

Research Article

Baclofen Treatment of Bulimia Nervosa and Binge Eating Disorder: An Internet Survey

Imbert S¹, Rat P² and de Beaurepaire R^{2*}¹7rue Louis Blériot, Plaisance, France²Groupe Hospitalier Paul-Guiraud, 54 Avenue de la République, France***Corresponding author:** Renaud de Beaurepaire, Groupe Hospitalier Paul-Guiraud, 54 Avenue de la République, 94806 Villejuif, France**Received:** August 11, 2017; **Accepted:** September 07, 2017; **Published:** September 14, 2017**Abstract**

Objective: Bulimia Nervosa (BN) and Binge Eating Disorder (BED) are conditions that are difficult to treat and for which there are very few approved treatments. Clinical studies have shown baclofen effectiveness in BED, but this must be confirmed.

Methods: The present study is an Internet survey targeting the use of baclofen for the treatment of BN and BED. Survey questions were released on the “Baclofène” Internet site. Questions relate to baclofen effectiveness, doses, treatment increase, adverse effects, and impact on quality of life.

Results: One hundred and eight responders met diagnostic criteria for BED and BN (61 BN, 47 BED). Forty-one percent of BN and 40% of BED participants reported total recovery, while 29% of BN and 34% of BED reported some improvement. BN participants were significantly younger than BED participants. Individual effective doses were highly variable (10-590 mg/d) and the average maximal dose was 174mg/d. There were no correlations between the maximal baclofen dose and the intensity of adverse effects, quality of life, or recovery.

Discussion: The high percentages of success in this study probably overestimate the reality of the effectiveness of baclofen in BN and BED because patients who were improved by baclofen were likely more prone to respond to the survey than those for whom the treatment had failed. Nevertheless, the results confirm the effectiveness of individually adjusted doses of baclofen in the treatment of many patients with BED and suggest its potential interest for BN. Controlled studies using individually adjusted doses of baclofen are needed.

Keywords: Eating disorder; Individual titration; Adverse effects; GABA-B; Quality of life

Introduction

Baclofen, a GABA-B agonist marketed more than 40 years ago for the treatment of spasticity, has recently emerged as a treatment of major interest for alcohol dependence. Studies have shown that low doses of baclofen (30-60 mg per day) have equivocal effects in the treatment of alcohol dependence [1-6], while high doses have demonstrated robust positive effects in case reports and observational studies [7-14]. These positive effects have been recently confirmed in a randomized, double-blind versus placebo study [15]. Baclofen has also shown effectiveness in Binge Eating Disorder (BED) at low [16,17] and high doses [18]. However, the strength of these BED studies is limited because of the low number of patients included (four in the Broft et al. study [16], 12 in the Corwin et al. study [17], five in the de Beaurepaire et al. case series [18]). Effectiveness of baclofen in BED needs to be confirmed; its potential effectiveness in BN [16] must be more thoroughly investigated; and doses need to be more precisely determined. In the present study, these issues were examined by using an Internet survey.

Since the publication by Olivier Ameisen in 2008 of a book relating the cure of his alcohol dependence with a high dose of baclofen [19], the use of baclofen in the treatment of alcoholism has become very widespread in France [20]. In 2014, the French Health Safety

Agency released a recommendation allowing for the prescription of baclofen up to 300mg/d, but not beyond, for the treatment of alcohol dependence (French Ministerial decree of June 13, 2014). Several Internet sites dedicated to the use of baclofen in the treatment of alcoholism now exist in France. These sites provide all kinds of information regarding baclofen, including its potential effectiveness in eating disorders. As a result, a number of patients suffering from BN or BED, but not alcoholism, have asked their physicians for a prescription of baclofen. Considering the high psychological distress of patients suffering from BN and BED, many physicians accepted to prescribe them off-label baclofen. One of the most popular Internet sites dedicated to the use of baclofen in France, the site “Baclofène”, receives more than 3000 visits per day on its forum. On this forum, where visitors relate and discuss their experience with baclofen, a recent substantial increase of discussions about its use in the treatment of eating disorders has been observed. Given this favorable context, the designer and administrator of the site, Sylvie Imbert, decided to make a survey targeting the use of baclofen in the treatment of BN and BED.

