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Article

Article

Tolerability of High-dose Baclofen in the Treatment of Patients with Alcohol Disorders: A Retrospective Study

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Abstract

Aims: The aim of this study was to describe the tolerability of high-dose baclofen taken by patients with alcohol disorders during their first year of treatment.
Methods: The medical records of all patients prescribed baclofen by one general practitioner were examined and all patients who could be contacted were retrospectively interviewed about adverse effects.
Results: Of the 146 eligible patients, 116 (79%) could be interviewed. Ninety (78%) reported at least one adverse effect (mean number per patient: 2.8 ± 2.7). The mean dosage of baclofen at the onset of the first adverse effect was 83 ± 57 mg/day. The most frequent group of adverse effects involved disruption of the wake–sleep cycle and affected 73 patients (63%). Persistent adverse effects occurred in 62 patients (53%). Eight patients (7%) had adverse effects that led them to stop taking baclofen. Their dosages were <90 mg/day at that time. Alertness disorders and depression were the adverse effects that most frequently led to stopping baclofen. Bouts of somnolence and hypomanic episodes were the most potentially dangerous adverse effects. Women reported significantly more adverse effects than men.
Conclusion: High-dose baclofen exposes patients with alcohol disorders to many adverse effects. Generally persistent, some adverse effects appear at low doses and may be dangerous.

INTRODUCTION

Baclofen, an agonist of the gamma-aminobutyric acid B receptor, is a muscle relaxant that has been used for around 40 years. It is indicated for the treatment of spasticity from diseases of the central nervous system, at doses <90 mg/day. In light of several case reports (Ameisen, 2005; Bucknam, 2007; Dore *et al.*, 2011; Pastor *et al.*, 2012) and several retrospective observational studies (de Beaurepaire, 2012; Rigal *et al.*, 2012a), it appears that high-dose (≥90 mg/day) baclofen can help some patients with alcohol disorders regain control of their consumption.

Nonetheless the benefit-to-risk ratio of high-dose baclofen remains unclear. The first two randomized controlled trials testing its efficacy against placebo are still underway in early 2015. Data about its safety and tolerability are equally fragmentary. Both because baclofen use in patients with neurological disorders began decades earlier and because some physicians are prescribing baclofen to patients with alcohol disorders in a compassionate approach (Rigal *et al.*, 2012b), some information is available about its safety and adverse-effect profile (Comité technique de pharmacovigilance, 2013). Overdoses (Leung *et al.*, 2006) and withdrawal syndromes (Leo and Baer, 2005) have been reported. Similarly, some co-morbidities have been

found to be associated with a higher risk of serious adverse effects [such as impaired renal function (Chen *et al.*, 1997)]. Nonetheless, the adverse-effect profile of high-dose baclofen over a long period by patients with alcohol disorders has not, to the best of our knowledge, been the object of a specific study, even though baclofen use appears to be associated with numerous adverse effects that might limit its use or hinder a dose increase up to the elevated doses at which it is expected to be efficacious.

The aim of the study was to assess the tolerability of high-dose baclofen taken by patients with alcohol disorders. More precisely, we describe here the adverse effects encountered by these patients during their first year of treatment and assess the patient characteristics associated with poor tolerance.

METHODS

Study design

This retrospective study was conducted among the patients of a general practitioner with specific expertize in treating patients with addictions who has been prescribing baclofen for >5 years, at high doses when appropriate, to treat 'high-risk' drinkers [that is, with consumption levels >40 g/day for women and 60 for men, as defined by the World Health Organisation (WHO, 2000)]. As previously described (Gache *et al.*, 2014), this physician prescribed baclofen at a progressively increasing dose until it allowed patients to reduce their consumption to the 'low-risk' level [≤20 g/day for women and 40 for men (WHO, 2000)] or even become abstinent. Neither detoxification nor alcohol dependence was a necessary precondition to treatment. Patients systematically received oral information about the treatment. The following points were always raised with them: the off-label nature of the prescription; the possibility of adverse effects, which required that the dosage be increased slowly, until the desire to drink disappeared; the ban on driving because of the risk of somnolence (the only adverse effect routinely mentioned), especially if taken with alcohol and the risk of either an overdose or withdrawal syndrome if the dose were to be changed suddenly. Management was not limited to baclofen alone but could include other aspects of the care generally used to treat patients with alcohol disorders (psychological and psychosocial interventions, management of comorbid mental conditions and physical complications) as recommended (NICE, 2011).

