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Review article

The influence of anxiety symptoms on clinical outcomes during baclofen treatment of alcohol use disorder: A systematic review and meta-analysis

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ABSTRACT

Given the high coexistence of anxiety symptoms in people with alcohol use disorder (AUD), we aimed to determine the influence of anxiety symptoms on outcomes in patients with AUD treated with the $GABA_B$ receptor agonist baclofen. A meta-analysis of 13 comparisons (published 2010–2020) including baseline and outcome data on alcohol consumption and anxiety after 12 weeks was undertaken. There were significantly higher rates of abstinent days in patients treated with baclofen compared to placebo ($p = 0.004$; high certainty evidence); specifically in those with higher baseline anxiety levels ($p < 0.00001$; high certainty evidence) compared to those with lower baseline anxiety levels ($p = 0.20$; moderate certainty evidence). The change in anxiety ratings over 12 weeks did not differ between those treated with baclofen or placebo ($p = 0.84$; moderate certainty evidence). This may be due to different anxiety constructs being measured by scales not validated in this patient group, or that anxiety is not a biobehavioral mechanism by which baclofen may reduce alcohol drinking. Given the prevalence of anxiety symptoms in AUD all these factors warrant further research.

1. Introduction

Baclofen (β-chlorophenyl-GABA) is a $GABA_B$ receptor full agonist, approved and long used in the treatment of muscle spasticity, which may also have analgesic properties independent of its myorelaxant effect (Balerio and Rubio, 2002; Enna and McCarson, 2016). The role of the $GABA_B$ receptor as a pharmacological target in the treatment of alcohol use disorder (AUD) has received increased attention in recent decades, with some clinical trials indicating that baclofen may reduce alcohol craving and drinking and promote abstinence [for review see de Beaurepaire et al., 2019]. However, human data are inconsistent (see meta-analytic studies: Bschor et al., 2018; Minozzi et al., 2018; Pierce et al., 2018; Rose and Jones, 2018), which may be due, at least in part, to the heterogeneity of the enrolled samples, and differences in study designs and dosage regimes. Baclofen has been approved for AUD treatment in France, in patients who have not responded to other approved treatments (de Beaurepaire et al., 2019).

Whilst the myorelaxant properties of baclofen are related to a 'dampening' of the spinal motor reflex (Bowery, 2016), its potential mechanism of action in AUD is less clear. Central $GABA_B$ receptors are involved in the regulation of a large number of systems and functions, including several neurotransmitter systems (e.g. dopamine, serotonin, norepinephrine, glutamate), transduction pathways, memory, and other cognitive functions (Bowery, 2016).

The optimal dosage of baclofen required to treat patients with AUD is also uncertain, with some patients being able to tolerate much higher

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doses compared to others (Agabio et al., 2018). Recent work suggests there may be a blunted sensitivity to baclofen in patients with AUD relative to controls, with no difference in pharmacokinetics suggesting a lower $GABA_B$ receptor sensitivity (Durant et al., 2018) and possibly a cross-tolerance between the effects of alcohol and baclofen on the $GABA_B$ receptor (Besheer et al., 2004; Addolorato et al., 2005).

Anxiety disorders and AUD are among the more prevalent mental disorders worldwide (Whiteford et al., 2013). Anxiety symptoms and disorders are frequent in patients with AUD (Schuckit and Hesselbrock, 1994), especially among women (Hasin and Grant, 2015). Social anxiety and post-traumatic stress disorder (PTSD) frequently pre-date AUD by many years and are an established risk factor in its aetiology (Oliveira et al., 2018; Debell et al., 2014; Berenz et al., 2017); panic attacks often occur in established AUD at high levels of daily drinking (Pacek et al., 2013); and anxiety symptoms are also common during alcohol withdrawal. Despite the high prevalence of co-occurrence, relatively little is known about the underlying neurobiological mechanisms involved, and even less about the effective management of this common co-morbid state (Ipser et al., 2015).

Preclinical and clinical findings indicate a key role of the $GABA_B$ receptor in depression and anxiety disorders (Felice et al., 2016; Jacobson et al., 2018) and the presence of psychiatric comorbidity may influence the response to baclofen treatment in patients with AUD (de Beaurepaire et al., 2019). A recent narrative review of clinical trials of baclofen in patients with AUD and comorbid mental disorders was not able to draw any definitive conclusions (Agabio and Leggio, 2018).

We speculated that a meta-analytic approach might better elucidate the role of anxiety symptoms in determining outcomes to treatment with baclofen in patients with AUD; in terms of alcohol consumption, anxiety symptoms, and the potential interaction between them. The different scales used to measure anxiety also require further exploration, as each is based on a different construct and there is little in the literature validating their use in patients with AUD. Accordingly, the aims of this study were to review how anxiety symptoms were measured in trials of patients with AUD treated with baclofen; and, using a meta-analytic approach, to evaluate whether, compared to placebo, baclofen induced significant changes in anxiety symptoms and drinking outcomes over the course of treatment, and how these were related.

2. Methods

2.1. Search strategy

We conducted a systematic review and meta-analysis in line with PRISMA guidelines, following an *a priori*–defined protocol, registered with PROSPERO (Baldwin et al., 2019). We searched PsycINFO; Embase; MEDLINE; PubMed; Cochrane Library, with no date limitation, using the following search strategy: "alcohol related terms" AND "anxiety related terms" AND "baclofen related terms" (see Baldwin et al., 2019 for full details). The last search was performed on February 26, 2019. References from included and excluded articles were reviewed to identify additional studies, and authors were contacted to identify studies in progress.

2.2. Inclusion criteria

2.2.1. Types of studies

Controlled clinical trials measuring the effects of baclofen on anxiety symptoms and alcohol consumption in patients with AUD. When a study reported more than one comparison, e.g. two different doses of baclofen and placebo, data for each comparison were included.

2.2.2. Types of participants

Men and women over 18 years with AUD, in whom levels of anxiety were also measured.

2.2.3. Types of interventions

Pharmacological treatment with baclofen alone or in combination with other medications or with psychosocial intervention.

2.2.4. Comparator(s)/control

Comparators initially included placebo, no intervention, other pharmacological interventions, and/or any psychological intervention.

2.3. Selection of the outcomes to evaluate alcohol consumption

There is a substantial range of outcome measures used in studies evaluating the efficacy of baclofen in the treatment of AUD (de Beaurepaire et al., 2019). Given the difficulty of comparing different outcome measures across studies, we selected a single measure (level of alcohol consumption) to evaluate the severity of alcohol use of participants at baseline.

Level of alcohol consumption at baseline (expressed in grams per week) was selected as a composite measure incorporating number of drinks per drinking day, and the number of drinking days per week. We used World Health Organization (WHO) criteria to classify the level of alcohol consumption into different categories of risk. WHO criteria consider 'high risk' as 60 −100 g/day for men (40−60 g/day for women), and 'very high risk' as greater than 100 g/day for men (60 g/day for women) (Mann et al., 2017): therefore, a week with seven drinking days at these levels would constitute 420 g to >700 g alcohol week for men (280 g to 420 g for women). Rate of abstinent days was used to evaluate the efficacy of baclofen at the end of the studies.

2.4. Outcomes and their measures

2.4.1. Primary outcomes

- Severity of anxiety expressed as
  - a Final score in continuous interviewer-rated and/or self-administered scales
  - b Difference between baseline and final scores in continuous interviewer-rated and/or self-administered scales
- Alcohol consumption levels expressed as rate of abstinent days.

2.4.2. Secondary outcomes

- Use of other substances with abuse liability
- Craving as measured by validated scales, e.g. Visual Analog Scale (VAS)
- Severity of AUD as measured by validated scales, e.g. Clinical Global Impression scale (CGI)
- Severity of other psychiatric symptoms diagnosed using standard criteria, e.g. Diagnostic and Statistical Manual of Mental Disorders (DSM) or measured by validated scales, e.g. Positive and Negative Syndrome Scale (PANSS).

2.5. Exclusion criteria

Studies were excluded if: (a) they did not report information on anxiety symptoms; (b) patients were not affected by AUD; (c) patients were < 18-years-old; (d) they were published in papers in languages other than English, Italian, Portuguese, or Spanish.

2.6. Data collection

Screening and data extraction were independently conducted by two authors (H.A. and R.A.; J.S. and R.A.). Disagreements were resolved by discussions with a third author (D.S.B. for topics related to anxiety; L.L. for topics related to AUD). From each selected study or comparison (when there was more than one comparison per study), the following information was abstracted: (a) type of study (comparative vs placebo

controlled trial), (b) number of participants assigned to baclofen and control group, (c) number of males and females, (d) mean age, (e) diagnostic criteria used for AUD and anxiety disorder, (f) duration of AUD and anxiety, (g) severity of AUD and anxiety at baseline, (h) dose of baclofen administered, (i) type of administration (fixed dose vs. titration), (j) scheduled duration of pharmacological treatment, (k) setting (inpatient or outpatient or a combination), (l) alcohol consumption at baseline (actively drinking or duration of abstinence), (m) presence of co-morbid mental or physical diseases (e.g. liver disease or mood disorders), (n) other pharmacological treatment offered, (o) other psychosocial treatment offered, (p) type of scale used to measure anxiety symptoms, and (q) outcome measures (see previous sections).

2.7. Assessment of risk of bias

Risk of bias of studies included in the meta-analysis was evaluated by two authors (J.S. and R.A.) and disagreements were discussed with a third author (D.S.B. or L.L.) according to the criteria indicated in Cochrane Reviews Handbook (Higgins and Green, 2011).

2.8. Data analysis

We analyzed continuous outcomes by calculating the mean difference (MD) with 95 % confidence interval (CI). When different scales were used to measure the severity of anxiety symptoms, the standardized mean difference (SMD) was used. We considered that participants differed in their response to baclofen compared to placebo when CIs excluded 0 (p-values < 0.05) and there was a lack of difference when CIs included 0 (p-values ≥ 0.05). The presence of significant heterogeneity was defined as I^2 value > 50 % or p-value for the chi-squared test ≤ 0.1 (Higgins and Green, 2011). Random effects models were used for all analyses. We assessed the overall quality of the evidence for the primary outcomes using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (Atkins et al., 2004) reporting the main findings in the 'Summary of findings' Tables 4a and 4b (Guyatt et al., 2011). Analyses were conducted using Review Manager 5.3.5.

3. Results

3.1. Studies selected and comparisons extracted

Two authors (RA, HA) independently screened the titles and abstracts of search hits to select studies of interest. The search identified 427 articles (4 from Cochrane reviews, 29 from Cochrane trials, 233 from Embase, 52 from Medline, 55 from PsycInfo and 54 from PubMed), of which 141 were duplicates. Six additional articles were identified through references (see Fig. 1).

