**THE USE OF BACLOFEN TO TREAT PATIENTS WITH ALCOHOL USE DISORDER:**

**THE *CAGLIARI* EXPERT CONSENSUS STATEMENT**

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Alcohol use disorder (AUD) is a leading cause of morbidity and mortality.1-2 Alcohol consumption is related to approximately 4% of the global burden of disease.1 It has been estimated that, in clinical settings and compared to the general population, the relative risk of mortality is 3.38 for male patients and 4.57 for female patients with AUD.2 Patients who reduce their alcohol consumption may halve this increased risk of mortality compared to patients with AUD who do not.3 However, currently the approved pharmacotherapies that may help patients with AUD to achieve abstinence and/or reduce alcohol consumption to lower drinking levels are limited in number and efficacy.4-5 Therefore, there is an urgent need to develop more effective treatments in this area.

Preclinical and human studies suggest that baclofen, a GABAB receptor agonist, might be a novel treatment for patients with moderate to severe AUD.6 Notably, a few years after initial randomized clinical trials (RCTs) were conducted, the potential use of this medication for AUD dramatically increased in its popularity due to a French case report describing the use of very high doses of baclofen to treat alcohol craving and drinking.7 This intriguing yet purely anecdotical case report led to significant scientific and mass media attention and to the use of baclofen (off-label) in the treatment of AUD, such that the French drugs regulatory agency became involved in evaluating the use of baclofen in AUD. However, clinical studies conducted in Europe, USA, Australia, Israel and that evaluated baclofen efficacy in AUD have yielded conflicting results with some but not all RCTs showing an effect of baclofen.6

The three recent meta-analyses do not draw definitive conclusions on the efficacy of baclofen in the treatment of AUD.8-10 In fact, one meta-analysis8 found no significant superiority of baclofen over placebo on the outcomes of each study whereas the other two found that baclofen treatment significantly increased the rate of abstinent patients9-10 and time to first lapse9 compared to placebo. Furthermore, one meta-analysis found larger effect sizes of baclofen among heavy drinkers and studies using lower doses.9 The other study found no significant efficacy of baclofen in reducing the severity of craving for alcohol, anxiety, and depression.10 In addition, these two meta-analyses reported no significant efficacy of baclofen on other important outcomes such as rate of abstinence days9-10 or rate of heavy drinking days.10 Chiefly, all three meta-analyses found overall a small effect size and substantial heterogeneity among studies.8-10 Following the publication of these meta-analyses,8-10 a further RCT has been completed and data analysis is currently under way (JC Garbutt, unpublished; ClinicalTrials.gov: NCT01980706). Despite the lack of consistent evidence of efficacy, baclofen is frequently used off-label to treat AUD, especially in some European countries and Australia. However, there is significant variability in the use of baclofen for clinical research and in medical practice, due to differences in treatment provision for AUD, clinical experience, and country-specific regulations and culture.

This Consensus Statement was developed by an international group of experts in the use of baclofen for AUD, based on the current evidence from clinical practice and research of baclofen in patients with moderate to severe AUD (see Panel). Most members of the Consensus had a meeting on May 25th, 2018 in Cagliari, Italy, at the GABAB Receptor Conference, in a post-conference closed session. To develop the Consensus Statement, we used a modified Delphi Process12 (see online Appendix for further methodological information). The 26 members of the *Cagliari* Expert Consensus Group were from seven countries and included 21 physicians, two psychologists, two researchers and a consultant nurse. The members’ backgrounds included addiction medicine, addiction psychiatry, biomedical research, clinical neuropsychopharmacology, emergency medicine, epidemiology, gastroenterology, hepatology, internal medicine, pharmacology, pharmacoepidemiology, primary care, psychiatry, public health and toxicology.