All the high-risk drinkers who had started baclofen more than one year before 1 November 2011, were eligible for this study, regardless of the length of their treatment or continued relationship with the doctor after the prescription of baclofen. They were identified through an exhaustive list of patients who had taken baclofen, compiled prospectively by the doctor.

Data collection

Data for each eligible patient were collected first by examining his or her medical record and then by an interview, either by the treating doctor during a regular consultation or by telephone, by a doctor-investigator, if the patient had stopped seeing the doctor (Fig. 1). The interview included the administration of a standardized questionnaire intended to obtain data not reported in the medical file and to ask patients systematically about how they tolerated the drug during their first year of treatment.

The list of distinct adverse effects that we looked for in the files and asked about at interviews included: disruption of the wake–sleep cycle (somnolence, bouts of somnolence, asthenia, insomnia), vertigo, headaches, higher function disorders (memory lapses, concentration and alertness disorders), reduced libido, increased libido, sweating, nausea, dysgeusia, joint pain, paresthaesia, tinnitus, hot flushes, constipation, rash, depression, diarrhoea, respiratory disorders, urinary disorders, excitement and hypomania. The latter two are the only ones that are mutually exclusive: no patient could have both of them, either simultaneously or consecutively. For each adverse effect, the following information was sought: the baclofen dosage at onset, its duration (dichotomized as transient or persistent, that is, not disappearing over time but not necessarily permanently present on a daily basis) and its consequences on the continuation of the treatment (classified as: no consequence, limitation of dose increase, introduction of symptomatic treatment or termination of the baclofen treatment).

Besides their adverse effects, we collected the following patient characteristics:

– sociodemographic data: age, sex, lives with a partner, has his/her own home (*vs* homeless or living in an institutional setting

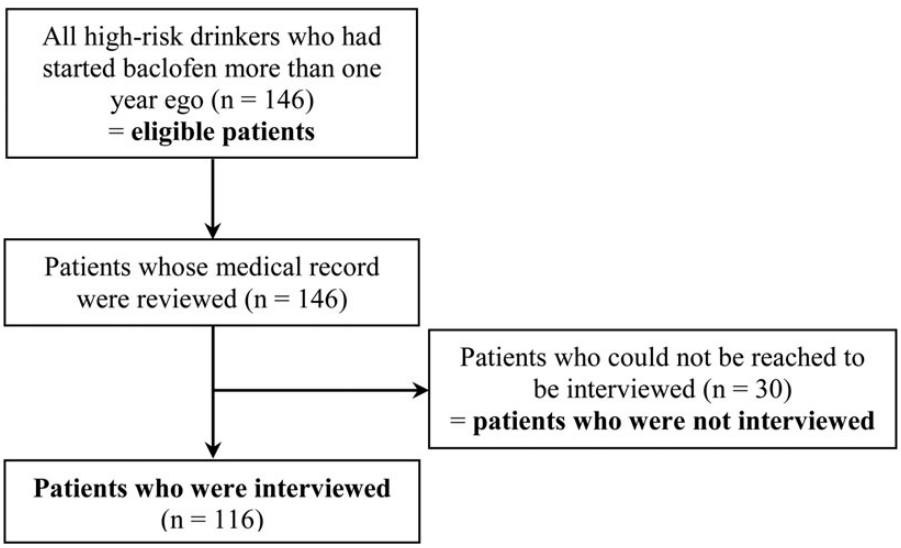

Fig. 1. Flow diagram.

