CASE REPORT

Gambling disorder: a side effect of an off-label prescription of baclofen—literature review

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Accepted 21 December 2016

SUMMARY

The use of high-dose baclofen emerged in 2008 in the treatment of alcohol-use disorders. Its prescription is still off-label in France, but recent trials have suggested the interest of using high doses for alcohol dependence, so we have to deal with an increase in its use. However, we still have few data about the adverse effects of a high-dose baclofen prescription, especially in complex addictive disorders. We present a case of a 32-year-old man who sought treatment for gambling disorders (GDs). He had complex addictive disorders, including alcohol-use disorders and GDs. He developed a severe GD, after treatment with a high dose of baclofen. The maximum dose was 160 mg/day, prescribed for his alcohol-use disorders. According to the Naranjo algorithm, the score was +7, it enabled to conclude that problem of gambling was probably imputable to baclofen. We discuss this case with reference to literature.

BACKGROUND

Baclofen is an agonist of γ -aminobutyric acid type B (GABA-B) receptors and has been used for spasticity since 1970s.¹ A few years ago, a major publication reported that a 30 mg/day dose of baclofen in patients with alcoholic liver cirrhosis could reduce the risk of relapse into alcohol dependence, with a very good safety level.² In France, the use of high-dose baclofen emerged in 2008, based on empirical findings, and has recently become a popular choice for treating alcohol dependence.^{3,4} Baclofen is still off-label but, due to a rapid increase in this prescribing practice, the French health authorities have decided to define it using an extraordinary regulatory measure named 'Temporary Recommendation for Use'. Trials have suggested the interest of using high doses for alcohol dependence.^{2,5} But some adverse effects are reported in the literature: sedative effects,⁶ deep coma and respiratory depression,^{7,8} confusion, delirium or seizures.⁹ However, the safety level of this therapeutic practice is uncertain in its use for chronic conditions and we find very little information on outcomes, least of all in complex patients with several addictive disorders.

The risk of developing an addiction is very high in someone presenting, or having presented, one or many addictive behaviours. Problem gambling is defined as a pattern of gambling behaviours that disrupt, compromise or damage personal, family and vocational pursuits.¹⁰ Given the similarities to non-substance addictions, in terms of biopsychosocial vulnerability and response to treatment,

gambling disorder (GD) has recently been classified as a non-substance addiction and has been included in the Diagnostic Statistical Manual (DSM-5) under the category 'Substance-related and Addictive Disorders'.¹¹

Among patients with substance-use disorders, the prevalence estimates of lifetime GDs (formerly pathological gambling in DSM-III and DSM-IV) are substantially higher and range from 7% to 39%.^{12–16} Thus, the most frequent comorbidity of GD is the use of psychoactive substances. Patients with a GD have a considerably higher consumption of psychoactive substances than the general population.¹⁷ This close association between substance-use disorders and GDs is well-known¹⁸ and patients may present alcohol disorder and GDs at the same time but they can also switch addiction: switch their alcohol-use disorder to GD, for example. This risk may also be exacerbated by medication.

We identified a close association between alcohol-use disorder and GD, and the occurrence of switching from alcohol-use disorder to pathological gambling, in a patient with high-dose baclofen medication. We found very few studies or reports about this topic in the literature. This case arouses risk factor issues, and clinical and pharmacological issues, concerning patients with treatment for complex addictive disorders. These points are discussed in this paper.

CASE PRESENTATION

A 32-year-old man presented for treatment of GDs. He attended our department, which specialises in the field of addictive disorders, especially behavioural addictions.

We identified no particular medical or psychiatric history apart from addictive disorders. Before the current disorder, he had no regular treatment.

He had worked in a family business for 10 years, but he had to sell the business 5 years ago because of financial problems. Since then, he was having difficulties in finding a job.

We identified a family history of addictive disorders, his father was alcohol dependent.

He described impulsivity, a tendency to act with little forethought, and having unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions. He did not present axis 1 mental disorders. However, treatment by olanzapine had been prescribed 1-month before he met us. This treatment was prescribed off the label, for anxiety and impulsivity, but the patient described a bad tolerance, with sedative effects.

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To cite: Guillou-Landreat M, Victorri Vigneau C, Gerardin M. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-217506

He presented an *alcohol-use disorder*. He started to drink alcohol in adolescence and daily consumption associated with craving and loss of control appeared at 24 years of age, after his brother's death.

