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Identification and Treatment of Alcohol Use Disorder

TO THE EDITOR: In his review article, Haber (Jan. 16 issue)[1] discusses ways of identifying and treating alcohol use disorder. We seek clarification regarding the use of pharmacotherapy for alcohol use disorder in patients with chronic liver disease, including cirrhosis. The oft-repeated statement that naltrexone should be avoided in patients with chronic liver disease is not firmly supported. Naltrexone previously carried a black-box warning that was issued by the Food and Drug Administration owing to concerns about hepatotoxicity — namely, transiently elevated liver-enzyme levels. This warning was removed in 2013. Evidence linking naltrexone to harm in patients with chronic liver disease is lacking. Conversely, alcohol is hepatotoxic. Several sources support that naltrexone is safe in patients with cirrhosis across the spectrum of disease severity.[2-4] Yet, many clinicians remain wary of prescribing naltrexone to patients with liver disease. One reason for this hesitancy is the perpetuation of the unsupported claim in literature and practice that naltrexone is harmful in patients with chronic liver disease.

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Dr. Tapper reports receiving grant funding from Madrigal Pharmaceuticals and Salix Pharmaceuticals and consulting fees from Ipsen. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: We believe that Haber's review could have been more emphatic in recommending against off-label use of baclofen and nalmefene for alcohol use disorder in the United States. Globally, marketing approval of baclofen has been granted only in France — a so-called "French exception." Our concern is that the usual European process for marketing approval may not have been followed and that it bypassed the assessment by the European Medicines Agency scientific committee that baclofen has a negative benefit-to-harm ratio. The scientific committee noted that evidence of efficacy was insufficient in two pivotal phase 3 trials and that a cohort study showed dose-dependent risks of hospitalization and death.[1-3] Furthermore, marketing approval of nalmefene — ostensibly to effect a reduction in drinking — in Europe was granted on the basis of a post hoc subgroup analysis of two thirds of the phase 3 trials; the effect sizes shown in these trials were minimal and possibly inflated owing to attrition bias.[4] No effect was shown for baclofen and nalmefene in terms of clinically relevant outcomes, including abstinence. However, use of these agents led to an increased incidence of adverse events.[3,4]

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The review by Haber, published within weeks of the U.S. Surgeon General's advisory on alcohol and cancer risk,[1] acknowledges that alcohol use disorder is widespread and undertreated, and the statistics paint a striking picture. In 2023, approximately 29 million people in the United States met the criteria for past-year alcohol use disorder, among whom only 7.9% received any form of treatment for the disorder and only 1.9% received medication.[2] One barrier to treatment engagement that we have observed in our clinical and research practices is patients' concern about denials of life insurance policy applications. Insurance companies within or outside the United States can reject policy applications on the basis of alcohol use and treatment — a possible example of the stigma against alcohol use disorder (and substance use more broadly).

Molly A. Bowdring, Ph.D.,[1] John Mendelson, M.D.,[2] and Judith J. Prochaska, Ph.D., M.P.H.[1]

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Dr. Bowdring reports having previously consulted for Pivot. Dr. Mendelson reports being employed by and having equity in Ria Health. No other potential conflict of interest relevant to this letter was reported.

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THE AUTHOR REPLIES: Blaney and Tapper note that naltrexone is safe and effective across the spectrum of liver disease severity and that it should be more widely used in the treatment of alcohol use disorder. I agree that growing experience supports this practice. Nevertheless, the most recent guidelines of the American College of Gastroenterology still recommend against the use of naltrexone in patients with decompensated liver disease.[1] The studies cited by Blaney and Tapper each included fewer than 25 patients with advanced decompensated cirrhosis. Therefore, caution remains appropriate in this population.

Braillon and Naudet express concerns about off-label use of baclofen and nalmefene for alcohol use disorder. These drugs were not recommended in my review article but were discussed as options for which there is mixed evidence. I largely share their concerns. Nevertheless, several treatment guidelines consider the cautious use of baclofen, particularly in persons with high baseline levels of alcohol consumption[2] and in those with liver disease.[1]

I agree with Bowdring et al. that the potential denial of insurance can affect a patient's willingness to undergo treatment for alcohol use disorder and is an understudied issue of concern. However, this issue is beyond the scope of my review.

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Since publication of the article, the author reports no further potential conflict of interest.

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