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REVIEW

Pharmacotherapy options for alcohol use disorder in patients with alcohol-associated liver disease: a brief guide for clinicians

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Quality care for patients living with alcohol-associated liver disease (ALD) includes identification and treatment of comorbid alcohol use disorder (AUD).[1] In addition to recommending behavioral interventions, providers caring for this population should feel comfortable prescribing AUD pharmacotherapy, which is safe, effective, and associated with reduced hepatic decompensation and mortality.[2–4] Many gastroenterologists, however, report discomfort prescribing these medications due to limited exposure in training as well as concerns about safety and efficacy.[5] Although a multidisciplinary approach involving an addiction specialist is ideal, a timely referral is not always feasible. For clinicians seeking to incorporate this evidence-based care into their practice, we herein provide a brief review of the pharmacology, evidence, and key prescribing considerations for AUD pharmacotherapy in patients with ALD. Table 1 provides a summary of key prescribing considerations, and Figure 1 offers an approach for selecting an initial agent.

Abbreviations: ALD, alcohol-associated liver disease; APA, American Psychiatric Association; AUD, alcohol use disorder; CP C, Child-Pugh-C; CrCl, creatinine clearance; FDA, Food and Drug Administration; GABA, γ-aminobutyric acid; GI, gastrointestinal; IM, intramuscular; VA, Veterans Health Administration.

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FOOD AND DRUG ADMINISTRATION–APPROVED PHARMACOTHERAPY OPTIONS

Acamprosate

Acamprosate attenuates alcohol-associated elevations in glutaminergic activity through action on N-methyl-D-aspartate receptors.[34] Its effectiveness in maintaining abstinence is well established.[7–11] It is well tolerated, with gastrointestinal symptoms and anxiety being the most common side effects, but rare.[7,9] Typically dosed at 666 mg 3 times a day, acamprosate dosed at 999 mg twice daily is bioequivalent and may improve adherence.[6] The American Psychiatric Association (APA) and UK National Institute for Health and Care Excellence recommend it as a first-line option for AUD.[13,35] The Veterans Health Administration (VA) recommends it as first line but qualifies the supporting evidence as weak.[36] The World Federation of Societies of Biologic Psychiatry cites high-quality evidence regarding its use, although it cautions that some trials do not show the effect on relapse prevention.[37] Acamprosate does not undergo hepatic metabolism and is likely safe in Child-Pugh A or B cirrhosis, although data regarding safety in liver disease is limited.[34,38] The dose should be reduced for renal impairment and avoided if creatinine clearance (CrCl) is <30 mL/min.[13] The American Association for the Study of Liver Diseases recommends consideration of acamprosate to treat AUD in ALD.[1]

TABLE 1 Summary of key prescribing considerations for alcohol use disorder pharmacotherapy

