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REVIEW

Efficacy, tolerability, and safety of low-dose and high-dose baclofen in the treatment of alcohol dependence: A systematic review and meta-analysis

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Abstract
A systematic review of the current literature on the efficacy of baclofen, particularly the effect of dosing, for the treatment of alcohol dependence (AD) is missing. We therefore conducted a systematic review and meta-analysis of currently available randomized placebo-controlled trials (RCTs). A systematic literature search for RCTs in AD patients comparing baclofen to placebo was performed in September 2017. The effect of baclofen treatment, and the moderating effects of baclofen dosing (low-dose (LDB) 30–60 mg versus high-dose (HDB) targeted as >60 mg/day), and the amount of alcohol consumption before inclusion were studied. Three treatment outcomes were assessed: time to lapse (TTL), percentage days abstinent (PDA), and percentage of patients abstinent at end point (PAE). 13 RCTs from 39 records were included. Baclofen was superior to placebo with significant increases in TTL (8 RCTs, 852 patients; SMD=0.42; 95% CI 0.19–0.64) and PAE (8 RCTs, 1244 patients; OR=1.93; 95% CI 1.17–3.17), and a non-significant increase in PDA (7 RCTs, 457 patients; SMD=0.21; 95% CI −0.24 to 0.66). Overall, studies with LDB showed better efficacy than studies with HDB. Furthermore, tolerability of HDB was low, but serious adverse events were rare. Meta-regression analysis showed that the effects of baclofen were stronger when daily alcohol

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consumption before inclusion was higher. Baclofen seems to be effective in the treatment of AD, especially among heavy drinkers. HDB is not necessarily more effective than LDB with low tolerability of HDB being an import limitation.

1. Introduction

Alcohol use is a component cause of more than 200 diseases and alcohol use disorders have a significant negative impact on global health with approximately 3.3 million deaths every year (World Health Organisation, 2014). About 70% of the disease burden from alcohol consumption stems from the 5 to 10% of heavy and dependent drinkers who are described as having alcohol dependence (AD) (Rehm et al., 2017). Effective treatments for AD could therefore significantly reduce alcohol-attributable morbidity and mortality.

Animal models of excessive alcohol consumption have suggested that the GABA-B receptor modulates dopamine release in brain areas involved in the positive reinforcing properties of alcohol intake (Colombo et al., 2004; Fadda et al., 2003; Koob and Volkow, 2010). It was therefore been suggested that baclofen, a GABA-B receptor agonist primarily used for muscle spasticity, is a promising novel pharmacotherapy for AD.

To date there have been eight randomized controlled trials testing the effects of low-dose baclofen (LDB; ≤ 60 mg), for AD in humans with inconsistent results. More recently in the light of preliminary evidence that baclofen has a dose-related effect in AD there has been a change towards the use of high-dose baclofen (HDB; >60 mg/day) (Addolorato et al., 2011).

HDB became popular after the publication of the autobiography of Dr Olivier Ameisen, a French cardiologist who claimed that HDB completely suppressed his craving for alcohol (Ameisen, 2005). Subsequently, several case reports, case series, and open-label cohort studies supported the efficacy of HDB and spurred the widespread use of baclofen in clinical practice, mainly in France, where in March 2014 a temporary recommendation for its medical prescription to AD patients was permitted for three years in dosages up to 300 mg/day (Rolland et al., 2014). This proposed maximum dose of 300 mg/day was then reduced to 80 mg/day in July 2017 motivated by the finding of a dose-dependent relationship between baclofen use and an increased risk of hospitalization and fatalities (Inserim; Cnamts; ANSM, 2017). Meanwhile, about 200.000 patients have been treated with HDB in France alone (Chaignot et al., 2015).

Remarkably, no HDB RCTs were available when the first temporary use recommendation for HDB was issued in France and even now – three years later – there is no review or meta-analysis available that critically evaluates the effect of baclofen in AD and the potential differences in effect of HDB versus LDB in AD. The only available meta-analysis on the efficacy and safety of baclofen for AD did not include HDB studies (Lesouef et al., 2014). Furthermore, although this meta-analysis supported the efficacy of LDB on the maintenance of abstinence, the robustness of the results was very weak. Meanwhile, additional LDB studies have been published along with a series of HDB studies. These new studies and the ongoing debate about the efficacy and safety of (HD) baclofen in the treatment of AD make a new review and meta-analysis highly relevant. The current systematic review and meta-analysis aims to investigate the efficacy, tolerability, and safety of both HDB and LDB in AD patients. In addition, we study the possible moderating effect of the amount of alcohol consumption at intake.

2. Experimental procedures

2.1. Search strategy and selection criteria

For the present systematic review and meta-analysis, we reviewed studies involving adult patients with a current DSM-IV or ICD-10 diagnosis of AD. To be eligible, studies needed to compare baclofen with placebo for a minimum of four weeks and have defined outcomes with data on days of abstinence or days to consumption of alcohol. Studies not presenting this data became eligible if data was provided on request. Trials reporting only on the use of baclofen for the treatment of alcohol withdrawal were excluded. Studies were limited to randomized, double-blind, placebo-controlled trials. Studies in languages other than English and unpublished studies that met the eligibility criteria were included if results and data could be attained.

A systematic literature search was performed in September 2017 using PubMed, the Clinical Trial Register (ClinicalTrials.gov), and the Netherlands Trial Register (trialregister.nl). This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher et al., 2009).

The following search strategy was conducted in PubMed: "alcoholism"[Mesh Terms] AND "baclofen"[Mesh Terms]; Filters: randomized controlled trial. Reference lists of all eligible articles were scanned for relevant articles.

Unpublished studies were identified, searching the Clinical Trial Register with "alcohol" AND "baclofen" and the Netherlands Trial Register with "baclofen".

Individual studies were assessed for bias using the Cochrane Collaboration's tool for assessing risk of bias. For data collection a data extraction sheet based on the *Cochrane Handbook for Systematic Reviews of Interventions* guidelines was used. First authors of papers were contacted in case of missing data.

2.2. Data analysis

This analysis was performed using Comprehensive Meta-Analysis (2017) software version 3. We chose three outcomes for the meta-analysis: time to lapse (TTL), percentage days abstinent (PDA), and percentage of patients abstinent at endpoint (PAE). For TTL (number of days until the first episode of alcohol consumption), eight studies were included with a total of 852 patients. For PDA (total number of days of abstinence divided by the number of days studied multiplied by 100), seven studies were included with a total

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