Screening the titles and abstracts of these records provided information that led to the exclusion of 208 articles (see References S1), while full text-review of the remaining 84 articles excluded a further 66 articles which did not meet all of the inclusion and none of the exclusion criteria. Nineteen studies were initially included in the qualitative synthesis, but one was excluded (Hauser et al., 2017) as although stating it measured anxiety, it only reported data from a broader scale of psychological distress.

Eighteen studies (Addolorato et al., 2002, 2006; Beraha et al., 2016; Farokhnia et al., 2017; Garbutt et al., 2010a, 2010b; Girish et al., 2016; Gulati et al., 2019; Gupta et al., 2017; Krupitsky et al., 1993, 2017; Leggio et al., 2013; Lyon et al., 2011; Morley et al., 2014, 2018; Müller et al., 2015; Reynaud et al., 2017; Rigal et al., 2020) evaluated the effects of baclofen on anxiety symptoms and alcohol consumption in patients with AUD. As these studies varied in the duration of pharmacological treatment, from less than 1 week to 12 months (see Table 1), studies with a duration of less than 12 weeks (a standard duration for many RCTs in AUD) were excluded from the meta-analysis

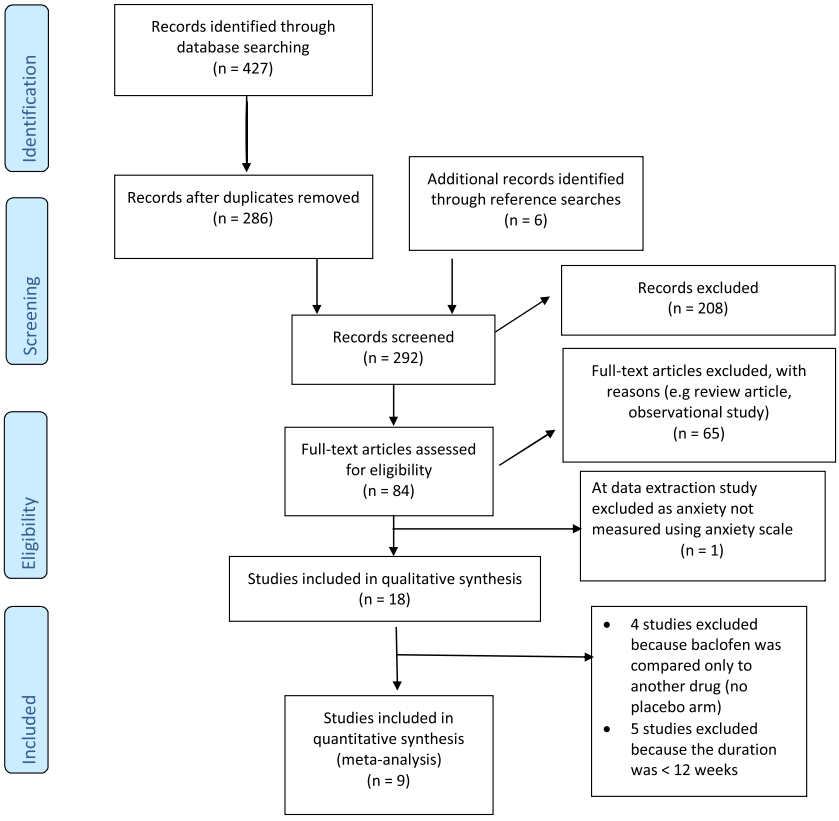


Fig. 1. Flow diagram of study selection.

Table 1
Main characteristics of the studies in which baclofen was administered to patients with AUD and anxiety symptoms were evaluated.

#	Study	Baclofen group	Control group	Baclofen		Treatment		Data available during and/or at the end of the study	
				Type of administration	Daily dose	Duration	Setting	Anxiety Symptoms	Alcohol
1	(Addolorato et al., 2002) 1 Drink =12 g	N = 20	**Placebo** **N = 19**	Fixed	30 mg	4 weeks	Outpatient	State STAI (baseline, 1,2,3,4 weeks)	CAD, DDD (baseline, 1,2,3,4 weeks) Abstinent participants (4 weeks)
2	(Addolorato et al., 2006)	N = 18	**Diazepam** **N = 19**	Fixed	30 mg	10 days	Outpatient	CIWA-Ar (anxiety item: day 1, 2, 3, 4, 5 and 10 days)	NR
3	(Beraha et al., 2016 [HD]) (Beraha et al., 2016 [LD]) 1 Drink =?	N = 58 N = 31	**Placebo** **N = 31** **Placebo** **N = 31**	Titration Fixed	Up to 150 mg 30 mg	16 weeks 16 weeks	Inpatient and outpatient Inpatient and outpatient	Trait STAI (baseline, 4 weeks, and 16 weeks) Trait STAI (baseline, 4 weeks, and 16 weeks)	TAC, CAD, Abstinent participants, Heavy drinkers (16 weeks) TAC, CAD, Abstinent participants, Heavy drinkers (16 weeks)
4	(Farokhnia et al., 2017) 1 Drink = 14 g	N = 18	**Placebo** **N = 16**	Fixed	30 mg	8 days	Outpatient laboratory	State and trait STAI (baseline and 8 days)	Alcohol self-administered Mini drinks self-administered
5	(Garbutt et al., 2010a) 1 Drink = 14 g	N = 40	**Placebo** **N = 40**	Fixed	30 mg	12 weeks	Outpatient	State STAI (baseline, 1, 2, 3, 4, 6, 8, 10 and 12 weeks) Trait STAI (baseline and 12 weeks)	Abstinent days, HDD (baseline, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 weeks)
6	(Garbutt et al., 2010b [1]) 1 Drink = 14 g (Garbutt et al., 2010b [2]) 1 Drink = 14 g Garbutt et al., 2010b [3] 1 Drink = 14 g	N = 10 Baclofen + Naltrexone N = 10 N = 10	**Placebo** **N = 10** Naltrexone + placebo **N = 10** **Naltrexone** **N = 10**	Fixed Fixed Fixed	30 mg 30 mg 30 mg	12 weeks 12 weeks 12 weeks	Outpatient Outpatient Outpatient	State STAI (baseline, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 weeks; graph) State STAI (baseline, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 weeks; graph) State STAI (baseline, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 weeks; graph)	HDD, Abstinent days (baseline and at 12 weeks) HDD, Abstinent days (baseline and at 12 weeks) HDD, Abstinent days (baseline and at 12 weeks) Time to first HDD (baseline, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 weeks; graph)
7	(Girish et al., 2016)	N = 30	**Chlordiazepoxide** **N = 30**	Fixed	30 mg	9 days	Inpatient	CIWA-Ar (anxiety item: baseline, 1, 2, 3, 4, 5, 6, 7, 8, and 9 days) Symptom free days	NR
8	(Gulati et al., 2019)	N = 34	**Lorazepam** **N = 32**	Fixed	30 mg	8 days	Inpatient	CIWA-Ar (baseline, 1, 2, 3, 4, 5, 6, 7, and 8 days; data on anxiety subscale NR)	NR
9	(Gupta et al., 2017)	N = 72	**Benfothiamine** **N = 50**	Fixed	30 mg	12 weeks	Outpatient	Decrease in HARS (12 weeks)	HDD, Time to relapse, CAD, Abstinent participants (12 weeks)
10	(Hauser et al., 2017) 1 Drink = 14 g	N = 88	**Placebo** **N = 92**	Fixed	30 mg	12 weeks	Outpatient	BSI and PLC (baseline, 6, and 12 weeks) BSI and PLC (diff between baseline and 12 weeks)	D and HDD per 2 weeks (graph)
11	(Krupitsky et al., 1993 [a]) (Krupitsky et al., 1993 [b])	N = 29 N = 29	**Placebo** **N = 23** **Diazepam** **N = 23**	Fixed Fixed	37.5 mg 37.5 mg	3 weeks 3 weeks	Inpatient Inpatient	State, Trait STAI and MMPI –Taylor at 3 weeks State, Trait STAI and MMPI –Taylor at 3 weeks	NR NR

(*continued on next page*)

Table 1 (*continued*)

#	Study	Baclofen group	Control group	Baclofen		Treatment		Data available during and/or at the end of the study	
				Type of administration	Daily dose	Duration	Setting	Anxiety Symptoms	Alcohol
12	(Krupitsky et al., 2017)	N = 16	**Placebo N = 16**	Fixed	50 mg	12 weeks	Outpatient	State, Trait STAI and HARS at 12 weeks	Time to relapse at 12 weeks
13	(Leggio et al., 2013) 1 Drink =?	N = 7	**Placebo N = 7**	Fixed	30 mg	7 days	Outpatient laboratory	Trait and State STAI at 7 days	NR (lab)
14	(Lyon et al., 2011) 1 Drink =?	N = 25	**Placebo N = 19**	Fixed	30 mg	3 days	Inpatient	NR	NR
15	(Morley et al., 2014 [HD]) 1 Drink = 10 g	N = 14	**Placebo N = 7**	Fixed	60 mg	12 weeks	Outpatient	State STAI at 12 weeks	DDD, HDD, Time to first lapse, Time to first relapse at 12 weeks
	(Morley et al., 2014 [LD]) 1 Drink = 10 g	N = 14	**Placebo N = 7**	Fixed	30 mg	12 weeks	Outpatient	State STAI at 12 weeks	DDD, HDD, Time to first lapse, Time to first relapse at 12 weeks
16	(Morley et al., 2018 [HD]) 1 Drink = 10 g	N = 35	**Placebo N = 16**	Fixed	75 mg	12 weeks	Outpatient	DASS (final score and diff betw baseline and final score) at 12 weeks	DDD, HDD, Time to first lapse, Time to first relapse, Abstinent days, Abstinent participants at 12 weeks
	(Morley et al., 2018 [LD]) 1 Drink = 10 g	N = 36	**Placebo N = 17**	Fixed	30 mg	12 weeks	Outpatient	DASS (final score and diff betw baseline and final score) at 12 weeks	DDD, HDD, Time to first lapse, Time to first relapse, Abstinent days, Abstinent participants at 12 weeks
17	(Müller et al., 2015)	N = 28	**Placebo N = 28**	Titration	Up to 270 mg	24 weeks	Outpatient	HAM-A (baseline, and 24 weeks)	CAD, Abstinent participants (baseline and 24 weeks)
18	(Reynaud et al., 2017)	N = 158	**Placebo N = 162**	Titration	Up to 180 mg	26 weeks	Outpatient	NR	Abstinent participants for 20 consecutive weeks from day 28 TAC & HDD (diff betw baseline and 6 months)
19	(Rigal et al., 2020) 1 Drink = 10 g	N = 162	**Placebo N = 158**	Titration	Up to 300 mg	12 months	Outpatients	HADS-A (baseline, 3, 6, and 12 months)	TAC, HDD, Abstinent days, Null or Low-risk alcohol drinkers, Heavy drinkers (baseline and 12 months)

ADS: Alcohol Dependence Scale.
CAD: Cumulative Abstinent Days.
CIWA-Ar: Clinical institute withdrawal assessment for alcohol scale – Revised.
DASS: Depression, Anxiety and Stress Scale.
DDD: Drinks per Drinking Day.
HADS-A: Hospital Anxiety and Depression Scale.
HAM-A or HARS: Hamilton Anxiety Rating Scale.
HD: High Dose Baclofen.
HDD: Heavy Drinking Day.
LD: Low Dose Baclofen.
NR: Not Reported.
TAC: Total Alcohol Consumption.

