and help with sleep deprivation–induced cravings.[42,43]

Acamprosate is available in 333-mg tablets and is dosed 666 mg by mouth three times daily. Unlike naltrexone or disulfiram, acamprosate is not affected by liver function, so it is safe for use in patients with liver disease. A significant component of the chemical structure of acamprosate is a calcium molecule, so it should be avoided in patients with hypercalcemia (total calcium > 10.3 mg/dL or ionized calcium > 5.4 mg/dL).[46,47] There are no psychotropic effects of acamprosate. Renal function should be monitored at baseline and at regular intervals as dose reduction is required for mild-to-moderate renal impairment. Acamprosate is not recommended for use in severe renal impairment (creatinine clearance less than 30 mL/min). Common side effects of acamprosate include flatulence, diarrhea, nausea, pruritus, and insomnia.

Clinical Pearls. Acamprosate is a first-line medication to consider for patients who desire complete abstinence from alcohol. It is especially effective after a period of sobriety, such as following inpatient treatment or incarceration. Although the initial period of sobriety has not been well-studied; 10 to

14 days would be a reasonable duration of time. Acamprosate can work well in those with negative emotional state cravings. Starting dose is 666 mg 3 times daily, although it is sometimes started at 333 mg 3 times daily to avoid gastrointestinal distress. This high frequency of dosing can cause a problem with adherence. Because of dosing frequency and requirement of a period of abstinence for optimal efficacy, naltrexone could often be the preferred first-line pharmacotherapy. However, physicians should be encouraged to consider treatment goal (eg, abstinence vs decreased heavy drinking) and evidence supporting the probability of achieving this outcome (ie, NNT for acamprosate and naltrexone) rather than relying on convenience of the once-per-day use. This medication often causes diarrhea and it should be used with caution in the setting of renal disease or hypercalcemia.

Disulfiram. Disulfiram was FDA approved in 1949 and has modest efficacy in relapse prevention, particularly when medication adherence is supervised. Disulfiram works by blocking aldehyde dehydrogenase 2 in the liver and the brain.[48] Aldehyde dehydrogenase 2 catalyzes the oxidation of the alcohol metabolite acetaldehyde into acetic acid; thus, its inhibition increases acetaldehyde levels after alcohol consumption.[49] Elevated acetaldehyde causes nausea, vomiting, headache, and flushing. These unpleasant effects, which develop after alcohol consumption, lead to negative reinforcement which in turn promotes alcohol avoidance in AUD.[50]

The target population for disulfiram is patients who desire abstinence who are without liver disease, psychotic disorders, or seizure disorder. They must also have motivation for supervised medication administration, either by a care giver or medical professional.[51-53] Studies show supervised ingestion provides significantly better outcomes than with unsupervised disulfiram use.[54] A meta-analysis of 22 RCTs showed an increase in total abstinence, percentage of abstinent days, mean days without alcohol, time to first drink, and a decreased likelihood of relapse with disulfiram as compared with control.[54] However, in a follow-up meta-analysis, success rates were only noted in open-label studies compared with blinded trials.[54]

TABLE 4. NNT for Different Primary Outcomes in Acamprosate Versus Naltrexone[a]

Primary outcome	Acamprosate	Naltrexone
Relative risk of first drink after abstinence	NNT = 12	NNT = 20
Relative risk of heavy drinking	No significant effect	NNT = 12

[a]NNT = number needed to treat.

Disulfiram is dosed 250 to 500 mg by mouth once daily. The most common side effect is moderate-to-severe drowsiness, which occurred in approximately 8% of patients during trials.[45] Less common side effects include hepatitis, neuropathy, optic neuritis, and confused states.[55] Disulfiram may also block dopamine beta-hydroxylase and increase dopamine concentration, which may cause psychosis.[49,56] Disulfiram-induced psychosis may be more likely to occur in patients with a pre-existing psychotic disorder, so caution should be used with these patients.[51-53]

Patients should be counseled to avoid exposure to products containing alcohol, such as cooking wine, vinegar, kombucha, or alcohol-containing mouthwash and cough syrups. Disulfiram should not be used if alcohol was ingested within the last 48 hours or if the patient has severe myocardial disease due to the potential for severe adverse effects.[51-53] Since disulfiram effects may last up to 2 weeks after the last dose because of the irreversible inhibition of alcohol dehydrogenase, it is also possible to have adverse effects from alcohol ingestion after the medication is discontinued.[51-53] Severe tachycardia, hypotension, bradycardia, congestive heart failure, convulsions, and death are rare but documented side effects, typically at high doses of disulfiram.[57,58] LFT should be reviewed at baseline and at regular intervals (eg, monthly for 3 mo and then quarterly thereafter) for elevated transaminases.

