Letters

Addressing the risks of antidepressants among people with alcohol use disorders

We thank Bahji and colleagues[1] and Elefante and colleagues[2] for their interest in the guideline on the management of alcohol use disorder (AUD).[3] We appreciate the opportunity to explain that the guideline's caution against prescribing certain antidepressants was based not only on the evidence that some antidepressants appear to be largely ineffective among those with AUD and comorbid depression or anxiety,[4,5] but also the literature demonstrating risks of increased alcohol use with certain antidepressants.

Bahji and colleagues cited several individual studies suggesting benefits of selective serotonin reuptake inhibitors (SSRIs), but most of these were not placebo-controlled trials. Conversely, various meta-analyses have found SSRIs to have no effect on depressive symptoms among people with AUD.[4–6] In particular, the Cochrane review by Agabio and colleagues[5] found no effect with SSRIs on final depression score, change in score, number of responders, or number of remissions relative to placebo. To Elefante and colleague's comments, the review also found no benefit of SSRIs versus placebo for either abstinent or heavy drinking days.[5] Similarly, the relevant Cochrane review by Ipser and colleagues[6] concluded that "the effectiveness of medication in treating anxiety disorders and comorbid alcohol use disorders is currently inconclusive."

Bahji and colleagues also cited a study showing efficacy for combined SSRI with naltrexone in the treatment of patients with AUD and major depressive disorder, but a subsequent meta-analysis including that study concluded SSRIs "either alone or in combination with relapse prevention medications such as naltrexone, had no significant effect on depressive symptoms."[4]

In addition, the guideline summarized an underappreciated literature demonstrating that certain antidepressants appear to increase alcohol use among some patients. Although Elefante and colleagues described a single trial,[7] at least 6 double-blind placebo-controlled trials have shown risks of increased alcohol use with SSRIs.[7–12] Elefante and colleagues are correct that, as reviewed in the guideline, some studies have found this concern most relevant among those who had earlier onset and more severe AUD. In addition, a functional polymorphism (5-HTTLPR) in the serotonin transporter gene may predispose those with AUD treated with SSRIs to either positive (i.e., less drinking) or negative outcomes (i.e., increased drinking).[6] A randomized controlled trial (RCT) that critically examined this question concluded that, since the genotype implicated in SSRI-induced heavier alcohol use was more common than the genotype affording benefit, an estimated twice as many patients would be "adversely affected" by SSRI prescribing and that the "widespread use of antidepressants suggest that the findings reported here are relevant to a substantial proportion of the US population."[7]

To the comments about trazodone, a serotonin receptor antagonist and reuptake inhibitor, this RCT was presented to further demonstrate the risks of increased alcohol use with another serotonergic medication that is commonly used in the treatment of AUD, in comparison to placebo.[13] Although increasing a medication's dose would generally not be expected to reduce adverse effects, additional studies would be required to assess the suggestion that increasing the trazodone dose or combining trazodone with anti-craving medications would limit the possible adverse effect of increased drinking.[13] In sum, the current evidence justifies the current recommendations in the guideline.

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References

1. Bahji A, Danilewitz M, Sloan M, et al. Concerns regarding the recommendation against prescribing selective serotonin reuptake inhibitors in the Canadian guideline for the clinical management of high-risk drinking and alcohol use disorder [letter]. *CMAJ* 2024;196:E346-7.
2. Elefante RJO, Lu C, Bach PJ. Navigating the nuances of the Canadian guideline's stance on selective serotonin reuptake inhibitors in concurrent alcohol use disorder and mood or anxiety disorders [letter]. *CMAJ* 2024;196:E348.
3. Wood E, Bright J, Hsu K, et al.; Canadian Alcohol Use Disorder Guideline Committee. Canadian guideline for the clinical management of high-risk drinking and alcohol use disorder. *CMAJ* 2023;195:E1364-79.
4. Stokes PRA, Jokinen T, Amawi S, et al. Pharmacological treatment of mood disorders and comorbid addictions: a systematic review and meta-analysis: traitement pharmacologique des troubles de l'humeur et des dépendances comorbides: une revue systématique et une méta-analyse. *Can J Psychiatry* 2020;65:749-69.
5. Agabio R, Trogu E, Pani PP. Antidepressants for the treatment of people with co-occurring depression and alcohol dependence. *Cochrane Database Syst Rev* 2018;(4):CD008581.
6. Ipser JC, Wilson D, Akindipe TO, et al. Pharmacotherapy for anxiety and comorbid alcohol use disorders. *Cochrane Database Syst Rev* 2015;(1):CD007505.
7. Kranzler HR, Armeli S, Tennen H, et al. A double-blind, randomized trial of sertraline for alcohol dependence: moderation by age of onset [corrected] and 5-hydroxytryptamine transporter-linked promoter region genotype. *J Clin Psychopharmacol* 2011;31:22-30.
8. Kranzler HR, Burleson JA, Brown J, et al. Fluoxetine treatment seems to reduce the beneficial effects of cognitive-behavioral therapy in type B alcoholics. *Alcohol Clin Exp Res*. 1996;2:1534-41.
9. Pettinati HM, Volpicelli JR, Kranzler HR, et al. Sertraline treatment for alcohol dependence: interactive effects of medication and alcoholic subtype. *Alcohol Clin Exp Res* 2000;24:1041-9.
10. Chick J, Aschauer H, Hornik K. Efficacy of fluvoxamine in preventing relapse in alcohol dependence: a one-year, double-blind, placebo-controlled multicentre study with analysis by typology. *Drug Alcohol Depend* 2004;74:61-70.
11. Charney DA, Heath LM, Zikos E, Palacios-Boix J, Gill KJ. Poorer drinking outcomes with citalopram treatment for alcohol dependence: a randomized, double-blind, placebo-controlled trial. *Alcohol Clin Exp Res* 2015;39:1756-65.
12. Anthenelli RM, Blom TJ, Heffner JL, et a l. Citalopram treatment for alcohol dependence: interactive effects of drinking goal and medication. Poster presented at the 33rd Annual RSA Scientific Meeting, San Antonio, Texas, June 2010.

13. Friedmann PD, Rose JS, Swift R, et al. Trazodone for sleep disturbance after alcohol detoxification: a double-blind, placebo-controlled trial. *Alcohol Clin Exp Res* 2008;32:1652-60.

Competing interests: Evan Wood is a physician who works for Vancouver Coastal Health in the area of withdrawal management and undertakes work in the area of occupational addiction medicine. Dr. Wood is also a professor of medicine based at the University of British Columbia (UBC), a position supported by a Canadian Institutes of Health Research (CIHR) Tier 1 Canada Research Chair and has received salary support from an R01 from the US National Institute on Drug Abuse, paid to UBC. Dr. Wood's research lab is further supported by CIHR grants to the Canadian Research Initiative in Substance Misuse. Dr. Wood has also undertaken consulting work in legal matters related to substance use disorders and for a mental health company called Numinus Wellness, where Dr. Wood is former chief medical officer; Dr. Wood has also received compensation in the form of equity in Numinus. Dr. Wood reports receiving honoraria for non-industry related lectures and presentations (e.g., at academic or educational conferences), including a talk at the Canadian Society of Addiction Medicine (CSAM) paid by CSAM conference; a Rounds Presentation at Dalhousie University (paid by the University); and an educational talk for the allied health educational platform, Executive Links (all outside the submitted work). Dr. Wood has also received payment for expert reports and expert testimony in legal matters pertaining to substance use disorder, including from the Canadian Medical Protective Association and from trade unions representing workers with possible substance use disorder. Dr. Wood has received travel support from the CIHR. No other competing interests were declared.