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LETTER TO THE EDITOR

Reply to Braillon et al.: Nalmefene Phase IV Study: A Seeding Flying in the Face of Evidence?

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Braillon et al. [1] state that nalmefene is a costly placebo. That deserves robust comment.

Nalmefene was approved by the European Medicines Agency after three randomized controlled trials, which enrolled 1997 patients, had been completed [2–4]. Interestingly, the authors suggest that two recent meta-analyses have concluded that nalmefene is not effective for alcohol dependence [5, 6]. However, a closer look at both analyses reveals nalmefene is indeed effective in reducing total alcohol consumption as compared to placebo. What meta-analyses fail to show is an effect on other health outcomes such as quality of life, mortality, or somatic health. However, it should be acknowledged that most randomized trials for alcohol medications are not specifically designed and are not sufficiently powered to detect differences in such outcomes. That being said, other studies suggest it is indeed clearly expected that reductions in alcohol consumption would lead to decreases in mortality and other health outcomes [7–9]. That, in fact, is in line with the concept of heavy drinking over time [10], which suggests that it is the amount of alcohol ingested that causes most harm to alcohol-dependent individuals (the authors themselves state this when detailing alcohol carcinogenic properties). Taken together, it means that reducing the amount of alcohol ingested is key to reducing the harm produced by alcohol.

We agree with the authors regarding the preferred goal of treatment—abstinence being, of course, the safest and most effective pathway to full recovery and better health outcomes. However, under a patient-centered approach [11] for individuals opting for a reduction in alcohol consumption, tools need to be provided so that their objective can be achieved. In fact, reduction aims have long been recognized as legitimate and feasible both nationally and professionally when dealing with alcohol-dependent patients [12–15].

We also agree that the basis of treatment remains always psychosocial in essence. However, at the same time we believe that a sterile discussion about whether to use medications should be avoided, and energies be directed to the provision of as many tools as possible for patients to achieve their objective. More so when there are efficacy-proven and approved medications for alcohol dependence (naltrexone, acamprosate, disulfiram and nalmefene) that remain underutilized [16, 17]. We believe that the key lies in treating patients with a holistic and integral approach, which means combining both psychosocial and pharmacological strategies. Worth mentioning, we believe that precluding patients from receiving pharmacological treatment enhances the moralistic and prejudiced view of alcohol dependence, instead of approaching it with the more desirable disease model.

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Finally, we are aware that a Phase IV study with no control group, conducted under routine clinical practice, has some relevant limitations such as a less exhaustive information recollection regarding adverse events or other relevant variables such as tobacco consumption. However, the fact that many of the effectiveness outcomes appear to be similar to the previous Phase III randomized trials supports our previous claim that, all data taken together, suggest that nalmefene is a well-tolerated and effective treatment for alcohol dependence.

Compliance with ethical standards

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Conflict of interest Dr. Barrio, Dr. Roncero, Dr. Guardia and Dr. Gual have received honoraria from Lundbeck. Dr. Barrio has also received honoraria from Pfizer. Dr. Roncero has also received honoraria from Janssen-Cilag, Otsuka, Server, GSK, Rovi, Astra, MSD and Sanofi. Dr. Yuguero and Dr. Ortega have no conflict of interest to declare.