or housed by a third party), child at home, work status (working, unemployed, ill or disabled, retired, otherwise not in the labour force);
- history of their alcoholism: episodes of detoxification, previous treatment with drugs approved for preventing relapses (acamprosate, naltrexone or disulphiram), participation in a therapy or discussion group such as Alcoholics Anonymous;
- alcohol consumption and dependence (DSM-IV criteria) at the beginning of treatment;
- psychiatric disorders (DSM-IV criteria): anxiety, depression, bipolar disorder, psychosis and borderline personality disorder;
- other addictions: tobacco, cannabis, cocaine and heroin;
- treatment at baseline with psychotropic drugs [anxiolytics, hypnotics, antidepressants, mood stabilizers, neuroleptics and opiate substitutes (methadone or buprenorphine)] as well as non-psychotropic drugs;
- maximum baclofen dosage;
- alcohol consumption during the twelfth month of baclofen treatment.

Statistical analyses

The patients who were interviewed (Fig. 1) were first described and the variation in their characteristics analysed according to sex and alcohol dependence. Their adverse effects were then described. To look for factors that might predispose patients to poor tolerance, we tested the associations of the following patient characteristics (sex, age, alcohol dependence, other addictions, psychiatric disorders, treatment at baseline and dose at the onset of the first adverse effect) with both the number of adverse effects and their consequences in terms of stopping treatment or limiting dose increases. It is possible that some patients who could not be reached for interviews had stopped seeing the physician who prescribed baclofen because of adverse effects that were more frequent and more bothersome for the continuation of treatment than those who were interviewed. To analyse this selection phenomenon, we compared characteristics and adverse effects between patients who were and were not interviewed (using data from the medical files for the latter). We used chi-square tests (or Fisher's exact tests if needed) and Student *t*-tests (or Kruskal–Wallis tests if needed) to compare percentages and means.

Ethical aspects

All patients included in the analysis were informed about the study's purpose. 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 as a retrospective study, it does not come within the scope of the French statutes regulating biomedical research. As required in France, the medical record database we used was reported to the National Data Protection Authority (*Commission Nationale de l'Informatique et des Libertés*), which is responsible for the protection of individual electronic data collection.

RESULTS

Patients' description

Of the 146 eligible patients, 116 (79%) were interviewed (Fig. 1). Complete information was available for all of them.

The patients' mean age when baclofen treatment began was 45 ± 11 years (43.1 for men *vs* 48.2 for women, $P = 0.01$). Overall, 59% of the patients were men (Table 1) and 25% were not alcohol-dependent (these patients nonetheless met at least one DSM-IV criterion for alcohol dependence: uncontrolled use). Their baseline alcohol consumption averaged 174 ± 100 g/day (194 g/day in men *vs* 146 g/day in women, $P = 0.011$; 191 g/day in the alcohol-dependent patients *vs* 124 g/day in those who were not $P < 0.0001$). Almost all the patients (94%) drank daily: 34.5% began in the morning, 22% at noon or in the afternoon (30% of the men *vs* 11% of the women, $P = 0.012$) and 43% only in the evening. Most of the patients (72%) had already tried a drug approved for relapse prevention.

One year after the initiation of their baclofen treatment 53 patients (45.7% of those interviewed and 36.3% of those eligible) were abstinent, 26 (22.4% of those interviewed and 17.8% of those eligible) were drinking but only below or at the 'low-risk' level and 37 (31.9% of those interviewed and 25.3% of those eligible) were drinking above that level. The maximum baclofen dose taken during their first year of treatment averaged 159 ± 87 mg/day (description of the maximum baclofen dose taken by patients during their first year of treatment:

Table 1. Characteristics of patients and comparison between patients who were and were not interviewed

