

Is baclofen effective in the treatment of alcoholism? The Bacloville study.

### Summary

Baclofen, an agonist of the gamma-aminobutyric acid B receptor, has been prescribed for more than 40 years for the treatment of spasticity at doses between 30 and 80mg/day. Since 2005 high dose baclofen is used in France for the treatment of alcohol dependence first off label then since 2014 with a recommendation from the French Health Safety Agency. The Bacloville trial is a multicentre (60 GP practices), randomised, placebo controlled, double-blind, pragmatic risk reduction study in heavy drinkers carried out entirely in the general practice over a one year period. The primary end point data showed 56.8% of the baclofen treated group achieved WHO criteria low risk alcohol consumption at 1 year compared to 35.8% of the placebo group, ( $p=0.003$ ). Baclofen induced more adverse effects compared to placebo, most of them moderate, and well tolerated. Having in mind the damage due to alcohol consumption the benefit: risk is in favour of baclofen.

### Introduction

Alcohol Use Disorders (AUD) are a worldwide public health problem. In France they affect around 6 million individuals of which 2 million are alcohol dependent. There is a death due to alcohol every 12 minutes, amounting to 49,000 deaths annually (1). The results obtained by the current forms of treatments and medications are that 20-30% of patients will still be abstinent after 1 year.

Baclofen is a new paradigm in the treatment of patients with an alcohol problem: abstinence is no longer an obligation in treatment, the focus being on risk reduction. This accords with the WHO safe drinking criteria that define the level of risk via levels of alcohol consumption (2).

Baclofen is a centrally acting muscle relaxant used since 1974 for spasticity (of CNS origin such as multiple sclerosis and in spinal cord diseases). It's a GABA B receptor agonist that inhibits the release of dopamine in the Nucleus Accumbens and the ventral tegmental area (VTA) (called the "reward centre")(3,4). The agonists reduce or even suppress the conditioned responses to addictive substances (alcohol, cocaine, methamphetamine, morphine, heroin, nicotine or even food in binge eating disorder) Craving, an irresistible need (5,6), is found in the Diagnostic and Statistical Manual of Mental Disorders (DSM 5) (7) as one of the 11 criteria for a diagnosis of "substance use disorder". It is now considered as a major element in the compulsive use of substances and is therefore a prime target for addiction treatments (6) and relapse prevention (8,9).

Used for the first time in patients with alcohol problems in 1993, baclofen has been shown to be superior to placebo in reducing anxiety and depression (10).

Since 2000, there have been numerous studies published which examine its effectiveness in alcoholism.

### The Bacloville Study (11)

#### Description and Methodology:

This study was financed in part by the French State (Hospital Program of Clinical Research of 2011) and a private donor and was supported by the Public Network of Parisian Hospitals (APHP). The research was authorised by the National Authority of Medication Security (ANSM) and was approved by the ethics committee, the Committee for the Protection of Persons (CPP) of the Ile-de-France Region.

The Bacloville study is a national multi-centre (60 centres in 8 regional areas), pragmatic, therapeutic (Phase IIb), randomised, double blind trial carried out in a Primary Care setting to evaluate the effectiveness and safety of baclofen up to 300mg/day against placebo over a duration of 1 year. It forms part of the care of patients with high risk alcohol consumption on WHO criteria (over 60g/day in men and over 40g/day in women). Bacloville was created as a pragmatic risk reduction study.

The principal objective of the study is to show the effectiveness of baclofen compared to placebo, specifically the proportion of patients achieving a low risk alcohol consumption (WHO criteria, (2)) or abstinence during the 12<sup>th</sup> month of the study. Low risk is an alcohol consumption of a maximum of 20g/day for women and 40g/day for men. The alcohol consumption were taken as those noted daily by the patient in their study follow-up diary. Analysis in the study was done by Intention to Treat (ITT).

The secondary objectives of the study were changes in the average monthly alcohol consumption of patients and the number of days of abstinence over the study year.