Agent	Dosage	Efficacy[a]	Considerations in liver disease	Special considerations, adverse effects (AE), and monitoring	FDA approved for AUD?
Acamprosate	Start at 666 mg TID; 999 mg BID is bioequivalent and simpler [6]	Significantly increased rates of abstinence vs. placebo [7–11] NNT to achieve additional cases of abstinence has been estimated between 7.5[11] and 9.09[7]	No hepatic metabolism and considered safe in liver disease, although it has not been studied in CP C cirrhosis[6] No known interaction with common antirejection medicines used after transplant[12]	Use 50% recommended dose in impaired renal function, avoid it completely if CrCl < 30 mL/min [6,13] GI side effects and anxiety are the most common AE[7,9] Monitor renal function in elderly patients	Yes
Naltrexone	Naltrexone hydrochloride: dose at 50 mg PO daily Naltrexone long-acting injection: dose at 380 mg IM q30 days	Significant improvement in abstinence and reduction in heavy drinking, when combined with counseling [9,14,15] NNT to prevent a return to heavy drinking has been estimated at 8.6[11]	Metabolism is altered in severe liver disease. Avoid in CP C cirrhosis[16] Historic concern for hepatoxicity, although experience and data suggest this is rare[17–19] No known interaction with common antirejection medicines used after transplant[12]	Caution with severe renal impairment. avoid initiating in patients who recently used opioids. Nausea, dizziness, vomiting, diarrhea, somnolence most common AEs[15,17] IM only: injection site reactions, hematoma[20] Check liver enzymes after 1 month of treatment and every 3 months thereafter.	Yes
Baclofen	Titrate from 5 mg TID to 10 mg TID[21] over 3 days	Improved abstinence rates among patients with cirrhosis[22] Studies in the general population are less promising[23,24]	Minimal hepatic metabolism. Only AUD medication studied in patients with cirrhosis, although those with pre-existing HE were excluded.[22] Avoid in HE. No known interaction with common antirejection medicines used after transplant[12]	Dose reduction by 33%, 50%, and 66% if CrCl 50–80 mL/min, 30–50 mL/min, and <30 mL/min, respectively[25] Sedation, vertigo, and paresthesias are known adverse effects[23] Routine monitoring of renal function	No
Gabapentin	Start at 300 mg daily, increase based on response and tolerability by 300 mg every 1–2 days to 600 mg TID target dose [26,27]	Increases abstinence and reduces heavy drinking, particularly among patients with higher self-reported withdrawal symptoms. NNT to achieve a case of abstinence estimated to be 8[26,27]	No hepatic metabolism. Avoid in HE. No known interaction with common antirejection medicines used after transplant[12]	Dose reduction required in renal dysfunction: manufacturer recommends daily dose not exceed 1400 mg if CrCl <59, 700 if CrCl <29, and 300 if CrCl < 15. Somnolence, headache, muscle aches, and GI upset are the most common AEs[28] Routine monitoring of renal function.	No
Topiramate	Begin at 25 mg per day, increase in 25–50 mg increments to 150 mg BID over 8 weeks[29]	Decreases drinks per day, decreases heavy drinking days, and increases percent days abstinent compared with placebo.[29–31]	Partial hepatic metabolism. Consider 30% dose reduction in severe hepatic disease[32] Avoid in HE. No known interaction with common antirejection medicines used after transplant[12]	Dose reduction of 50% recommended in renal impairment (CrCl <70) Cognitive impairment, paresthesia, nephrolithiasis, and anorexia are known AEs [33] Routine monitoring of renal function	No

[a]Common clinically relevant efficacy metrics include rates of abstinence and heavy drinking. Study definitions for abstinence duration are provided when available in the text. Heavy drinking is typically defined as 4 or more drinks per day for women and 5 or more drinks per day for men.

Abbreviations: AUD, alcohol use disorder; CP C, Child-Pugh-C; CrCl, creatinine clearance; FDA, Food and Drug Administration; GI, gastrointestinal; IM, intramuscular; NNT, number needed to treat.

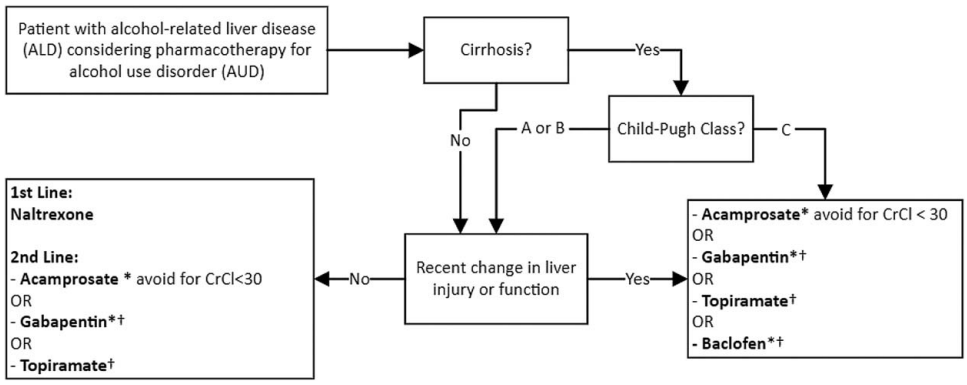

FIGURE 1 Approach to selecting initial alcohol use disorder pharmacotherapy option in alcohol-associated liver disease. This algorithm represents the authors best synthesis of AUD-focused and ALD-focused society guideline recommendations for AUD pharmacotherapy in the ALD population, it is intended as a reference only and has not been validated or tested in clinical practice. *Adjust dose for renal function. †Use with caution in HE. Abbreviation: CrCl, creatinine clearance.

