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## CASE REPORT

## Speaking fluently with baclofen?

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**SUMMARY**

Baclofen is a new and promising pharmacological compound for the treatment of alcohol dependence (AD). Although several randomised trials found a reduction of craving and higher abstinence rates with low and high doses of baclofen, others failed to show positive effects. In this case study, the successful treatment of a patient with AD with daily 120 mg of baclofen is described. In addition to a decrease in alcohol use, we observed the cessation of stuttering during treatment with baclofen, reoccurrence of stuttering following discontinuation, and cessation of stuttering after reinstatement of the treatment. Based on this observation, the direct effects of baclofen on muscle relaxation and anxiety reduction and its indirect effect on dopaminergic inhibition, we believe that baclofen might be a new treatment for stuttering. Further research into the effect of baclofen on stuttering is warranted.

**BACKGROUND**

Based on estimates of the WHO, 3.3 million global deaths are attributable to harmful alcohol use. Furthermore, drinking alcohol is associated with health problems such as liver cirrhosis, cancer and injuries and is a highly social and economic burden.<sup>1</sup> Alcohol dependence (AD), the most extreme form of harmful alcohol use, is a chronic disease characterised by high relapse rates of up to 60% after 1 year.<sup>2</sup> AD can be treated with psychotherapy (eg, motivational enhancement therapy, cognitive behaviour therapy) and/or pharmacotherapy. To date, only disulfiram, acamprosate, and naltrexone are approved by the Food and Drug Administration and the European Medicines Agency. However, although efficacy of these agents could be proven in several clinical trials, other trials failed to find significant effects and treatment effects were often relatively small.<sup>3</sup> Therefore, new effective medications are needed for the treatment of AD. One such promising medication is baclofen, a central acting muscle relaxant. Baclofen is a gamma-aminobutyric acid (GABA)-B receptor agonist, which is widely used for the treatment of muscle spasticity, resulting from multiple sclerosis or spinal cord diseases. It is commonly administered in oral doses between 30 and 100 mg, but also higher doses are used.<sup>4</sup> Furthermore, baclofen has been found to successfully stop chronic hiccup.<sup>5,6</sup>

GABA-B receptors are located in the same areas of the brain as the mesolimbic dopamine neurons, which play a role in the mediation of alcohol intake and reinforcement.<sup>7,8</sup> It is assumed that activation of GABA-B receptors inhibits the surrounding dopamine neurons,<sup>9</sup> leading to a decrease of dopamine

release in response to alcohol consumption and a reduction in craving. First animal studies showed a positive effect of baclofen on rat's drinking behaviour,<sup>10,11</sup> and this effect was replicated in two double-blind randomised placebo-controlled trials (RCT) where a dose of 30 mg/day resulted in a reduction of craving and higher abstinence rates in alcohol-dependent patients<sup>12,13</sup> (but see the RCT of Garbutt *et al*,<sup>14</sup> Ponizovsky *et al*<sup>15</sup> and Krupitsky *et al*<sup>16</sup> that failed to observe such effects of daily 30–60 mg baclofen). In addition, two case studies, which showed that a dose up to 270 mg of daily baclofen could completely suppress alcohol craving,<sup>17,18</sup> suggest the presence of a dose-dependent effect. The benefit of higher doses of baclofen was further demonstrated in a double-blind RCT, where doses up to 270 mg/day (mean 180 mg/day) resulted in significant higher abstinence rates compared with placebo.<sup>19</sup> However, in a recent study, we could not replicate this finding,<sup>20</sup> but there were three important differences between the studies: our dosage was lower (up to 150 mg), patients received cognitive behavioral therapy (CBT) (not in the study of Müller *et al*), and had lower drinking levels before treatment. Due to these contrasting results, further studies have to be awaited to draw final conclusions about the efficacy of baclofen in the treatment of AD. To further illustrate the effect of a high dose of baclofen in the treatment of AD, the present study reports on a successful and interesting case using daily 120 mg of baclofen (as part of an RCT on high-dose effects of baclofen). Besides a strong reduction of alcohol use, a remarkable positive effect on stuttering was observed.

**CASE PRESENTATION**

A 61-year-old Irish man attended an outpatient addiction treatment clinic (The Home Clinic) in the Netherlands for the treatment of AD. At first glance, he looked rather thin and this was confirmed by the combination of a height of 190 cm and a weight of 75 kg (body mass index=20.8). The patient reported to be socially isolated, unable to work and having lost several relationships. During the first visit, the patient showed withdrawal symptoms and reported daily drinking of 2–3 L of wine. He reported to have drinking problems for the last 20 years. In the past, he received several inpatient and outpatient treatments consisting of detoxification and rehabilitation followed by a maximum period of 30-month abstinence. The patient had no somatic problems, but reported sleeping problems and a history of depression, treated with 45 mg mirtazapine for 1 year. The treating physician further noted that the patient



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was stuttering, which the patient himself perceived as 'a problem of finding the right words in a foreign language, not facing the problem in his native language'.

In November 2014, the patient decided to participate in a double-blind, placebo-controlled RCT that was conducted to study the efficacy of high doses of baclofen for the treatment of AD (Netherlands Trial Register, number NTR3681; for a detailed description see Beraha *et al*<sup>20</sup>). The patient met all inclusion and none of the exclusion criteria of that study and informed consent were obtained.