Methods

General methods

The survey, opened to people with BN and BED, was released on

Table 1: Variables investigated.

Item	total	BN	BED	P
N	108	61	47	-
Age (years)	40.2±1.0	37.8±1.2	43.4±1.6	<0.01
Men/women	5/103	2/59	3/44	-
Effect: recovered+improved	78 (72%)	43 (70.5%)	35 (74.5%)	NS
Treatment duration (months)	19.75±1.9	18.5±2.3	21.2±2.5	NS
Treatment increase (day/10mg)	6.0±0.3	6.1±0.4	6.0±0.5	NS
Current dose (mg/day) (n=65)	76.3±8.8	77.9±11.6	74.3±13.5	NS
Maximal dose (mg/day)	174.3±11.3	185.5±16.1	159.5±15.2	NS
Number of episodes per week	8.6±0.5	8.8±0.6	8.3±0.7	NS
AE intensity (1-7 scale)	4.1±0.2	4.2±0.3	3.8±0.3	NS
AE Incidence on quality of life (1-5 scale)	2.8±0.1	2.9±0.2	2.7±0.2	NS

P-values: comparisons between BN and BED. AE: Adverse Effects.

the “Baclofène” Internet site over the course of one month, between November 6 and December 5, 2016. It consisted of a series of 14 questions (in addition to age and gender):

1. Type of eating disorder: BN or BED (criteria provided, including: 1: Eating, in less than a 2-hour period, an abnormally high amount of food; 2. Loss of control during binge eating episodes; 3. Compensatory behaviors),
2. Concomitant psychiatric and somatic illnesses, and medications,
3. Previous alternative non-pharmacologic treatments that have failed (psychotherapy, nutritionist, sophrology, hypnosis),
4. Number of binge episodes per week before treatment,
5. Treatment initiation date (to determine the length of treatment),
6. Stepwise treatment increase,
7. Dose of baclofen taken the day of the survey (current dose),
8. Maximal baclofen dose taken,
9. Effect of the treatment. 1: no effect (similar number of binge episodes); 2: improvement but incomplete recovery (decreased number, but not suppression, of binge episodes); 3: complete recovery (no further binge episodes),
10. A list the occurring adverse effects,
11. Intensity of adverse effects, with severity ranging from 1 to 7. 1: no adverse effects; 2: very mild; 3: mild; 4: average; 5: strong; 6: very strong; 7: adverse effects unbearable (treatment had to be stopped),
12. Professional activity during treatment (full time activity; part-time activity; no activity),
13. For those who work: effect of the treatment on professional activity. 1: no particular incidence; 2: a significant incidence but the subject keeps on working; 3: stops working,
14. Adverse effects/related changes in quality of life during treatment, ranging from 1 to 5 (patient’s self-appraisal). 1: no change;

2: life minimally hampered; 3: life significantly hampered; 4: life strongly hampered; 5: so hampered that treatment had to be stopped.

Given the non-interventional nature of this Internet-based survey, the fact that the participation was voluntary and anonymous, the fact that there are no established ethical recommendations in the Declaration of Helsinki for internet surveys, the fact that Ethical Committees are not trained to address the question of internet surveys (for which there is no consensus), and as in other Internet surveys of the same type [21], specific ethical approval was not required.

Statistical analyses

Global results are expressed in percentage and were analyzed by using a χ^2 test with $\alpha=0.05$. Mean’ comparisons between the different subgroups were analyzed by ANOVA (one-way analysis of variance) followed, in case of significance, by a Fisher’s PLSD test for post hoc analysis (Statview V4.57 Abacus Software, USA), $p<0.05$ was recognized as statistically significant. Correlations were analyzed by performing a linear regression and calculating the linear correlation coefficient r whose significance is tested by Fisher’s F-test (Epi Info™ 7.1.5); $p<0.05$ was recognized as statistically significant.