Clinical Pearls. Disulfiram is a second-line agent that works best in a controlled environment wherein the patient is supervised taking medication on a daily basis (250 mg) or thrice weekly (500 mg). Given the intense adverse effects of consuming alcohol while on this medication, it is only used for complete abstinence. Patients should be counselled on disulfiram interactions and should avoid mouthwash, hand sanitizer, or any other alcohol-containing products such as cough or cold medicine. Alcohol should not be consumed within 2 weeks of last dose of disulfiram. Drowsiness is the most common side effect. Extreme caution should be exercised if the patient has a history of cardiovascular disease or psychosis, as rare but severe adverse reactions can occur if alcohol is consumed with this medication.

Treatment Efficacy. Efficacies of these medications are compelling when comparing with other medications used routinely as standard care for other common medical conditions. As mentioned earlier, the NNT for naltrexone in reduced heavy drinking is 12 and that for complete abstinence is 20. Acamprosate is similar with an NNT of 12 for return to any drinking and 9 for reduced drinking. For comparison, the NNTs for other commonly prescribed medications include: aspirin for prevention of cardiovascular disease has an NNT of 50,[59] antibiotics for symptom reduction of acute otitis media has an NNT of 16,[60] antihypertensive medications for prevention of stroke has an NNT of 67 and prevention of death has an NNT of 125,[61] and metformin for mortality improvement has an NNT of 14 over 10 years.[62] It would be considered a deviation from standard to not offer or prescribe the medications above for their respective conditions. For example, approximately 70% of patients with hypertension are treated with antihypertensive medication in the United States.[63] However, despite the lower NNT, less than 10% of those with AUD receive treatment.[2,4]

Non–FDA-Approved Pharmacotherapy

Nalmefene. Nalmefene is closely related to naltrexone and approved in Europe for AUD, although it is unavailable in the United States for this indication. Similar to naltrexone, nalmefene is an inverse agonist at the μ-opioid receptor but also an antagonist at the δ-opioid receptor and partial agonist at the κ-opioid receptor.[23] Unlike naltrexone, nalmefene has a longer half-life and is not associated with liver dysfunction. It is the first medication specifically approved for reduced alcohol consumption as opposed to alcohol abstinence and is taken on an as-needed basis as opposed to scheduled.

The target population for nalmefene is patients who want to reduce alcohol consumption, but who are not necessarily interested in complete abstinence. In a meta-analysis of 5 RCTs, nalmefene was associated with a reduction of 1.65 more heavy-drinking days per month than placebo at 6 months and 1.60 more heavy-drinking days per month than placebo at 1 year. It has also been associated with decreased total alcohol consumption.[64] The studies used in these trials were largely retrospective and head-to-head comparisons are lacking.[65]

Nalmefene is dosed 18 mg by mouth once daily as needed, ideally 1 to 2 hours before drinking.[42] Adverse effects from nalmefene include nausea, dizziness, insomnia, headache, vomiting, and fatigue.[66] Similar to naltrexone, nalmefene should not be used in patients who are either receiving or expect to receive opioids.

Clinical Pearls. Nalmefene is not approved in the United States for AUD. It has some evidence supporting its use in reducing alcohol consumption when used on an as-needed basis. Similar to naltrexone, nalmefene should be avoided in those on chronic opioid therapy, although it may be used in patients with liver disease. The starting dose is 18 mg daily as needed.

Gabapentin. Gabapentin is FDA approved for post-herpetic neuralgia in adults and as adjunctive therapy in the treatment of partial seizures in patients age 3 years and older.[23] A specific formulation, gabapentin enacarbil, is also approved for restless legs syndrome. Gabapentin is structurally similar to

GABA, although it has no activity at GABA receptors; the exact mechanism of action for gabapentin is unknown although it is speculated that it works as an α-2-Δ calcium channel ligand.[67] Small studies have shown gabapentin to be superior to placebo in greater abstinence and reduced heavy drinking.[68] Recent larger follow-up studies have not found any significant improvement in AUD-related outcomes in patients receiving gabapentin.[69]

The target population for gabapentin may be patients who have multiple other comorbid conditions such as neuropathic pain, restless leg syndrome, insomnia, or those who would like to continue the medication after it was started to treat acute alcohol withdrawal–related symptoms. Off-label, three placebo-controlled trials (n=231) have shown gabapentin to aid in symptoms of alcohol withdrawal, increase abstinence rates, decrease heavy drinking days, decrease alcohol craving, decrease anxiety, and help with insomnia.[23] These findings are based on of three peer-reviewed RCTs (n=231).[68] In contrast, preliminary findings of a multicenter trial of 346 patients with AUD found no significant results for any of the drinking measures evaluated.[69] However, this trial used a different formulation of gabapentin, the pro-drug gabapentin enacarbil ER; therefore, comparison to the other studies is imperfect.

