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COMMENTARY

Off-label use of baclofen for alcohol use disorders in India: no ethics without science

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Abstract

Off-label use of drugs, when not supported by sound scientific evidence, hinders the development of evidence-based medicine and therapeutic innovation, is costly to the healthcare system, and exposes patients to unnecessary risks, including mortality, for an uncertain benefit. Off-label use of baclofen is the preferred pharmacotherapy for alcohol use disorders in India, despite its negative benefit/harm ratio, and the fact that acamprosate or naltrexone have long been established as robustly evidence-based medicines. This unacceptable state of affairs only illustrates the fact that the marketing strategies of industry cannot be the sole basis for prescribing a drug.

Keywords: *off-label use, EBM, acamprosate, naltrexone, BACLOVILLE, ALPADIR, drug safety, scientific integrity*

Ghosh and colleagues' analysis of clinicians' attitudes towards pharmacotherapies in patients with alcohol use disorder (AUD) found a preference for baclofen, an off-label use [1]. This deserved robust comment, as Ghosh and colleagues flew in the face of evidence by claiming this "(reflected) its cost and safety profile" [1] and the editor of the *Indian Journal of Psychological Medicine,* refused to open this up to scientific debate.

We have to repeat that the benefit-harm balance of baclofen has been deemed negative by the Scientific Committee of the French Medicines Agency. However, France remains the only country to have granted marketing authorisation in AUD, not for abstinence as is usual, but for "a reduction in alcohol consumption", the director of the Agency having by-passed this negative assessment [2-4].

First, it is an understatement when Ghosh and colleagues assert that "the evidence for the efficacy of baclofen in AUD is far from clinching."[1] In Baclofen's first pivotal trial, ALPADIR (NCT01738282; 320 patients), designed to explore abstinence, the results were negative. The second pivotal trial BACLOVILLE (NCT01604330; 320 patients) had a composite primary endpoint: abstinence or low-risk consumption. Its data were sold by the sponsor AP-HP (The Paris Public Hospitals Authority), to Ethypharm laboratory [2]. This French pharmaceutical company switched the primary endpoint for its marketing authorisation application. We documented major problems in the study, questioning its ethics and scientific inconsistencies when the results were published, four years after the end of the study [3]. In summary, at best, baclofen could only have a modest effect on daily consumption vs placebo, if one can believe that these highly dependent patients can reliably monitor their own consumption [3]. Indeed, as for other treatments, meta-analyses fail to show any convincing benefit from baclofen in harm reduction [5]. Regarding safety, the BACLOVILLE trial identified a higher incidence of harms in the baclofen group, specifically more serious adverse events associated with baclofen [3]. This result was in line with a French cohort study (n= 165,334) in which patients exposed to baclofen had a higher risk of hospitalisation and death than with approved drugs for abstinence (acamprosate and naltrexone), these risks increasing with dosage [6]. It is therefore wrong to suggest that baclofen possesses an acceptable safety profile [7]. Similarly, it is, at best, naïve to claim that baclofen has an acceptable cost. Without proven efficacy, effectiveness is unlikely in the real setting, and potential toxicity must be factored into the cost. For instance, drug poisonings and self-poisonings resulting in convulsions, lethargy, somnolence and coma [7], if not death [6], are particularly expensive to manage in intensive care settings.

Second, off-label use, when it is not supported by sound scientific evidence hinders the development of evidence-based medicine and therapeutic innovation, is costly to the healthcare system, and exposes patients to the unnecessary risk of many adverse events, including mortality, for an uncertain benefit. Why is there only inertia, despite clear warnings in 2004 from Dr Ranjit Roy Chowdhury, then president of the Delhi Medical Council, that "If individual doctors or medical associations take on the role of drug regulators, we'll have therapeutic chaos", and from Dr Sanjay Nagral, chairperson of the Forum for Medical Ethics in Mumbai, that "It is dangerous to suggest that doctors should be free to decide about off-label use based on their experience and knowledge."[8] Why has the proposal of Dr Chandra Gulhati, editor of the *Monthly Index of Medical Specialities India,* that "drugs should be considered for unapproved indications only in highly controlled environments such as hospitals in situations where the potential benefits of the drug clearly outweigh its risks and with the approval of ethics committees and patients' consent" been ignored for two decades? [8]

Third, the finding that more clinicians reported having prescribed baclofen than naltrexone or acamprosate illustrates a shipwreck [1]. Indeed, it indicated that baclofen is frequently prescribed as a first–line drug, despite there

being an accumulation of meta-analyses and reviews confirming the positive benefits/harms ratio of naltrexone and acamprosate, the most recent one concluding that "with psychosocial interventions, oral naltrexone at 50 mg/d and acamprosate are … first-line pharmacotherapies for alcohol use disorder." [9]

We ask: why are doctors not using their common sense on this globally important issue of off-label use of baclofen? Indeed, as Ambroise Paré, a French military barber-surgeon from the 16th century, stated in his *Forty rules of surgery,* "Remedies known and approved by use and reason, are to be preferred before such as are unknown, or but lately found out."[10] Quoting Philippe Pinel, French psychiatrist (1745–1826), "it is no small art to prescribe drugs correctly, but it is an art of much greater difficulty than knowing when to stop or not to prescribe them." We assert that the marketing campaigns of a drug company cannot be the sole basis for putting the health and safety of patients at undue risk [11].

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