

## TREATMENT

### Abstinence and ‘Low-Risk’ Consumption 1 Year after the Initiation of High-Dose Baclofen: A Retrospective Study among ‘High-Risk’ Drinkers

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**Abstract** — **Aims:** The aim of the study was to assess the proportions of ‘high-risk’ drinkers’ abstinent or with ‘low-risk’ consumption levels 1 year after the initiation of high-dose baclofen. **Methods:** This is a retrospective ‘open’ study; the outcome of this study was to assess the level of alcohol consumption in the 12th month of treatment. **Results:** Of the 181 patients included, a follow-up evaluation was possible in 132 patients. The initial alcohol consumption of the 132 patients analysed averaged  $182 \pm 92$  g/day. After 1 year, 80% of the 132 (i.e. 58% of 181) were either abstinent ( $n = 78$ ) or drinking at low-risk levels ( $n = 28$ ) in their 12th month of treatment. The mean baclofen dose at 1 year was  $129 \pm 71$  mg/day. **Conclusion:** High-dose baclofen should be tested in randomized placebo-controlled trials among high-risk drinkers.

## INTRODUCTION

Baclofen, a gamma-aminobutyric acid ‘B-receptor’ agonist, has long been used to treat spasticity from neurological diseases, at a dose of 30–90 mg/day. It appears today to be a promising but controversial candidate for treating alcoholic patients (Enserink, 2011), by reducing or even suppressing their craving (which we define here as an irrepressible sense of needing) to drink. A few case reports (Ameisen, 2005; Bucknam, 2007; Dore *et al.*, 2011) suggest that some patients might respond favourably to baclofen at doses  $>90$  mg/day. Although no randomized controlled trial testing such doses has yet been conducted, some physicians are prescribing high-dose baclofen off-label to informed patients in a compassionate approach. To date, published randomized controlled trials have tested 30 mg/day dosage (Addolorato *et al.*, 2002, 2007; Garbutt *et al.*, 2010).

This study presents two physicians’ clinical experience of prescribing high-dose baclofen in patients with ‘high-risk’ consumption levels, as defined by the World Health Organization (WHO; i.e.  $>40$  g/day for women and  $>60$  g/day for men; World Health Organization, 2000). As part of their usual clinical practice, they prescribed baclofen at a progressively increasing dose (steps of 15 mg/week, then 30 if possible, according to tolerance) until it abolished craving, to the extent possible, thereby allowing patients to reduce their consumption to the WHO’s ‘low-risk’ level (i.e.  $\leq 20$  g/day for women and  $\leq 40$  g/day for men; World Health Organization, 2000) or even become abstinent.

The aim of the study was to assess the proportions of ‘high-risk’ drinkers who had either one of the two satisfactory alcohol consumption profiles (full abstinence or ‘low-risk’ consumption) during the 12th month of high-dose baclofen treatment. Our secondary objectives were to examine the patient characteristics associated with these profiles and to analyse the tolerance for and safety of high doses of baclofen.

## MATERIALS AND METHODS

This retrospective study is based on two physicians’ study of the records of patients to whom they had prescribed baclofen. Both worked in the Paris metropolitan area: one general practitioner in private practice and one hospital-based psychiatrist, both of whom prescribed baclofen to outpatients with drinking problems. Neither practitioner applied any absolute contraindications to baclofen, except for allergies. Neither detoxification nor alcohol dependence was a necessary precondition to treatment. No particular management (pharmacological or non-pharmacological) was systematically offered, and the physicians were free to prescribe as they thought appropriate. Patients systematically received complete information about various characteristics of the treatment (off-label prescription, increasing dose potentially higher than for neurological indications, list of adverse effects and in particular the risk of hypersomnolence, especially if taken with alcohol, and the risk of withdrawal symptoms if the medication were to be stopped suddenly).

Patients eligible for this study were all ‘high-risk’ drinkers who had started baclofen more than a year before 1 November 2010, regardless of the length of their treatment or follow-up. Each physician kept an exhaustive list of patients who had taken baclofen, and subjects were identified from that list.

