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Safety and Tolerability of Medications for Alcohol Use Disorder

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This summary reviews Shenoy A, Jasty FS, Uttal S, et al. Medications for Alcohol Use Disorder Are Increasingly Being Prescribed in American Patients With Advanced Liver Disease. Am J Gastroenterol 2025; doi: 10.14309/ajg.0000000000003328.

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STRUCTURED ABSTRACT

Question: What is the safety and tolerability of various FDA-approved medications for alcohol use disorder (AUD) among patients with mild versus severe alcohol-related liver disease (ALD)?

Design: Retrospective cohort study of adult patients who were diagnosed with AUD and ALD using *International Classification of Diseases, Ninth or Tenth Revision* (*ICD-9/10*) codes and received naltrexone, acamprosate, or disulfiram. Patients were stratified into 2 cohorts: A) Advanced alcohol-associated cirrhosis or alcohol-associated hepatitis, B) Mild ALD. Mild ALD was defined by lack of jaundice or coagulopathy. Cirrhosis was determined by a biopsy, imaging, decompensating event, or clinical criteria based on imaging, FibroScan, varices, or biochemical parameters defined in the supplemental appendix. Clinical data were collected at 3 time points: 6 months prior to initiation of AUD treatment, during treatment and 6 months after completion of AUD treatment.

Setting: University of Michigan Health System from January 2013 to January 2023.

Patients: Records were screened utilizing *ICD-9* and *ICD-10* codes for alcohol-associated liver disease. Patients were excluded if therapy for AUD was not started, patients declined treatment, exposure to treatment was less than 1 month, history of liver transplant, lost to follow-up, missing data.

Intervention: The intervention was receipt of 1 of 3 FDA-approved medications for AUD.

Outcome: The outcomes were the percentage of patients who remained on AUD medication, completed treatment with sustained sobriety, or discontinued treatment due to adverse effects.

Data analysis: Chi-square analysis with Pearson's test and Wilcoxon-ranked sum test were used to compared dichotomous and continuous variables, respectively.

Funding: Support from Kezar Pharmaceuticals and Takeda Pharmaceuticals.

Results: A total of 213 patients were included with 112 patients in cohort A and 101 patients in cohort B. Majority of patients (88%) were White, 50% were female, and the median age was 51 years. Most patients were privately insured (54%).

Patients in the mild liver disease group had significantly lower MELD 3.0: 7 compared to the advanced group (MELD 3.0: 11). Similarly, prior to initiation of AUD treatment, patients with advanced disease had significantly higher bilirubin, INR, and lower albumin and ALT compared to the mild disease group. While on treatment, there were no differences in peak serum AST, total bilirubin, or albumin. Of the entire cohort, naltrexone, acamprosate and disulfiram were prescribed in 65%, 26% and 9%, respectively.

In 77% of cases, AUD medication was prescribed in the outpatient setting by an Internal Medicine provider, and least likely to be prescribed in the Emergency Department setting (1.9%). Patients in the advanced liver disease group were more likely to have concurrent use of an anxiolytic but less likely to be enrolled in an AUD behavioral program as compared to the mild liver disease group.

Over a 10-year period, there were significant increases in use of AUD medications in both the advanced and mild liver disease cohorts, *P*=0.012 and *P*=0.016, respectively (**Figure 1**). The most prescribed medication for AUD was naltrexone (65%), followed by acamprosate (26%), and disulfiram (9%) for a median of 360, 252 and 190 days, respectively.

There was no significant difference regarding time to death. There were 38 deaths in the entire cohort, with most (N=35) in the advanced disease group. As expected, the leading cause of death was from ALD. There was no evidence of drug induced liver injury in either group.

There were no differences in medication discontinuation or completion of therapy rates. However, 43% of patients were lost to follow up and only 17% completed treatment. At the last follow-up time point, the rate of AUD medication discontinuation for adverse events was similar in both groups (14% vs 12%). PETH was monitored more frequently in the advanced liver disease cohort in 34% of cases whereas this occurred in only 4% of mild ALD cases.

COMMENTARY

Why Is This Important?

