**Systematic review: Baclofen dosing protocols for alcohol use disorders used in observational studies**

**Short title: Baclofen protocols for alcohol use disorders**

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**Abstract**

The popularity of baclofen as an anti-craving agent in the treatment of alcohol use disorders (AUDs) has increased, especially in patients with established liver disease. However,evidence-based guidelines to inform practice are lacking. The aim of this systematic review is explore the prescribing practices of baclofen in AUD treatment.Electronic databases were searched for relevant articles from 2002. Assessment of eligibility criteria for inclusion was performed independently by two investigators. The main outcomes of interest were maximum dose, starting dose, titration regimen, effectiveness, and tolerability. Twenty-five studies reporting outcomes in 613 patients treated with baclofen for an AUD were identified. Starting doses ranged between 5 and 50 mg/d. Titration was study-dependent, and doses were increased until either therapeutic target (abstinence or study-defined low risk drinking) was achieved or adverse events resulted in a dose reduction or discontinuation. The maximum dose for individual patients ranged between 20 and 630 mg/d. Seven studies reported at least one patient using >300 mg/d. In studies with 10 or more patients, we found a negative correlation between dose and proportion of patients achieving the therapeutic goal. However, this was skewed by one study. A range of serious adverse events were reported. Most were reported at doses over 100 mg/d, but others presented at lower doses.Baclofen is a promising therapeutic in this area. Evidence is required, however, to support practitioners in prescribing doses that optimise outcomes and reduce adverse events.

**Keywords:** Baclofen; alcohol use disorders; abstinence; tolerability

**Introduction**

Baclofen, a selective γ-aminobutyric acid B (GABAB) receptor agonist, has been extensively used as an anti-spasticity agent for several decades (Davidoff, 1985). More recently, however, baclofen has been utilised as an anti-craving agent in the treatment of alcohol use disorders (AUDs). Development and progression of AUDs have been associated with modulation of dopaminergic neurotransmission and amino acid stimulation of GABAB receptors in the mesolimbic reward system of the brain (Agabio, Leite-Morris, Addolorato, & Colombo, 2016). Therefore, as a GABAB receptor agonist, baclofen is a biologically plausible therapeutic in the prevention of progression of AUDs. Furthermore, baclofen can be used in patients with established liver disease because it is predominantly excreted via the kidneys (Addolorato, Mirijello, Barrio, & Gual, 2016; Wuis, Dirks, Vree, & Van der Kleijn, 1990).

Initial randomised placebo-controlled trials (RCTs) of baclofen in patients with alcohol dependence in the presence or absence of liver cirrhosis utilised a dose of 30 mg/day (mg/d). These trials had both positive (Addolorato et al., 2002; Addolorato et al., 2007) and null outcomes (Garbutt, Kampov‐Polevoy, Gallop, Kalka‐Juhl, & Flannery, 2010). Animal models (Colombo et al., 2003) and anecdotal reports (Ameisen, 2005; Thomas, 2012) proposed that baclofen’s efficacy may be dose-dependent, with higher doses potentially improving outcomes. Two publications from the International Baclofen Intervention Study reported improved efficacy in participants randomised to 60 mg/d vs. placebo compared with those allocated 30 mg/d vs. placebo, but this was a *post-hoc* analysis (Addolorato et al., 2011; Morley et al., 2014). A placebo controlled trial conducted in Germany individually titrated participants based on effectiveness to a maximum dose of 270 mg/d with a mean dose of 180 mg/d (Müller et al., 2015). No serious adverse events were observed and the treatment group reported greater total and cumulative abstinence than the placebo group. A further trial used a maximum dose of 150 mg/d (mean dose 94 mg/d) (Beraha et al., 2016). The authors reported no differences in the time to first relapse between three groups (placebo, 30 mg/d and high dose baclofen). One patient developed severe constipation that resulted in hospitalisation in the high dose baclofen group. The most recently published RCT, the ALPADIR study, used a maximum dose of 180 mg/d, and also reported a null outcome when compared to placebo (Reynaud et al., 2017). Overall, the direction of outcomes from these studies are not universal, sample sizes are generally small but have increased in recent publications, and heterogeneity between trials in baclofen dose, titration regimens, baseline alcohol consumption, and psychosocial support make comparisons problematic and translation into practice unclear.

The number of pharmacological options for AUD is low. In the UK, The National Institute for Health and Care Excellence (NICE) recommend the use of acamprosate, naltrexone, disulfiram and nalmefene depending on the treatment objective. The popularity of prescribing off-label baclofen for AUD has grown in recent years, and we recently published our own observational findings in this area (Owens et al., 2017). However, there is limited formal evidence on which to base baclofen prescribing. This is particularly pertinent in patients with liver disease given the dearth of evidence on how different disease states influence pharmacokinetics, and whether robust moderators exist on which dosing can be stratified to maximise the benefit-risk ratio of baclofen.