Adverse effect were categorised using the international classification Medical Dictionary for Regulatory Activities (MedDRA). As for any pragmatic study, the *inclusion criteria* were very wide. The study could include any adult patient between 18 and 65 years of age voluntarily presenting to a participating GP for an alcohol problem and with an high risk alcohol consumption (WHO criteria, (2)) during the previous 3 months who expressed the wish to be abstinent or achieve a low risk alcohol consumption, who was willing to participate in the study and gave informed consent in writing. The patient could be non-detoxed (still drinking) or detoxed for less than a month. The *exclusion criteria* were reduced to a minimum to reflect “real life” practice. Patients could not be included if they were currently taking baclofen, had previously taken baclofen, were pregnant or breast feeding, were homeless, had no access to the social security system or were incapable of correctly filling out the study diary for 1 year. For patients with severe psychiatric illnesses (psychosis, schizophrenia, bipolar affective disorder) or severe physical illness which could compromise their adherence to the study, the investigating GP, who knew the patient, decided whether or not they would be suitable to enter the study.

The study medication (baclofen or placebo) was given for a maximum of 52 consecutive weeks. In the first three days, patients received the study medication at a dose of 5mg three times daily (but it could be 4 or 5 doses per day). The maximum dose authorised was 300mg/day. There were no restrictions on the regime of dose titration used although a suggested titration regime was given, consisting of an increase of 5mg in the total daily dose every 3 days to start off with. It was not necessary to stop drinking alcohol. In the case of side effects to the study medication, it was permitted to decrease the dose, to increase the time between dose increases and so do the study medication titration more slowly. Once the effective dose was successfully reached, the patient could decrease the dose or stop the study medication all together. Some patients who refused to continue the study medication (because they felt it was not effective) were then given unblinded baclofen for the rest of the study period but were considered as failures of their study medication. Patients who

die during the study were considered as failures of their study medication if their death could be attributed to alcohol.

The statistical analysis method allowed imputations to manage missing data (12,13) and was validated by three independent experts. The analysis was carried out with the Logiciel R version 3.2.2. The multiple imputations were carried out with help of package mice. The General Estimating Equation (GEE) models were done with the help of the geeglm function (Gaussian linear models) of the geepack package. The mixed linear modelling was done with the lme function of the package nlme (Linear and Non-Linear Mixed Effects Models).

### Bacloville Study Results

Figure 1 is the study flow chart. Three hundred and twenty patients were randomised (162 in the baclofen arm and 158 in the placebo arm). The median age of the patients was 48 years old (range 23-65) in the two arms, consisting of 70% men. The prior daily consumption of alcohol of the study participants averaged 128g/day in the baclofen group and 129g/day in the placebo group. Twenty seven patients regularly smoked cannabis, four regularly used cocaine and two took heroin. Twenty patients were on buprenorphine (11 Bac/9 Plac) and seventeen on methadone (11 Bac/6 Plac) for opiate substitution therapy. Twenty three patients had behavioural addictions. Twenty two patients had bipolar affective disorder (13 Bac/9 Plac). In 61.9% of patients there was family history of alcoholism and 31.8% had suffered a severe traumatic event during childhood or adolescence.

The principal outcome measure was the average daily consumption of alcohol during the 12<sup>th</sup> month of the study, success being defined as a low risk consumption or abstinence. In the case of missing data on a patient's alcohol consumption, the data was imputed. The comparison of baclofen vs placebo (taking into account to intra-centre correlation, 95% IC= confidence interval at 95% with data imputation) give the result of 56.8% success with baclofen vs 35.8% success with placebo ie an absolute difference of 21% (risk ratio 1.59 (1.17 : 2.15)). In the baclofen arm, the median dose of baclofen was 180mg/day. The Wald test for estimating the combined rate ratio gave a p value of 0.003. As part of the statistical analysis, two sensitivity analyses were undertaken and validated the result.

The main secondary outcome measures were in favour of baclofen without reaching statistical significance, apart from the average days of abstinence where the difference was significant at each time point during the 12 months.

With regard to tolerance, the side effects reported the most frequently were sleepiness (63% in the baclofen arm and 52% in the placebo arm), fatigue (60%/39%), insomnia (43%/44%), excessive sweating (35%/30%), dizziness (40%/25%), nausea (33%/27%), concentration problems (33%/23%), parasthesias (31%/23%), memory difficulties (27%/22%), headaches (28%/22%), and depressed mood (25%/18%).

