DISCUSSION

Reconsidering the ethics of off-label medication use: A response to Braillon and Naudet on baclofen use in alcohol use disorders in India

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Abstract

High diffusion of the use of baclofen in patients with alcohol use disorders (AUD) in India has raised concerns from Braillon and Naudet. They say the practice is based on poor evidence and ignores possible harms to patients. This article critiques their arguments and makes a reasoned, ethical, and evidence-informed case for baclofen as a treatment option for AUD, albeit a second-line one, especially because of issues with acceptability and cost of other approved pharmacotherapies.

Keywords: *Off-label medication, baclofen, ethics, drug regulation, alcohol use disorder*

Recently, I peer reviewed an article by Alain Braillon and Florian Naudet for the *Indian Journal of Medical Ethics* [1]. The editor invited me to write a commentary based on my critical comments as a reviewer. As an addiction psychiatrist practising in India, I welcome the discussion of pharmacological treatment for AUD and the ethics that should guide us.

In their article, the authors raise concerns about the high diffusion of the use of baclofen in the treatment of alcohol disorder in India, as reported by Ghosh et al [2]. They say the use of Baclofen is unethical due to safety issues and a lack of evidence for efficacy. While I agree that more evidence for baclofen is always welcome, I find their article lacking in balance and a global outlook, ignoring the latest evidence, and overlooking local factors for clinical practice in India. In this response, I critically evaluate their claims, discuss the ethics of off-label use of medications, and make a pragmatic case for baclofen use in alcohol use disorders.

Critique of the Braillon and Naudet article

Background

Braillon and Naudet have been critics of baclofen use in AUD for many years and have written many letters to editors and commentaries in scientific journals on the subject [3-7]. Their main critique arises out of questions regarding clinical trial integrity, safety concerns, and scepticism about the regulatory body. They critiqued [3] a review of an Indian academic, Professor Chittaranjan Andrade, who reviewed the randomised controlled trials (RCTs) and meta-analyses available by 2020 and gave a nuanced argument for baclofen use [8]. Prof Andrade gave a point-by-point counterargument against each point that was raised in their critique [9]. Similarly, their queries and comments have drawn logical and nuanced responses from the authors they had commented upon [10-13]. They have now raised the same queries, despite those having been answered adequately. Though their intention to ensure patient safety is good, their narrative suggests a distrust of regulators and practitioners.

Cherry picking evidence

They reference the 2018 network meta-analysis by Palpacuer et al [14] in their argument about the poor efficacy of baclofen in AUD; but ignore the latest meta-analysis by Agabio et al [15], which shows that baclofen decreases the risk of relapse to any drinking and increases the percentage of abstinent days after detoxification, without being associated with more adverse effects or dropouts [14,15]. Baclofen studies often involve complex populations, making comparisons with other drugs in AUD more difficult. Braillon and Naudet have ignored guidelines that attest to the utility of baclofen in AUD management. They fail to acknowledge that guidance from France itself has been provided after a 10-year-long period of off-label use and research [16]. When the baclofen dose is titrated in a flexible manner, clinical experience in diverse settings has shown better outcomes [17].

Ignoring aspects of the global South

Their critique reflects the perspective of the global North and ignores the challenges, such as limited healthcare infrastructure, availability of medication, and monetary constraints, that are central to treatment decisions in the global South. In India, Naltrexone and Acamprosate are expensive and are out of the reach of average citizens. Some patients do not tolerate these medications. Baclofen, on the other hand, is widely available, affordable, and acceptable, making it a pragmatic option in Indian settings. One cannot use a one-size-fits-all approach, especially when it is not aligned with the lived experiences of clinicians and patients in countries like India. Many Indian AUD patients have comorbid anxiety, which may benefit from baclofen's GABA-B agonist properties [18].

Misrepresentation of safety profile

The tone of Braillon and Naudet's article [1] is likely to create fear in the reader. However, it is important to note that, like other drugs used in AUD, baclofen has a dose-dependent risk. Otherwise, it is safe even in those with comorbidities [19]. There is a greater risk of misuse with benzodiazepines, which are standard treatment in alcohol withdrawal, than

with baclofen [20]. Therefore, the argument flagging addiction risk also fails.