The aim of this systematic review was to explore the prescribing practices of baclofen in real-world settings. Therefore, we decided to explore drug utilisation and outcomes using observational published data to assess the degree of variation in baclofen utilisation outside of carefully executed randomised controlled trials, which do not always reflect real-world clinical practice. Additionally, RCTs were also excluded because there have been a limited number of publications since recent systematic reviews (Jonas et al., 2014) and meta-analyses (Lesouef, Bellet, Mounier, & Beyens, 2014). The primary variable of interest was maximum dose per day prescribed to patients. Secondary variables of interest included starting dose, titration regimen, effectiveness, and tolerability.

**Experimental procedures**

*Search methods*

PubMed/MEDLINE and Scopus were the electronic databases that were searched from 2002 onwards. Each database was searched twice; the first was performed on 15 October 2015, and an update was performed 8 August 2016. The complete search strategy for each database is provided in Table 1. The reference lists of the identified publications were manually explored for additional relevant articles.

*Eligibility criteria*

Original English language case reports and case series in humans were eligible if they were: 1) published in a peer-reviewed journal; 2) provided real world examples of baclofen prescribing for AUDs; and 3) reported a maximum dose that was achieved through titration supervised by a healthcare professional. Non-case reports such as clinical trials, reviews, basic research, and commentaries were excluded. Evidence of an AUD was presumed if: 1) diagnostic criteria (e.g. DSM-IV) was used to confirm an AUD; or 2) the authors defined the patient as having an AUD as part of their clinical assessment. We excluded papers where baclofen was wholly self-administered, doses were consumed by mistake, or authors only reported baclofen ingestion as part of a suicide attempt. Information on the maximum dose achieved by a single patient was extracted; where multiple patients were included, we extracted the range of maximum doses reported.

Relevant papers were selected by screening the titles (phase one), abstracts (phase two) and complete articles (phase three) retrieved during the database searches. Assessment of eligibility criteria for inclusion or exclusion studies was performed independently by two investigators (AT and LO). Any disagreement during the selection procedure was resolved by discussion and consensus. The level of agreement during full-text screening was 88.9%.

*Data extraction and study variables*

For each article matching our inclusion criteria, we extracted the time of publication, country of origin, number of participants and gender distribution, age at commencing baclofen, AUD diagnosis, and maximum dose. We also extracted, where available, duration of treatment with baclofen, starting dose, titration regimen, effectiveness outcomes, and tolerability. Tolerability was defined as any reported side effect that was defined as ‘serious or severe’ within the article or resulted in the drug being discontinued or reduced. Effectiveness was defined as abstinence or drinking at levels considered controlled by health organisations (e.g. WHO, 2010).

The variables included are summarised in Table 2.

**Results**

*Literature search*

The final literature search identified 951 articles (PubMed/MEDLINE, 308 titles; SCOPUS, 643 titles). Combining the results from the two databases and removing both within- and between-database duplicates resulted in 657 unique articles for screening. Screening of the titles and abstracts resulted in 36 appearing to match the inclusion criteria. Out of the 36 full-texts assessed for eligibility, 11 were excluded because they reported self-administration (Ameisen, 2005; Thomas, 2012), reported intoxication only (Pape et al., 2014), reported findings from an RCT (Leggio et al., 2015), the full text was not written in English (Chaignot, Weill, Ricordeau, & Alla, 2014; Thill et al., 2016), they did not report the primary variable of interest (Rolland, Labreuche, et al., 2015; Rolland, Valin, et al., 2015; Shukla et al., 2015), the indication for treatment assumed AUD (Dupouy et al., 2014), or there was no evidence of an AUD (Olivier et al., 2016). This left 25 papers that were included in the review (Figure 1).

*Article characteristics*

The first included papers were published in 2007 (Agabio, Marras, Addolorato, Carpiniello, & Gessa, 2007; Bucknam, 2007). The year with most publications was 2015 (n=6; 24%). Of the included articles, 13 originated from France, three from Australia, two each from India, Switzerland and the USA, and one each from Italy, Japan and the UK. The follow-up periods ranged between three days (Saddichha, Jayaram, Manjunatha, & Benegal, 2011) and 67 months (de Beaurepaire, 2014). A total of 613 patients were included in the review, of which 214 (34.9%) were female. Number of patients per article ranged from 1 to 132. The median of the patients mean age for all included articles was 47.2 years (interquartile range = 10.2), and the age range was 23 to 85 years (Table 2).

*Baclofen dosing*

Thirteen articles reported a starting dose. Starting doses ranged between 5 and 50 mg/d, and there were seven different starting doses reported. Three articles reported a starting dose of ≥30 mg/d (Table 2 and Figure 2) (Heydtmann et al., 2015; Pastor, Jones, & Currie, 2012; Simioni et al., 2016).