Data for each eligible patient were collected first by examining his or her medical record and then by an interview of the patient, either in the physician’s office during a regular consultation or by telephone, by a physician–investigator. The aim of the interview was to obtain all of the necessary data (completing data for patients who had stopped treatment with the physician before a year had elapsed) and to obtain high-quality measurements of some patient characteristics (initial alcohol dependence, alcohol consumption during the 12th month after the initiation of baclofen and adverse effects) about which they were systematically questioned.

The other characteristics collected came from the medical files.

We defined two satisfactory alcohol consumption profiles, based on the patient reports of their alcohol consumption during the 12th month of baclofen treatment:

- (1) full abstinence (vs any alcohol consumption) and
- (2) 'low-risk' consumption (vs more than low risk consumption), that is, which might include occasional periods of abstinence, but had no days above 20 g (women) or 40 g (men), as defined by the WHO.

Besides consumption levels during the 12th month of treatment, the following information was collected:

- (1) sociodemographic data: age, sex, whether the patient was living with a partner;
- (2) history of their alcoholism: number of episodes of detoxification, previous treatment with drugs approved for preventing relapses (acamprosate, naltrexone or disulfiram);
- (3) alcohol consumption and smoking at the beginning of treatment;
- (4) initial alcohol dependence (diagnosed in accordance with DSM-IV, without using a questionnaire);
- (5) psychiatric disorders (diagnosed in accordance with DSM-IV criteria, without using questionnaires): anxiety, depression, bipolar disorder, psychosis or other psychiatric disorders;
- (6) addictive behaviour (food, i.e. binge eating, shopping, gambling, work or sex, without using questionnaires);
- (7) treatment with psychotropic drugs: anxiolytics, antidepressants, mood stabilizers and neuroleptics;
- (8) baclofen dosage: maximum and at 12 months;
- (9) perceived diminution in craving intensity: binary measure corresponding to the patient's perceived diminution in craving between the beginning of treatment and 12 months afterwards and
- (10) adverse effects, both those reported spontaneously and on questioning.

The patients included in the analysis were those who were eligible for the study and for whom the alcohol consumption during the 12th month of treatment could be determined, as opposed to the patients lost to follow-up. For the latter, alcohol consumption at their last visit, the number of visits and the length of the follow-up were extracted from the files. We also asked the physicians for their opinion about the principal reason that the patient stopped coming.

The patients analysed were first described, and the variations in their characteristics according to sex and alcohol dependence were examined. The two satisfactory profiles were then described, and their variations according to characteristics tested. The same analysis was conducted for the maximum baclofen doses and the doses at 1 year. Next, the adverse effects were described. Finally, we described the patients lost to follow-up and compared them with the patients analysed as a function of age, sex, alcohol dependence, initial alcohol consumption and proportion of adverse

effects. We used  $\chi^2$  tests (or Fisher's exact tests if needed) and Student *t*-tests (or Kruskal–Wallis tests if needed) to compare percentages and means.

All patients were informed about the study's purpose and design (and about our intention to publish the results) and gave their consent to participate. Patients seen in the physician's office signed a consent form and those interviewed by telephone gave their consent verbally. This study was not reviewed by a research ethics committee, because it is inherently an 'audit' of two physicians, which was not deemed within the purview of ethics committees.

## RESULTS

Of the 181 patients eligible, 132 (73%) were included in the analysis, while 49 were lost to follow-up. Complete information was available for all of the patients analysed: all their medical records were evaluated, and all were interviewed. The 49 patients lost to follow-up had stopped seeing their physician regularly before a full year was completed; even though their files had been examined, their alcohol consumption during the 12th month of treatment could not be determined because they could not be interviewed. Among this group, four patients had died; none from a cause attributable to baclofen.