References

1. Braillon A, Taiebi F, Bernoussi A. Nalmefene phase IV study: a seeding flying in the face of evidence? Clin Drug Investig. 2018. https://doi.org/10.1007/s40261-018-0628-2.
2. Mann K, Bladström A, Torup L, Gual A, van den Brink W. Extending the treatment options in alcohol dependence: a randomized controlled study of as-needed nalmefene. Biol Psychiatry. 2013;73:706–13.
3. Gual A, He Y, Torup L, van den Brink W, Mann K, ESENSE 2 Study Group. A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence. Eur Neuropsychopharmacol. 2013;23:1432–42.
4. van den Brink W, Sørensen P, Torup L, Mann K, Gual A, SENSE Study Group. Long-term efficacy, tolerability and safety of nalmefene as-needed in patients with alcohol dependence: a 1-year, randomised controlled study. J Psychopharmacol. 2014;28:733–44.
5. Palpacuer C, Laviolle B, Boussageon R, Reymann JM, Bellissant E, Naudet F. Risks and benefits of nalmefene in the treatment of adult alcohol dependence: a systematic literature review and meta-analysis of published and unpublished double-blind randomized controlled trials. PLoS Med. 2015;12:e1001924.
6. Palpacuer C, Duprez R, Huneau A, et al. Pharmacologically controlled drinking in the treatment of alcohol dependence or alcohol use disorders: a systematic review with direct and network meta- analyses on nalmefene, naltrexone, acamprosate, baclofen and topiramate. Addiction. 2017. https://doi.org/10.1111/add.13974 **(Online 80 Sep 20)**.
7. Roerecke M, Gual A, Rehm J. Reduction of alcohol consumption and subsequent mortality in alcohol use disorders: systematic review and meta-analyses. Clin Psychiatry. 2013;74(12):e1181–9. https://doi.org/10.4088/JCP.13r08379.
8. Rahhali N, Millier A, Briquet B, Laramée P, Aballéa S, Toumi M, François C, Rehm J, Daeppen JB. Modelling the consequences of a reduction in alcohol consumption among patients with alcohol dependence based on real-life observational data. BMC Public Health. 2015;21(15):1271. https://doi.org/10.1186/s12889-015-2606-4.
9. Roerecke M, Kaczorowski J, Tobe SW, Gmel G, Hasan OSM, Rehm J. The effect of a reduction in alcohol consumption on blood pressure: a systematic review and meta-analysis. Lancet Public Health. 2017;2(2):e108–20. https://doi.org/10.1016/S2468-2667(17)30003-8 **(Epub 2017 Feb 7)**.
10. Rehm J, Marmet S, Anderson P, Gual A, Kraus L, Nutt DJ, Room R, Samokhvalov AV, Scafato E, Trapencieris M, Wiers RW, Gmel G. Defining substance use disorders: do we really need more than heavy use? Alcohol Alcohol. 2013;48(6):633–40. https://doi.org/10.1093/alcalc/agt127 **(Epub 2013 Aug 7. Review)**.
11. Bradley KA, Kivlahan DR. Bringing patient-centered care to patients with alcohol use disorders. JAMA. 2014;311(18):1861–2. https://doi.org/10.1001/jama.2014.3629.
12. Luquiens A, Reynaud M, Aubin HJ. Is controlled drinking an acceptable goal in the treatment of alcohol dependence? A survey of French alcohol specialists. Alcohol Alcohol. 2011;46(5):586–91.
13. Gastfriend DR, Garbutt JC, Pettinati HM, Forman RF. Reduction in heavy drinking as a treatment outcome in alcohol dependence. J Subst Abuse Treat. 2007;33(1):71–80.
14. Gottheil E, Thornton CC, Skoloda TE, Alterman AI. Follow-up of abstinent and nonabstinent alcoholics. Am J Psychiatry. 1982;139(5):560–5.
15. European Medicines Agency. Guideline on the development of medicinal products for the treatment of alcohol dependence. 2010. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500074898.pdf. Accessed Jan 2018.
16. Harris AH, Oliva E, Bowe T, Humphreys KN, Kivlahan DR, Trafton JA. Pharmacotherapy of alcohol use disorders by the Veterans Health Administration: patterns of receipt and persistence. Psychiatr Serv. 2012;63(7):679–85. https://doi.org/10.1176/appi.ps.201000553.
17. Mark TL, Kassed CA, Vandivort-Warren R, Levit KR, Kranzler HR. Alcohol and opioid dependence medications: prescription trends, overall and by physician specialty. Drug Alcohol Depend. 2009;99(1–3):345–9. https://doi.org/10.1016/j.drugalcdep.2008.07.018 **(Epub 2008 Sep 25)**.