Lacking nuance in argument regarding ethics

The authors believe that off-label use of drugs is inherently unethical without evidence from randomised controlled trials. Off-label use refers to prescribing a medication for an indication, age group, dosage, or route of administration that is not approved by regulatory agencies like the Food and Drug Administration (FDA) or the Drugs Controller General of India (DCGI). A drug used for a particular indication has already gone through safety checks. Use of such a medication for a new indication based on a scientific rationale is sound scientifically and ethically [21]. How else do you get case reports and case series, which become the basis for clinical trials, which would also be the basis for regulatory approval and clinical guidelines? Informed consent, clinical justification, and patient monitoring are all central to ethical practice, all of which can be expected in Indian clinical settings.

Can we ethically use off-label medications? If yes, how?

We have an obligation to help patients by using all the tools available to improve health and provide relief from suffering, based on the principle of beneficence. Off-label use of medication may be the only, or the most effective, treatment available. For example, one may use tramadol to treat a person dependent on heroin, when there is no access to approved drugs like buprenorphine or methadone. The principle of non-maleficence can be adhered to, especially if the patient is monitored well as, usually, the drug which is to be prescribed has been used for other indications for a long time and has a well-established safety profile. When patients are provided with adequate information about the condition, rationale for use, the truth about the use being "off-label", and the uncertainties about response and adverse effects — and patients make informed choices — the principle of autonomy can be considered to have been followed. It is also important that the decision aligns with the principle of providing equitable access to treatment and being cost-effective, thereby upholding the principle of justice [22].

A pragmatic case for baclofen use in AUD

Mechanism of action

Baclofen is an agonist at GABA-B receptors. It reduces alcohol cravings by dampening mesolimbic dopamine release [23]. It is especially useful in patients with comorbid benzodiazepine use, anxiety disorders, or liver dysfunction.

Clinical evidence

A systematic review from the Cochrane Collaboration has concluded that baclofen increases the percentage of days abstinent from alcohol and probably decreases the risk of relapse to any drinking [15]. There is meta-analytic evidence for safety even in liver disease [19]. There is a consensus among international experts in the form of the Cagliari statement on baclofen use (off-label) to treat AUD patients [24]. Several studies from India have also demonstrated its safety and efficacy [25-27].

Suitability in Indian settings

Baclofen is cost-effective and suitable for use in low-resource or rural settings. It would cost about Rs 50 per day in comparison to naltrexone, which would cost about Rs 75 per day, and acamprosate, which would cost about Rs 120 per day [28]. Additionally, it does not require monitoring of liver enzymes like naltrexone and has a benign renal clearance profile compared to acamprosate.

Conclusion

While it is important not to see baclofen as a magic pill in the treatment of AUD, and to exercise caution while using it, outright rejection based on selective evidence and improper ethical arguments undermines the interests of patients. Baclofen, when used appropriately, could be a valuable second-line treatment option for AUD, particularly in resource-constrained settings like India.

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Conflict of Interest: The author is an alumnus of AIIMS, New Delhi, a sister institution of AIIMS, Bhopal, the institution affiliated with authors critiqued by Braillon and Naudet. He is also the Associate Editor of the *Indian Journal of Psychological Medicine,* the journal where the original article was published.

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DISCUSSION

Off-label use of baclofen: A response to Kattula

FLORIAN NAUDET, ALAIN BRAILLON

Abstract

The "discussion" on our commentary about baclofen use in India perpetuates misconceptions. We want to: a) highlight the flood of overlapping and conflicting meta-analyses that obscure rather than clarify baclofen's effects; b) stress the importance of pivotal trials which support hypothetico-deductive reasoning and provide the basis for regulatory decisions. Such trials use only high-dose baclofen without proven benefit but serious safety concerns, including mortality. Practitioner enthusiasm, lived experience, or off-label consensus — whether in the global North or recycled in the global South — cannot replace rigorous trial evidence. We call for careful evaluation of pivotal evidence and robust research.

Keywords: *Off-label medication, baclofen, ethics, drug regulation, alcohol use disorder*

The publication of a "discussion" [1] on our "commentary" [2] was a welcome surprise, as stimulating debate is always valuable. The work of reviewers certainly deserves recognition, and making reviews accessible is an excellent initiative. However, we believe Dr Kattula's response [1] perpetuates serious misconceptions that we are eager to address in this response.

Ignoring the latest evidence?

First, on the issue of meta-analyses, Dr Kattula suggests that we are cherry-picking evidence. We are happy to clarify this point, since the implication of cherry-picking is dishonesty, something we reject.

We cited the network meta-analysis by Palpacuer et al in support of our statement: "indeed, as for other treatments, meta-analyses fail to show any convincing benefit from baclofen in harm reduction." That reference supports two key points: comparative effectiveness and lack of evidence for harm reduction. Indeed, as for other medications, no evidence exists that baclofen reduces alcohol-related harm.