Table 2
Scales used to evaluate anxiety in studies of baclofen in AUD.

Scale	Construction	Form	Rating	Primary samples	Use in Baclofen studies
BSI (Derogatis and Melisaratos, 1983)	Adapted from SCL-90-R Good psychometric properties for whole scale Sensitive to change	Nine subscales, including one on 'anxiety' 6 items on anxiety sub-scale (Q1,12,19,38,45,49) Timeframe: last 7/7	0 (not at all) - 4 (extremely) Max score on anxiety subscale = 24. ***Or 63+ cut off for case in whole BSI***	Designed to reflect the psychological distress and symptom patterns of psychiatric and medical patients, as well as community samples	(Hauser et al., 2017) (Used full BSI, not anxiety subscale)
CIWA-Ar (Sullivan et al., 1989)	Clinical rating scale for the monitoring of the severity of alcohol withdrawal	Ten questions Single question on anxiety 'Do you feel nervous?' Time frame: currently	0 (no anxiety – at ease) 4 (Moderately anxious, or guarded, so anxiety is inferred) 7 (Equivalent to acute panic states as seen in severe delirium)	Patients in alcohol withdrawal	(Addolorato et al., 2002) (Girish et al., 2016) (Gulati et al., 2019)
DASS (Lovibond and Lovibond, 1995)	Three scales to measure depression, anxiety and stress Sensitive to change	Each scale contains 14 items, including Anxiety scale Burden: <2 minutes Timeframe: 'over the past week'	0 (not at all) – 3 (very much) Range 0-42 0-7 normal; 8-9 mild; 10-14 moderate 15-19 severe 20+ extremely severe ***Or 8+ cut off for case***	Range of populations, developed in non-clinical setting	(Morley et al., 2018)
HADS-A (Zigmond and Snaith, 1983)	Not confounded by physical illness Some sensitivity to change Good correlation with BDI and GHQ	Self-assessment/ or interviewer Burden: <5 mins 7 items (anxiety) Time frame: currently	0 (not present) – 3 (severely) Range 0-21 0-7 normal; 8-10 mild; 11-14 moderate 15-21 severe ***Or 8+ cut off for case***	Screening for significant anxiety in medically unwell patients.	(Reynaud et al., 2017) (Rigal et al., 2020)
HAM-A or HARS (Hamilton, 1959)	More accurate than self-report Good inter-rater reliability Reasonable sensitivity to change	Clinician rated Burden: 10-15 mins 14 items Time frame: in the last week	0 (not present) - 4 (severe) Range 0-56 0-5: no anxiety 6-14: minor anxiety 15-56: major anxiety ***Or 14+ cut off for case***	Based on clinical anxious samples Severity rating not diagnosis/ screening Includes depressive symptoms	(Gupta et al., 2017) (Krupitsky et al., 2017) (Müller et al., 2015)
STAI Y (Spielberger, 1983)	S (State) has lower reliability than T (Trait) T not sensitive to change Limited discrimination from depressive states	Self-report Burden: 20 mins S-20 items State – 'now' T- 20 items Trait – 'in general'	0 (almost never) – 4 (almost always) Range 0-80 ***Or 52+ cut off for case in Epilepy sample***	Used extensively in patients with chronic medical conditions Most commonly used, but developed for non-clinical conditions	(Addolorato et al., 2002) (Beraha et al., 2016) (Farokhnia et al., 2017) (Garbutt et al., 2010a) (Garbutt et al., 2010b) (Krupitsky et al., 1993) (Krupitsky et al., 2017) (Leggio et al., 2013) (Morley et al., 2014)

BDI: Beck Depression Inventory.
BSI: Brief Symptom Inventory.
SCL-90-R: Revised 90 item Symptom checklist from.
DASS: Depression, Anxiety and Stress Scale.
GHQ: General Health Questionnaire.
HADS-A: Hospital Anxiety and Depression Scale.
HAM- A: Hamilton Rating Scale for Anxiety.
HARS: Hamilton Anxiety Rating Scale.
STAI: State-Trait Anxiety Inventory.

to decrease the variability in response related to differences in duration (Addolorato et al., 2002, 2006; Farokhnia et al., 2017; Girish et al., 2016; Gulati et al., 2019; Krupitsky et al., 1993; Leggio et al., 2013; Lyon et al., 2011).

Comparisons of baclofen with another drug (i.e. diazepam, naltrexone, chlordiazepoxide, lorazepam, and benfothiamine), rather than placebo were also excluded (Addolorato et al., 2006; Garbutt et al., 2010b3; Krupitsky et al., 1993). Studies comparing baclofen to naltrexone (Garbutt et al., 2010b) or benfothiamine (Girish et al., 2016) were excluded because there was no placebo comparison. Despite benfothiamine being defined by the authors as a 'placebo' (Gupta et al., 2017) we included it in the comparator drug category, as benfothiamine (a nutritional supplement) has been found to modify anxiety symptoms in patients with AUD (Manzardo et al., 2015). This is consistent with FDA guidelines for the development of medications for AUD, which highlight that, while an active comparator of proven efficacy can *also* be included, in general a placebo comparator *should* be used (FDA, 2015). Studies comparing baclofen to diazepam (Addolorato et al., 2009; Krupitsky et al., 1993b), chlordiazepoxide (Girish et al., 2016) or lorazepam (Gulati et al., 2019) were excluded both due to lack of a placebo arm in addition to their short duration (see above) as a treatment for alcohol withdrawal, which is a distinct clinical treatment beyond the scope of this work.

Study characteristics are shown in Table 1. As three studies used two different doses of baclofen (Beraha et al., 2016; Morley et al., 2014, 2018), two different comparisons were extracted from each. Patients assigned to placebo were divided into two groups, one for each comparison. One study compared baclofen treatment with naltrexone and their combination (Garbutt et al., 2010b), enabling three potential comparisons [(1) baclofen (n = 10) *vs* placebo (n = 10); (2) the combination baclofen plus naltrexone (n = 10) *vs* the combination placebo plus naltrexone (n = 10); (3) baclofen (n = 10) *vs* naltrexone (n = 10)].

3.2. Scales used to evaluate anxiety symptoms

Table 2 shows the main characteristics of the scales used to evaluate anxiety symptoms (Derogatis and Melisaratos, 1983; Sullivan et al., 1989; Lovibond and Lovibond, 1995; Zigmond and Snaith, 1983; Hamilton, 1959; Spielberger, 1983). The majority of studies (Addolorato et al., 2002; Beraha et al., 2016; Farokhnia et al., 2017; Garbutt et al., 2010a, 2010b; Krupitsky et al., 1993, 2017; Leggio et al., 2013; Morley et al., 2014) used Spielberger's State-Trait Anxiety Inventory (STAI); three studies (Krupitsky et al., 2017; Müller et al., 2015; Gupta et al., 2017) used the Hamilton Anxiety Rating Scale (HAM-A or HARS); three studies (Addolorato et al., 2006; Girish et al., 2016; Gulati et al., 2019), not ultimately included in the meta-analysis, only used the single anxiety question in the Clinical Institute Withdrawal Assessment for Alcohol, revised scale (CIWA-Ar). Two studies (Reynaud et al., 2017; Rigal et al., 2020) used the Hospital Anxiety and Depression Scale (HADS-A), and one study (Morley et al., 2018) used the Depression, Anxiety and Stress Scale (DASS). One final study (Hauser et al., 2017) stated that 'symptoms of anxiety were measured by self-report using the Brief symptom Inventory (BSI)': however, only the full BSI (rather than the anxiety sub-scale) findings were reported in the paper (see section below), so after contacting the authors to confirm that it was not the anxiety measure that was presented, and they could not provide specific data for this, it was excluded from the analysis.

3.2.1. Spielberger State-Trait Anxiety Inventory (STAI) (Spielberger, 1983)

There is limited evidence for the validity of the STAI as a measure of categorical diagnoses of anxiety in general population samples. Mean values of both State and Trait STAI range between 30–40 (Knight et al., 1983). One recent study demonstrated that, among patients with epilepsy, a cut-off score $\geq$ 52 for both State and Trait STAI showed the best psychometric properties for the diagnoses of anxiety disorders (Wiglusz et al., 2019). As far as we are aware, no study has evaluated 'cut-off' values for the diagnoses of anxiety disorders among patients with AUD. Therefore, consistent with Wiglusz et al. (Wiglusz et al., 2019), we used $\geq$ 52 as the cut-off value to categorize if samples in the present meta-analysis reached the threshold for an anxiety disorder.

3.2.2. Hamilton Anxiety Rating Scale (HAM-A or HARS) (Hamilton, 1959)

The HAM-A is well validated as a symptom rating scale in patients with anxiety disorders. Scores of 14 and higher are often taken to designate a case (McDowell, 2006). Accordingly, we used the cut-off value $\geq$ 14 to categorize if samples compared in the present meta-analysis reached the threshold for an anxiety disorder.

3.2.3. Depression, Anxiety and Stress Scale (DASS) (Lovibond and Lovibond, 1995)

The DASS comprises three separate scales, well validated in clinical samples, to evaluate depression (DASS-D), anxiety (DASS-A), and stress (DASS-S) (McDowell, 2006). The cut-off value suggestive for the presence of anxiety disorders is $\geq$ 8 for the anxiety scale.

3.2.4. Hospital Anxiety and Depression Scale (HADS-A) (Zigmond and Snaith, 1983)

The HADS-A is validated for screening for anxiety and depression in medically unwell patients (McDowell, 2006). Scores of >8 higher on the anxiety sub-scale are often taken to designate a case including in one report of patients with rheumatological conditions (Julian, 2011). To our knowledge, no study has evaluated cut-off values for probable anxiety disorder among patients with AUD; therefore we used the standard cut-off value to categorize if samples compared in the present meta-analysis reached the threshold for an anxiety disorder.

