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A prospective cohort study examining the effectiveness of baclofen in the maintenance of abstinence in alcohol use disorder patients attending a joint liver and alcohol treatment clinic

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ABSTRACT

Objective: Alcohol-related liver disease (ARLD) is the leading cause of alcohol-related mortality in the UK. Helping patients with ARLD to stop drinking is an important treatment goal. The aim of this study is to explore baclofen's utility in maintaining abstinence.
Methods – a prospective cohort study: Patients with ARLD were commenced on baclofen; the dose was titrated according to tolerability and response up to 30 mg three times daily. Severity of physical dependence and biochemical markers of liver injury were assessed at baseline, 3 months, and 12 months.
Results: Length of follow-up differed. Of 219 patients in the original cohort, 186 and 113 were evaluated at 3 months and 12 months, respectively. Loss to follow-up was due to death, baclofen non-adherence, and failure to attend appointments. Comparison of baseline and 1-year biochemical markers showed significant reductions in GGT (median change = 82.0; 95% CI = −149.0 to −40.0; $p < 0.0005$), ALT (−10.5; 95% CI = −16.5 to −5.0; $p = 0.001$), and bilirubin (−4.5; 95% CI = −7.0 to −2.0; $p < 0.001$). The proportion of eligible patients reporting complete abstinence at 3 and 12 months was 55% and 53%, respectively. A significant reduction in alcohol consumption and Severity of Alcohol Dependence Questionnaire score was observed at both follow-up time points.
Conclusion: Adherence to the baclofen was good, and it had a positive impact on measures of alcohol consumption. A limitation of our study is its observational nature. Further randomized studies alongside investigation of dosing strategies are required.

Introduction

In the previous 50 years, the UK has observed a dramatic rise in alcohol consumption with a corresponding increase in alcohol-related disease (Department of Health, 2014). In particular, the incidence of alcohol related liver disease (ARLD) has risen sharply, while rates in most other EU countries are declining (Zatoński et al., 2009). In England and Wales, 63% of all alcohol-related deaths in 2012 were caused by ARLD, with 16% of these deaths occurring in a relatively young age group (55–59 years) (ONS, 2014). Importantly, all of these deaths are potentially preventable by abstinence from or reduction in alcohol consumption. There is therefore an urgent need to optimize treatment pathways to support individuals with evidence of ARLD to prevent disease progression and associated mortality.

The National Institute for Health and Care Excellence (NICE) has approved several pharmacotherapies (acamprosate, naltrexone, and disulfiram) to treat alcohol-use disorders (AUD) (NICE, 2010). However, both naltrexone and disulfiram are contraindicated in ARLD, and data on the safety of acamprosate in the presence of severe hepatic impairment are limited to one study (Delgrange, Khater, Capron, Duron, & Capron, 1991). As liver disease is common in AUD patients (Blachier, Leleu, Peck-Radosavljevic, Valla, & Roudot-Thoraval, 2013; Mann, Smart, & Govoni, 2003), patients usually receive no treatment (Drummond et al., 2005), or

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occasionally they may receive psychosocial support alone.

Baclofen is a γ-aminobutyric acid-B ($GABA_B$) receptor agonist that has been extensively used as an anti-spasticity agent. More recently, however, it has been posited that the stimulation of $GABA_B$ receptors by baclofen inhibits the release of the excitatory amino acids glutamate and aspartate, which reduces the rewarding and/or pleasurable effects of alcohol. Importantly, excretion of baclofen is mainly via the kidneys (Wuis, Dirks, Vree, & Van der Kleijn, 1990), and it is therefore not contraindicated in patients with liver disease. Thus, baclofen may provide a much-needed pharmacological option, especially in patients where other pharmacological interventions have failed or liver impairment is present.

Findings from preclinical studies (Anstrom, Cromwell, Markowski, & Woodward, 2003; Chester & Cunningham, 1999; Maccioni et al., 2005; Walker & Koob, 2007) and open-label trials (Addolorato et al., 2000; Flannery et al., 2004; Yamini, Lee, Avanesyan, Walter, & Runyon, 2014) generally support the role of baclofen in the reduction of both alcohol drinking and alcohol-seeking behavior. Subsequent randomized, placebo-controlled clinical trials reported positive results (Addolorato et al., 2002, 2007). Addolorato et al. (2007) randomized 84 patients with alcohol dependence and comorbid liver cirrhosis to receive baclofen 30 mg/day or placebo (1:1) for 12 weeks, and reported significantly higher rates of abstinence, a greater number of cumulative days without consuming alcohol, and improved markers of liver injury. However, a US-based trial that recruited 80 patients with DSM-IV criteria for current alcohol dependence was unable to replicate these positive findings (Garbutt, Kampov-Polevoy, Gallop, Kalka-Juhl, & Flannery, 2010). Moreover, a French-language meta-analysis concluded that evidence for the efficacy of low-dose baclofen in maintaining abstinence was weak (Lesouef, Bellet, Mounier, & Beyens, 2014). However, the value of this meta-analysis is limited, given the small number of studies included. The inconsistency in findings presents a position of uncertainty.