	Interviewed ($N = 116$) %	Not interviewed ($N = 30$) % (*n* missing values, if any)	*P*
Male	59	67	0.5
Lived with a partner	53	53	0.9
Has his/her own home	84	83	1.0
Child at home	34	47	0.2
Work status		(1)	0.9
Working	60	52	
Unemployed	13	14	
Ill or disabled	13	17	
Retired	9	10	
Otherwise not in the labour force	4	7	
Alcohol dependence	75	88 (5)	0.2
Drinks daily	94	93 (1)	1.0
Had already			
tried a drug approved for relapse prevention	72	70	0.8
undergone detoxification	34	63	0.004
participated in therapy or discussion groups	29	37	0.4
Other addictions			
Smoking	86	87	1.0
Cannabis	43	33	0.3
Cocaine	24	20	0.6
Heroin	19	20	0.9
Psychiatric disorders	92	93	1.0
Depression	61	63	0.8
Psychosis	7	20	0.03
Anxiety	86	90	0.8
Bipolar disorders	10	13	0.6
Borderline personality	25	30	0.6
Treatment at baseline	78	88	0.3
Anxiolytics	64	83	0.04
Hypnotics	42	43	0.9
Antidepressants	38	53	0.1
Neuroleptics	12	30	0.01
Mood regulators	3	10	0.1
Opiate substitutes	18	3	0.04
Non-psychotropic drugs	39	20	0.054

minimum 30 mg/day, first quartile 90 mg/day, median 150 mg/day, third quartile 210 mg/day, maximum 400 mg/day).

Description of adverse effects

During their first year of treatment, three patients were hospitalized following misuse of the treatment: two patients had hallucinations after overdoses (intake of 400–500 mg) and a third had withdrawal syndrome (after abruptly stopping a dosage of 180 mg/day).

During that year, 78% ($n = 90$) of the patients had at least one adverse effect (Table 2). The mean number of adverse effects per patient was 2.8 ± 2.7. The most frequent group of adverse effects was disruptions of the wake–sleep cycle (somnolence, bouts of somnolence, asthenia and insomnia), which affected 63% ($n = 73$) of the patients.

The mean dosage of baclofen at the onset of the first adverse effect was 83 ± 57 mg/day (description of the baclofen dose taken by patients at the onset of their first adverse effect: minimum 20 mg/day, first quartile 30 mg/day, median 60 mg/day, third quartile 120 mg/day, maximum 300 mg/day).Urinary and alertness disorders were the adverse effects with the lowest mean dose at onset (all episodes of these two adverse effects appeared at doses <90 mg/day). Contrarily, sweating, tinnitus and diarrhoea had the highest mean doses at onset.

Persistent adverse effects occurred in 53% ($n = 62$) of the patients (i.e. almost 70% of those with adverse effects). Sweating and alertness disorders were the most frequently persistent adverse effects (in >85% of cases).

Eight patients (7%) had adverse effects that caused them to stop taking baclofen. The dosage at the time of the decision to stop was <90 mg/day for all of them. Alertness disorders and depression were the effects that most frequently led to stopping treatment. Higher function disorders (memory lapses, concentration and alertness disorders) affected 20% ($n = 23$) of the patients and were seen in 7 of the 8 patients who stopped baclofen for poor tolerance. These adverse effects appeared at doses that varied from 30 to 270 mg/day.

A planned dose increase was interrupted for 10 patients (9%) because of poor tolerance. The maximum dosage of baclofen that they could tolerate ranged from 30 to 240 mg/day. Paraesthesia and tinnitus were the adverse effects most frequently associated with limiting dose increases.

Diarrhoea, hot flushes, rashes, dysgeusia (distorted taste perception), excitation and libidinal disorders had the fewest consequences on continued treatment. All adverse effects were resolved by stopping baclofen.