Before the introduction of baclofen in hospitalisation, he consumed alcohol every day; he said he always consumed over 6 standard units, so 30 heavy drinking days (HDD) per month. The average consumption was 20 standard units per day.

After baclofen prescription during hospitalisation, he significantly reduced the average consumption, which was 4 standard units per drinking day, and he consumed alcohol maximum once or twice during a month, and with any HDD during the previous month before the first meeting.

Baclofen was prescribed off-label after all treatments for alcohol-use disorders authorised in France at that time had failed (acamprosate, naltrexone). It was prescribed according to the guidelines of the 'Temporary Recommendation for Use' as a slow growing protocol. The dose had been increased 10 mg daily/week for 15 weeks up to 160 mg/day, which was the maximum dose. About 160 mg/day was maintained because it aimed to reduce alcohol craving. He described a reduction in alcohol craving and consumption with baclofen, according to his personal objectives. The alcohol consumption reduction was significant, around 75% of reduction, and the frequency reduction too, with no more daily consumption. Medication was taken as directed; no misuse was described but he said that he experienced the effects of euphoria which increased as the day progressed, 'as if he was drunk'.

GDs appeared after financial problems. He fulfilled three criteria between 28 and 33 years old: he was often preoccupied with gambling, he often gambled when he was feeling distressed and he sometimes chased losses. But he fulfilled all the GD criteria (DSM 5) immediately after baclofen treatment was prescribed at 160 mg/day.¹¹ Gambling craving increased as alcohol craving decreased. He described an irresistible need to gamble, to bet, despite being aware of the damage. From this point, he started to feel unable to stop or limit gambling and described

feeling a craving rated between 9 or 10/10 every day. He said that he had spent from 90% to 100% of his money on gambling, despite all the debts and his rent and bills. He said that 'money burns a hole in his pocket' or 'runs through his fingers'. He sought sensation and positive reinforcement in gambling which became the only source of pleasure, despite the damage. He described financial and legal damage, for example, he stole money from his business, as well as damage to family due to his GD.

Figure 1 presents a longitudinal analysis of his life events, his addictive disorders history and his treatment.

INVESTIGATIONS

This case has been reported in the French pharmacovigilance database (BR20160922).

We did not lead more investigations.

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis of GD is the manic episode. Moreover, baclofen can induce manic symptoms.¹⁹ GD was not explained by a manic episode. He did not present manic symptoms: there was no inflated self-esteem, no decreased need for sleep, no flight of ideas and no increase in psychomotor activity or agitation.

TREATMENT

- Medication he had before the first meeting:
 - Baclofen 120 mg/day
 - Zopiclone: 1/day
 - Oxazepam 150 mg/day
 - Olanzapine: 5 mg/day
- Medication he had after the first meeting:
 - Baclofen: slow tapering 10 mg every 3 days
 - After baclofen stopped: nalmefene 18 mg/day
 - Zopiclone: 1/day
 - Oxazepam 100 mg/day

Figure 1 Life event and addictive disorders history.

OUTCOME AND FOLLOW-UP

We decided, after we met the first time, to decrease and then stop baclofen treatment, with the patient's approval. Baclofen brought about a large reduction in alcohol craving, but the high-dose baclofen medication coincided with the appearance and severity of the GD. Damages due to the GD were dramatic, concerning his financial, familial situations and were inducing psychological distress. Our supposition was that baclofen had lowered inhibitions and that had encouraged switching addictions and pathological gambling.

Opioid antagonists have been approved for the treatment of alcohol-use disorders, and nalmefene has been approved in alcohol consumption reduction recently in France.^{20 21} Moreover, in the literature, some studies supported the use of opioid antagonists, namely naltrexone and nalmefene, in GD.^{22 23}

We introduced nalmefene treatment to reduce alcohol craving and consumption, as well as to treat gambling craving and to help the patient to control gambling. His objective was to control gambling.

Slowly tapering off baclofen reduced the gambling craving and, 1-month after the introduction of nalmefene, he described a maximum gambling craving of around 4–5/10, less than half the rating he assigned to the craving when we first met. He said that he was feeling much more able to control his gambling and he had not increased his alcohol consumption.

Oxazepam treatment was reduced; we led a slow tapering after alcohol withdrawal management.

Olanzapine was stopped, because the patient described a sedative effect with this treatment, and the patient did not present any axis 1 disorders.