Gabapentin is dosed 300 to 600 mg by mouth three times a day.[42] Side effects of gabapentin include dizziness, somnolence, ataxia, and peripheral edema; at high doses, intoxication has also been reported.[70] There have been reports of abuse potential associated with gabapentin and prescribers should be watchful for this possibility.[71]

Clinical Pearls. Gabapentin can be considered in those with neuropathy, restless legs syndrome, insomnia, or anxiety. A unique feature of gabapentin is that it can be used for acute alcohol withdrawal to prevent withdrawal symptoms and can be continued to help with cravings. It should be started at 300 mg three times daily for prolonged abstinence or reduced cravings, although it may require higher doses in acute withdrawal, which is not discussed in this article. This medication may cause drowsiness, suggesting benefit from starting with bedtime dose with subsequent upward titration. Use with caution in the setting of renal disease. Approximately 1% of the general population has misused gabapentin for recreation purposes, self-medication, or intentional self-harm, either alone or in combination with other substances (including alcohol).[70]

Topiramate. Topiramate is indicated for treatment of seizures, migraine prophylaxis, weight loss, and chronic weight management (in combination with phentermine).[23] Topiramate works by facilitating GABA-A receptors and antagonizing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and kainate glutamate receptors.[72-75] These activities reduce dopamine levels in the mesocorticolimbic system and decrease alcohol induced reinforcement and the propensity to drink.[76]

Off label, topiramate can be considered for those with AUD and with heavy-eating disorder. It serves as an appetite suppressant and is sometimes used to treat heavy-eating disorder. In AUD, topiramate has been shown to increase abstinence from alcohol and lower the rate of heavy drinking compared with placebo.[77] Topiramate has been shown in some trials to have greater efficacy than naltrexone in reducing heavy drinking, although it has not been shown to improve rates of abstinence.[77]

Topiramate is dosed 25 to 150 mg by mouth two times per day.[23] The most common side effects of topiramate include cognitive dysfunction including mental slowing and modest reduction in verbal fluency and working memory (dose related),[78,79] paresthesia,[80] taste abnormalities,[81] anorexia, nervousness, dizziness, and renal stones.[23] Extended release formulations are contraindicated for use with metformin in patients with metabolic acidosis.[82]

Clinical Pearls. Topiramate could be considered as a second-line medication to reduce heavy drinking, especially in those with comorbid migraine headaches or obesity/binge eating disorder, as it is used off-label for weight loss and appetite suppression.

It should be started at 25 to 50 mg daily with dose increases no more frequently than weekly.[23] Common side effects of topiramate include mental fogginess and altered taste. These can be mitigated by starting at the lowest effective dose with slow upward titration. This medication is contraindicated in patients with comorbid metabolic acidosis, should be avoided in patients with renal stones, and used with caution in patients with renal disease.

Baclofen. Baclofen is indicated for spasticity resulting from multiple sclerosis.[23] In 2014, it was also given a temporary recommendation in France for treating AUD.[23] Baclofen is a $GABA_B$ receptor agonist that helps restore the GABA supply, which is chronically depleted in AUD.[23]

Off-label, it could also be considered for AUD in patients who have generalized muscle spasticity, Tourette syndrome, or tardive dyskinesia, as it is used to treat these conditions.[23] Previously for AUD, a meta-analysis of 13 RCTs showed that baclofen was associated with greater time to first lapse of drinking and greater likelihood of abstinence versus placebo.[83] A more recent Cochrane review did not replicate these positive results or any other positive alcohol-related outcome.[84]

Baclofen is dosed 30 to 80 mg by mouth daily.[23] The primary side effect of baclofen is sedation; it may also cause dizziness, headache, confusion, muscle stiffness, excessive perspiration, itching, abnormal muscle movements, numbness, central sleep apnea, and slurred speech.[23]

Clinical Pearls. Baclofen may be a reasonable alternative medication, especially in the setting of muscle spasms. Although lacking FDA approval for AUD in the United States, it is approved for this use in France. Baclofen should be dosed at 60 mg daily initially. The most common side effect is sedation or drowsiness. Use with caution in renal failure. As this medication is renally metabolized it can be used in the setting of liver failure or liver cirrhosis.