All included papers reported a maximum dose, and those with a sample greater than one generally reported the range of maximum doses achieved by individual patients. The highest maximum dose of baclofen achieved by any one patient was 630 mg/d, which was taken for 1.5 months (de Beaurepaire, 2014). There were 19 articles that reported maximum doses ≥100 mg/d (Akosile & Klan, 2016; Auffret et al., 2014; Bence et al., 2014; Bucknam, 2007; de Beaurepaire, 2012, 2014; Dore, Lo, Juckes, Bezyan, & Latt, 2011; Franchitto, Pelissier, Lauque, Simon, & Lançon, 2014; Geoffroy et al., 2014; Heydtmann et al., 2015; Pastor et al., 2012; Perogamvros et al., 2015; Reichmuth, Blanc, & Tagan, 2015; Rigal, Alexandre-Dubroeucq, de Beaurepaire, Le Jeunne, & Jaury, 2012; Rigal et al., 2015; Rolland, Deheul, Danel, Bordet, & Cottencin, 2012; Rolland, Jaillette, et al., 2014; Simioni et al., 2016; Weibel, Lalanne, Riegert, & Bertschy, 2015), seven of which reported doses ≥300 mg/d (Akosile & Klan, 2016; de Beaurepaire, 2012, 2014; Heydtmann et al., 2015; Rigal et al., 2012; Rigal et al., 2015; Simioni et al., 2016). There were 10 articles that reported individual patients receiving maximum doses of less than 50 mg/d (Table 2 and Figure 2) (de Beaurepaire, 2012; Dore et al., 2011; Franchitto et al., 2014; Heydtmann et al., 2015; Holla et al., 2015; Macaigne, Champagnon, Harnois, Cheiab, & Chayette, 2011; Rigal et al., 2012; Rigal et al., 2015; Saddichha et al., 2011; Yamini, Lee, Avanesyan, Walter, & Runyon, 2014).

*Titration*

Of the studies included, 12 reported information on their titration regimen. The extent of detail provided was variable. Some studies used a slightly different dosing regimen; giving five doses per day instead of the usual three, the rationale being that baclofen has a short half-life. This approach was adopted by Heytmann and colleagues who used a starting dose of 25 mg/d (5 x 5 mg) (Heydtmann et al., 2015). Ten studies reported sufficient information to allow extraction of data (amount and timing) on first dose increase:

* Three studies had a first dose increase of 5 mg/d, which was initiated on either day 1 or 4 after treatment commenced (de Beaurepaire, 2012, 2014; Dore et al., 2011).
* Six studies had a first dose increase of 15 mg/d, which was initiated 3-7 days after treatment commenced (Agabio et al., 2007; Auffret et al., 2014; Rigal et al., 2012; Rolland et al., 2012; Simioni et al., 2016; Yamini et al., 2014).
* One study had a first dose increase of 20 mg/d, which was initiated 4 days after treatment commenced (Soufia et al., 2010).

One study reported a *pro rata* dose increase of 50-75 mg/d, which was proceeded by ‘steady escalation’ (Akosile & Klan, 2016). The remaining study reported an increase from 15 mg/d to 150 mg/d over 5 weeks; no details on how the maximum dose was achieved were provided (Weibel et al., 2015).

Titration after the first dose increase was variable, but appeared to range between 5 and 30 mg/d increasing over 2-7 day intervals. One study reported an increase from 30 mg/d to 75 mg/d, approximately 17 weeks after the smaller dose was commenced because of relapse (Agabio et al., 2007). Increases across studies were generally reported to be dependent on tolerance and effectiveness. The measures used to determine the need for increased dose included persistent alcohol consumption (i.e. desired effect not achieved), lapse or relapse to drinking following abstinence on baclofen, and subjectively or objectively measured craving. Some patients requested, and received, increased doses despite the emergence of side effects.

*Effectiveness*

Seventeen of the included studies provided some evidence of effectiveness. Abstinence was the most commonly reported outcome, whilst others reported a metric of reduced alcohol intake (e.g. ‘controlled drinking’, ‘reduced consumption’). Two studies reported that at least one patient achieving abstinence subsequently relapsed (Holla et al., 2015; Weibel et al., 2015). There were seven articles that had a sample of 10 or more and included outcomes for effectiveness (de Beaurepaire, 2012, 2014; Dore et al., 2011; Heydtmann et al., 2015; Rigal et al., 2012; Rigal et al., 2015; Yamini et al., 2014); the proportion of patients reporting abstinence or lower risk drinking ranged between 18.9% and 97.1% (median = 45.7%) in these articles. Delineating the relationship between dose and effectiveness is problematic because of the range of doses at which abstinence is reported. Running a Pearson correlation for the relationship between dose and proportion of patients achieving the article-specific drinking goal in the seven articles with a sample of 10 or more gave an r = -0.34 (*P* = 0.416). This negative relationship was weighted heavily by the Yamini paper that reported abstinence in 97.1% of patients using 30 mg/d of baclofen (Yamini et al., 2014). Several of the included case studies reported that some patients needed very high doses (i.e. >300 mg/d) to achieve the desired consumption goal.