Table 2. Characteristics of adverse effects

	% (n)[a]	Baclofen dosage at initiation—mg/day					Persistent %	Consequence for continuation of treatment—% (n)			
		m ± sd[b]	≤90	[90–120]	[120–180]	>180		Stopped	Dose increase limited	Symptomatic treatment	None
Somnolence	45 (52)	93 ± 55	58	23	11	8	48	10 (5)	4 (2)	42 (22)[c]	44 (23)
Bouts of somnolence	26 (30)	124 ± 85	47	23	10	20	43	7 (2)	7 (2)	43 (13)[c]	43 (13)
Asthenia	23 (27)	97 ± 63	56	22	15	7	56	15 (4)	3 (1)	41 (11)	41 (11)
Insomnia	20 (23)	117 ± 68	52	17	17	13	52	4 (1)	0 (0)	43 (10)	52 (12)
Vertigo	20 (23)	87 ± 54	65	13	18	4	35	26 (6)	13 (3)	4 (1)	57 (13)
Headaches	13 (15)	102 ± 52	60	13	20	7	33	13 (2)	27 (4)	0 (0)	60 (9)
Memory lapses	12 (14)	116 ± 80	57	0	21	21	64	36 (5)	7 (1)	43 (6)	14 (2)
Concentration disorders	11 (13)	118 ± 82	46	15	15	23	46	23 (3)	8 (1)	54 (7)	15 (2)
Excitation	10 (12)	84 ± 72	58	25	8	8	50	0 (0)	0 (0)	8 (1)	92 (11)
Increased libido	9 (11)	68 ± 45	73	18	9	0	55	0 (0)	0 (0)	0 (0)	100 (11)
Sweating	9 (11)	132 ± 67	18	55	18	9	91	9 (1)	9 (1)	9 (1)	73 (8)
Nausea	9 (11)	73 ± 51	82	0	18	0	55	36 (4)	0 (0)	36 (4)	27 (3)
Dysgeusia	8 (9)	80 ± 58	67	11	22	0	56	0 (0)	0 (0)	0 (0)	100 (9)
Reduced libido	8 (9)	108 ± 33	33	44	22	0	33	0 (0)	0 (0)	11 (1)	89 (8)
Hypomania	7 (8)	80 ± 34	88	0	13	0	63	25 (2)	0 (0)	13 (1)	63 (5)
Joint pain	7 (8)	90 ± 53	50	38	13	0	38	25 (2)	0 (0)	0 (0)	75 (6)
Alertness disorders	6 (7)	44 ± 15	100	0	0	0	86	71 (5)	14 (1)	0 (0)	14 (1)
Tinnitus	6 (7)	163 ± 84	14	43	14	29	14	0 (0)	28 (2)	14 (1)	57 (4)
Paresthaesia	6 (7)	93 ± 68	57	14	14	14	57	29 (2)	43 (3)	14 (1)	14 (1)
Urinary disorders	4 (5)	16 ± 9	100	0	0	0	60	20 (1)	20 (1)	20 (1)	40 (2)
Depression	3 (4)	60 ± 42	75	25	0	0	50	50 (2)	0 (0)	50 (2)	0 (0)
Rash	3 (4)	98 ± 51	50	25	25	0	0	0 (0)	0 (0)	0 (0)	100 (4)
Constipation	3 (4)	64 ± 40	75	25	0	0	75	25 (1)	0 (0)	50 (2)	25 (1)
Hot flushes	3 (4)	105 ± 39	50	25	25	0	25	0 (0)	0 (0)	0 (0)	100 (4)
Respiratory disorders	3 (3)	70 ± 46	67	33	0	0	33	33 (1)	0 (0)	0 (0)	67 (3)
Diarrhoea	3 (3)	203 ± 119	0	33	33	33	33	0 (0)	0 (0)	0 (0)	100 (3)

[a]Classification in decreasing order of frequency (number of patients = 116).

[b]Mean ± standard deviation.

[c]Piracetam is a nootropic that can be used to reduce this adverse effect (with positive results, in our experience).

Table 3. Association of patient characteristics with the number of adverse effects and with their consequences for continuation of treatment (stopping baclofen or limiting dose increases)