Across whole of the baclofen and placebo groups the proportion of patients reporting a side effect (93%/87%) was not statistically significant.

In contrast, the severe side effects (SSE), principally insomnia, sleepiness, depression and much more rarely hallucinations and hypomania, were more frequent in the baclofen group (44%/31%,  $p=0.015$ ). For patient who had at least one SSE related to treatment (19%/7%) the difference was also statistically significant ( $p=0.002$ ). None of the deaths occurring during the study implicated baclofen and the difference in the number of deaths in the two groups was not statistically significant.

## Discussion

In order to discuss the results, it is useful to revisit the previous published studies. The first positive study was published in 2000 with baclofen prescribed at a dose of 30mg/day (14). In 2004, an alcoholic doctor, basing his ideas on animal studies, showed that baclofen is a medication capable of suppressing alcohol dependence with a dose dependent effect (15-17) by experimenting on himself with baclofen at high dose (270mg/day). His abstinence was achieved without a prior detoxification (18). The doctor published his story in 2008 in a book designed for the general public (19), setting off an explosion of interest from the media and patients.

After this, numerous studies were published using small doses of baclofen (less than 60mg/day) with often positive results for the principal outcome criteria (table 1) (14, 20-29). There were also successful case reports with high doses of baclofen up to 270mg/day (18, 30-32). From 2010 onwards, observational studies using high doses of baclofen had positive results (table 2)(33-39). More recently there have been four randomised controlled studies carried out, double blind studies with baclofen vs placebo. All except Bacloville had abstinence from alcohol as both criteria for entry into the study and as the principal outcome measure. All of these had a duration of treatment (4-6 months) shorter than Bacloville (1 year). Two of them used doses limited to 150 or 180mg/day and had negative results (41,42). The two studies, including Bacloville, permitted higher doses up to 270 -300mg/day and had positive results (40,11). See Table 3.

These results appear to confirm the need to use high dose for effective treatment in certain patients. In our study, the median dose used was 180mg/day.

It's important to remember that our study patients were asked to record (in a diary) everything they noticed from pimples to hallucinations and including a common cold or backache. There were therefore numerous unpleasant symptoms reported. As a whole, they reflect the known and expected side effect profile of baclofen (36). Their frequency requires prescribing doctors to have knowledge of the wide range of potential baclofen side effects. Given the health problems related to alcohol (1), the risk: benefit ratio favours the use of baclofen.

The main limitation of the Bacloville study was the use of unblinded baclofen in 76 patients, which makes analysis of the secondary criteria (average monthly alcohol consumption and number of abstinent days over the year) hard to interpret when using Intention to Treat (ITT). In addition, the patients had to fill out their diary every day and, despite all the efforts of the investigators, there were numerous time points of data missing. This can be partly explained by the difficulty for people, often living in great distress, in filling out the diary every day for a year. The management of the missing data in Bacloville was carried out by the methods recommended in the literature in the area of treatment trials in alcoholism (12,13). The two sensitivity studies planned as part of the statistical analysis corroborated the results and allowed the imputations to be validated.

One of the strengths of the study was its pragmatic approach. In addition, Bacloville shows the feasibility of doing multi-centre, double blind, placebo-controlled therapeutic treatment trials in an ambulatory setting and that GPs are able to successfully treat alcohol dependent patients in their practices.

Questions can be asked about the high rate of success of the placebo group (35.8%). This result may be due to the strong demand for baclofen treatment by patients (and therefore their motivation). But it may also be due to quality of the therapeutic interaction and follow up, which were done by their own doctor who knows them well.

#### Conclusions:

Baclofen treatment successfully treated more than half the patients with alcohol problems. With baclofen treatment, it is no longer necessary to remain abstinent and this increases the number of alcohol dependence patients who will accept to be treated. Baclofen treatment is challenging, requiring a slow and steady dose titration and managing the frequent side effects. In some patients, the baclofen dose needs to be high to get the therapeutic effect. The Bacloville study suggests that the dose should probably rise over 180mg/day for these patients.