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THE USE OF BACLOFEN TO TREAT PATIENTS WITH ALCOHOL USE DISORDER: THE *CAGLIARI* EXPERT CONSENSUS STATEMENT

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 $GABA_B$ 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-analysis[8] 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 patients[9-10] and time to first lapse[9] 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 days[9-10] 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 $GABA_B$ Receptor Conference, in a post-conference closed session. To develop the Consensus Statement, we

used a modified Delphi Process[12] (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 $GABA_B$ 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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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).

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THE USE OF BACLOFEN TO TREAT PATIENTS WITH ALCOHOL USE DISORDER: THE *CAGLIARI* EXPERT CONSENSUS STATEMENT

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 $GABA_B$ 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]

~~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.~~ ~~Even if T~~the ~~conclusions of~~ three recent meta-analyses ~~are not in full agreement~~ do not draw definitive conclusions on the efficacy of baclofen in the treatment of AUD.[8-10] In fact, one meta-analysis[8] 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 patients[9-10] and time to first lapse[9] 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 days[9-10] or rate of heavy drinking days.[10] ~~they converge in that baclofen appears superior to placebo, even if the overall effect is small.[8-10] Since then~~ 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). ~~reported a significant effect of baclofen in the treatment of AUD, compared to placebo.[11]~~ 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

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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 $GABA_B$ Receptor Conference, in a post-conference closed session. To develop the Consensus Statement, we used a modified Delphi Process[12] (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 ~~is~~ a promising pharmacotherapy for AUD, however baclofen's superiority versus placebo cannot be considered to be established. ~~However, c~~Compared to approved medications for AUD,[4-5] the level of evidence for baclofen is lower and further clinical trials are required. Furthermore~~, the work on baclofen supports~~ future studies on the $GABA_B$ receptor as a target ~~via~~ 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

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Declaration of 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~~	~~All clinical decision-making should be based on a balance of the evidence base, the clinical state and circumstances of the patient, the patient's preferences and actions, and the clinical expertise of the physician. Each clinical decision requires a risk/benefit analysis balancing these aspects.~~[~~12~~]
1~~2~~	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~~3~~	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~~4~~	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~~5~~	Baclofen is not licenced as an approved treatment of AUD and its use is therefore "off label".
5~~6~~	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~~7~~	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~~8~~	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~~9~~	Daily baclofen dose should be ~~personalized~~ based on safety, tolerability and patient's response.
9~~10~~	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~~11~~	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~~12~~	There is no evidence on the use of baclofen in combination with other medications for AUD (e.g. disulfiram, naltrexone, acamprosate, or nalmefene).
12~~13~~	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~~14~~	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~~15~~	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~~16~~	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~~17~~	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~~18~~	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~~19~~	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).

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Title: THE USE OF BACLOFEN TO TREAT PATIENTS WITH ALCOHOL USE DISORDER: THE CAGLIARI EXPERT CONSENSUS STATEMENT

Response to the Editor and Reviewers

Note: Reviewers comments are listed in normal typeface with **author responses in bold.**

Editor:

You will see that the reviewer approves the statement contents, as depicted in the panel, but that a more critical discussion of the published literature is required. You can add up to 150 words to the text, a few more if required, but please keep to the reference limit of 12.

We have revised the manuscript and provided a more critical discussion of the published literature, with special attention to a more detailed description of the results of each of the three meta-analyses (142 words; see lines 26-36, Clean draft) and the reference are 10.

Reviewer #1:

Agabio et al. provide an instructive consensus statement on the use of baclofen in patients with alcohol use disorders. The statement itself is sound and may improve clinical pratice. In particular, it is positive that the authors caution against combining baclofen with other pharmacological treatments of AUD, against the use of baclofen in alcohol withdrawal, against its sole use w/o social and psychological treatment, and against abruptly ending baclofen treatment.

We thank the Reviewer for their positive and supportive comments, and for their helpful suggestions. We appreciate the questions raised by the Reviewer and believe that we have carefully attended to them in our revised manuscript.

Other statements appear unnecessary for the general readership, such as the admonition that treatment decisions be based on evidence, the situation of the patient, and the experience of the doctor (statement 1), or should be re-phrased, such as statement 9 that invokes the lofty term „personalized" when it simply states that dosage should adapted according to tolerability.

We have removed statement 1 and have re-worded statement 9 (re-numbered now as statement 8).

What seems exaggerated to me is the presentation of the evidence. In my reading of the meta-analyses, they do not „converge in that baclofen appears to be superior to placebo" (line 32). The most comprehensive meta-analysis (Bschor et al. 2018), based on > 1500 patients, shows no statistically significant superiority of baclofen vs placebo, a finding suported by several pre-specified subgroup analyses, including among low risk of bias studies. In fact, there are only four to five studies in this field conducted with low risk of bias. For example, many studies changed considerably and unexplained between study protocol and publication. Against this backdrop, Pierce and co-workers' bold statmenent, in their meta-analysis (2018), that study quality was

generally „good" is hard to understand even if one accepted the results of their own risk of bias table. Rose & Jones (2018), in their meta-analysis, also conclude that the current use of baclofen is „premature". What the three meta-analyses indeed agree on is the large heterogeneity in this field, another reason for caution against strong claims.

The Reviewer makes an excellent point. We have revised the manuscript accordingly. In particular, we have now provided a more detailed description of the results of each of the three meta-analyses (see lines 26-36, Clean draft).

As a result, it seems a little rash to write that baclofen is a „promising pharmacotherapy for AUD" and that „work on baclofen supports future studies on the GABA-B receptor as a target". While such research can hardly do much damage, the baclofen story does not seem remotely similar to, say, the development of antipsychotics that clearly justified interest in the dopamine system. Consequently, while it is certainly a possibility that baclofen will turn out as a moderately effective treatment, at this point in time, I think it is too early to claim such an effect. Thus, I would considerably tone down this part of the statement and add that baclofen's superiority versus placebo cannot be considered to be established.

We agree with the Reviewer. We have revised and toned down those statements referenced by the Reviewer. Furthermore, we have added a sentence stating that baclofen's superiority versus placebo cannot be considered to be established (see lines 56-57).

A minor point: It is said that, after the publication of the three meta-analyses, „a further RCT has reported a significant effect of baclofen" (line 33), and this statement is supported by a congress abstract (ref 11). However, this very abstract does not provide any statement, much less data, regarding baclofen's superiority. What it says is simply that there were unexpectedly high numbers of drop-outs and side-effects. It may very well be that the authors presented data in favor of baclofen during the meeting, but the general reader cannot follow the authors' claim. Therefore, and since the results have not been published in a peer-reviewed journal, this statement should be changed.

This is an excellent point. The Reviewer is correct that Dr. Garbutt's team presented data in favor of baclofen during the meeting, but the results have not been published yet, nor are they available in the abstract. We have revised that sentence accordingly. Furthermore, we have removed the abstract citation and have rather referenced the clinicaltrials.gov NCT# in the text (see lines 36-38, Clean draft).

Necessary Additional Data

Click here to download Necessary Additional Data: 18-580 Agabio Baclofen Appendix_R2.pdf

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