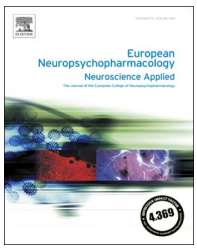
European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

www.elsevier.com/locate/euroneuro



REVIEW

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

Andrew Thompson[a,*], Lynn Owens[a,b], Paul Richardson[b], Munir Pirmohamed[a]

[a]*Wolfson Centre for Personalised Medicine, Institute of Translational Medicine, University of Liverpool, United Kingdom*
[b]*Gastroenterology and Hepatology, Royal Liverpool University Hospital Trust, Ward 5z Link, Prescot Street, United Kingdom*

Received 25 May 2017; received in revised form 10 August 2017; accepted 30 August 2017

KEYWORDS
Baclofen;
Alcohol use disorders;
Abstinence;
Tolerability

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

*Correspondence to: Wolfson Centre for Personalised Medicine, Institute of Translational Medicine, University of Liverpool, Block A Waterhouse Building, Liverpool L69 3GL, United Kingdom.
E-mail address: andrew.thompson@liverpool.ac.uk (A. Thompson).

http://dx.doi.org/10.1016/j.euroneuro.2017.08.434

Please cite this article as: Thompson, A., et al., Systematic review: Baclofen dosing protocols for alcohol use disorders used in observational studies. European Neuropsychopharmacology (2017), http://dx.doi.org/10.1016/j.euroneuro.2017.08.434

in this area. Evidence is required, however, to support practitioners in prescribing doses that optimise outcomes and reduce adverse events.

1. Introduction

Baclofen, a selective γ-aminobutyric acid B ($GABA_B$) 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 $GABA_B$ receptors in the mesolimbic reward system of the brain (Agabio et al., 2016). Therefore, as a $GABA_B$ 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 et al., 2016; Wuis et al., 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, 2007) and null outcomes (Garbutt et al., 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 et al., 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.

2. Experimental procedures

2.1. 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.

2.2. 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

Please cite this article as: Thompson, A., et al., Systematic review: Baclofen dosing protocols for alcohol use disorders used in observational studies. European Neuropsychopharmacology (2017), http://dx.doi.org/10.1016/j.euroneuro.2017.08.434