*Tolerability*

Twenty of the included studies reported at least one adverse event that was defined as “serious/severe”, and/or resulted in the reduction or discontinuation of baclofen. The proportion of patients within these 20 studies with a relevant adverse event ranged between 7% and 100%; there were 13 studies where 100% of the sample had an adverse event that matched our inclusion criteria, but the highest sample size in any of these studies was 12 (Franchitto et al., 2014) and eight studies were single patient case reports (Akosile & Klan, 2016; Geoffroy et al., 2014; Macaigne et al., 2011; Perogamvros et al., 2015; Reichmuth et al., 2015; Rolland et al., 2012; Soufia et al., 2010; Weibel et al., 2015). Details relating the dose reductions and any rechallenge are provided in Table 3. Some of the included articles had a specific baclofen-related adverse event as their focus, whilst others reported adverse events that presented over the observation period. The adverse events included: tinnitus (dose(s) at which adverse event initially occurred: 180-210 mg/d); oedema (75-250 mg/d); delirium (210 mg/d); depression (unknown); back pain 120 mg/d); somnolence/tiredness with other adverse events (275-370 mg/d); mania (180 mg/d); irritability (unknown); dizziness (150 mg/d); gastroesophageal reflux (unknown); decreased libido (unknown); acute hepatitis (30 mg/d); sleep apnoea (200 mg/d); morbilliform rashes (20-60 mg/d); behavioural disinhibition (60 mg/d); and seizures (240 mg/d). Three articles reported a dose reduction or discontinuation due to an adverse event, but the details of the adverse events and dose reduction were not provided (Rigal et al., 2012; Rigal et al., 2015; Simioni et al., 2016).

Several studies showed good practice and utilised an adverse drug reaction causality assessment tool to formally assess the likelihood of baclofen as the casual factor (Bence et al., 2014; Geoffroy et al., 2014; Macaigne et al., 2011; Rolland et al., 2012; Rolland, Jaillette, et al., 2014; Saddichha et al., 2011). Other studies that have not used such tools may need to be interpreted with caution.

There was also evidence of poor compliance or misuse by patients. The case study by Akosile and Klan (2016) reported symptoms suggestive of baclofen withdrawal following abrupt cessation by a patient at a dose of 500 mg/d. The symptoms were reported by the patient as similar to those experienced during alcohol withdrawal. Baclofen withdrawal following potential baclofen abuse (up to 2000 mg ingested) was also reported by Rolland et al. (2014) , where the symptoms were initially mistaken for alcohol withdrawal and benzodiazepines were initiated with minimal effect. Direct suicide attempts via ingestion of high doses of baclofen following periods of stable use were also reported (Franchitto et al., 2014; Holla et al., 2015); although direct causality was not established.

**Discussion**

Given the societal costs of alcohol (Rehm et al., 2009; WHO, 2010) and the modest efficacy of licenced anti-craving pharmacotherapies (Jonas et al., 2014), gaining an improved understanding of current and novel AUD treatments is an important and urgent challenge.

Interest in baclofen as a treatment for AUDs was catalysed by the auto-case report of a French physician who used doses up to 270 mg/d as an anti-craving therapy to achieve abstinence after failing with other therapies (Ameisen, 2005). Despite the contradictory data from clinical trials as outlined above, there has been substantial uptake of baclofen in clinical practice in recent years. Our aim in this systematic review was to examine real-world evidence of the clinical use of baclofen in AUDs. We included 25 studies that ranged from single patient case studies to case series with more than 100 patients.

We found the prescribing of baclofen to be disparate. The maximum doses used ranged between 20 and 630 mg/d across the included studies. Starting dose and subsequent titration varied, although this range appears relatively small except for a 10-fold difference in starting dose across several studies [i.e. 5 (de Beaurepaire, 2012, 2014) vs. 50 mg/d (Heydtmann et al., 2015)]. However, a rationale was rarely given to support the different titration regimens. We were unable to associate dose with effectiveness because of good outcomes reported at both low and high doses. Adverse events appeared to be more commonly associated with high dose baclofen (>100 mg/d), but this was not exclusive as several studies also reported serious adverse effects at lower doses.

The range of maximum doses within the included studies demonstrated the wide variation in baclofen prescribing in current clinical practice. Indeed, this is perhaps best supported by a study in France in which 81.2% of 221 surveyed physicians reported prescribing maximum doses between 71 and 284 mg/d, and a further 5% used doses over 350 mg/d (Rolland, Paille, et al., 2014). Several articles included in our review reported patients achieving doses of >300 mg/d (Akosile & Klan, 2016; de Beaurepaire, 2012, 2014; Heydtmann et al., 2015; Rigal et al., 2012; Rigal et al., 2015; Simioni et al., 2016). The popularity of high dose baclofen has increased in recent years as patients and prescribers attempt to find the dose at which baclofen begins to elicit the desired effects. Whether higher doses result in better clinical outcomes cannot be confirmed from this review.