Worldwide, 283 million people are diagnosed with AUD, one-third of whom develop ALD.[1] Currently, ALD is the leading cause of cirrhosis worldwide, and in the United States and Europe, it is the leading etiology for liver transplantation.[2] The burden of disease is immense and efforts to achieve abstinence are critical since it is the key factor in improving survival in ALD. Pharmacotherapies are only one part of the multi-disciplinary approach to addressing ALD. However, AUD medications are underutilized due to knowledge gaps, and lack of comfort and familiarity with prescribing these medications.[3]

To address these gaps and variability in comfort levels, there should be a focus on increased educational experiences for providers who care for those with AUD/ALD, especially those in training via addiction medicine electives, rotations, and intensive immersion programming.[4]

This study demonstrates similar tolerability and efficacy of 3 FDA approved AUD medications regardless of severity of liver disease. The authors also demonstrate an increase in total AUD medication prescriptions over the 10-year study period likely due to their initiation in 2018 of the “MAIN” (University of Michigan Alcohol Improvement Network) clinic. Centers across the US should consider this model and other models of care when designing clinical care pathways.

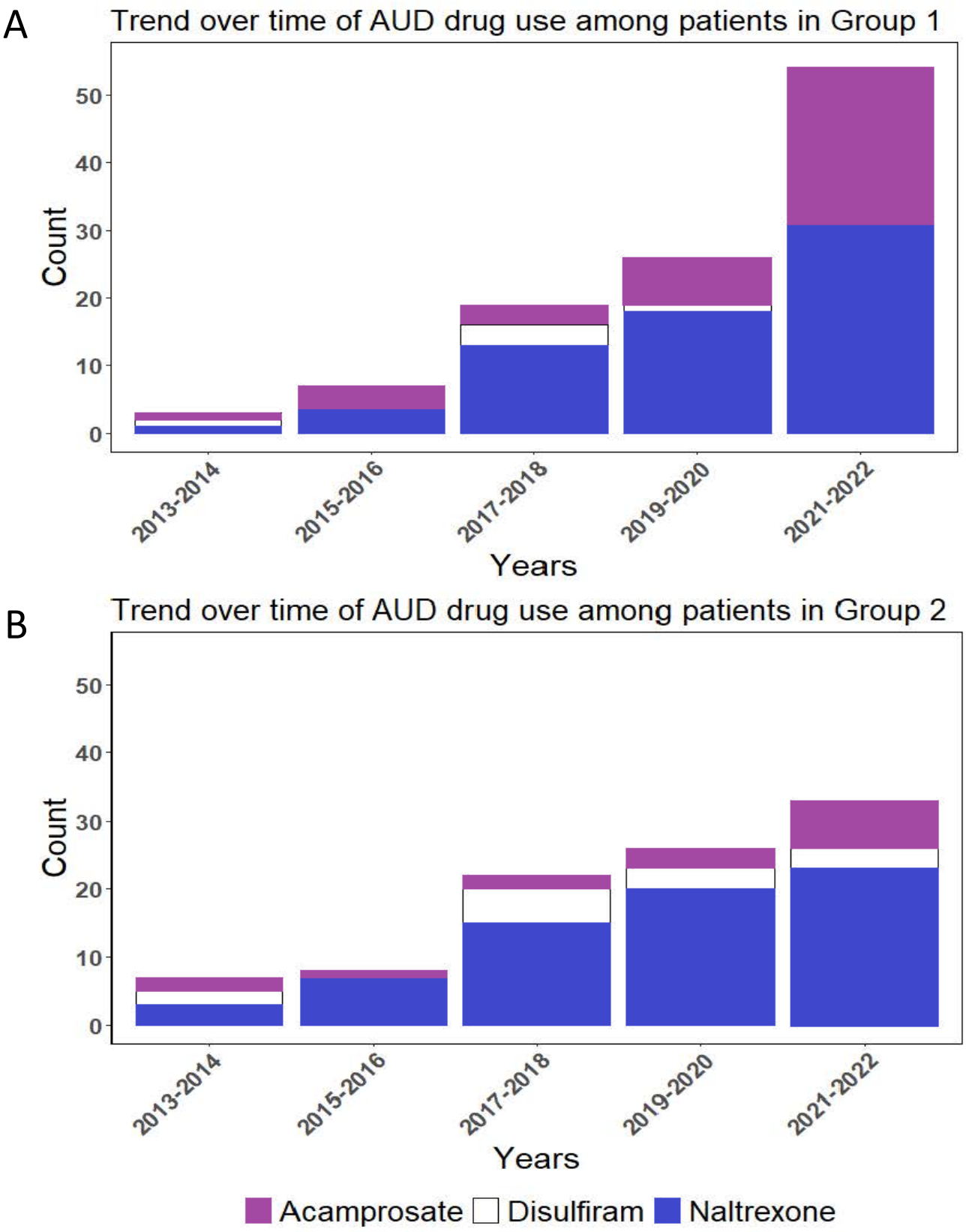

Figure 1. The number of prescriptions for individual alcohol use disorder (AUD) medications in 2-year intervals between 2013 and 2023. The total number of prescriptions (**a**) in patients with advanced liver disease (group 1) and (**b**) patients with mild liver disease (group 2) increased significantly over time (P = 0.012 and 0.016, respectively, per Mann-Kendall trend test).