Overall, 63% of the patients were men, 52% lived with a partner and only 9% were not alcohol dependent (these 12 patients nonetheless met at least the fourth DSM-IV criterion for alcohol dependence: uncontrolled use). The patients' mean age was  $47 \pm 11$  years. Their baseline alcohol consumption averaged  $182 \pm 92$  g/day ( $197$  g/day in men vs  $157$  g/day in women,  $P=0.04$ );  $190$  g/day in the alcohol-dependent patients vs  $120$  g/day in those who were not ( $P=0.04$ ). Eighty per cent of the patients had psychiatric disorders (92% of the men vs 73% of the women,  $P=0.02$ ), detailed in Table 1. Most (85%) of the patients had already tried a drug approved for relapse prevention and 44% had undergone detoxification at least once. In addition to baclofen, 77% of the patients took psychotropic drugs (90% of the men vs 70% of the women,  $P=0.008$ ; 75% of the alcohol-dependent vs 100% of those who were not,  $P=0.048$ ), also listed in Table 1. The smokers (71%) consumed a mean of  $22 \pm 11$  cigarettes/day.

At 1 year, 78 patients (59% of those analysed and 43% of those eligible) were abstinent, 28 (21% of those analysed and 15% of those eligible) were drinking but only below or at the 'low risk' level and 26 (20% of those analysed and 14% of those eligible) were drinking above that level.

The proportion of psychiatric disorders (and especially of anxiety disorders) was significantly lower among patients with either satisfactory alcohol consumption profile (Table 1). The patients with eating disorders or who took psychotropic drugs (anxiolytics and anti-depressants in particular) were significantly less frequent among abstinent than among non-abstinent patients. Among patients with either satisfactory profile, a perceived diminution in craving was significantly more frequent. No satisfactory profile varied significantly by initial alcohol consumption, alcohol dependence, sex or physician consulted.

One year after the initiation of baclofen, 83% of the patients were still taking it. The maximum dose averaged

Table 1. Patient characteristics and their associations with outcome measures

Description	% among patients analysed (n = 132)	Association with full abstinence			Association with no or 'low-risk' consumption		
		% among abstinent patients (n = 78)	% among non-abstinent patients	P-value*	% among patients with no or 'low-risk' consumption (n = 106)	% among patients with above 'low-risk' consumption	P-value*
Any psychiatric disorders	80	12	48	0.0007	4	24	0.02
Anxiety disorders	75	15	49	0.0005	6	24	0.02
Depression disorder	56	—	—	—	—	—	—
Bipolar disorder	11	—	—	—	—	—	—
Psychosis	11	—	—	—	—	—	—
Other psychiatric disorders	28	—	—	—	—	—	—
Any addictive behaviours	29	—	—	—	—	—	—
Eating disorders	11	37	71	0.01	—	—	—
Any psychotropic drugs	77	23	46	0.03	—	—	—
Anxiolytics	64	23	51	0.002	—	—	—
Antidepressants	44	28	57	0.0009	—	—	—
Mood stabilizers	9	—	—	—	—	—	—
Neuroleptics	11	—	—	—	—	—	—

\*Only the figures related to a significant association are presented.

145 ± 75 mg/day (min = 30, max = 400, median 145, first quartile = 85, third quartile = 200; 150 in the alcohol-dependent patients vs 93 in those who were not,  $P = 0.01$ ) and the dose taken at 1 year averaged 129 + 71 mg/day (min = 20, max = 300, median = 120, first quartile = 65, third quartile = 180; 134 in the alcohol-dependent patients vs 76 in those who were not,  $P = 0.006$ ). No dose was associated with sex, initial alcohol consumption, psychiatric disorders or addictive behaviours.

Overall, 86% of the patients (69% of the men vs 84% of the women,  $P = 0.04$ ) had experienced adverse effects. Most of them were transient, during dose increases, and some occurred while drinking alcohol. The physicians reported that baclofen seemed to potentiate somnolence and probably also the mental confusion induced by alcohol. In the order of decreasing frequency, the principal adverse effects were fatigue or somnolence, insomnia, vertigo and digestive disorders. None required hospitalization. Because of intolerance, six patients (<5%) stopped their treatment and four had to interrupt a dosage increase (although all four maintained their 'low-risk' consumption level, although the craving had not completely disappeared).