Ondansetron. Ondansetron is approved for postoperative and chemotherapy-induced nausea.[41] It is a selective 5-HT_3 receptor antagonist. Activated by serotonin when alcohol is consumed, this receptor causes dopamine release in the mesocorticolimbic region of the brain.[41] Alcohol consumption was inversely related to expression of 5-HT_3 receptors in the amygdala in mice.[85]

The target population for ondansetron may be patients with early-onset AUD. Some studies showed benefit in reducing drinks per day as well as increasing abstinence, but only in patients with a biological predisposition to AUD before age 25 years.[86-88] Other studies have not confirmed this finding.[86-88]

For AUD, ondansetron is dosed 1 to 4 μg/kg by mouth two times a day.[42] Common side effects of ondansetron include constipation, diarrhea, and headache; rarely, it can prolong the QT interval and may increase the risk for serotonin syndrome when used with other serotonergic medications.

Clinical Pearls. Ondansetron may be most effective in those who developed features of alcohol use disorder before age 25 years. In this subcategory, it decreases heavy drinking and increases abstinence. The starting dose is lower than for other indications, at 1 μg/kg two times a day. Common side effect includes diarrhea and should be used cautiously in those with prolonged QT interval.

GUIDELINES FOR TREATMENT

The American Psychiatric Association (APA) guidelines recommend naltrexone or acamprosate be offered first-line to patients with moderate-to-severe AUD. It recommends disulfiram, topiramate, and gabapentin as second-line options for patients who prefer one of these agents and are intolerant to or have not responded to naltrexone or acamprosate.[45] It further recommends against the use of acamprosate in severe renal impairment and against the use of naltrexone in severe hepatic impairment or concomitant opioid use. It does not comment on the use of baclofen or ondansetron. The relative hesitation of the APA guidelines in picking specific agents suggests that an individualized approach to AUD treatment may be warranted and ideal

therapy may depend on goals of therapy, patient preferences, and underlying medical conditions.

The APA also recommends patients with AUD being screened for psychiatric comorbidities and dual diagnosis capable services should be sought out when appropriate. Patients with co-occurring disorders have more complex treatment needs and poorer outcomes; that being double the average number of emergency department visits as those with substance use disorder alone. Dual diagnosis also increases use of health resources, emergency department length of stay, and hospitalizations. Despite high comorbidities, in the United States only 18% of addiction treatment and 9% of mental health programs met criteria for dual diagnoses–capable services.[89] It is recommended against using antidepressant therapy for AUD unless evidence of co-occurring disorder in which antidepressant is indicated. It is also recommended against using benzodiazepines unless treating acute alcohol withdrawal or unless co-occurring disorder exists for which a benzodiazepine is an indicated treatment. Finally, the APA recommends against using pharmacologic treatment for AUD in pregnant patients unless treating acute alcohol withdrawal with benzodiazepines or unless a co-occurring disorder exists that warrants pharmacologic treatment.

PERSONALIZED MEDICINE

Pharmacogenomics is the study of how genetic factors affect individual drug response and represents an emerging approach in treatment of AUD. Although current evidence is insufficient to support broad implementation of personalized medicine for AUD, genetic variation has been shown to influence the response to several AUD medications. Naltrexone has been the most widely studied to date and has the most promising results with more than 20 replicated trials.[89] A specific polymorphism, A118G (rs1799971) in the μ-opioid receptor gene OPRM1, has been associated with naltrexone response. Patients with the OPRM1 118G allele appear to have a better treatment response compared with carriers of the 118A allele, making it a likely indicator for personalized naltrexone treatment.[90,91] These findings seem to be most promising in patients with East Asian ancestry, although other ethnic populations have also shown correlation.[91] However, two recent trials which attempted to replicate these findings were unsuccessful, making the role of OPRM1 genetics in predicting naltrexone response unclear.[14,92] Other AUD medications, including disulfiram, acamprosate, topiramate, nalmefene, and ondansetron, have fewer pharmacogenetics studies at this time.

CONCLUSION

Alcohol use disorder can be effectively treated with recurrence rates no higher than those for other chronic illnesses such as asthma or diabetes. Well-supported scientific evidence shows that medications can be effective in treating serious alcohol use disorders, but they remain under-used. The FDA has approved three medications for alcohol use disorder: naltrexone, acamprosate, and disulfiram. Additionally, other medications including gabapentin, baclofen, topiramate, and ondansetron show promise off-label for treating alcohol use disorder. The choice of medication should be based on guidelines with individualization according to comorbidities and patient goals for treatment. Per APA guidelines, appropriate psychiatric evaluation and treatment for dual diagnosis should also be sought for appropriate patients.

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Abbreviations and Acronyms: **AUD** = alcohol use disorder; **FDA** = Food and Drug Administration; **GABA** = γ-aminobutyric acid; **NNT** = number need to treat; **RCT** = randomized controlled trial; **UAU** = unhealthy alcohol use; **RD** = risk difference; **RR** = relative risk

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