

Alcohol-related liver disease treatment and EBM

Alain Braillon (1) M.D., Ph.D., and Florian Naudet (2) M.D., Ph.D.

(1) Previously chief of alcohol treatment unit, university hospital, Amiens, France.
braillon.alain@gmail.com

(2) Professor in Therapeutics, Adult Psychiatry Department and Clinical Investigation Center (INSERM 1414), Rennes university hospital, Rennes, France.

CoI: AB and FN are among industry independent experts from Jeanne Lenzer's list. (<https://jeannelenzer.com/list-independent-experts>)

No funding

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: EBM; off-label use; harm-benefit ratio; scientific integrity

351 words + 5 references (limit 400 words + 5 references)

The unbalanced recommendation from France about alcohol-related liver disease claiming that “The presence of liver disease does not generally affect the prescribing of baclofen at the doses recommended by the marketing authorization” deserved comment when considering the international impact of the Journal.¹ Indeed, baclofen use is off-label, except in France. The French Alcohol Society cannot ignore that the director of the French medicines agency granted a marketing approval despite the Special Scientific Committee concluding that benefits/harms ratio was negative. We warned, the Chairman of the Committee dared to comment “(he) well understood that the benefit-risk assessment [of baclofen] was only one element, among others, (behind the decision)”.² The first pivotal trial Alpadir (NCT01738282) was negative regarding abstinence rates. Further, results of the second pivotal trial, Bacloville (NCT01604330), are most questionable, having been published without acknowledging: a) major changes to the initial protocol affecting the primary outcome; the change in the initial statistical team when data were sold to the French pharmaceutical company applying for the marketing authorization in France.^{2,3} Based on a tortured analysis, the report of Bacloville claimed that baclofen was effective in reducing alcohol consumption, a non-

validated surrogate outcome, while serious adverse events were greater with baclofen than placebo. The latter was expected when accounting a large-scale pharmaco-epidemiological study in the real-life setting showing a dose-dependent increase in mortality with baclofen vs acamprosate and naltrexone.⁴ The French approval retained lower doses, in a total vacuum of evidence from pivotal trials. Ironically, the guideline promotes baclofen for “controlling consumption” with the very idea of a harm-reduction strategy but there are converging signals for harms – and this included 30-75mg doses.⁴ Why can prescribers fly in the face of wise adages: a) the Hippocratic dictum “First, do no harm”; b) the #3 of the “40 rules of surgery” by Ambroise Paré, a French King’s barber-surgeon from the 16th century (1510-1590) “Remedies knownd and approved by use and reason, are to be preferred before such as unknowned, or but lately found out”.⁵

Lastly, could the authors and the professional organizations provide a disclosure of their links of interest with pharmaceutical companies?

References

- 1 Louvet A, Trabut JB, Moreno C, et al. Management of alcohol-related liver disease: the French Association for the Study of the Liver and the French Alcohol Society clinical guidelines. *Liver Int.* 2022. Online Apr 29. doi:10.1111/liv.15221
- 2 Braillon A, Naudet F, Cristea IA, Lexchin J. Baclofen and Alcohol Use Disorders: Breakthrough or Great White Elephant? *Alcohol Alcohol.* 2020;55(1):49-50.
- 3 Naudet F, Braillon A, Cristea IA, Lexchin J. Restoring the Bacloville trial: efficacy and harms. *Addiction.* 2020;115(11):2184-2186.
- 4 Chaignot C, Zureik M, Rey G, Dray-Spira R, Coste J, Weill A. Risk of hospitalisation and death related to baclofen for alcohol use disorders: comparison with nalmefene, acamprosate, and naltrexone in a cohort study of 165 334 patients between 2009 and 2015 in France. *Pharmacoepidemiol Drug Saf.* 2018;27(11):1239–48.
- 5 Paré A. *Workes* (translated out of Latine by Johnson T). Th. Cotes and R. Young, London, 1634 (first English edition). p. 1119. Available at <https://wellcomecollection.org/works/hamvcbsv> (p1061/1143) accessed 30 April 2022.