

Treatment of alcohol-use disorders

In the treatment of alcohol dependence, Marc Schuckit (Feb 7, p 492)¹ omits baclofen. This is most regrettable for two reasons.

First, Schuckit's proposed treatment excludes patients with liver cirrhosis from receiving any anticraving medication. Alcohol intake in patients with cirrhosis is associated with high mortality.² With cirrhosis, naltrexone is contraindicated and the safety of acamprosate, topiramate, and disulfiram has not been tested because these agents undergo extensive liver metabolism. Baclofen is the only anticraving medication shown in a randomised trial³ to be safe and effective at promoting abstinence in patients with cirrhosis. Depriving cirrhosis patients of baclofen would deprive them of the benefit patients without cirrhosis get from standard anticraving treatment.

Second, a new translational model of treatment based on animal studies has been proposed, in which medication-induced suppression of craving could translate into effortless suppression of dependence in alcohol-dependent patients.⁴ In animals, baclofen is the only drug that has been shown to suppress the urge to consume alcohol. All other anticraving medications used in the treatment of alcohol-dependence only reduce this urge.⁵ In alcoholic patients, suppression of dependence through suppression of craving has never been reported with naltrexone, acamprosate, or topiramate despite thousands of patients trialled on these drugs.

Baclofen should be offered to patients with cirrhosis, and craving suppression should be tested in randomised trials.

I declare that I have no conflicts of interest.

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Marc Schuckit¹ clearly highlights the psychosocial and pharmacological aspects of alcohol-use disorders. As regards the topic of medications, however, he cites topiramate—a GABA-ergic drug—despite the fact that it is still not approved for the treatment of alcoholism, but he does not consider γ hydroxybutyric acid (GHB)—a further GABA-ergic medication—which has been approved for more than 10 years and which is currently used in some European countries.

The efficacy of GHB both for the treatment of alcohol withdrawal syndrome and as an anticraving drug has been well documented by several clinical trials in more than 700 patients.² In particular, when GHB has been used to treat alcohol withdrawal syndrome, an efficacy similar to diazepam and to clomethiazole has been shown;² additionally, when GHB is used as an anticraving drug, almost 60% of patients remain completely abstinent from alcohol during the treatment period.^{3–5}

Although craving for and abuse of GHB remain a crucial point during the clinical administration of this drug, a very limited number of treated patients with alcoholism (less than 10%) are really at risk of this unfavourable effect.^{3,5}

Thus, the therapeutic relevance of GHB for the treatment of alcohol addiction has to be mentioned. If

physicians are well informed and follow correct guidelines for administration^{3–5} (strict medical control with supervision by a family member), GHB is manageable and safe.

We declare that we have no conflicts of interest.

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Authors' reply

Olivier Ameisen and Fabio Caputo and colleagues highlight several important issues. A brief Seminar cannot comprehensively cover all clinically interesting topics for a disorder as complex as alcohol dependence, and I had to make decisions about which findings I felt to be most central to the overview. Many additional drugs and psychological approaches have been proposed for the alcohol-use disorders, but they could not be adequately discussed. These letters highlight two drugs that I considered in the original draft of the Seminar, but were deleted because of space constraints.

Regarding baclofen, given at 5–10 mg three times per day, this interesting direct agonist of the GABA_B receptor has some potential



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benefits in the treatment of alcoholism, including in patients with liver cirrhosis. Rats decrease alcohol-seeking behaviour with baclofen,¹ and there are some promising results on the maintenance of abstinence in human beings.² However, my review of the literature supported the conclusion that, although the results are promising, future research is required to determine whether the benefits of baclofen outweigh the liabilities (eg, possible adverse cognitive effects and enhanced intoxication with alcohol³).

My initial review also revealed potential promising effects of the second GABA-boosting substance, γ hydroxybutyric acid (GHB), mostly for alcohol detoxification, but also, possibly, for rehabilitation. In a recent study⁴ of 18 patients treated with GHB who completed the research protocol, results suggested that this drug (50 mg per kg per day divided into three doses), either alone or in combination with naltrexone, is worthy of future study. However, there is no convincing evidence that GHB is superior to the more easily available and widely tested benzodiazepines in treating withdrawal, and only small, brief studies have assessed this agent in rehabilitation. There are concerns about dangers when this medication is mixed with alcohol, as well as the misuse potential for GHB.⁵ Therefore I am not convinced that the assets of this agent outweigh the liabilities.

In summary, these letters raise interesting and potentially important issues about two drugs that deserve further careful assessment in the treatment of alcohol-use disorders.

I declare that I have no conflicts of interest.

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We declare that we have no conflicts of interest.

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- 1 Alio AP, Nana PN, Salihu HM. Spousal violence and potentially preventable single and recurrent spontaneous fetal loss in an African setting: cross-sectional study. *Lancet* 2009; **373**: 318–24.

Authors' reply

The first issue raised by James Shelton and Jacob Adetunji concerns the lack of a biological explanation that could link domestic violence to fetal loss. We would like to highlight findings from previous studies that do present at least two biological pathways through which spousal violence could lead to stillbirth.

First, pregnant victims of domestic violence have a more than threefold likelihood of having a small-for-gestational-age fetus than those who do not experience such violence (odds ratio 3.42, 95% CI 1.26–9.29).¹ Having a small-for-gestational-age fetus is a well established precursor of stillbirth.² Indeed, the relation is so strong that some believe the greatest potential to reduce stillbirth involves enhanced detection of unappreciated small-for-gestational-age fetuses through timely antenatal testing.³ Hence, the strong association between domestic violence and having a small-for-gestational-age fetus could partly explain the reported increase in the likelihood of stillbirth among victims of spousal violence.

Second, pregnant women who receive trauma as minor as massage have been shown, by use of serial doppler ultrasound, to carry fetuses with brain lesions⁴ similar to those found at autopsy on stillborn fetuses (eg, germinal matrix or intraventricular haemorrhage).⁵ It is therefore reasonable to expect that other forms of trauma sustained by pregnant women (including domestic violence) could cause the same pathology. In fact, it might be that many instances of unexplained sonographically demonstrable fetal brain lesions in ongoing

Spousal violence and spontaneous fetal loss

Amina Alio and colleagues (Jan 24, p 318)¹ make an admirable effort to unravel a myriad of confounders to explain their finding of a statistical relation between spousal violence and spontaneous fetal loss. Spousal violence is clearly deplorable. But, as Alio and colleagues note, it included a wide range of behaviours, including "saying something to humiliate" and pushing and twisting the arm, as well as more violent acts. A biological explanation for such spousal violence "ever" to account for a 50% increase in fetal loss "ever" does not seem obvious.

Another explanation is major misclassification with induced abortion. Although the 2004 Demographic and Health Survey instrument for Cameroon attempted to distinguish between the two, responses on numbers of induced abortions, spontaneous abortions, and stillbirths were contained within the same question. It would be easy for respondents to report induced abortions as spontaneous. Induced abortion is notoriously under-reported, especially in countries such as Cameroon where it is illegal. On the other hand, both induced abortion and spousal violence might be common markers of other factors such as relationship stress or other dysfunction and thus lead to a spurious finding.



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