Disulfiram

Although Food and Drug Administration has approved AUD since the 1950s, disulfiram is hepatically metabolized and associated with hepatotoxicity and liver failure.[39] Given these risks and the availability of safer treatments for this population, disulfiram is not recommended for AUD in patients with ALD.[1]

Naltrexone

Naltrexone is an opioid receptor antagonist that decreases cravings through additional effects on the hypothalamic-pituitary axis.[40] It improves rates of abstinence and reduces the risk of return to heavy drinking.[9,14,15] In addition to gastrointestinal side effects, dizziness and somnolence have also been reported.[15,17] Naltrexone has simple dosing, available as a 50-mg tablet taken once daily or a monthly 380 mg intramuscular injection. The APA, National Institute for Health and Care Excellence, and VA recommend naltrexone as the first line for AUD, and the WFSB characterizes evidence supporting its use as "abundant."[13,35–37] The US Substance Abuse and Mental Health Services Administration guidelines recommend several days of abstinence before initiating naltrexone.[41] There are historical concerns for naltrexone-related hepatoxicity, and although liver function should be monitored frequently while on therapy, experience and data suggest that this is rare.[17–19] Nonetheless, the metabolism of naltrexone is altered in liver disease, and it should be avoided in patients with recent changes in liver function and Child-Pugh-C cirrhosis, pending additional safety data.[16] Naltrexone should not be initiated in patients recently taking opioids.

OFF-LABEL PHARMACOTHERAPY OPTIONS

Baclofen

Baclofen is a γ-aminobutyric acid $(GABA)_B$ agonist that suppresses dopamine release and attenuates alcohol-associated reward pathways.[42] It is the only medication discussed that has been studied in cirrhosis. In a randomized controlled trial (RCT), 10 mg administered 3 times daily improved 12-week abstinence rates compared with placebo.[22] Higher doses have been used for AUD in the general population, although lower doses (5–10 mg 3 times a day) may be more effective and better tolerated.[21,43] Sedation is common, particularly if abstinence is not achieved before use. Up and down titration over several days is needed to ensure tolerability and prevent discontinuation reactions. It is not recommended in patients with HE, and dose reduction should be considered in patients with reduced renal function.[21,43] Despite the favorable findings in cirrhosis, studies in the general population are less promising.[23,24] Thus, the American Association for the Study of Liver Diseases recommends baclofen for the treatment of AUD in ALD, but it is not included in guidelines for the general population.[1]

Gabapentin

Gabapentin is a GABA analog that reduces excitatory neurotransmission and affects the downstream mediation of neurologic changes associated with withdrawal and abstinence in heavy drinkers.[28] Compared with a placebo, gabapentin significantly increases 12-week abstinence rates and reduces heavy drinking.[26] These effects are greatest among patients with alcohol

withdrawal symptoms.[27] Somnolence, dizziness, and headache are the known side effects.[28] For AUD, gabapentin is initiated at 300 mg daily and increased in 300 mg increments, based on response and tolerability, every 1–2 days to a target dose of 600 mg 3 times daily.[26,27] In cirrhosis, lower initial doses may be considered. The APA and VA recommend gabapentin as second line in AUD.[13,36] Gabapentin can precipitate HE, and extra caution is advised for patients with decompensated cirrhosis.[44] It also must be dose-reduced in kidney disease.

Topiramate

Topiramate likely improves AUD by dampening excitatory activity through the potentiation of GABA and inhibition of glutamate.[29] Topiramate reduces heavy drinking days and increases percent days abstinent when compared with a placebo.[29–31] Dosing requires slow escalation; trials typically start with 25 mg daily, increasing to a maximum of 300 mg per day in 2 divided doses over 8 weeks.[29,31] Confusion, somnolence, paresthesias, and nephrolithiasis have been reported.[29,31,33] Cognitive effects may limit tolerability and confound the clinical picture in patients with HE.[12] There is minimal hepatic metabolism, but a dose reduction of 30% has been recommended for severe hepatic impairment.[32] The manufacturer suggests halving the dose for CrCl <70. The VA and APA recommend it as a first-line and second-line option in the general population, respectively.[13,36]

CONCLUSIONS

Pharmacotherapy for AUD is safe and effective in improving drinking outcomes in the general population. For patients with concurrent ALD, however, evidence is mostly limited to retrospective data. More prospective studies involving chronic liver disease, including decompensated cirrhosis, are needed. Despite this, the ongoing risk alcohol use poses for negative outcomes should make barriers for accessing AUD pharmacotherapy low. Armed with the essential knowledge of how to prescribe these medications, those caring for patients with ALD should feel confident offering this evidence-based care.

AUTHOR CONTRIBUTIONS

All: study concept and design; Christopher Coe: drafting of manuscript; all: critical revision of manuscript; Arpan Patel and David Lawrence: study supervision.

CONFLICTS OF INTEREST

The authors have no conflicts to report.

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