In conclusion, baclofen remains a promising pharmacotherapy for AUD, however baclofen's superiority versus placebo cannot be considered to be established. Compared to approved medications for AUD,4-5 the level of evidence for baclofen is lower and further clinical trials are required. Furthermore, future studies on the GABAB receptor as a target using other pharmacological approaches like positive allosteric modulators are desirable in further understanding the potential mechanism of action in AUD.6 Research is also needed to understand baclofen dose-response relationships and precision medicine approaches, including its use in specific sub-groups (e.g. AUD patients with liver disease), as well as characterization of responders versus non-responders. However, as it is frequently used in clinical practice, this paper offers a Consensus of international experts on baclofen use (off-label) to treat AUD patients.

**Contributors**

RA served as the Chair of the *Cagliari* Expert Consensus Group and oversaw all stages of the process to ensure consistency across the stages of development of the Consensus. RA, LL, and JMAS served as the coordinating workgroup of the *Cagliari* Expert Consensus Group and led all stages of the development of the manuscript. RA, RdB, PdLS, PSH, MH, and PJ drafted the initial document before the expert meeting. RA, EMB, PJ, and AS revised the initial document based on the outcomes of the expert meeting. RA, LL, and JMAS drafted the full-text manuscript. RA, LL, and JMAS led and coordinated revisions before and after each round up to completion of the manuscript and submission. All authors contributed to the manuscript and approved its final version.

**Declaration of interests**

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CAM reports personal fees from Silence Therapeutics, outside the submitted work. BR reports personal fees from Ethypharm, outside the submitted work. WvdB reports personal fees from Lundbeck, personal fees from Eli Lilly, personal fees from Indivior, personal fees from Mundipharma, personal fees from Bioproject, personal fees from D&A Pharma, personal fees from Novartis, personal fees from Opiant Pharmaceuticals, outside the submitted work. All other authors declare no competing interests.

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| **Panel. Consensus Statement of the *Cagliari* Expert Consensus Group on the use of baclofen to treat patients with moderare to severe alcohol use disorder (AUD)** | |
| ***I. General statements*** ***on the treatment of patients with AUD*** | |
| 1 | Each country differs regarding medication regulations, laws, models of care, and reimbursement systems which need to be considered in the prescribing of medications and the provision of treatment. |
| 2 | Pharmacotherapy is only one component of the treatment of moderate to severe AUD. Patient-centred individualized treatment plans should be employed. These plans should also include psychotherapy, in-person and/or web-based treatments, and/or community and peer support groups. |
| 3 | The goal of a pharmacological treatment for patients with AUD may be both abstinence and/or reducing alcohol consumption to lower drinking levels, ideally below harmful levels. However, in certain subgroups of patients, the goal should be complete abstinence.4-5 |
| ***II. Effectiveness of baclofen in the treatment of patients with AUD*** | |
| 4 | Baclofen is not licenced as an approved treatment of AUD and its use is therefore “off label”. |
| 5 | Clinical research evidence is not clear about the most effective treatment setting for baclofen treatment but AUD patients may be treated in a range of treatment settings by clinicians with appropriate experience and training. |
| 6 | The majority of clinical trials started baclofen after detoxification and obtaining abstinence. In clinical practice, some physicians prescribe off-label baclofen while the patient is still drinking. These patients should be warned of the risks of side effects (e.g. excessive sedation; see also Section III) due to the pharmacological interaction of baclofen and alcohol. |
| 7 | Baclofen should be considered a second-line pharmacotherapy in patients who have not responded to approved pharmacological treatments for AUD. However, the off-label use of baclofen may be considered among the first-line pharmacological treatments in those patients with contra-indication to approved medications (e.g. patients with advanced liver disease for which the use of disulfiram or naltrexone may be contraindicated). |
| 8 | Daily baclofen dose should be based on safety, tolerability and patient’s response. |
| 9 | The daily dose of baclofen required to achieve abstinence, or a significant reduction in alcohol consumption, and/or a significant decrease in craving for alcohol may vary widely between patients, over a 10-fold range. |
| 10 | Baclofen must be started at a low dose (5 mg three times per day) and slowly titrated upwards (e.g. 5-10 mg/day, every three days) to minimize possible side effects, including sedation and overdose. |
| 11 | There is no evidence on the use of baclofen in combination with other medications for AUD (e.g. disulfiram, naltrexone, acamprosate, or nalmefene). |
| 12 | Baclofen should not be used instead of benzodiazepines in the treatment of alcohol withdrawal syndrome (AWS) as there is no evidence of its efficacy in preventing the development of potentially life-threatening complications of AWS like seizures and delirium tremens. |
| ***III. Safety of baclofen in the treatment of patients with AUD*** | |
| 13 | History of renal impairment needs to be considered before starting baclofen as it is mainly excreted by the kidneys. If prescribed, the management of baclofen in patients with renal impairment requires close supervision because of the higher risk of baclofen toxicity. |
| 14 | Most frequent side effects observed among patients with AUD include: sedation, fatigue, drowsiness, tiredness, somnolence, sleep disorders/insomnia, dizziness, headache, dry mouth, paresthesia, fasciculations, nausea, myalgia, and arthralgia. Most side-effects occur at the beginning of baclofen treatment or if the dose is increased too rapidly. |
| 15 | Many side-effects tend to be dose-related, although the contribution of other factors to the onset and/or severity of side-effects cannot be ruled out. |
| 16 | Particular caution is needed for the combination of baclofen with other sedative medications (including alcohol) since there are additive side-effects (e.g. sedation, drowsiness, somnolence). |
| 17 | Particular caution is needed among AUD patients with other comorbidities, e.g. patients with a history of epilepsy as baclofen may lower the seizure threshold, patients with mood disorders as baclofen may increase the risk of (hypo)manic episodes and patients with suicidal ideation and/or history of suicide attempts due to the risk of intentional overdose. |
| 18 | Treatment with baclofen should not be abruptly interrupted to avoid the risk of withdrawal symptoms. The daily dose should be slowly reduced (e.g. 5-10 mg/week). |