The patients lost to follow-up had seen the physician for an average of 6.2 ± 5.9 consultations over an average follow-up period of 5.6 ± 5.2 months. During their last contact with the physician, 36% of them were abstinent, 22% were drinking but only below or at the 'low risk' level and 42% were drinking above that level. They had significantly fewer ( $P = 0.01$ ) adverse effects (69%) than the patients analysed (86%). The physicians considered that an adverse effect was responsible for only three of the patients' stopping treatment, one because of mental confusion that occurred when he drank. The most frequent reason for stopping ( $n = 10$ ) was a lack of motivation. The patients analysed and those lost to follow-up did not differ significantly by age, sex, initial alcohol consumption levels, alcohol dependence, psychiatric disorders or psychotropic drugs.

## DISCUSSION

Our observational study has some limitations. First of all, it had no control group. Some of the satisfactory responses might therefore have been due to regression towards the mean, to a classification (memory or social desirability) bias, or to the other medications they received, as well as to the physicians' support. Next, some patients had expressed the desire to be treated with baclofen even before the physician suggested this medication, which might have accentuated the placebo effect. Another limitation is that we cannot present corroborative evidence, by family reports or biological markers.

This study is innovative in several ways: its length, its large number of patients from only two centres, the dosage higher than in the published trials (Addolorato *et al.*, 2002, 2007; Garbutt *et al.*, 2010), and its pragmatic prescription on an outpatient basis (Garbutt and Flannery, 2007). It is also atypical compared with the studies that most often target only alcohol-dependent patients. These doctors also treated several 'high-risk' drinkers who were not alcohol dependent. Indeed, the majority of patients with alcohol use disorders are not alcohol dependent (Reid *et al.*, 1999), and the benefit-risk ratio may be favourable for some of them (especially those who cannot control their 'high-risk' consumption).

This study also renews the questions about abstinence. A reduction in craving allowed some patients to advance towards abstinence and to maintain this state without having to experience the personal hardships of detoxification (Ameisen, 2008). This change is likely to modify the individual's experience of treatment by limiting the usual feelings of guilt and failure. Abstinence is neither a preliminary requirement nor an objective that can be met only in pain. And, if some patients succeed in maintaining moderate consumption, should we not prefer consumption at low risk to abstinence as the principal endpoint of trials (European Medicines Agency, 2010)?

The larger doses taken by alcohol-dependent patients compared with their non-dependent counterparts might be interpreted as the adaptation of dosage to disease severity. Proposals for modifying the fifth revision of the DSM eliminate the abuse/dependence dichotomy and suggest a dimensional approach to 'alcohol use disorders' (O'Brien, 2011); using such a diagnostic approach, we suggest that perhaps the more severe the use disorder, the higher the dose of baclofen that might be prescribed.

Some authors (Garbutt *et al.*, 2010) have hypothesized that high levels of alcohol dependence or anxiety may be predictive of a favourable response to baclofen. We did not find evidence that alcohol dependence was a good prognostic factor in our study, but this finding might have differed had we used a criterion of dependence severity, for example, based on the number of DSM-IV criteria met or the severity of alcohol withdrawal symptoms. Moreover, although several studies have consistently reported that baclofen is effective in reducing anxiety in alcoholic patients (Addolorato *et al.*, 2009), we found a negative association between the existence of an anxiety disorder and a satisfactory profile at 1 year. However, no causal relation could be deduced from our finding, unlike, for example, the studies by Garbutt *et al.* (2010) and those reviewed by Addolorato *et al.* (2009) which were prospective and used a placebo control group.

Finally, we found that baclofen, including at a high dose and in patients with psychiatric disorders, appears to be well tolerated and manageable, thus confirming other reports (Agabio *et al.*, 2007; Dore *et al.*, 2011).

## CONCLUSIONS

Our encouraging results must be interpreted in the light of the finding that psychiatric diseases, frequent (Regier *et al.*, 1990) among alcoholics, might modulate the efficacy of baclofen and that tolerance to it at high doses and over the long-term is not known with any certainty (Smith *et al.*, 1991). These must be confirmed by randomized placebo-controlled trials.

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