LETTER TO THE EDITOR

A Point-by-Point Response to Braillon

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In his letter [1], Braillon comments our article recently published in CNS Neuroscience and Therapeutics, which synthesized the French recommendations on the pharmacotherapy of alcohol dependence [2]. He questions the thoroughness of the recommendations issued by the Société Française d'Alcoologie (SFA, i.e., French Alcohol Society) on both nalmefene and baclofen and suggests that the statements of the SFA members and the external experts who participated in writing or reviewing the French guidelines were influenced by the pharmaceutical industry. This calls for a point-by-point response, as we deem that Braillon's argumentation is largely based on misunderstood or erroneous facts.

Regarding the recommendation issued on nalmefene, and according to the official national grading system detailed in our article, the A grade means that the recommendation is based on the results of large-sample clinical trials or meta-analyses. This was precisely the case here, since, when the guidelines were being written, the efficacy of nalmefene had been assessed by nine randomized placebo-controlled trials [3], including three large-sample phase 3 trials [4–6]. The arguments developed by Braillon regarding these trials are similar to those of his previous letter published in the *British Medical Journal* [7], and we will only refer the reader to the detailed answer provided by van den Brink et al.

[8]. Braillon subsequently paraphrases the conclusive sentences of a recent meta-analysis on nalmefene [3]. However, he omits to remind that this meta-analysis found significant differences between nalmefene and placebo on the primary endpoints, namely the monthly number of heavy drinking days at both 6 months and 1 year, and on the total alcohol consumption at 6 months. Consequently, nalmefene appears to show a small but significant efficacy on drinking reduction. It is warranted to mention that the same statement can be given on the previously labeled medications for alcohol dependence, as both acamprosate and naltrexone showed small effect sizes, that is, high number-needed-to-treat (NNT) values, when compared to placebo [9]. Moreover, both nalmefene and baclofen support treatment paradigms of drinking reduction, which may allow patients unwilling to engage into abstinence to enter in a therapeutic program [10–12]. The adjunction of a drug to psychosocial interventions is felt by most clinicians to be a useful approach to engage patients in treatment, even when drugs have a limited pharmacologic effect compared to placebo.

Furthermore, Braillon's statements on baclofen are off the mark. First, the "temporary recommendation for use" (TRU) measure on baclofen was not "requested" by the French Drug Agency but entirely written and issued by them. Second, when he states

that the TRU measure “is not implemented by French doctors” because “only 6000 patients of an estimated 100,000 receiving the drug off-label are registered,” Braillon mixes up the TRU online registry, which is actually very poorly filled in by baclofen prescribers, and the TRU patient follow-up protocol (i.e., prescription indications and contraindications, dose-tapering procedures, maximum authorized dose...) [13]. Braillon writes that the baclofen maximum authorized oral dose for spasticity in France is 40 mg/day, whereas it is actually 120 mg/day [14]. Braillon floats the hypothesis that the results of the NCT01738282 industrial efficacy clinical trial on high-dose baclofen have not been published yet because there are negative. First, there are actually two clinical trials in this situation (NCT01738282 and NCT01604330), and the second of these trials was not conducted by a pharmaceutical company. Moreover, a communication on the results of these trials

has been planned at the ISBRA-ESBRA congress in Berlin in September 2016 (<http://isbra-esbra-2016.org/>). Braillon states that “off-label drug use is a slippery slope,” whereas careful off-label prescriptions can actually be useful and warranted in numerous situations [15]. Last, regarding the conflict of interests of the members of the recommendation working group, they are fully available to any reader on the SFA website (<http://www.sfalcoologie.asso.fr/>), as mentioned in our initial article. The public and industrial funding of the SFA is mentioned in the online Good Practice Recommendation publication [16]. Industrial funders are not involved in the scientific work provided by the SFA.

Conflict of Interest

The authors declare no conflict of interest.

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