Results

General

One hundred and eighteen participants responded during the month following the release of the survey. Ten were excluded because they did not meet criteria for BN or BED. The 108 remaining participants were 103 women (95%) and 5 men (6%), including 61 BN (56%) and 47 BED (44%), average age 40.2±1.0 (BN: 37.8±1.2; BED: 43.4±1.6 [$p=0.01$]), and an average of 8.6±0.5 binge episodes per week of before treatment (Table 1). Forty-four participants met the criteria of recovery (less than one episode per week) (41%), 34 were improved (31%), and the treatment failed in 30 (28%). Regarding diagnostic subgroups, 25 BN participants (41%) and 19 BED participants (40%) met the criteria of recovery, 18 BN participants (29%) and 16 BED participants (34%) improved, and the treatment failed in 18 BN participants (29%) and 12 BED participants (25%). The average stepwise treatment increase was 10mg more every 6.0±0.3 days, the average maximal daily dose of baclofen taken was 174±11mg (extremes: 10-590), and the average daily current dose was 76.3±8.8 (n=65:43 participants had stopped their treatment before the survey)

(extremes: 10-350) (BN: 77.9±11.6; BED: 74.3±13.5). The average length of the treatment was 19.75 months, and 43 participants had stopped their treatment at the time of the survey. Among the 43 participants who had stopped their treatment, 22 did so because side effects were unbearable, eight because the treatment had failed, seven because the treatment was a success and they considered themselves cured, and six for "other reasons" (undetermined).

Adverse effects and quality of life

Almost all participants (93%) reported at least one adverse effect, and 45 different kinds of adverse effects were reported. The most common (expressed by at least 20% of the participants) were fatigue (76%), somnolence (68%), falling suddenly asleep (40%), insomnia (39%), loss of concentration (38%), dizziness (29%), sexual dysfunction (28%), memory loss (26%), nausea (26%), muscular pain (25%), sweating (24%), nightmares (24%), headache (24%), tinnitus (23%), paresthesia (20%), and freezing of emotions (20%). Adverse effects were rated absent or unimportant (rated 1 and 2) in 12 participants (11%), and unbearable (rated 7) in 21 participants (19.4%). Among the 85 participants who claimed a professional activity, the treatment had no incidence on work in 35 participants (41%), a significant incidence in 36 participants who nevertheless kept on working (42%), while four participants (5%) stopped working because of the treatment, and 10 (12%) chose to stop baclofen to continue to work. Regarding the subjective appraisal of the consequences of adverse events on quality of life (107 responses), 51 participants considered that the treatment did not change or only slightly altered their quality of life (rated 1 or 2) (48%), 23 reported a significant but not severe alteration of their quality of life (rated 3) (21%), and 23 considered that the treatment very severely altered their quality of life (rated 4 or 5) (21%).

Concomitant illnesses, medications and other forms of treatment

Thirteen participants reported a concomitant somatic illness (one subject may have several illnesses): hypertension (four cases), diabetes (three cases), fibromyalgia, asthma, stroke, ataxia, scoliosis, primary biliary cirrhosis, hypothyroidism, renal insufficiency; all were taking appropriate somatic medications. Fifty-four (50%) participants reported a concomitant psychiatric illness (one subject can have several illnesses): depression (43 cases), anxiety disorder (15 cases), alcohol dependence (seven cases), bipolarity (five cases), and obsessive-compulsive disorder (one case). Forty-five participants reported taking a psychotropic medication: antidepressant (27 cases - mostly fluoxetine, prescribed for the treatment of the eating disorder in most of the cases), anxiolytic (nine cases), mood stabilizer (seven cases), antipsychotic (three cases). In addition, 99 participants (92%) reported that they tried alternative non-pharmacologic treatments before starting baclofen. These included psychotherapy (any kind) in 89 cases (82%), dietary regimen prescribed by a nutritionist (74 cases, 68%), sophrology (31 cases, 29%), hypnosis (28 cases, 26%).