	N	Number of adverse effects		Stopping baclofen or limiting dose increases	
		m ± sd[a]	*P*	%	*P*
Male (Yes/No)	69/47	2.3 ± 1.7/3.5 ± 2.7	0.02	9/26	0.01
Alcohol dependence (Yes/No)	87/29	2.8 ± 2.9/2.9 ± 2.1	0.9	17/10	0.6
Other addictions					
Smoking (Yes/No)	100/16	2.9 ± 2.7/2.4 ± 2.9	0.6	13/31	0.1
Cannabis (Yes/No)	50/66	2.5 ± 2.4/3.0 ± 2.9	0.3	12/18	0.4
Cocaine (Yes/No)	28/ 88	2.3 ± 1.9/3.0 ± 2.9	0.1	7/18	0.2
Heroin (Yes/No)	22/94	2.0 ± 1.8/3.0 ± 2.8	0.05	9/17	0.5
Psychiatric disorders					
Depression(Yes/No)	71/45	3.2 ± 3.0/2.2 ± 2.1	0.07	18/11	0.3
Psychosis (Yes/No)	8/108	0.9 ± 1.7/2.9 ± 2.7	0.04	12/16	1.0
Anxiety (Yes/No)	100/16	3.0 ± 2.8/1.6 ± 1.9	0.06	18/0	0.07
Bipolar disorders (Yes/No)	12/104	3.0 ± 2.9/2.8 ± 2.7	0.8	17/15	1.0
Borderline personality (Yes/No)	29/87	2.9 ± 2.5/2.8 ± 2.8	0.8	14/16	1.0
Treatment at baseline					
Anxiolytics (Yes/No)	74/42	2.5 ± 2.7/3.3 ± 2.8	0.1	15/17	0.8
Hypnotics (Yes/No)	49/67	2.6 ± 2.6/2.9 ± 2.8	0.6	12 /18	0.4
Antidepressants (Yes/No)	44/72	2.5 ± 2.5/3.3 ± 3.0	0.1	22/11	0.09
Neuroleptics (Yes/No)	14/102	1.5 ± 1.6/3.0 ± 2.8	0.008	14/16	1.0
Mood regulators (Yes/No)	4/112	0.8 ± 1.5/2.9 ± 2.7	0.12	0/16	1.0
Opiate substitutes (Yes/No)	21/95	2.0 ± 1.8/3.0 ± 2.9	0.06	10/17	0.5
Non-psychotropic drugs (Yes/No)	45/71	3.2 ± 2.8/2.5 ± 2.6	0.2	18/14	0.6

[a]Mean ± standard deviation.

Patient characteristics associated with poor tolerance

The analyses of the patient characteristics associated with poor tolerance showed that patients with a history of psychosis had fewer adverse effects than the others, as did patients treated with neuroleptics (Table 3). Women also reported more adverse effects than men, and more often stopped taking baclofen or limited the dosage increase. Neither the patients′ age nor the dosage at the first adverse effect was associated with either the number of adverse effects or their consequence for baclofen usage (stopping or limiting increases).

Comparison between patients who were and were not interviewed

Of the 146 eligible patients, 30 (21%) could not be reached for interviews (Fig. 1). We had nevertheless data about them, extracted from their medical records.

The patients who were not interviewed had stopped seeing the physician an average period of 4.6 ± 3.3 months after they started using baclofen. During their last contact with the physician, 40% of them were abstinent ($n = 12$), 20% were drinking but only below or at the 'low-risk' level and 40% were drinking above that level.

They did not differ significantly for age, sex, initial alcohol consumption (6 missing values) or alcohol dependence from those who were interviewed (Table 1). Nonetheless the patients not interviewed had a history of psychosis and also took neuroleptic treatment more often than the patients interviewed. They had also undergone detoxification more frequently (mean number of detoxifications: 2.5 ± 3.1 *vs* 1.5 ± 2.5, $P = 0.01$). Finally, they received anxiolytic medication more often and opiate substitute treatment less often ($P = 0.04$, Table 1).

The patients not interviewed did not have more adverse effects than the patients who were interviewed ($n = 2.0 \pm 2.3$, $P = 0.12$) but they did have (Table 4) more respiratory disorders ($P = 0.01$) and fewer bouts of somnolence ($P = 0.02$) and vertigo ($P = 0.03$). No significant difference was observed for the frequency of adverse effects related to continuation of baclofen use (that is, related to stopping it or limiting its dosage).