There is evidence from a small-scale pharmacokinetic/dynamic modelling study to suggest dose and duration of exposure might be important factors in response. Firstly, a population pharmacokinetic (PK) model with 67 alcohol dependent patients using up to 180 mg/d of baclofen found that the inclusion of various covariates (e.g. demographics, liver biochemistry measures) did not improve the PK model fit (Imbert, Alvarez, & Simon, 2015). Results based on the 95% confidence intervals from this model, and another model created by the same group in a separate study (Marsot et al., 2014), were similar to those reported in healthy (Kochak et al., 1985) and other clinical populations (Wuis et al., 1990). However, the confidence intervals were relatively wide. Secondly, a pharmacodynamic (PD) model used the Obsessive-Compulsive Drinking Scale (Anton, Moak, & Latham, 1995) as a measure of baclofen’s effectiveness in 50 patients (Imbert et al., 2015). Categorisation of responders and non-responders revealed that some patients needed a higher dose or longer duration to respond. Furthermore, non-responders were more likely to have higher creatinine and alkaline phosphate levels, suggesting that impaired liver and/or kidney function might have modulated the response to baclofen. Unfortunately, the data available in the literature on PK modelling do not particularly help in determining the doses that need to be used in patients with AUD. Further studies which explore more sophisticated PKPD modelling approaches in patients with different degrees of liver and renal impairment need to be conducted to establish a relationship between exposure and the pharmacodynamic response.

Although no dose-effectiveness relationship was found in our review, we believe it is of clinical interest to highlight the evidence for potential benefits of baclofen through reduced drinking or abstinence. Seventeen studies included in this systematic review reported improved drinking status for at least one patient, and evidence suggests that some patients achieved positive outcomes after failing with other pharmacotherapies. The challenge will be to identify the factors (clinical and non-clinical) that determine whether a patient is a responder or a non-responder.

Trivial adverse effects are common within clinical trials of baclofen in AUD, particularly headache, drowsiness, nausea, and vertigo. Here we documented evidence of adverse effects that resulted in baclofen being reduced or discontinued. Studies generally reported issues with tolerability as doses increased, but the actual dose at which adverse effects occurred was variable between studies and individual patients. Furthermore, the reactions reported were diverse and may represent off-target effects of baclofen, alternatively there may be no causal association with baclofen. This again makes it difficult to define baclofen dosing in a population where high alcohol consumption and compromised organ pharmacokinetics may interact with the drug to alter exposure.

The Summary of Product Characteristics (SPC) for baclofen published in the UK suggest a starting dose of 5 mg three times daily for three days, which is then titrated by 15 mg/d every third day. It is also recommended that the dose should not exceed 100 mg/d unless the patient is in hospital and under close medical supervision. However, this SPC is for spasticity and might not be relevant in AUD treatment, where baclofen is used off-label. The only current national guidelines are provided in a temporary recommendation of use (RTU) in France that was implemented in March 2014 and subsequently amended in July 2017. The RTU permits use of baclofen in patients with alcohol dependence. The original protocol provided guidance on starting doses (15 mg/d) and titration (5-10 mg/d), with a maximum dose of 300 mg/d. However, analysis of data collected between 2009 and 2015 by the Agence Nationale de Sécurité du Médicament et des Produits de Santé has shown a dose-dependent increase in the risk of hospitalisation and death compared with other treatments for alcohol dependence, leading to revised guidance limiting the maximum dosage to 80 mg/d (ANSM, Cnamts, & Inserm, 2017). The limitations of anecdotal and observational evidence are well documented, and therefore their adoption into clinical guidelines, such as the RTU in France, is potentially problematic and may have contributed to aforementioned situation. The lack of basic underpinning knowledge is especially stark in the setting of liver disease where the need for abstinence is paramount. Taken together, this only further corroborates the need for early phase dose-finding studies of baclofen in AUD patients.

The utility of baclofen in the treatment of AUD remains equivocal. However, some patients seem to have substantial benefits in terms of achieving abstinence or reduced consumption. Coupled with the moderate efficacy of other pharmacotherapies, such as acamprosate and naltrexone (Jonas et al., 2014), it is not difficult to see the appeal of baclofen. Furthermore, the minimal hepatic excretion of baclofen makes it a potentially safer option for clinicians treating patients with concomitant impaired liver function. However, the speed at which baclofen has been adopted in this patient cohort has meant that some of the underlying science that goes towards ensuring a maximal benefit-risk ratio has yet to be established. Although baclofen is considered relevantly safe as evidenced by its use as an anti-spasticity agent for several decades, the interactions with high exposure to alcohol with/without the presence of significant alcohol-related comorbidities (e.g. liver cirrhosis) needs to be explored. Moreover, baclofen’s effectiveness is not universal and whether this is dependent on alcohol intake at presentation, lifetime consumption, craving, and/or other moderating factors such as genetics is not yet understood and requires well-designed studies to elicit evidence that can be utilised in practice.