Analyses of variance

Analyses of variance show that treatment doses were more elevated in BN than in BED, but the difference was not significant. BN participants were significantly younger than BED participants ($p < 0.01$). There were no correlations between baclofen doses and age, intensity of adverse effects, quality of life, and recovery. Intensity of adverse effects correlated with a worse outcome ($p < 0.0001$), and with

a worse quality of life ($p < 0.0001$). Adverse effects were significantly more intense in the group "treatment failed" compared with the group "recovered+improved" ($p < 0.01$). Intensity of adverse effects and treatment-induced alterations in quality of life were not different in BN and BED. There were no correlations between length of treatment and effect, and no correlations between stepwise treatment increase and effect.

Discussion

The present Internet survey shows that a fairly high number of patients were interested in responding to a questionnaire investigating their experience of baclofen for the treatment of BN and BED. One hundred and eighteen participants responded rapidly to the questionnaire, yielding 108 results that were eligible for analysis (61 BN, 47 BED). Although there are no established criteria for treatment-resistance in the case of BED and BN, one can consider that the participants had some degree of resistance to treatments, since 92% of them had previously tried other forms of treatment, including antidepressants, psychotherapy, sophrology, health food, and hypnosis. Globally, the results show that baclofen treatment was followed by an improvement or a complete recovery in 70.5% of the BN participants and 74.5% of the BED participants (41% of the BN and 40% of the BED completely recovered; 29% of the BN and 34% of the BED improved). Given that there are very few approved medications for BN and BED worldwide (fluoxetine for BN, and, only in the US, lisdexamfetamine for BED), the results are very encouraging. However, these results should be cautiously interpreted. They do not mean that baclofen will be effective in 70 to 75% of patients with BN and BED. It is very likely that participants with positive results were more prone to respond to the survey than those for whom the treatment had failed, and individuals who visited the site and chose to complete the survey may not be representative of the general population of people suffering from BN and BED. Besides, in a number of patients, a decrease in binge episodes may have been circumstantial or a placebo effect. Nonetheless, the results of the present study confirm the results of previous studies suggesting that baclofen may be helpful in the treatment of BED [16-18]. Further randomized placebo-controlled studies using individually adjusted baclofen are needed.

The treatment did not differ in terms of efficacy in BN and BED. BN participants were significantly younger, and tended to receive higher doses of baclofen, even though the results were not statistically significant. The fact that BN participants were younger is in accordance with the literature, which shows that the prevalence of BED increases much more with age than that of BN [22]. No correlations were found between the dose and the effect (recovery, improvement, or no effect), the intensity of adverse effects, and the quality of life. These results may appear surprising given that a dose-response to baclofen has been suggested in the case of alcohol dependence [3]. However, the present study, in line with other studies [12-15], does not support the existence of such a dose-response. As in alcohol dependence, some patients needed low doses, others high doses. The reasons for such individual variations are unknown. It is likely that those participants who best tolerate baclofen (low occurrence of adverse effects) more easily reach an optimal dose (that can be low or high), feel better and have a better quality of life, while those for whom the dose increase is hampered by adverse effects have difficulties in reaching an effective

dose, may remain at doses that are too low, feel less improved by the treatment, suffer from adverse effects, and thus have a worse quality of life. This is supported by the significant correlation found in the present study between the intensity of adverse effects and worse outcome and quality of life. The key element is that doses need to be individually adjusted very carefully. The average dose in the present study was 174,3mg/d. This is in accordance with studies on alcohol dependence. Effective doses have also been found to be highly variable in alcohol-dependent patients, with an average of 147mg/d in one study [13] and 180mg/d in another [15].