DISCUSSION

A French team of experts has recently published recommendations to address the causality of baclofen for alcohol dependence in the occurrence of adverse effects. We followed these five recommendations to address causality.²⁴ We provided a validated causality assessment. In this case, the causality of baclofen can be evaluated according to Naranjo's criteria.²⁵ The scoring was 7, which enabled us to conclude that it had probably produced a severe adverse reaction. We checked all the causality factors for this case (table 1). We also led a longitudinal description of the baclofen dosing before, during and after the adverse event, and a longitudinal description of alcohol and other substance (figure 1). We provided a longitudinal description of the dosing of psychotropic drugs. And we described precisely the history of the psychiatric underlying condition(s) of the patient.

We did not find any exacerbation of behavioural addiction nor its appearance as a potential adverse effect of baclofen neither in the authorisation labelling (in spasticity indication), nor in the extraordinary regulatory measure named 'Temporary Recommendation for Use'. We analysed the European pharmacovigilance database (Eudravigilance). Among 16 747 cases of adverse effects of baclofen, two cases of pathological gambling were reported. In the USA, among 16 161 adverse effects, we identified 4 cases of pathological gambling (between 2004 and 2012 but very little information is available about these cases (treatment, baclofen dose etc).

We analysed the literature (PubMed, ScienceDirect) with keywords: 'baclofen' AND 'pathological gambling' OR 'gambling disorder'. Seven articles matched this search; four were animal studies and only three articles concerned clinical studies.

Table 1 Naranjo algorithm²⁵

Criteria	Yes	No	Do not know
Are there previous conclusive reports on this reaction?	+1	0	0
Did the adverse events appear after the suspected drug was given?	+2	–1	0
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	–1	0
Did the adverse reaction appear when the drug was re-administered?	+2	–1	0
Are there alternative causes that could have caused the reaction?	–1	+2	0
Was the drug detected in any body fluid in toxic concentrations?	+1	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0
SCORE	+7		

Scoring: ≥9, definite adverse drug reaction; 5–8, probable adverse drug reaction; 1–4, possible adverse drug reaction; 0, doubtful adverse drug reaction.

Terrier *et al* explored the influence of the baclofen dose (20 vs 50 mg) on reinforcement learning in healthy male participants. They found that low doses of baclofen caused a disinhibition of dopamine neurons, an increase in DA levels and thus facilitated reinforcement learning in a gambling task.²⁶ They often chose the correct symbol associated with the highest probability of winning money. But no differences were found at 50 mg/day. It corresponds to the model of a bi-directional control of dopamine activity by increasing doses of baclofen, as proposed by Cruz *et al*.²⁷ Low doses of baclofen would preferentially inhibit GABA neurons activity. Conversely, high-dose baclofen inhibits the firing of dopamine neurons, resulting in a decrease of neurotransmitter release to the NAc in the ventral striatum.²⁷

Following this study, the Technical Committee of the CEIP (Centre for Information and Evaluation of Pharmacodependence) stressed baclofen's potential to induce GD. They suggested that an item be added to the Temporary Recommendation for Use statement regarding foreseen adverse effects which would enable research into those side effects of baclofen which were deemed to be pleasant or rewarding (Technical committee CEIP-A. CT022014033-22 July 2014). However, there were no studies concerned with really high doses of baclofen, despite the fact that, in alcohol-use disorders, daily doses are higher than in market authorisation guidelines.²¹

Different methods of pharmacological treatment have actually been discussed in GD research. Dannon *et al* reported a trial of baclofen treatment as a treatment for GD among nine gamblers. Baclofen was prescribed at a daily dose from 10 to 50 mg. It concluded that baclofen was not effective in reducing gambling.²⁸ Treatment strategies may differ according to clinical, psychological or biological situations, as proposed by Pettorrusso *et al*.²⁹

Given the high prevalence of disordered gambling among those with substance-use disorders, screening for GD in the substance-use treatment setting is strongly advisable. It seems necessary that physicians who prescribe high-dose baclofen also carefully supervise their patients and report any adverse event they have encountered in the use of this treatment.

Learning points

- ▶ Alcohol-use disorder and gambling disorder (GD) are closely linked and occur frequently as comorbidity.
- ▶ The choice of alcohol-use disorder treatment has to take into account associated comorbidity.
- ▶ A high dose of baclofen may induce disinhibition and elevated gambling craving in patients with comorbidity.
- ▶ Opioid antagonists may be a better choice when alcohol-use disorder is associated with GD.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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