3.2.5. Brief Symptom Inventory (BSI) (Derogatis and Melisaratos, 1983)

The BSI (Derogatis and Melisaratos, 1983) is a shortened, 53-item version of the Symptom Checklist-90. Participants have to rate from 0 (not at all) to 4 (extremely) the items corresponding to different subscales investigating anxiety, phobic anxiety, somatization, obsessive-compulsive, sensitivity, depression, hostility, paranoid ideation, and psychoticism. The cut-off for clinical 'caseness' for psychological distress is $\geq$ 63.

3.2.6. Clinical Institute Withdrawal Assessment for alcohol, revised scale (CIWA-Ar) (Sullivan et al., 1989)

The CIWA-Ar is a 10-item scale used clinically to measure the severity of alcohol withdrawal and response to medication. There is a single question relating to anxiety (scored 0−7), which is observer-rated. We excluded all studies in which only the CIWA single item question was used as the measure of anxiety symptoms.

3.3. Scales and outcomes used to evaluate alcohol consumption

The measures used to evaluate AUD severity varied widely including the Alcohol Dependence Scale (ADS), Alcohol Use Disorder Identification Test (AUDIT), and CAGE screening questions. The outcomes selected by the different studies to evaluate alcohol consumption or abstinence from alcohol comprised: the number or rate of Cumulative Abstinent Days (CAD), the number of Drinks per Drinking Day (DDD), the number or rate of Heavy Drinking Days (HDD), the Total Alcohol Consumption (TAC) expressed in grams of alcohol per day or grams per week, the number or rate of abstinent participants, the rate of heavy drinkers, the time to first relapse, the time to first lapse, and time to first Heavy Drinking Day.

3.4. Comparisons included in the meta-analysis

We included 13 comparisons in the meta-analysis (Beraha et al., 2016 (HD); Beraha et al., 2016 (LD); Garbutt et al., 2010a; Garbutt et al.,

Table 3
Comparisons included in the meta-analysis in which baclofen was compared to placebo for at least 12 weeks.

	Study	N patients	Males and Females	Baseline values				Data available at 12 weeks or later			
				Anxiety			Alcohol	Anxiety			Alcohol
				Scale used and mean baseline score	Cut-off values for cases	Anxiety disorders	Mean consumption in g/week	Scale used and mean final score	Scale used and mean difference between basal and final scores	Reduction in anxiety symptoms (% of basal score)	Abstinent days (%)
1	(Beraha et al., 2016 [HD])	B: 58 P: 31	M: 62 (69.66%) F: 27 (30.34%)	Trait STAI B: 49.7 (12.4) P: 48.6 (10.6)	52	NO	B: 896.7 P: 864.4	Trait STAI at 16 weeks B: 37.3 (12.1) P: 38.0 (11.1)	Trait STAI at 16 weeks B: 12.40 (24.50) P: 10.60 (21.70)	At 16 weeks B: 24.9% P: 21.8%	At 16 weeks B: 71.0 (34.94) P: 69.8 (28.98)
2	(Beraha et al., 2016 [LD])	B: 31 P: 31	M: 42 (67.74%) F: 20 (32.26%)	Trait STAI B: 52.1 (9.5) P: 48.6 (10.6)	52	Unclear	B: 808.2 P: 864.4	Trait STAI at 16 weeks B: 42.2 (14.1) P: 38.0 (11.1)	Trait STAI at 16 weeks B: 9.90 (23.60) P: 10.60 (21.70)	At 16 weeks B: 19.0% P: 21.8%	At 16 weeks B: 67.7 (34.94) P: 69.8 (28.98)
3	(Garbutt et al., 2010a)	B: 40 P: 40	M: 44 (55.00%) F: 36 (45.00%)	State STAI B: 34.1 (10.8) P: 38.5 (12.7) Trait STAI B: 38.3 (8.7) P: 42.1 (11.4)	52	NO	B: 623.4 P: 598.9	State STAI at 12 weeks B: 27.5 (13.5) P: 32.2 (16.7)	State STAI at 12 weeks B: 6.6 (24.30) P: 6.3 (29.40)	At 12 weeks B: 19.3% P: 16.4%	At 12 weeks B: 49.9 (27.9) P: 50.6 (25.9)
4	(Garbutt et al., 2010b [1])	B: 10 P: 10	M: 12 (60.00%) F: 8 (40.00%)	State STAI in a graph	52	NO	N.A.	N.A.	N.A.	N.A.	At 12 weeks B: 69.8 (34.94) P: 33.4 (28.98)
5	(Garbutt et al., 2010b [2])	B + N: 10 P + N: 10	M: 9 (45.00%) F: 11 (55.00%)	State STAI in a graph	52	NO	N.A.	N.A.	N.A.	N.A.	At 12 weeks B: 55.4 (34.94) P: 58.9 (28.98)
6	(Krupitsky et al., 2017)	B: 16 P: 16	M: 26 (81.25%) F: 6 (18.75%)	State STAI B: 43.2 (SE: 1.8) P: 37.2 (SE: 2.3) Trait STAI B: 45.5 (1.7) P: 41.7 (1.9)	52	NO	B: 8.5 (SE: 1.3) P: 9.7 (SE: 1.4)	State STAI at 12 weeks B: 34.8 (SE: 2.4) P: 33.8 (SE: 1.0)	State STAI at 12 weeks B: 8.4 (16.80) P: 3.4 (13.20)	At 12 weeks B: 19.4% P: 9.1%	At 12 weeks B: 79.1 (34.94) P: 78.7 (28.98)
7	(Morley et al., 2014 [HD])	B: 14 P: 7	M: 7 (33.33%) F: 14 (66.67%)	State STAI B: 35.93 (30.33-41.53) P: 36.62 (30.68-42.55) Trait STAI B: 39.50 (33.79-45.21) P: 43.08 (35.71-50.44)	52	NO	B: 594.7 (475.7) P: 765.1 (655.8)	State STAI at 12 weeks B: 36.61 (28.24-44.98) P: 32.44 (22.59-42.29)	State STAI at 12 weeks B: -0.68 (26.67) P: 4.18 (30.13)	At 12 weeks B: -1.9% P: 11.4%	At 12 weeks B: 33.2 (31.2) P: 22.6 (29.1)
8	(Morley et al., 2014 [LD])	B: 14 P: 7	M: 12 (57.14%) F: 9 (42.86%)	State STAI B: 42.23 (33.39-51.07) P: 36.62 (30.68-42.55) Trait STAI B: 46.92 (40.20-53.65) P: 43.08 (35.71-50.44)	52	NO	B: 617.0 (466.4) P: 765.1 (655.8)	State STAI at 12 weeks B: 33.18 (24.13-42.22) P: 32.44 (22.59-42.29)	State STAI at 12 weeks B: 9.05 (33.95) P: 4.18 (30.13)	At 12 weeks B: 21.4% P: 11.4%	At 12 weeks B: 30.9 (34.7) P: 22.6 (29.1)
9	(Morley et al., 2018 [HD])	B: 35 P: 16	M: 36 (70.59%) F: 15 (29.41%)	DASS B: 11.82 (8.92) P: 10.56 (8.58)	8	YES	B: 720.3 (581.3) P: 708.2 (509.5)	DASS at 12 weeks B: 7.83 (7.55) P: 9.91 (15.74)	DASS at 12 weeks B: 3.99 (16.47) P: 0.65 (24.32)	At 12 weeks B: 33.8% P: 6.2%	At 12 weeks B: 64.56 (SE: 7.69) P: 43.35 (SE: 7.60)

(*continued on next page*)

Table 3 (*continued*)

	Study	N patients	Males and Females	Baseline values				Data available at 12 weeks or later			
				Anxiety			Alcohol	Anxiety			Alcohol
				Scale used and mean baseline score	Cut-off values for cases	Anxiety disorders	Mean consumption in g/week	Scale used and mean final score	Scale used and mean difference between basal and final scores	Reduction in anxiety symptoms (% of basal score)	Abstinent days (%)
10	(Morley et al., 2018 [LD])	B: 36 P: 17	M: 38 (71.70%) F: 15 (28.30%)	DASS B: 14.72 (10.00)	8	YES	B: 934.4 (764.7) P: 708.2 (509.5)	DASS at 12 weeks B: 7.65 (9.72)	DASS at 12 weeks B: 7.07 (19.72)	At 12 weeks B: 48.0%	At 12 weeks B: 68.54 (SE: 5.90)
11	(Müller et al., 2015)	B: 28 P: 28	M: 39 (69.64%) F: 17 (30.36%)	HAM-A B: 2.1 (2.3) P: 3 (3.5)	14	NO	N.A.	HAM-A at 24 weeks B: 1.9 (5) P: 0 (0)	HAM-A at 24 weeks B: 0.2 (7.30) P: 3.00 (3.50)	At 24 weeks B: 9.5% P: 100%	At 24 weeks B: 49.3 (34.94) P: 39.8 (28.98)
12	(Reynaud et al., 2017)	B: 158	M: 225 (72.58%)	HADS-A	8	NO	N.A.	N.A.	N.A.	N.A.	N.A.
13	(Rigal et al., 2020)	B: 162 P: 158	M: 224 (70.00%) F: 96 (30.00%)	HADS-A B: 10.4 (4.4) P: 10.6 (4.6)	8	YES	N.A.	HADS-A at 12 weeks B: 9 (4) P: 9 (5)	HADS-A at 12 weeks B: 1.4 (8.4) P: 1.6 (10.0)	At 12 weeks B: 13.5% P: 15.1 %	At 48 weeks B: 53.6 P: 39.3

Legend Mean (SD).
ADS: Alcohol Dependence Scale.
B: Baclofen.
B+N: Baclofen + Naltrexone.
BSI: Brief Symptoms Inventory.
CAD: Cumulative Abstinent Days.
DASS: Depression, Anxiety and Stress Scale.
HADS-A: Hospital Anxiety and Depression Scale.
HAM-A: Hamilton Anxiety.
HARS: Hamilton Anxiety Rating Scale.
HD: High Dose Baclofen.
HDD: Heavy Drinking Day.
LD: Low Dose Baclofen.
N: Naltrexone.
N.A.: Not Available.
P: Placebo.
SD: Standard Deviation.
SE: Standard Error.
T: Total.
TAC: Total Alcohol Consumption.

Table 4a
Summary of findings: Baclofen compared to placebo for patients with AUD in studies in which anxiety symptoms were evaluated (studies of 12 weeks).