Adverse effects are a major concern during baclofen treatment. A commonly used strategy that supposedly minimizes the occurrence of adverse effects is to slowly increase the baclofen dosage. Different stepwise treatment increase options have been proposed, including an increase of 10mg every three days, or the use of much slower increases [23]. In the present study, participants reported highly variable dose increase strategies, ranging from 10mg every three days to less than 10mg per week (average 10mg increase every 6days). The general idea that the slower the dose increase, the fewer the adverse effects is not supported by the present study: the results show no correlation between stepwise treatment strategies and the occurrence of adverse effects. In a recent study in alcohol-dependent patients, baclofen was increased 6 times faster than the average in the present study (approximately 10mg more every day), yet no particular seriousness of adverse effects was reported [15]. The question of the optimal stepwise increase strategy during baclofen treatment is still unresolved, and the relationship between a given strategy and the occurrence of adverse effects has not been demonstrated.

In the case of alcohol dependence, baclofen treatment is not supposed to be a lifelong treatment, and a previous study has shown that 20% of alcohol-dependent patients who recovered with baclofen stopped baclofen within two years following recovery, while still remaining abstinent [13]. In the present study, 43 participants had stopped their treatment at the time of the survey. Fifteen of them (19.2% of those who recovered), had stopped their treatment because they considered themselves as being cured or sufficiently improved. Longer follow-ups are needed to determine if such a treatment arrest after recovery is long-lasting or associated with a risk of relapse. Among the 28 remaining participants, 22 had stopped baclofen because adverse effects were unbearable. Among them, the maximal dose reached was often low (less than 100mg in nine patients), showing that poor tolerance of baclofen can jeopardize chances of recovery.

The study has important limitations, in large part related to the method used: an Internet survey designed to be simple enough so as not to discourage potential responders. The first limitation is that there were no thorough investigations or use of validated protocols to assess the diagnoses and the number of binge episodes, thus limiting the validity of the results and their interpretation. However, regarding the diagnosis, questions included the major DSM5 criteria for the diagnosis of BN and BED (number of binge episodes, eating rapidly high amounts of food, loss of control, and compensatory behaviors), so that it has been possible to exclude those who did not respond to the criteria. Nevertheless, errors remain possible, in particular the case of anorexia nervosa binge-eating/purging subtype. A second limitation

is that concomitant somatic or psychiatric illness, including substance use and use of medications with potential impact on the response to baclofen may have had an incidence with the response to treatment. Indeed, such associations were frequent (13 participants reporting a concomitant somatic illness, seven an alcohol dependence, 45 taking a psychotropic medication). Concomitant alcohol use and psychotropic medications may have worsened adverse effects, since it has been shown that psychotropic medications and baclofen may interact to produce adverse effects [24], and that sedation produced by baclofen is potentiated by concomitant alcohol use [25]. However, it is not possible, given the methodology of the study, to precisely evaluate the extent to which such concomitant illnesses and treatments could have impacted the response to baclofen. Given that the results show that adverse effects could have limited the efficacy of baclofen in certain patients, we can speculate that a potentiation of the adverse effects by concomitant illnesses and medications may have decreased its effectiveness in certain cases. Another limitation is inherent to all anonymous Internet surveys: an individual, using different pseudonyms and e-mail addresses, could have filled out more than one questionnaire. Other limitations are that patients had to remember treatment dosages that sometimes occurred years before (recollection that may have been inaccurate), and the large predominance of females with BED in the present study (while BED very frequently occurs in males [22]).

In conclusion, the present study shows that, thanks to an Internet survey, it has been possible to very rapidly individualize a considerable number of participants who took baclofen for the treatment of their BN and BED, and to analyze with fairly good precision information regarding the treatment. The results confirm the effectiveness of baclofen in the treatment of BED and suggest its potential interest in BN. Important similarities seem to exist between baclofen treatment of BN and BED and baclofen treatment of alcohol dependence, which have in common the existence of compulsive craving episodes (whatever the substance). Controlled studies using individually adjusted doses baclofen are needed.

Acknowledgement

The authors thank the GHPG for baclofen research sponsoring.

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