Our review has limitations. First, there is a risk of publication bias. It is likely that examples of high dose baclofen and those demonstrating serious or unexpected adverse events are more likely to be accepted for publication. This may distort the perception of actual prescribing practices. However, the physician survey in France would suggest that utilisation of high doses is relatively common; whether this is representative of other countries is unknown. Second, the language selection criteria could introduce a selection bias as several articles in French were excluded. Third, all studies stated that patients had an AUD, usually alcohol dependence, but criteria for diagnosis varied between studies. However, we are confident that all studies included patients with significant alcohol use problems.

In summary, baclofen as an anti-craving agent in AUD seems to be promising, albeit that prescribing practices are haphazard. There are currently many starting and maximum doses that are used with no clear titration schedules, and recent evidence from France suggests potential safety concerns at higher doses. We believe that this review has highlighted the need to invest in research necessary to ensure that utilisation of any new or repurposed therapeutics (including baclofen) is supported by good quality evidence, including on dosing, which maximises effectiveness and reduces the risk of adverse events.

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**Table 1:** Search strategies for each database

|  |  |
| --- | --- |
| **MEDLINE/**  **PubMed** | (("baclofen"[MeSH Terms] OR "baclofen"[All Fields]) OR baclofene[All Fields] OR baclofeno[All Fields] OR ("baclofen"[MeSH Terms] OR "baclofen"[All Fields] OR "lioresal"[All Fields]) OR gablofen[All Fields]) AND ("alcohol dependence"[All Fields] OR "alcohol dependency"[All Fields] OR ("alcoholism"[MeSH Terms] OR "alcoholism"[All Fields]) OR ("alcoholics"[MeSH Terms] OR "alcoholics"[All Fields] OR "alcoholic"[All Fields]) OR "alcohol use disorder"[All Fields] OR ("craving"[MeSH Terms] OR "craving"[All Fields]) OR ("alcohol drinking"[MeSH Terms] OR ("alcohol"[All Fields] AND "drinking"[All Fields]) OR "alcohol drinking"[All Fields] OR ("alcohol"[All Fields] AND "consumption"[All Fields]) OR "alcohol consumption"[All Fields]) OR abstinence[All Fields]) – 2002 onwards |
| **Scopus** | TITLE-ABS-KEY ( baclofen  OR  baclofene  OR  baclofeno  OR  lioresal  OR  gablofen  AND  "alcohol dependence"  OR  "alcohol dependency"  OR  alcoholism  OR  "alcohol use disorder"  OR  "alcoholics"  OR  craving  OR  "alcohol consumption"  OR  abstinence )  AND  PUBYEAR  >  2001 |