Patient or population: Patients with AUD (studies of 12 weeks)						
Setting: Outpatient						
Intervention: baclofen						
Comparison: placebo						
Outcomes	Type of patients	N° of participants (comparisons)	Certainty of the evidence (GRADE)	Anticipated absolute effects* (95% CI)		Heterogeneity
				Risk with placebo	Risk difference with baclofen	
Rate of abstinent days at the end of treatment	All patients	298 (8 comparisons)	⨁⨁⨁◯ MODERATE [a]	The mean rate of abstinent days ranged from 22.6–78.7	MD **11.24 higher** (1.29 higher to 21.19 higher)	$Tau^2 = 78.44$; $Chi^2 = 11.69$, df = 7 (p = 0.11); $I^2 = 40$ %
	Anxious patients	104 (2 comparisons)	⨁⨁⨁◯ MODERATE [a]	The mean rate of abstinent days ranged from 43.35–43.35	MD **23.47 higher** (9.53 higher to 37.41 higher)	$Tau^2 = 0.00$; $Chi^2 = 0.08$, df = 1 (p = 0.78); $I^2 = 0$%
	Not anxious patients	194 (6 comparisons)	⨁⨁⨁◯ MODERATE [a]	The mean rate of abstinent days ranged from 22.6–78.7	MD 5.54 higher (4.56 lower to 15.64 higher)	$Tau^2 = 32.63$; $Chi^2 = 6.25$, df = 5 (p = 0.28); $I^2 = 20$ %
Anxiety symptoms expressed as final score at the end of treatment	All patients	477 (7 comparisons)	⨁⨁⨁⨁ HIGH	The mean final score of anxiety symptoms ranged from 9 to 33.8	SMD 0.07 SD lower (0.25 lower to 0.12 higher)	$Tau^2 = 0.00$; $Chi^2 = 2.71$, df = 6 (p = 0.84); $I^2 = 0$%
	Anxious patients	323 (3 comparisons)	⨁⨁⨁◯ MODERATE [a]	The mean final score of anxiety symptoms ranged from 9 to 9.91	SMD 0.05 SD lower (0.28 lower to 0.17 higher)	$Tau^2 = 0.00$; $Chi^2 = 0.56$, df = 2 (p = 0.75); $I^2 = 0$%
	Not anxious patients	154 (4 comparisons)	⨁⨁⨁◯ MODERATE [a]	The mean final score of anxiety symptoms ranged from 32.2–33.8	SMD 0.09 SD lower (0.41 lower to 0.23 higher)	$Tau^2 = 0.00$; $Chi^2 = 2.11$, df = 3 (p = 0.55); $I^2 = 0$%
Anxiety symptoms expressed as difference between basal and final score at the end of treatment	All patients	578 (7 comparisons)	⨁⨁⨁⨁ HIGH	The mean difference between basal and final score of anxiety symptoms ranged from 0.65 to 6.3	SMD 0.02 SD higher (0.15 lower to 0.19 higher)	$Tau^2 = 0.00$; $Chi^2 = 2.66$, df = 6 (p = 0.85); $I^2 = 0$%
	Anxious patients	424 (3 comparisons)	⨁⨁⨁⨁ HIGH	The mean difference between basal and final score of anxiety symptoms ranged from 0.65 to 2	SMD 0.00 SD (0.19 lower to 0.19 higher)	$Tau^2 = 0.00$; $Chi^2 = 1.67$, df = 2 (p = 0.43); $I^2 = 0$%
	Not anxious patients	154 (4 comparisons)	⨁⨁⨁◯ MODERATE [a]	The mean difference between basal and final score of anxiety symptoms ranged from 3.4–6.3	SMD 0.07 SD higher (0.25 lower to 0.39 higher)	$Tau^2 = 0.00$; $Chi^2 = 0.86$, df = 3 (p = 0.84); $I^2 = 0$%

Explanations.
CI: confidence interval; MD: mean difference; SMD: standardized mean difference.
GRADE Working Group grades of evidence.
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[a] Downgraded one level for imprecision: fewer than 400 participants included in the analysis.
* **The risk in the intervention group** (and its 95 % confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95 % CI).

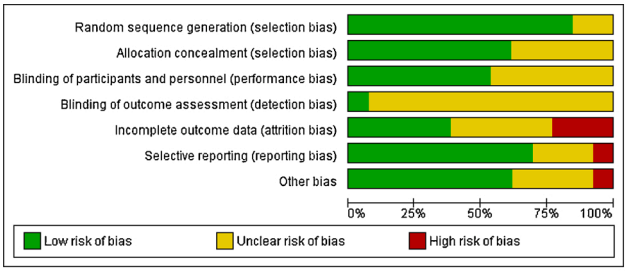
Table 4b
Summary of findings: Baclofen compared to placebo for patients with AUD in studies in which anxiety symptoms were evaluated (studies of 12 weeks or longer).

Patient or population: Patients with AUD (studies of 12 weeks or longer)						
Setting: Outpatient						
Intervention: baclofen						
Comparison: placebo						
Outcomes	Type of patients	N° of participants (comparisons)	Certainty of the evidence (GRADE)	Anticipated absolute effects* (95% CI)		Heterogeneity
				Risk with placebo	Risk difference with baclofen	
Rate of abstinent days at the end of treatment	All patients	825 (12 comparisons)	⨁⨁⨁⨁ HIGH	mean rate of abstinent days ranged from 22.6–78.7	MD **9.01 higher** (2.85 higher to 15.16 higher)	$Tau^2 = 36.19$; $Chi^2 = 16.78$, df = 11 (p = 0.11); $I^2 = 34$ %
	Anxious patients	424 (3 comparisons)	⨁⨁⨁⨁ HIGH	mean rate of abstinent days ranged from 39.3–43.35	MD **16.5 higher** (9.67 higher to 23.32 higher)	$Tau^2 = 0.00$; $Chi^2 = 1.34$, df = 2 (p = 0.51); $I^2 = 0$%
	Not anxious patients	339 (8 comparisons)	⨁⨁⨁◯ MODERATE [a]	mean rate of abstinent days ranged from 22.6–78.7	MD 4.35 higher (2.25 lower to 10.95 higher)	$Tau^2 = 0.00$; $Chi^2 = 6.80$, df = 7 (p = 0.45); $I^2 = 0$%
Anxiety symptoms expressed as final score at the end of treatment	All patients	684 (10 comparisons)	⨁⨁⨁⨁ HIGH	mean final score of anxiety symptoms ranged from 0 to 38	SMD 0.02 SD higher (0.13 lower to 0.17 higher)	$Tau^2 = 0.00$; $Chi^2 = 8.64$, df = 9 (p = 0.47); $I^2 = 0$%
	Anxious patients	323 (3 comparisons)	⨁⨁⨁◯ MODERATE [a]	mean final score of anxiety symptoms ranged from 9 to 9.91	SMD 0.05 SD lower (0.28 lower to 0.17 higher)	$Tau^2 = 0.00$; $Chi^2 = 0.56$, df = 2 (p = 0.75); $I^2 = 0$%
	Not anxious patients	299 (5 comparisons)	⨁⨁⨁◯ MODERATE [a]	mean final score of anxiety symptoms ranged from 0 to 38	SMD 0.05 SD higher (0.21 lower to 0.32 higher)	$Tau^2 = 0.02$ $Chi^2 = 6.18$, df = 5 (p = 0.29); $I^2 = 19$ %
Anxiety symptoms expressed as difference between basal and final score at the end of treatment	All patients	785 (10 comparisons)	⨁⨁⨁◯ MODERATE [a]	mean difference between basal and final score of anxiety symptoms ranged from 0.65 to 10.6	SMD 0.01 SD lower (0.16 lower to 0.13 higher)	$Tau^2 = 0.00$; $Chi^2 = 5.96$, df = 9 (p = 0.74); $I^2 = 0$%
	Anxious patients	424 (3 comparisons)	⨁⨁⨁⨁ HIGH	mean difference between basal and final score of anxiety symptoms ranged from 0.65 to 2	SMD 0 SD (0.19 lower to 0.19 higher)	$Tau^2 = 0.00$; $Chi^2 = 1.67$, df = 2 (p = 0.43); $I^2 = 0$%
	Not anxious patients	299 (6 comparisons)	⨁⨁⨁◯ MODERATE [a]	mean difference between basal and final score of anxiety symptoms ranged from 3 to 10.6	SMD 0.03 SD lower (0.27 lower to 0.2 higher)	$Tau^2 = 0.00$; $Chi^2 = 4.24$, df = 5 (p = 0.52); $I^2 = 0$%

Explanations.
CI: Confidence interval; MD: Mean difference; SMD: Standardised mean difference.
GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[*] **The risk in the intervention group** (and its 95 % confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95 % CI).

[a] Downgraded one level for imprecision: fewer than 400 participants included in the analysis.



Caption

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Fig. 2. Risk of bias.

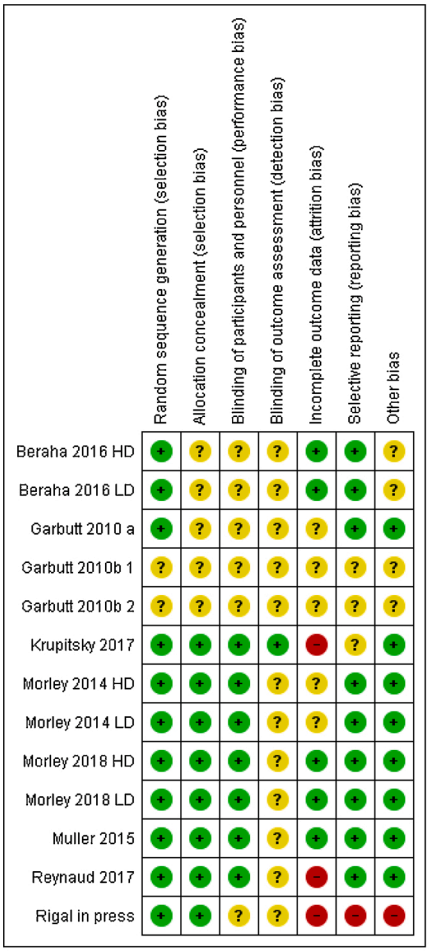
2010b(1); Garbutt et al., 2010b(2); Krupitsky et al., 2017; Morley et al., 2014 (HD); Morley et al., 2014 (LD); Morley et al., 2018 (HD); Morley et al., 2018 (LD); Müller et al., 2015; Reynaud et al., 2017; Rigal et al., 2020; 1143 participants) between baclofen (610 participants) and placebo (533 participants) extracted from studies lasting 12 weeks or longer (see Table 3).