Key Study Findings

Between 2013 and 2023, there was a significant increase in the prevalence of patients with mild and severe alcohol associated liver disease in this single center, retrospective study. Among the 3 FDA approved medications for AUD, naltrexone was the most prescribed, in 65% of patients, and most frequently prescribed by Internal Medicine providers. Disulfiram was rarely used and is not recommended for AUD in the setting ALD. In terms of tolerability, the rates of AUD medication discontinuation were low and comparable between both cohorts.

Therefore, despite these medications being safe and increasingly utilized, they are still infrequently prescribed by gastroenterology and hepatology providers.

Caution

By nature of the retrospective design of this study, only associations are noted but causality cannot be established. The sample sizes are modest despite the study spanning a full decade. There may also be selection bias in that the overwhelming majority were White and privately insured. Therefore, this study may not adequately reflect the diverse range of patients affected by ALD in the US.

My Practice

In my practice, I care for patients with ALD and often Met-ALD frequently. I often find that these clinical scenarios pose a different challenge than managing a patient with autoimmune hepatitis where steroids and immunosuppressive therapy are the clear answer, most often. I tell my patients that I can empower them, provide objective data, and arrange for close follow-up, while providing various resources, however they truly are in the "driver seat" and I am there to guide.

I practice in a culturally competent manner while abiding by the principles of cultural safety.[5] This requires minimizing presumptive narratives and incorporating social determinants of health into every treatment plan. It often requires several visits to build rapport with patients while encouraging them to bring their loved ones to clinic, and learning about their perceived barriers to abstaining from alcohol, until I am able to broach the topic of introducing pharmacotherapy or behavioral therapies. It often requires a multi-disciplinary approach and I may refer to our Addiction Medicine colleagues or prescribe AUD medications on my own, depending on the clinical situation. It is important for us as a Gastroenterology/Hepatology community to continue to educate ourselves and offer evidence-based therapies for AUD to curb the rapidly rising rates of ALD in this country.

For Future Research

The authors are to be commended for highlighting an important topic that addresses the leading cause for liver transplant in many parts of the world. Future

multi-center randomized controlled trials with a diverse representation of patients with ALD with mild and advanced liver disease are needed to understand the true safety of AUD medications. In addition, cost analyses would be important to determine the public health burden of prescribing AUD medications. Preliminary reports have noted that prescribing medicines for alcohol use disorder leads to a large reduction in 30 day rehospitalization in those admitted for an alcohol related complication.[6] Studies such as these would also provide information regarding the barriers that patients may face in accessing pharmacotherapy for AUD. Furthermore, understanding the complex factors at the systems, provider and patient level that impact the underutilization of AUD therapy are critical in addressing care gaps.

Conflicts of Interest

The authors have no reported conflicts of interest.

REFERENCES

1. Asrani SK, Mellinger J, Arab JP, et al. Reducing the global burden of alcohol-associated liver disease: A blueprint for action. *Hepatology*. 2021;73:2039–2050.
2. Younossi ZM, Stepanova M, Al Shabeeb R, et al. The changing epidemiology of adult liver transplantation in the United States in 2013-2022: The dominance of metabolic dysfunction-associated steatotic liver disease and alcohol-associated liver disease. *Hepatol Commun.* 2023;8:e0352.
3. Im GY, Mellinger JL, Winters A, et al. Provider Attitudes and Practices for Alcohol Screening, Treatment, and Education in Patients With Liver Disease: A Survey From the American Association for the Study of Liver Diseases Alcohol-Associated Liver Disease Special Interest Group. *Clin Gastroenterol Hepatol*. 2021 Nov;19(11):2407-2416.e8.
4. Klimas J, Ahamad K, Fairgrieve C, et al. Impact of a brief addiction medicine training experience on knowledge self-assessment among medical learners. *Subst Abus* 2017;38(2):141–144.
5. Nikzad, N., Duong, N. & Paul, S. Improving culturally safe engagement with sexual and gender minority populations. *Nat Rev Gastroenterol Hepatol* 21, 372–373 (2024).
6. Bernstein EY, Baggett TP, Trivedi S, Herzig SJ, Anderson TS. Outcomes After Initiation of Medications for Alcohol Use Disorder at Hospital Discharge. *JAMA Netw Open.* 2024;7(3):e243387.