**Table 2:** Overview of included studies

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **N (sex)** | **Mean age commencing baclofen (range if n > 1); unless stated otherwise** | **Alcohol use disorder diagnosis (Criteria cited)** | **Starting dose** | **Treatment duration** | **Maximum dose (range provided where possible and applicable)** | **Titration regimen (if reported)** | **Effectiveness for alcohol use disorder (if reported)** | **Tolerability (i.e. severe side effects or those resulting in discontinuation or decrease nmdose. If reported)** |
| (Agabio et al., 2007) | 1 M | 55 | Alcohol dependence (DSM-IV) | 15 mg/d | 12 months | 75 mg/d | Day 1 to 3 – 15 mg/d;  Day 4 to ~ week 18 – 30 mg/d;  Week 18 onwards – 75 mg/d | Abstinence – 1 lapse at week 18 | NA |
| (Akosile & Klan, 2016) | 1 M | 26 | Alcohol use disorder (criteria not stated) | 25 mg/d | 5 months | 500 mg/d | 50–75 mg as a pro re nata. Followed by steady escalation (details not reported) | NA | Abrupt cessation resulting in baclofen withdrawal |
| (Auffret et al., 2014) | 2 (1 F; 1 M) | 52.5 (45-60) | Alcohol dependence | NA | 12-15 months | 240-250 mg/d | 15 mg/d each week | Abstinence achieved by both | 2/2 gradual reduction: severe tinnitus (2). |
| (Bence et al., 2014) | 3 (2 F; 1 M) | 48.7 (35-60) | Alcohol Dependence (DSM‐IV-TR) | NA | 5 weeks – 12 months | 75-250 mg/d | NA | 1/3 abstinent | 2/3 discontinued baclofen: oedema (2). |
| (Bucknam, 2007) | 1 M | 59 | Self-diagnosed alcohol dependence | NA | NA | 140 mg/d | NA | Controlled drinking | NA |
| (de Beaurepaire, 2012) | 100 (30 F; 70 M) | 47.3  SD = 10.8 | Alcohol dependence (DSM-IV) | 5 mg/d | Up to 2 years | 20-330 mg/d | Day 1: 5 mg/d; day 2 10 /d; day 3-7: 15 mg/d; Day 8-14: 45 mg/d; day 15-21: 75 mg/d; then escalated by 30 mg/w until effectiveness obtained | At 2 years: 13 lost to follow-up; 50/87 low risk drinkers (WHO criteria) | NA |
| (de Beaurepaire, 2014) | 17 (2 F; 15 M) | 41.1 (28-59) | Alcohol dependence (DSM-IV) | 5 mg/d | 7-67 m | 310-630 mg/d | Day 1: 5 mg/d; day 2 10 /d; day 3-7: 15 mg/d; Day 8-14: 45 mg/day; day 15-21: 75 mg/d; then escalated by 30 mg/week until effectiveness obtained | 7/17 Abstinence at most recent visit | 4/17 severe side effect:  Somnambulism (1); nocturnal delirium (1); depression (1); baclofen intoxication (1) |
| (Dore et al., 2011) | 13 (3 F; 10 M) | 49.1 (41-62) | alcohol dependence  (criteria not stated) | 15 mg/d | 4d – 27m | 10-275 mg/d | Day 1-3: 5 mg/d;  Day 4 onwards: 10 mg/d  Final dose at the discretion of the treating clinician | 4/13 abstinent during follow-up | 2/13 severe side effects:  severe back pain (1); tiredness and somnolence, with occasional bedwetting and dizziness and feeling faint (1) |
| (Franchitto et al., 2014) | 12 (7F; 5M) | 37.7 (23-56) | Alcohol dependence syndrome (F10.2 ICD-10) | NA | NA | 30-120 mg/d | NA | NA | 12/12 with baclofen self-intoxication with suicidal intent |
| (Geoffroy et al., 2014) | 1 M | 49 | Alcohol dependence (DSM-IV-TR) | NA | 5 months | 180 mg/d | NA | NA | Baclofen discontinued; Mania |
| (Heydtmann et al., 2015) | 53 (22 F; 31 M) | NA | Alcohol dependence syndrome (F10.2 ICD-10) | 25 to 50 mg/d | 0.05 to 18 months | 5 to 400 mg/d | NA | 10/53 (19%) reported abstinence | 21/53 were assessed in detail.  4/21 reported side-effects resulting in dose reduction:  drowsiness (1), irritability, and urinary and faecal incontinence (1), dizziness, unsteadiness and gastroesophageal reflux (1) and decreased libido (1) |
| (Holla et al., 2015) | 2 M | 32 (29-35) | Alcohol dependence syndrome (F10.2 ICD-10) | NA | 0.25 to 1 month | 40-60 mg/d | NA | 2/2 abstinent for short period before relapse | 2/2 with baclofen self-intoxication with suicidal intent |
| (Macaigne et al., 2011) | 1 F | 46 | Chronic alcoholism (criteria not stated) | NA | 2 months | 30 mg/d | NA | Reduced alcohol consumption | Baclofen discontinued; acute hepatitis |
| (Pastor et al., 2012) | 4 (1F; 3M) | 39 (31-46) | Alcohol dependence  (criteria not stated) | 30 mg/d | 9-13 months | 75-125 mg/d | NA | 4/4 achieved abstinence – 2/4 had short periods relapse | NA |
| (Perogamvros et al., 2015) | 1 M | 61 | Alcohol use disorder (criteria not stated) | NA | 24 months | 200 mg/d | NA | Decreased consumption | Baclofen discontinued; severe central sleep apnoea |
| (Reichmuth et al., 2015) | 1 M | 66 | Chronic alcohol overuse (criteria not stated) | NA | 5 months | 180 m/d | NA | Controlled consumption | Baclofen discontinued; unintentional intoxication |
| (Rigal et al., 2012) | 132 (49 F; 89 M) | 47  SD = 11 | Alcohol Dependence (DSM-IV) n =120;  Matching DSM-IV criteria for uncontrolled alcohol use n = 12 | NA | Up to 12 months | 30-400 mg/d | 15 mg/week, then 30 mg/week if possible, according to tolerance | 78/139 abstinent | 6/139 patients stopped their treatment and 4/139 had to interrupt a dosage increase because of intolerance. Specific effects for these cases NA. |
| (Rigal et al., 2015) | 116 (48 F; 68 M) | 45  SD = 11 | Alcohol Dependence (DSM-IV) n =87;  Matching DSM-IV criteria for uncontrolled alcohol use n = 29 | NA | Up to 12 months | 30-400 mg/d | NA | 53/116 abstinent | 8 patients stopped their treatment |
| (Rolland et al., 2012) | 1 M | 46 | Alcohol dependence  (criteria not stated) | 15 mg/d | 18 weeks | 240 mg/d | 15 mg/d each week | NA | Reduced dose: Two episodes of seizures after a short relapse. |
| (Rolland, Jaillette, et al., 2014) | 3 M | 44.3 (35-63) | Alcohol use disorder (criteria not stated) | NA | 3-4 months | 120-240 mg/d | NA | NA | 3/3 Baclofen discontinuation / reduction: intoxication / withdrawal |
| (Saddichha et al., 2011) | 4 (1 F; 3 M) | 36.5 (25-42) | Alcohol dependence  (criteria not stated) | 10-20 mg/d | 3-8 days | 20-60 mg/d | NA | NA | 4/4 Baclofen discontinued or reduced: morbiliform rashes |
| (Simioni et al., 2016) | 107 (31 F; 76 M) | 49.6  SD = 10.9 | Alcohol dependence (ICD-10) | 30 mg/d | Up to 12 months | 300 mg/d | Initiated at 30 mg/d; increased by 15 mg/d every three days | NA | 25/107 discontinued over the 12 months: side effects – specific details NA. |
| (Soufia et al., 2010) | 1 M | 66 | Alcohol abuse (criteria not stated) | 20 mg/d | ~7 days | 60 mg/d | Initiated at  20 mg/d. Day 5, increased to 40 mg/d; day 7, 60 mg/d | NA | Baclofen Discontinuation:  Behavioural disinhibition |
| (Weibel et al., 2015) | 1 F | 40 | Alcohol use disorder (criteria not stated) | 15 mg/d | ~3 months | 150 mg/d | Initiated at 15 mg/d. increased to 150 mg/d over 5 weeks | Abstinence for 2m; followed by relapse | Reduced dose: dizziness and fatigue |
| (Yamini et al., 2014) | 35 (15 F; 20 M) | 50.5 (27-85) | alcohol dependence or abuse (DSM-IV) | 15 mg/d | Up to 12 months (mean 5.8) | 30 mg/d | Initiated at 15 mg/d. Day 5, increased to 30 mg/d | 34/35 abstinent while taking baclofen | NA |

