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Efficacy of Baclofen on Abstinence and Craving in Alcohol-dependent Patients: a Meta-analysis of Randomized Controlled Trials

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Abstract – Purpose. We conducted a meta-analysis in order to estimate the efficacy of baclofen on the maintenance of abstinence and the decrease of craving in alcohol-dependent patients. **Methods.** All randomized controlled clinical trials assessing baclofen for at least four weeks' treatment duration *versus* placebo or other comparators were included. The primary outcome measure was the percentage of patients who had not consumed alcohol at the end of the treatment. Measures of cumulative abstinence and indexes of craving were also assessed. **Results.** Compared to placebo, baclofen was associated with a significant increase of 179% in the percentage of abstinent patients at the end of the trial, without heterogeneity. For secondary outcome measures, based on a random-effect model, no significant effect of baclofen was observed compared to placebo. **Conclusions.** Our meta-analysis brings weak support towards an efficacy of low dosages of baclofen on the maintenance of abstinence in alcohol-dependent patients.

Mots clés :
baclofène ; résultats de traitement ; essais contrôlés randomisés/sujet ; méta-analyse/sujet ; consommation d'alcool ; troubles liés à l'alcool ; alcoolisme

Résumé – Efficacité du baclofène sur l'abstinence et le craving chez les patients alcoolo-dépendants : une méta-analyse des essais cliniques randomisés et contrôlés. Objectif. Nous avons réalisé une méta-analyse afin d'estimer l'efficacité du baclofène sur le maintien de l'abstinence et la réduction du craving chez les patients alcoolo-dépendants. **Méthode.** Tous les essais cliniques contrôlés et randomisés évaluant le baclofène pendant au moins 4 semaines de traitement *versus* placebo ou autres comparateurs étaient inclus. Le critère d'évaluation principal était le pourcentage de patients qui n'avaient pas consommé d'alcool à la fin du traitement. Les mesures du nombre de jours cumulatifs d'abstinence et du craving étaient également évaluées. **Résultats.** Comparé au placebo, le baclofène était associé à une augmentation significative de 179 % du pourcentage de patients abstinents à la fin de l'essai clinique, sans hétérogénéité. Pour les critères d'évaluation secondaires, basés sur un modèle aléatoire, aucun effet significatif du baclofène était observé. **Conclusion.** Notre méta-analyse apporte une faible évidence de l'efficacité du baclofène à faibles doses sur le maintien de l'abstinence chez les patients alcoolo-dépendants.

Abbreviations: see end of article.

1. Introduction

Alcohol consumption is approximately responsible to 4% of the global burden of disease.[1] Craving is a significant component of alcohol dependence which represents psychological dependence. Its main clinical symptoms are malaise, the compulsive urge to consume alcohol, withdrawal syndrome, a loss of reasoning and a loss of integration of dependence information.

However, to date, drugs with proven efficacy are very few[2-4] and do not ensure complete abstinence in patients. An important step forward in the treatment of patients would be the discovery of new medications able of positively affecting the components of alcohol-dependence syndrome, such as craving and loss of control on drinking or proacted abstinence symptoms.[2] Several drugs, including baclofen (Lioresal®), are currently being tested and/or are under investigation as new treatments for alcohol dependence.

Baclofen is a stereoselective gamma-aminobutyric acid B (GABA-B) receptor agonist with an approved indication to control spasticity.[5] The experimental evidence suggests that mesolimbic dopamine neurons are involved in the mediation of alcohol intake and reinforcement.[6] Remarkably, GABA-B receptors are located in the ventral tegmental area where mesolimbic dopamine neurons originate, both on the cell body of dopamine neurons and on the terminals of glutamaergic afferent neurons.[7] Baclofen as the GABA-B receptor agonist may exert an inhibitory action on the dopamine neurons,[8] which is the possible mechanism *via* which baclofen suppresses alcohol-stimulated dopamine release and, in turn, dopamine-mediated, alcohol-reinforced and motivated behaviors. Efficacy of baclofen on abstinence and craving was retrieved in preclinical experiments.[9] A preliminary study showed that baclofen was effective to decrease alcohol craving and to increase abstinence in alcohol-dependent patients.[10] The first case report of the withdrawal of the alcohol consumption without difficulties after few weeks of baclofen's treatment taken after the failure of all other medicines available in alcohol-dependence was published in 2005.[11]

To determine the efficacy of baclofen in alcohol-dependant patients; we have realized a meta-analysis of randomized controlled trials in order to precisely quantify the effect of baclofen compared to placebo or active treatments on the maintenance of abstinence and the decrease of craving.

2. Methods

2.1. Search methods for identification of studies

2.1.1. Electronic searches

The search for trials was performed using Medline, Embase and Science Direct through June 2012. The search method is as follow: *([alcohol] AND [withdraw* OR detox* OR craving* OR abstinen* OR abstain* OR randomized* OR controlled*] AND [baclofen])*. We have used the function "related articles" in Medline to exclude duplicate studies.

We identified unpublished or published studies in the registries of ongoing clinical trials of www.clinicaltrial.gov and www.controlled-trial.com with a search strategy containing the indexing terms "baclofen" and "alcohol". We identified unpublished studies in Google Scholar according to the search method presented as follow: *[baclofen AND randomized AND alcohol AND (congress or meeting])*. The research of unpublished studies was also performed looking for abstract containing the indexing terms "baclofen" and "baclofene" in the proceedings of the main psychiatry and addictology congresses that were hold from 2002 onwards. These congresses were the following:

- French congress of psychiatry 2009, 2010 and 2011;
- encephale congress 2012;
- congress of American Psychiatry Association (APA) from 2002 to 2011;
- congress of Research Society of Alcoholism (RSoA) from 2003 to 2009;
- congress of American Academy of Addiction Psychiatry (AAAP) from 2003 to 2011.

2.1.2. Searching other resources

All references of randomized controlled clinical trial reviews corresponding to our inclusion criteria were analyzed. We contacted researchers, pharmaceutical industries and the main authors of unpublished or incomplete studies. The search was conducted without date or language restriction.

2.2. Criteria for considering studies for this review

2.2.1. Type of studies

Randomized controlled clinical trials which evaluated baclofen *versus* placebo or other comparators in alcohol-dependant patients according to the diagnostic and statistical manual of mental disorders, 4th edition (DSM-IV) classification or 10th revision of the International statistical classification of diseases and related health problems (ICD-10) were included. Clinical trials without measured abstinence outcome and less than four weeks' treatment duration were excluded, as we have considered that the effects of baclofen on abstinence may start from that period. Duplicate studies were excluded.

2.2.2. Types of outcome measures

Primary outcome: the primary outcome measure was the percentage of patients who had not consumed alcohol at the end of the treatment.

Secondary outcomes:

- *abstinence outcome*: as a secondary outcome, we evaluated the cumulated number of days of abstinence during the period of study;
- *craving outcomes*: the indexes of craving were assessed at the end of the treatment using the Penn alcohol drinking scale (PACS) and obsessive compulsive drinking scale (OCDS), as well as the variation of craving between the inclusion of patients and the end of the study by OCDS scale as a secondary outcome.