Despite RCTs providing gold standard evidence, some of the strict inclusion criteria can often bias samples and limit generalizability of outcomes. For example, trials often exclude patients with underlying disease or require patients to be abstinent for a number of days before joining the study, possibly resulting in a sample that is predisposed to abstinence. Here we aim to explore the clinical utility of baclofen, using an observational dataset from a real-world treatment setting. It is hypothesized that prescribing baclofen will result in improvements of subjective and objective measures of alcohol consumption and liver damage. Patients had a diagnosis of ARLD or biochemical evidence of liver damage where previous attempts to remain abstinent using other pharmacotherapies had been unsuccessful, or where approved pharmacotherapies were contraindicated.

Patients and methods

Design

We conducted a prospective, cohort study of AUD patients prescribed baclofen with the therapeutic aim of maintaining abstinence. These patients presented with an AUD and either confirmed ARLD or biochemical evidence of liver damage where previous attempts to remain abstinent using other pharmacotherapies had been either unsuccessful or were contraindicated. Patients were commenced on baclofen 10 mg three times daily (TDS), and the dose titrated according to tolerability and response up to 30 mg TDS. As part of usual clinical care, all patients were referred to community services for adjunct psychosocial support.

Consecutive patients attending a joint liver and alcohol treatment clinic and who were prescribed baclofen were selected with no *a priori* sample size determined. This decision reflected the time available to monitor patients and the pragmatic nature of the study design.

Setting

Patients were recruited from a nurse-led joint hepatology and alcohol treatment clinic in an acute hospital.

Data collection

A prospective dataset was completed by an independent administrator. Information was taken from patient case notes and hospital electronic information systems. This included demographics, comorbidities, alcohol consumption measures [i.e., quantity/frequency utilizing Time Line Follow Back methodology (Sobell & Sobell, 1992) and AUDIT (Babor, Higgins-Biddle, Saunders, & Monteiro, 2001), Severity of Alcohol Dependence Questionnaire (SADQ) score (Stockwell, Hodgson, Edwards, Taylor, & Rankin, 1979)], and biochemical and imaging reports.

Statistical analysis

Differences between baseline and 3-month follow-up, and baseline and 12-month follow-up were analyzed. The distribution of the change scores between each pair was assessed for normality. Where the assumption of normality was violated, log transformation was performed. Following this process, some data were still not normally distributed and, therefore, Wilcoxon signed rank tests were applied for analysis of the entire dataset without transformation. Effect sizes were calculated using Cohen's *d* statistic and interpreted according to guidelines (Cohen, 1992). Secondary analysis was conducted to explore the effect of the presence of liver disease on drinking outcomes. The significance level was set at $p < 0.05$. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies have been followed in the reporting of our results.

Results

Our cohort included a convenience sample of 219 patients, with a median age of 48 years (range: 25–76 years); 112 (51%) were male (Fig. 1). Baseline characteristics, including drinking status (i.e., alcohol consumption measures), and liver parameters, are provided in Table 1. Eighty-two (37.5%) patients had cirrhosis; 50 (22.8%) had ARLD but no evidence of cirrhosis indexed radiologically, or by clinical and/or biochemistry assessment. The remaining patients

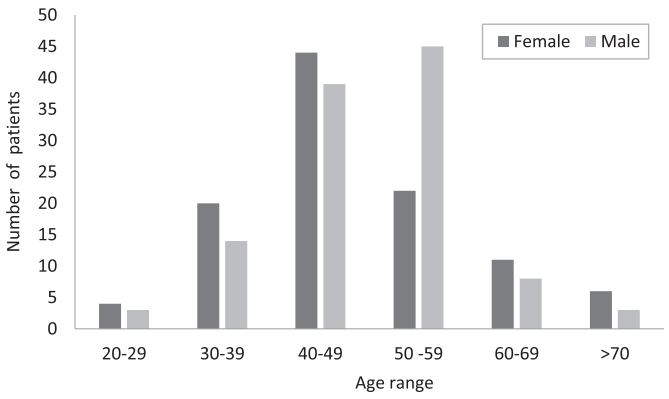

Fig. 1. Age and sex distribution of the cohort.