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## **The underutilization of medications for alcohol use disorders is a sensible choice**

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Antonelli and colleagues' review about perspectives on the pharmacological management of alcohol use disorders and their effectiveness rightly concluded that "medications are still markedly underutilized in clinical practice and many patients do not have access to specialized treatment" [1]. However, one must rather question the roots of this state of affairs.

There is no magic pill. Treatment should combine psychosocial interventions and pharmacological therapy and even the combination have a limited effectiveness. This is evidenced by the high drop out in randomized clinical trials, roughly 30%, despite patients being highly selected - being not representative of those with more severe and complex conditions encountered in the real-life setting- and benefit from highly specialized professionals with adequate resources with a quality assurance program. One must acknowledge there are too few robust randomized clinical trials, as evidenced by off-label use (e.g. sodium oxybate...). Furthermore the informativeness of existing randomized clinical trials is a concern. E.g. for nalmefene or baclofen: a) the comparator was a placebo and not an effective treatment (e.g. acamprosate or naltrexone) as required by the Helsinki declaration; b) non-validated surrogate outcomes

were used as total consumption and heavy drinking days replaced abstinence, an outcome that is still required by U.S Food and Drug Administration for granting marketing authorization.

The claim “nalmefene too shows its major efficacy in the reduction of heavy drinking days, although it seems to be more effective than naltrexone in reducing total alcohol consumption” [1] deserved comment. A reduction of one drink per day with nalmefene vs a placebo, obtained from a post-hoc analysis in a subgroup of patients from the pivotal trials represents very weak evidence for a “major efficacy” [2] and nalmefene has shown a very small efficacy on consumption outcomes [3]. The assumption that such small differences will result in harm reduction (i.e. reduction of accidents, injuries and mortality) is highly speculative and is not evidence based yet. Evidence for such an approach has never been provided from randomized controlled trials or when follow-up is adequate. Of course, certain heavy drinkers may benefit from lower consumption but expecting that a dependent patient can maintain alcohol use at low level is an oxymoron per se. Last, there is no evidence of comparative effectiveness versus naltrexone, the claim for superiority comes from an industry sponsored indirect comparison [ref. 27 in 1] whose flaws had been extensively described [4,5] and were explored systematically [6].

The evidence base for baclofen is even worse. Its marketing authorization in France is a global exception. The director of the French medicines agency granted the approval by overturning the Special Scientific Committee conclusion that benefits/harms ratio was negative. We previously reported that the Chairman of the Committee declared that “(he) well understood that the benefit-risk assessment [of baclofen] was only one element, among others, (behind the decision)” [7]. The first pivotal trial Alpadir (NCT01738282) was negative on its primary outcome. Results of the second pivotal trial, Bacloville (NCT01604330) have been published without acknowledging major changes to the initial protocol affecting the primary outcome and the change in the initial statistical team when data were sold to the French pharmaceutical company applying for the marketing authorization in France [8]. The final report of Bacloville claimed that baclofen was effective in reducing alcohol consumption while serious adverse events were greater with baclofen than placebo. In other words, the harm reduction approach with baclofen increases harm! This result that was corroborated by a pharmaco-epidemiological study that evidenced a dose-dependent increase in mortality with baclofen vs acamprosate and naltrexone [9]. Last, the French National Authority for Health, the independent public scientific advisory body in charge of assessing medicinal products, recognized the lack of added benefit in clinical practice [10]. Despite these critical flaws, uncritical reviews are accumulating with these concerns being swept under the rug despite we repeatedly warned.

Last, Antonelli and colleagues, claimed that the Number Needed to Treat for antidepressants was 5 to 9 [1]. There has been accumulating evidence of the limited efficacy of antidepressants on clinically relevant outcomes when compared to psychotherapies [11,12] while solely the former expose to serious harms. As patients with alcohol use disorders are most frequently medicated with antidepressants one should rather recall that antidepressants have modest effect size if any, for relieving depression in alcohol users and that observational data suggest that antidepressant use in alcohol use disorders may be associated with a loss of self-control, memory impairment, and occasionally serious violence, suicide and homicide [13].

We therefore see reasons to regret that patients are too frequently pillled with non-evidence based or even harmful medications.

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