Focus on hypomanic episodes

The hypomanic episodes (of the patients who were and were not interviewed) were all resolved by adding divalproex sodium treatment (if no mood stabilizer had already been prescribed) and/or by reducing the baclofen dose. Of the 10 patients with a hypomanic episode, 5 had a history of bipolar disorder but only one was currently treated with a mood stabilizer. Of the 16 patients with a history of bipolar disorder, 7 were taking mood-stabilizing drugs (and only one of these had a hypomanic episode); and 9 were not (and 4 of them had a hypomanic episode).

DISCUSSION

Summary

Our results show that baclofen is associated with very frequent and various adverse effects that appear at relatively low doses and are generally persistent. Disruption of the wake–sleep cycle was the most frequent adverse effect. Alertness disorders appeared at low doses and very often led to the interruption of baclofen.

Limitations and strengths

Our observational study has some limitations. The retrospective data collection certainly results in underestimating the frequency of its adverse effects. This recall bias is nonetheless probably reduced for the most annoying adverse effects, such as those that led to stopping baclofen or limiting any increase in its dosage. Beyond that, it is

Table 4. Characteristics of adverse effects among patients who were not interviewed ($n = 30$)

	% (n)	Baclofen dosage at initiation—mg/day Minimum–Maximum	Consequence for continuation of treatment—% (n)			
			Stopped	Dose increase limited	Symptomatic treatment	None
Somnolence	40 (12)	30–180	0 (0)	17 (2)	25 (3)	58 (7)
Bouts of somnolence	7 (2)	30–45	0 (0)	50 (1)	50 (1)	0 (0)
Asthenia	17 (5)	30–120	0 (0)	20 (1)	0 (0)	80 (3)
Insomnia	20 (6)	60–150	0 (0)	0 (0)	50 (3)	50 (3)
Vertigo	3 (1)	240	0 (0)	0 (0)	0 (0)	100 (1)
Headaches	13 (4)	60–120	0 (0)	0 (0)	25 (1)	75 (3)
Memory lapses	7 (2)	120	0 (0)	0 (0)	0 (0)	100 (2)
Concentration disorders	3 (1)	60	0 (0)	0 (0)	0 (0)	100 (1)
Excitation	3 (1)	90	0 (0)	0 (0)	0 (0)	100 (1)
Increased libido	3 (1)	120–160	0 (0)	0 (0)	0 (0)	100 (2)
Sweating	10 (3)	120–150	0 (0)	33 (1)	0 (0)	67 (2)
Nausea	10 (3)	30–120	0 (0)	0 (0)	67 (2)	33 (1)
Dysgeusia	0 (0)	–	–	–	–	–
Reduced libido	7 (2)	30–120	0 (0)	0 (0)	0 (0)	100 (2)
Hypomania	7 (2)	30–60	0 (0)	50 (1)	0 (0)	50 (1)
Joint pain	3 (1)	120	0 (0)	0 (0)	0 (0)	100 (1)
Alertness disorders	0 (0)	–	0 (0)	0 (0)	0 (0)	0 (0)
Tinnitus	7 (2)	60–120	0 (0)	0 (0)	0 (0)	100 (2)
Paresthaesia	17 (5)	90–150	0 (0)	20 (3)	40 (2)	40 (2)
Urinary disorders	0 (0)	–	–	–	–	–
Depression	0 (0)	–	0 (0)	0 (0)	0 (0)	0 (0)
Rash	0 (0)	–	0 (0)	0 (0)	0 (0)	0 (0)
Constipation	0 (0)	–	–	–	–	–
Hot flushes	0 (0)	–	–	–	–	–
Respiratory disorders	17 (5)	60–150	20 (1)	0 (0)	40 (2)	40 (2)
Diarrhoea	0 (0)	–	–	–	–	–

probable that some of the patients who could not be reached for interviews had stopped seeing the physician who prescribed baclofen because they could not tolerate it and that this also led to an underestimation of the frequency of these adverse effects. Moreover, neuroleptic treatment and a history of psychosis were more frequent among the patients not interviewed and also associated with fewer adverse effects. It is probable that psychotic patients and those taking neuroleptics who had poor tolerance and many adverse effects dropped out of treatment and were not interviewed. Accordingly, these two patient characteristics may be associated with tolerance only through a selection effect. Female sex, a new finding to the best of our knowledge, appears to be the only patient characteristic clearly associated with poorer tolerance for baclofen in our study.