**Supplementary Appendix**

**Methods – Additional Information**

A modified Delphi Process was used.1 Six members (RA, RdB, PdLS, PSH, MH, PJ) drafted an initial document that was circulated by e-mail to all members before the initial meeting on May 25th, 2018. This was held in Cagliari, Italy, at the GABAB Receptor Conference, in a post-conference closed session.

Participants to the group were experts in the use of baclofen for AUD in clinical research and/or clinical practice. Eighteen members (RA, RdB, LL, JMAS, GA, HJA, EMB, NF, JCG, PSH, PJ, ARLH, LO, AP, LMP, FP, BR, AS) joined the expert meeting. Another eight members (FC, JDC, PdLS, MH, KCM, CAM, AT, WvdB) were unable to participate but provided written comments before the meeting, and/or significantly contributed to the iterations after the meeting. The Chair (RA) led each phase of the process to ensure consistency across the stages of the consensus.

During the meeting, an initial discussion took place on the scope of the consensus statement and differences in experience and opinion. Then, each sentence of the initial document was removed, approved, or approved after modification, based on the discussion and a vote (for/against).

The modified and approved items were then drafted by another group (RA, EMB, PJ, AS). This first draft of the Consensus Statement was sent to all 26 members (Round 1) with a request to rate each item on a 1-5 scale (1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree, 5 = strongly agree). All members were also asked to comment on any aspects of the wording that may require modification. Statements were then further modified, and any statement that one or more members rated < 3 was revised to address the areas of non-consensus. These revised statements were drafted and finalized, together with a draft of the full-text manuscript, by the coordinating workgroup (RA, LL, JMAS). The second draft was then sent to all members (Round 2) for a further iteration of rating, as described for Round 1. Statements were again revised by the coordinating workgroup and then sent to all members (Round 3). The final statements were approved by all members of the *Cagliari* Expert Consensus Group.

This study adhered to the tenets of the Declaration of Helsinki2 and was evaluated by, and considered exempt from, ethical committee oversight at the University of Cagliari, Italy.

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