3.4.1. Risk of bias in included comparisons (see Figs. 2 and 3)

Random sequence generation: eleven comparisons were considered to have low risk of bias. No information about methods of sequence random generation was available in two comparisons, so were judged as at unclear risk of bias.

Allocation concealment: eight comparisons were considered at low risk of bias, three comparisons did not report methods of allocation concealment, so were judged as at unclear risk of bias. Two other comparisons, during the trial, the inclusion of patients in a scheduled group was interrupted, and it is unclear that it may have constituted a risk of bias (Beraha et al., 2016 (HD); Beraha et al., 2016 (LD)).

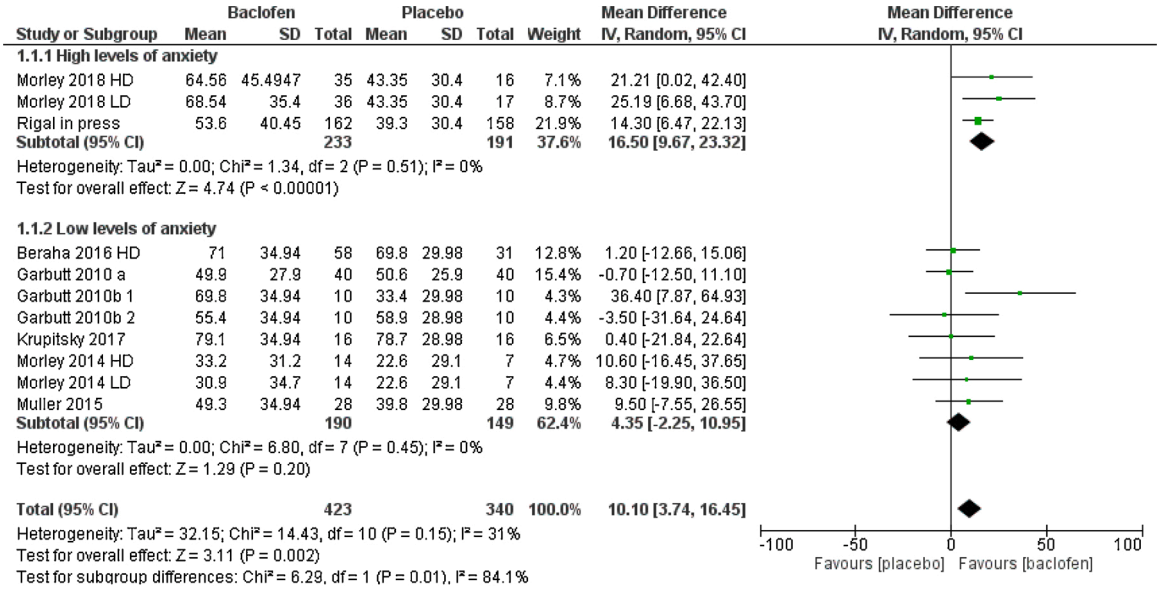
Blinding of participants and personnel: seven comparisons were judged at low risk of bias; three comparisons did not report details about blinding so were judged at unclear risk of bias; two comparisons, during the study, the inclusion of patients in a scheduled group was interrupted and it is unclear that it may have constituted a risk of bias (Beraha et al., 2016 (HD); Beraha et al., 2016 (LD)) in another it was unclear if the high



Caption

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Fig. 3. Risk of bias summary.



Caption

Forest plot of comparison: Baclofen vs placebo: Abstinent days (rate) at 12 weeks or longer.

Fig. 4. Forest plot of the comparison "baclofen *vs* placebo" in the rate of abstinent days.
CI: confidence interval
HD: high dose
IV: inverse variance
ID: low dose
SD: standard deviation

dose of baclofen may constitute a risk of bias (Rigal et al., 2020).

Blinding of outcome assessment: only one comparison was judged at low risk of bias (Krupitsky et al., 2017) for the other comparisons information about blinding was not available so were judged as at unclear risk of bias. Incomplete outcome data: five comparisons were considered low risk of bias; five comparisons did not report numbers and reasons of dropouts or missing data, so were judged as at unclear risk of bias. Three comparisons were judged to be at high risk of bias: one study as patients who relapsed were excluded (Krupitsky et al., 2017), one reported the primary outcome as "an estimated percentage of abstinent patients during 20 consecutive weeks" without providing an explanation of how these figures were reached (e.g. how the authors deal with drop out (Reynaud et al., 2017), and one as a high number of patients discontinued before the end of the study (Rigal et al., 2020).

Selective reporting: nine comparisons were considered at low risk of bias; three comparisons did not report enough information, so were judged as at unclear risk of bias. In one comparison a high number of patients discontinued before the end of the study and were moved to an open-label baclofen study, and so considered as at high risk of bias (Rigal et al., 2020).

Other biases: eight comparisons were considered as at low risk of bias; four comparisons did not report enough information, so were judged as at unclear risk of other bias. In one comparison not all patients had an AUD, and so was considered as at high risk of bias (Rigal et al., 2020).

3.4.2. *Severity of anxiety at baseline*

Only three comparisons (Morley et al., 2018 HD; Morley et al., 2018 LD; Rigal et al., 2020) met the criteria at baseline (based on mean scores on anxiety scales) for the sample to be considered within the clinically anxious range. One comparison (Beraha et al., 2016 LD) reported mean baseline anxiety scores that spanned the threshold for the presence of anxiety disorders based on the defined cut-off levels (see Table 3), and so was not included in the analyses divided according to the presence or not of anxiety disorders at baseline. In all other comparisons, mean baseline scores were lower than the cut-off values suggestive of clinically significant anxiety.

3.4.3. *Alcohol consumption at baseline*

As study samples varied considerably in terms of proportions of men and women included, it was not possible to differentiate between high and very high risk levels of alcohol consumption at baseline within samples (see above). However, using WHO drinking risk level criteria, seven comparisons [Beraha et al., 2016 HD; Beraha et al., 2016 LD; Garbutt et al., 2010a; Morley et al., 2014 HD; Morley et al., 2014 LD; Morley et al., 2018 HD; Morley et al., 2018 LD] were in participants whose drinking level at baseline were within or above the high risk range, regardless of gender (see Table 3). No data were available to calculate the drinking risk level for three comparisons (Garbutt et al., 2010b1; Garbutt et al., 2010b2; Rigal et al., 2020), and one study (Krupitsky et al., 2017) recorded a very low drinking risk level at baseline.

4. Meta-analysis

4.1. *Abstinent days (%, studies = 12 weeks)*

The rate of abstinent days at 12 weeks was available for 8 comparisons (Garbutt et al., 2010a; Garbutt et al., 2010b1; Garbutt et al., 2010b2; Krupitsky et al., 2017; Morley et al., 2014 HD; Morley et al., 2014 LD; Morley et al., 2018 HD, Morley et al., 2018 LD), involving 298 patients. The analysis found a significantly higher rate of abstinent days among patients treated with baclofen ($p = 0.03$; moderate certainty evidence) (see Tables 3 and 4a).

One comparison had a high risk of bias (Krupitsky et al., 2017): the analysis found a higher rate of abstinent days among patients treated with baclofen after exclusion of this study ($p = 0.02$), without evidence of heterogeneity [7 comparisons (Garbutt et al., 2010a; Garbutt et al., 2010b1, Garbutt et al., 2010b2; Morley et al., 2014 HD; Morley et al., 2014 LD; Morley et al., 2018 HD, Morley et al., 2018 LD), 266 patients,

MD: 12.96, 95 % CI 1.78–24.13; $Tau^2 = 97.61$; $Chi^2 = 11.00$, df = 6 (p = 0.09); $I^2 = 45$ %].

4.1.1. Studies divided into subgroups according to anxiety

Two comparisons (Morley et al., 2018 HD; Morley et al., 2018 LD), involving 104 patients reported mean baseline anxiety scores suggestive of reaching the threshold for an anxiety disorders based on the cut-off values of the scale used to evaluate anxiety symptoms. The analysis found a significantly higher rate of abstinent days among patients with levels of anxiety reaching the threshold for an anxiety disorder treated with baclofen rather than placebo (p = 0.0010; moderate certainty evidence): none of them had a high risk of bias (see Tables 3 and 4a).

Six comparisons (Garbutt et al., 2010a; Garbutt et al., 2010b1; Garbutt et al., 2010b2; Krupitsky et al., 2017; Morley et al., 2014 HD; Morley et al., 2014 LD) involving 194 patients reported mean baseline anxiety scores not reaching the threshold for an anxiety disorders according to the cut-off values of the scales used to evaluate anxiety symptoms. The analysis found no difference in the rate of abstinent days between baclofen and placebo in the low anxiety group (p = 0.28; moderate certainty evidence) (see Tables 3 and 4a). One comparison had a high risk of bias (Krupitsky et al., 2017). The analysis found no difference after its exclusion (p = 0.24) without evidence of heterogeneity [5 comparisons (Garbutt et al., 2010a; Garbutt et al., 2010b1; Garbutt et al., 2010b2; Morley et al., 2014 HD; Morley et al., 2014 LD), 162 patients, MD: 7.56, 95 % CI -5.18–20.31; $Tau^2 = 72.75$; $Chi^2 = 6.12$, df = 4 (p = 0.19); $I^2 = 35$ %].

4.2. Abstinent days (%, studies ≥ 12 weeks)

The rate of abstinent days at 12 weeks or longer was available for 12 comparisons (Beraha et al., 2016 HD; Beraha et al., 2016 LD; Garbutt et al., 2010a; Garbutt et al., 2010b1; Garbutt et al., 2010b2; Krupitsky et al., 2017; Morley et al., 2014 HD; Morley et al., 2014 LD; Morley et al., 2018 HD; Morley et al., 2018 LD; Müller et al., 2015; Rigal et al., 2020), involving 825 patients. The analysis found high certainty evidence (see Table 4b) for a significantly higher rate of abstinent days among patients treated with baclofen (p = 0.004). Two comparisons had a high risk of bias (Krupitsky et al., 2017; Rigal et al., 2020). The analysis found a higher rate of abstinent days among patients treated with baclofen after their exclusion (p = 0.03), without evidence of heterogeneity [10 comparisons (Beraha et al., 2016 HD; Beraha et al., 2016 LD; Garbutt et al., 2010a; Garbutt et al., 2010b1; Garbutt et al., 2010b2; Morley et al., 2014 HD; Morley et al., 2014 LD; Morley et al., 2018 HD; Morley et al., 2018 LD; Müller et al., 2015), 473 patients, MD: 8.50, 95 % CI 0.99–16.01; $Tau^2 = 47.87$; $Chi^2 = 13.73$, df = 9 (p = 0.13); $I^2 = 34$ %].