It is important to point out that adverse effects cannot be attributed to baclofen with any certainty. Our study aimed first of all to describe, without any suggestion of causality, the symptoms patients experience while taking baclofen in real prescription conditions. The fact that many patients were taking other psychotropic drugs and/or were drinking alcohol means that some adverse effects could have had another cause or been due to interaction phenomena. Baclofen could for example have potentiated somnolence as well as the mental confusion induced by other psychotropic medications. Moreover, even though studies have shown good tolerability of low-dose baclofen co-administered with alcohol (Evans and Bisaga, 2009; Leggio *et al.*, 2013), high baclofen doses taken by patients with alcohol disorders can cause severe adverse effects, such as convulsions (Rolland *et al.*, 2012).

Although we have, for convenience, talked about adverse effects that led to stopping baclofen, it would have been more accurate to say that these effects contributed to the decision to stop. That is, this decision depends on an entire set of elements including adverse effects, but others may well play a role, including treatment efficacy, the patient's motivation and preferences, as well as his or her personal problems at that moment.

Finally, our study does not take the pharmacokinetics and pharmacodynamics of baclofen into account. Nonetheless the wide inter-patient variation in baclofen pharmacokinetics, due to the fact that similar doses of baclofen do not produce the same plasma concentrations in all patients (Marsot *et al.*, 2014), may explain the variety in the doses at which adverse effects appeared.

This study is innovative in several ways: its length, its large number of patients, its high dosage and its setting in general practice (Garbutt and Flannery, 2007). Our results appear to be consistent with the scientific literature, which is, however, limited and composed principally of case reports. Several observational studies are available (Smith *et al.*, 1991; de Beaurepaire, 2012; Rigal *et al.*, 2012a) but provide little information about tolerance. The four placebo-controlled randomized clinical trials that used baclofen in patients with alcohol disorders were small (maximum number = 84), administered low dosages (maximum dosage = 60 mg/day), and focussed primarily on efficacy (Addolorato *et al.*, 2002, 2007, 2011; Garbutt *et al.*, 2010).

Implications for practice and research

Our results lead us to offer three pieces of practical advice. First, more than a quarter of the patients reported bouts of somnolence, and some described these sudden episodes as close to narcolepsy. These can be very dangerous for both the patients and for others, when, for

example, the patient is driving a vehicle. These risks must be clearly explained to the patients, and they must be advised to avoid these risky activities at least during the periods when the baclofen dosage is being increased. Second, some patients presented alertness disorders that appeared at a low dose and persisted until baclofen was finally stopped. In patients with severe and dangerous adverse effects that begin at low dosages, it appears necessary to reassess the indications for baclofen immediately and, if necessary, stop this treatment, which may be more dangerous than beneficial for them. Third, because of the potential danger of hypomanic episodes, we think that it is preferable to avoid prescribing baclofen to patients with bipolar disorders.

A larger prospective study should be conducted to look for rare and serious adverse effects. Such a study might also make it possible to specify more precisely the different disorders of daytime somnolence induced by baclofen and to improve both our understanding of interaction phenomena that can modulate patient tolerance for baclofen and the characterization of the patients at greatest risk of finding this drug intolerable. This latter objective seems relevant because tolerance problems are frequent and negatively affect treatment [in our study 16% of the patients stopped taking baclofen (7%) or limited dosage increases because they found it intolerable (9%)] and because we found few significant associations between patient characteristics and tolerability.

CONCLUSION

The use of high-dose baclofen in patients with alcohol disorders appears manageable but difficult in view of the large number of adverse effects, some of which may lead to stopping the treatment or limiting its dosage. It also exposes patients to severe consequences, such as hypomanic episodes. To help patients decide about taking baclofen and to ensure their safety, this information must be clearly described when treatment begins. Problems of tolerance at low doses should raise questions about the value of continuing this treatment.

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