NA – Information not available; mg/d - mg per day.

**Table 3:** Overview of studies that reduced dose because of an adverse event

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Adverse event (n)** | **Dose at which ADE occurred** | **Reduced dose / rechallenge** | **Symptoms returned** | **Final outcome** |
| (Akosile & Klan, 2016) | Baclofen Withdrawal | 500 mg/d – following abrupt cessation | ~200 mg/d | Yes | Baclofen withdrawn |
| (Auffret et al., 2014) | Tinnitus (2) | 180-210 mg/d | 60 mg/d | No | Baclofen continued |
| (Dore et al., 2011) | Back pain | 120 mg/d | Unknown | Yes. Mild | Baclofen continued |
| (Dore et al., 2011) | tiredness and somnolence, with occasional bedwetting and dizziness and feeling faint (1) | 275 mg/d | 200 mg/d | No | Baclofen continued |
| (Heydtmann et al., 2015) | drowsiness (1), irritability, and urinary and faecal incontinence (1), dizziness, unsteadiness and gastroesophageal reflux (1) and decreased libido (1) | Unknown | NA | No | Baclofen continued |
| (Perogamvros et al., 2015) | severe central sleep apnoea (1) | 200 mg/d | 100 mg/d | Yes | Baclofen withdrawn |
| (Rigal et al., 2012) | Unknown (4) | Unknown | Titration regimen interrupted – dose NA | Unknown | Baclofen titration resumed |
| (Rolland et al., 2012) | Tonic–clonic seizure (1) | 240 mg/d | 100 mg/d | No | Baclofen withdrawn |
| (Rolland, Jaillette, et al., 2014) | Baclofen intoxication / withdrawal (2) | 120-240 mg/d | 60-240 mg/d | No | Baclofen withdrawn after 3m (n=1).  Unknown (n=1) |
| (Saddichha et al., 2011) | morbiliform rashes (4) | 20-60 mg/d | 20-40 mg/d | Yes, mild (n =1)  No (n=3) | Baclofen continued in all |
| (Soufia et al., 2010) | Behavioural disinhibition (1) | 60 mg/d | 10 mg/d | Yes | Baclofen withdrawn |
| (Weibel et al., 2015) | dizziness and fatigue | 150 mg/d | 120 mg/d | Milder symptoms persisted | Baclofen continued. Titrated to 150 mg/d |

NA – Information not available; mg/d - mg per day

**Figure captions**

**Figure 1:** Flowchart of the literature search

**Figure 2**: Dot plot of starting and maximum dose of baclofen used in each study. Grey squares – starting dose; Black circles – Maximum dose.