4.2.1. Studies divided into subgroups according to anxiety

Three comparisons in studies with outcome data at 12 weeks or longer (Morley et al., 2018 HD; Morley et al., 2018 LD; Rigal et al., 2020) involving 424 patients reported mean baseline anxiety scores suggestive of anxiety disorders based on the cut-off values of the scale used to evaluate anxiety symptoms. The analysis found high certainty evidence (see Table 4b and Fig. 4) for a significantly higher rate of abstinent days among patients treated with baclofen (p < 0.00001). One comparison had high risk of bias (Rigal et al., 2020). After its exclusion, the analysis still found a significantly high rate of abstinent days among patients treated with baclofen (p = 0.0010), without evidence of heterogeneity [2 comparisons (Morley et al., 2018 HD; Morley et al., 2018 LD), 104 patients, MD: 23.47, 95 % CI 9.53–37.41; $Tau^2 = 0.00$; $Chi^2 = 0.08$, df = 1 (p = 0.78); $I^2 = 0\%$).

Eight comparisons (Beraha et al., 2016 HD; Garbutt et al., 2010a; Garbutt et al., 2010b1; Garbutt et al., 2010b2; Krupitsky et al., 2017; Morley et al., 2014 HD; Morley et al., 2014 LD; Müller et al., 2015), involving 339 patients, reported mean baseline anxiety scores that did not reach the defined threshold for an anxiety disorder (see Table 3 and Fig. 4). There was no difference in the rate of abstinent days between baclofen and placebo (p = 0.20; moderate certainty evidence). One comparison had high risk of bias (Krupitsky et al., 2017). After its exclusion, the analysis still did not find any difference in the rate of abstinent days among patients (not reaching the defined threshold for an anxiety disorder) treated with baclofen and placebo (P = 0.18), without evidence of heterogeneity [7 comparisons (Beraha et al., 2016 HD; Garbutt et al., 2010a; Garbutt et al., 2010b1; Garbutt et al., 2010b2; Morley et al., 2014 HD; Morley et al., 2014 LD; Müller et al., 2015), 307 patients, MD: 5.19, 95 % CI -2.33 to 12.70; $Tau^2 = 10.64$; $Chi^2 = 6.67$, df = 6 (p = 0.35); $I^2 = 10$ %].

4.3. Anxiety: final score (studies = 12 weeks)

The outcome rating on an anxiety scale at 12 weeks was available (or we calculated it) for 7 comparisons (Garbutt et al., 2010a; Krupitsky et al., 2017; Morley et al., 2014 HD; Morley et al., 2014 LD; Morley et al., 2018 HD; Morley et al., 2018 LD; Rigal et al., 2020), involving 477 patients. The analysis found no difference between groups treated with baclofen or placebo for anxiety outcome rating (p = 0.48, without heterogeneity, high certainty evidence, see Tables 3 and 4a). Two comparisons had high risk of bias (Krupitsky et al., 2017; Rigal et al., 2020). After their exclusion, the analysis still did not find any difference between anxiety outcome ratings (p = 0.23), without evidence of heterogeneity, [5 comparisons (Garbutt et al., 2010a; Morley et al., 2014 HD; Morley et al., 2014 LD; Morley et al., 2018 HD; Morley et al., 2018 LD), 226 patients, SMD: -0.17, 95 % CI -0.44 to 0.10; $Tau^2 = 0.00$; $Chi^2 = 1.61$, df = 4 (p = 0.81); $I^2 = 0\%$].

4.3.1. Studies divided into subgroups according to anxiety

Three comparisons (Morley et al., 2018 HD; Morley et al., 2018 LD; Rigal et al., 2020), involving 323 patients, with mean baseline anxiety scores that reached the defined threshold for an anxiety disorder (see Table 3) reported an outcome anxiety rating at 12 weeks. The analysis of these comparisons found no difference between baclofen and placebo on the outcome anxiety rating (p = 0.63, without evidence of heterogeneity, moderate certainty evidence; see Table 4a). One of them had high risk of bias (Rigal et al., 2020). After its exclusion, the analysis still found no difference in outcome anxiety rating (p = 0.46) [2 comparisons (Morley et al., 2018 HD; Morley et al., 2018 LD), 104 patients, MD: -2.17, 95 % CI -7.91 to 3.57; $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 1 (p = 0.98); $I^2 = 0\%$).

Four comparisons (Garbutt et al., 2010a; Krupitsky et al., 2017; Morley et al., 2014 HD; Morley et al., 2014 LD), involving 154 patients, with mean baseline anxiety scores that did not reach the defined threshold for an anxiety disorder (see Table 3) reported an outcome anxiety rating at 12 weeks. The analysis found no difference in outcome anxiety rating between baclofen and placebo (p = 0.58, without evidence of heterogeneity, moderate certainty evidence, see Table 4a). One comparison had a high risk of bias (Krupitsky et al., 2017). After its exclusion, the analysis still found no difference in outcome anxiety rating (p = 0.54, without evidence of heterogeneity) [3 comparisons (Garbutt et al., 2010a; Morley et al., 2014 HD; Morley et al., 2014 LD), 122 patients, MD: -1.63, 95 % CI -6.83 to 3.57; $Tau^2 = 0.72$; $Chi^2 = 2.06$, df = 2 (p = 0.36); $I^2 = 3\%$].

4.4. Anxiety: Final score (studies ≥ 12 weeks)

The outcome score on an anxiety rating at 12 weeks or longer was available (or could be calculated) for 10 comparisons (Beraha et al., 2016 HD; Beraha et al., 2016 LD; Garbutt et al., 2010a; Krupitsky et al., 2017; Morley et al., 2014 HD; Morley et al., 2014 LD; Morley et al., 2018 HD; Morley et al., 2018 LD; Müller et al., 2015; Rigal et al., 2020), involving 684 patients. The analysis found no difference between groups treated with baclofen or placebo for anxiety outcome rating (p = 0.79, without heterogeneity, high certainty evidence, see Tables 3 and 4b). Two studies had high risk of bias (Krupitsky et al., 2017; Rigal et al.,

2020). After their exclusion, the analysis still did not find any difference between anxiety outcome ratings (P = 0.80, without evidence of heterogeneity), [8 comparisons (Beraha et al., 2016 HD; Beraha et al., 2016 LD; Garbutt et al., 2010a; Morley et al., 2014 HD; Morley et al., 2014 LD; Morley et al., 2018 HD; Morley et al., 2018 LD; Müller et al., 2015), 433 patients, SMD: 0.03, 95 % CI -0.19 to 0.25; $Tau^2 = 0.02$; $Chi^2 = 8.51$, df = 7 (p = 0.29); $I^2 = 18$ %].

4.4.1. Studies divided into sub-groups according to anxiety

Three comparisons (Morley et al., 2018 HD; Morley et al., 2018 LD; Rigal et al., 2020), involving 323 patients, with mean baseline anxiety scores that reached the defined threshold for an anxiety disorder (see Table 3) reported an outcome anxiety rating at 12 weeks. The analysis of these three comparisons found no difference between baclofen and placebo on the outcome anxiety rating (p = 0.63, without evidence of heterogeneity, moderate certainty evidence, see Table 4b). One of them had a high risk of bias (Rigal et al., 2020). After its exclusion, the analysis still found no difference in outcome anxiety rating (p = 0.46) after its exclusion [2 comparisons (Morley et al., 2018 HD; Morley et al., 2018 LD), 104 patients, MD: -2.17, 95 % CI -7.91 to 3.57; $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 1 (p = 0.98); $I^2 = 0\%$).

Six comparisons (Beraha et al., 2016 HD; Garbutt et al., 2010a; Krupitsky et al., 2017; Morley et al., 2014 HD; Morley et al., 2014 LD; Müller et al., 2015), involving 299 patients, with mean baseline anxiety scores that did not reach the defined threshold for an anxiety disorder (see Table 3) reported an outcome anxiety rating at 12 weeks. The analysis found no difference in outcome anxiety rating between baclofen and placebo (p = 0.70, without evidence of heterogeneity, moderate certainty evidence, see Table 4b). One comparison had high risk of bias (Krupitsky et al., 2017). After its exclusion, the analysis still found no difference in outcome anxiety rating (p = 0.75) [5 comparisons (Beraha et al., 2016 HD; Garbutt et al., 2010a; Morley et al., 2014 HD; Morley et al., 2014 LD; Müller et al., 2015), 267 patients, SMD: 0.05, 95 % CI -0.27 to 0.37; $Tau^2 = 0.05$; $Chi^2 = 6.10$, df = 4 (p = 0.19); $I^2 = 34$ %].

4.5. Anxiety: Delta score (studies = 12 weeks)

The difference between baseline and final score at 12 weeks was available (or we calculated it) for 7 comparisons (Garbutt et al., 2010a; Krupitsky et al., 2017; Morley et al., 2014 HD; Morley et al., 2014 LD; Morley et al., 2018 HD; Morley et al., 2018 LD; Rigal et al., 2020), involving 578 patients. The analysis found no difference between baclofen and placebo for the change in anxiety level over 12 weeks (p = 0.82, without heterogeneity, high certainty evidence, see Tables 3 and 4a). Two comparisons had high risk of bias (Krupitsky et al., 2017; Rigal et al., 2021), but after their exclusion, the analysis still found no difference in change of anxiety score (p = 0.45, without evidence of heterogeneity) [5 studies (Garbutt et al., 2010a; Morley et al., 2014 HD; Morley et al., 2014 LD; Morley et al., 2018 HD; Morley et al., 2018 LD), 226 patients, SMD: 0.10, 95 % CI -0.17 to 0.38; $Tau^2 = 0.00$; $Chi^2 = 1.00$, df = 4 (p = 0.91); $I^2 = 0\%$].

4.5.1. Studies divided into sub-groups according to anxiety

Three comparisons (Morley et al., 2018 HD; Morley et al., 2018 LD; Rigal et al., 2020), involving 424 patients, with mean baseline anxiety scores that reached the defined threshold for an anxiety disorder (see Table 3) reported a change in anxiety score at 12 weeks. The analysis of these comparisons found no difference between baclofen and placebo for the change in anxiety score over 12 weeks (p = 0.99, without evidence of heterogeneity, high certainty evidence, see Table 4a). One study had high risk of bias (Rigal et al., 2020). After its exclusion, the analysis still found no difference in change of anxiety score (p = 0.31) without evidence of heterogeneity [2 comparisons (Morley et al., 2018 HD; Morley et al., 2018 LD), 104 participants, MD: 4.87, 95 % CI -4.45 to 14.18; $Tau^2 = 0.00$; $Chi^2 = 0.11$, df = 1 (p = 0.75); $I^2 = 0\%$).

Four comparisons (Garbutt et al., 2010a; Krupitsky et al., 2017; Morley et al., 2014 HD; Morley et al., 2014 LD), involving 154 patients, with mean baseline anxiety scores that did not reach the defined threshold for an anxiety disorder (see Table 3) reported a change in anxiety score at 12 weeks. The analysis found no difference between baclofen and placebo for the change in anxiety score over 12 weeks (p = 0.66, without evidence of heterogeneity, moderate certainty evidence, see Table 4a). One comparison had high risk of bias (Krupitsky et al., 2017). After its exclusion, the analysis still found no difference in change of anxiety score (p = 0.97) [3 comparisons (Garbutt et al., 2010a; Morley et al., 2014 HD; Morley et al., 2014 LD), 122 patients, MD: 0.11, 95 % CI -9.97 to 10.20; $Tau^2 = 0.00$; $Chi^2 = 0.24$, df = 2 (p = 0.88); $I^2 = 0\%$].

4.6. Anxiety: Delta score (studies ≥ 12 weeks)

The difference between baseline and final score at 12 weeks or longer was available (or we calculated it) for 10 comparisons (Beraha et al., 2016 HD; Beraha et al., 2016 LD; Garbutt et al., 2010a; Krupitsky et al., 2017; Morley et al., 2014 HD; Morley et al., 2014 LD; Morley et al., 2018 HD; Morley et al., 2018 LD; Müller et al., 2015; Rigal et al., 2020), involving 785 patients. The analysis found no difference between baclofen and placebo for the change in anxiety score over 12 or more weeks (p = 0.84, without heterogeneity, moderate certainty evidence, see Table 3 and 4b). Two comparisons had high risk of bias (Krupitsky et al., 2017; Rigal et al., 2020), but after their exclusion, the analysis still found no difference in change of anxiety score (p = 0.99) without evidence of heterogeneity [8 comparisons (Beraha et al., 2016 HD; Beraha et al., 2016 LD; Garbutt et al., 2010a; Morley et al., 2014 HD; Morley et al., 2014 LD; Morley et al., 2018 HD; Morley et al., 2018 LD; Müller et al., 2015), 433 participants, SMD: -0.00, 95 % CI -0.20 to 0.19; $Tau^2 = 0.00$; $Chi^2 = 4.85$, df = 7 (p = 0.68); $I^2 = 0\%$].

4.6.1. Studies divided into sub-groups according to anxiety

Three comparisons (Morley et al., 2018 HD; Morley et al., 2018 LD; Rigal et al., 2020), involving 424 patients, with mean baseline anxiety scores that reached the defined threshold for an anxiety disorder (see Table 3) reported a change in anxiety score at 12 weeks or longer. The analysis found no difference between baclofen and placebo for the change in anxiety score over 12 or more weeks (p = 0.99, without evidence of heterogeneity, high certainty evidence, see Table 4b). One study had high risk of bias (Rigal et al., 2020). After its exclusion, the analysis still found no difference in change of anxiety score (p = 0.31) without evidence of heterogeneity [2 comparisons (Morley et al., 2018 HD; Morley et al., 2018 LD), 104 participants, MD: 4.87, 95 % CI -4.45 to 14.18; $Tau^2 = 0.00$; $Chi^2 = 0.11$, df = 1 (p = 0.75); $I^2 = 0\%$) without evidence of heterogeneity.

Six comparisons (Beraha et al., 2016 HD; Garbutt et al., 2010a; Krupitsky et al., 2017; Morley et al., 2014 HD; Morley et al., 2014 LD; Müller et al., 2015), involving 299 patients, with mean baseline anxiety scores that did not reach the defined threshold for an anxiety disorder (see Table 3) reported a change in anxiety score at 12 weeks or longer. The analysis found no difference between baclofen and placebo for the change in anxiety score over ≥ 12 weeks (p = 0.78, without evidence of heterogeneity, moderate certainty evidence, see Table 4b). One study had a high risk of bias (Krupitsky et al., 2017). After its exclusion, the analysis still found no difference in change of anxiety score [5 comparisons (Beraha et al., 2016 HD; Garbutt et al., 2010a; Morley et al., 2014 HD; Morley et al., 2014 LD; Müller et al., 2015), 267 patients, SMD: -0.08, 95 % CI -0.32 to 0.17; $Tau^2 = 0.00$; $Chi^2 = 3.12$, df = 4 (p = 0.54); $I^2 = 0\%$].

5. Discussion

This study is the first to analyze systematically the impact of anxiety symptoms on the outcome of treatment with baclofen in patients with

AUD, as well as explore the range and validity of the tools used to assess anxiety. We focused the analysis on those studies which had outcome data at 12 or more weeks, to enhance the stability of the results found, and limit the impact of acute alcohol withdrawal on measuring anxiety symptoms. There were limited differences between baclofen and placebo in the change on outcome measure at 12 weeks or more than 12 weeks suggesting that baclofen-placebo differences in anxiety symptoms at this point are relatively stable, as found in other treatment studies in patients with generalized anxiety disorder, social anxiety disorder and panic disorder (Rutherford et al., 2015).

There were significantly higher rates of abstinent days among patients treated with baclofen compared to placebo after 12 or more weeks (with moderate and high certainty of evidence, respectively). This remained so in the small number of comparisons where patients had high levels of anxiety at baseline (moderate and high certainty of evidence, respectively); however, the analysis found moderate certainty of evidence that patients treated with baclofen did not differ in the rate of abstinent days, after 12 or more weeks treatment, from those treated with placebo among those with low anxiety levels. We also found that, regardless of levels of anxiety at baseline, patients treated with baclofen did not differ from those treated with placebo in final anxiety rating expressed as final score and difference between basal and final score after 12 or more weeks (with moderate to high certainty of evidence).

These findings suggest that baclofen *may* be more effective in patients with higher baseline anxiety levels compared to those with lower baseline anxiety levels. There has been much speculation that a better response to the anti-alcohol effects of baclofen may be related to its anxiolytic actions (de Beaurepaire et al., 2019; Agabio and Leggio, 2018; Addolorato et al., 2009; Addolorato and Leggio, 2010; Agabio and Colombo, 2014; Agabio et al., 2016; Breese et al., 2011; de Beaurepaire, 2018; Goh and Morgan, 2017; Gorsane et al., 2012; Haass-Koffler et al., 2014; Heilig and Egli, 2006; Kalueff and Nutt, 2007; Kiefer, 2009; Leggio, 2009; Leggio et al., 2010; Lev-Ran et al., 2012; Lingford-Hughes et al., 2012; Muzyk et al., 2012; Soyka and Lieb, 2015; Tambour and Quertemont, 2007). However, our results demonstrate that this apparently better response among patients with higher baseline anxiety levels is not related to an anxiolytic effect induced by baclofen, as we found no differences in the final anxiety levels between patients treated with baclofen and placebo. As such, it is conceivable to speculate that reduction in anxiety is not a biobehavioral mechanism by which baclofen may reduce alcohol drinking. It is plausible that higher levels of anxiety represent an indirect proxy of a specific endophenotype of patients with AUD who may better respond to baclofen in terms of alcohol-related outcomes (e.g. patients with higher severity of AUD).

We also note the wide confidence intervals around the baseline anxiety levels which suggests significant inter-personal variation within the samples we analysed. We also observed that the measurement of anxiety symptoms was highly variable. Of those included in the meta-analysis, four studies used the Spielberger State anxiety subscale, two the Spielberger Trait anxiety subscale, two used the DASS, and one each the HAM-A and HADS-A. Of these the DASS, HAM-A and HADS-A have some evidence of sensitivity to change. Although the most widely used, the Spielberger Trait scale scores were reported as either State or Trait in different studies. Trait anxiety measures although constructed as a more stable phenomenon showed reductions over time in the samples in which it was used, and so its usefulness as a construct in clinical populations with AUD is hard to assess. Overall the STAI was not constructed for use in clinical samples or treatment studies and the only validation study against a diagnostic measure of anxiety was undertaken in patients with epilepsy (Wiglusz et al., 2019), and so this reference point was used as the cut off to define clinically significant anxiety in this analysis.

Levels of anxiety at baseline were also highly variable, and using the cut off points for potential 'caseness' from the literature only two studies included patients who (at a group level) scored sufficiently highly to meet the criteria for an anxiety disorder (Morley et al., 2018; Rigal et al., 2020). Despite this variety, all but one study (Morley et al., 2014) showed a reduction in anxiety symptoms from baseline over time in both cases and controls, suggesting that the reduction of anxiety symptoms in early abstinence is a consistent phenomenon in need of further research.

The study is limited by the fact that anxiety levels could only be measured at the sample mean level and not individual level, making it difficult to draw firm conclusions about the impact of baclofen treatment in individual patients based on their level of anxiety.

Anxiety symptoms are frequently seen as a factor across many mental disorders (including depression, PTSD and OCD, autistic spectrum disorder) (Howland et al., 2009; Straus et al., 2018; Ressel et al., 2020; Lochner and Stein, 2010). Their presence is frequently associated with higher suicide risk, longer duration of illness, and greater likelihood of treatment nonresponse (Kupfer, 2015). Given anxiety symptoms are an important predictor of outcome across a range of disorders, validated measures of severity and change are needed. Specifically, in AUD, the substantial coexistence of anxiety symptoms, and the potential impact of this on outcomes, requires further research to establish the optimal method for measuring anxiety constructs in this patient group. The STAI has been the most frequently used measure of anxiety symptoms in patients with AUD; however, given that both state and trait measures reduced over the 12 weeks of the study, its utility is questionable and future studies are needed to investigate the value of using the STAI to assess anxiety levels in patients with AUD. Of note the General Anxiety Disorder -7 (GAD-7) questionnaire (Spitzer et al., 2006) has not been used in any of the studies in this analysis. It is a specific measure of anxiety symptom severity and has been shown to be sensitive to change in clinical populations (Beard and Björgvinsson, 2014; Rutter and Brown, 2017), and consisting of only 7 questions (unlike 40 for the STAI) it would be less burdensome to use in clinical practice and research trials than the STAI, but needs validation in this population.

Given the putative mechanism of action of baclofen and the findings of this meta-analysis which suggest that levels of anxiety may be a predictor of outcome, there is a real need to reach consensus on how best to measure anxiety levels in patients with AUD. Improving the consistency of measures would enhance the quality of gathered evidence, and extend understanding of the potential role of anxiety in patients treated with baclofen, and help to clarify the role of anxiety on treatment outcomes in AUD.

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Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neubiorev.2020.12.030.

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