## TREATMENT

Baclofen treatment was started with 10 mg baclofen orally three times a day. During the first week, the patient continued taking 30 mg/day. Depending on the occurrence of side effects and the level of craving, from the second week on, the dosage was increased with 10 mg baclofen every other day, resulting in an increase of the dose with 30 mg/week (following study protocol). After the 6-week titration period, the patient reached a dose of 120 mg/day and he continued taking this dosage during the 10-week high-dose phase until the end of the study.

## OUTCOME AND FOLLOW-UP

After a 14-day detoxification period with 10 mg diazepam daily as necessary, injections of 300 mg intramuscular thiamine for 3 days followed by four times 25 mg oral thiamine, vitamin B complex and ascorbic acid, the patient started with the baclofen titration. In the first week, taking 30 mg of baclofen, the patient reported drinking two glasses of wine on two separate occasions but completely stopped drinking thereafter for the whole study period of 16 weeks. Interestingly, when the patient reached 90 mg baclofen/day, the physician recognised that the patient stopped stuttering. However, the patient reported sleepiness, stiff muscles and heavy legs as prolonged side effects, starting at a dose of 90 mg/day. At the end of the study, the patient wished to reduce baclofen because of side effects, and the dose was reduced with 10 mg every 2 days. Once he completely stopped taking baclofen, the patient relapsed to a daily intake of 2 L of wine. In addition, he started to stutter again. Therefore, the physician advised to restart the treatment with baclofen, and the baclofen dose was titrated up to 90 mg/day, followed by a period of prolonged abstinence and cessation of stuttering.

## DISCUSSION

This case illustrates the potential efficacy of high-dose baclofen treatment of patients with AD. Although baclofen was effective in reducing alcohol intake in this patient, he reported some important adverse events, including sleepiness, stiff muscles, and heavy legs. Because of these side effects, the dose of baclofen was tapered down to 0 mg, which resulted in a relapse to excessive alcohol use comparable to the time before starting the treatment. Unexpectedly, the high dose of baclofen was associated with a cessation of the patient's stuttering. When baclofen dosage was tapered down or stopped, stuttering reappeared but disappeared again when baclofen treatment resumed.

Three possible explanations for the positive effect of baclofen on stuttering are discussed. First, since it is assumed that one important factor in stuttering is muscle tension<sup>21</sup> and baclofen is known as a muscle relaxant, the cessation of stuttering could be related to the relaxation of muscles in the region of the respiratory muscles or in the neck or face.<sup>21</sup> Furthermore, earlier studies show that baclofen leads to a reduction of anxiety in patients with a history of AD,<sup>12-14 22</sup> and it is suggested that baclofen

might be more effective in patients with AD with comorbid anxiety.<sup>23</sup> Since it has been shown that anxiety is closely related to stuttering,<sup>24</sup> baclofen could also have reduced stuttering through a reduction of anxiety. Another possible explanation is the indirect effect of baclofen on the dopamine system. It has been shown that stuttering is related to higher levels of dopamine activity<sup>25</sup> and that dopamine antagonists like haloperidol or risperidone can improve stuttering.<sup>26</sup> Baclofen will lead to a stimulation of GABA-B receptors, resulting in the inhibition of dopamine release in the surrounding dopaminergic neurons, which in turn may cause an amelioration of stuttering.

The patient himself perceived his stuttering as a problem of finding the right words and reported not facing the problem in his mother tongue. However, his environment also recognised the spontaneous cessation of stuttering. Since stuttering was

## Patient's perspective

- ▶ The worst side effects which I experienced were pain in all my joints, severe constipation and sleepiness (somnolence). The severe sleepiness was experienced when I used mirtazapine 45 mg/day in combination with baclofen. Mirtazapine causes increase in appetite + sleepiness during the first hour or so and seemed to work stronger in combination with high-dosage baclofen (+70 mg/day). All of these combined caused an increase in my body weight (from 65 to 75 kg) during the first couple of months. Sleepiness and overeating ceased when I stopped or decreased my dosage of mirtazapine. In June 2016, I tapered down my baclofen from 60 mg/day to zero. I was comfortable with 60 mg/day with no disturbing side effects, although I did lack some energy, considering eating a healthy diet and plenty of vitamin supplements but was concerned about slightly low blood pressure and heart rate (nothing severe) and somehow felt I could do without baclofen. So I discussed it with my physician who advised me to stop. I continued using mirtazapine 30 mg/day and do so up to today. I have had no return of comorbid anxiety which always led to a relapse previously whenever I stopped using baclofen. I feel I have learnt how to pace myself somehow. There are moments where I can sense nervousness or anxiety coming on or can predict a possibility of anxiety depending on my task for the day. At these moments I use baclofen 10–20 mg and it helps me get through the day amazingly. This happens on average once or twice a week. Even though the taste, effect and consequences of drinking alcohol do not appeal to me anymore, I have on two occasions at social gatherings indulged in a couple of beers, mainly to test myself and see how I would react. I did feel totally confident and in control when I made this decision and without fear somehow. The results were I did not enjoy the taste so much that warming feeling felt uncomfortable and I could just stop after a couple (2–3) of bottles and not drink again or have any desire to drink.
- ▶ Stuttering: Personally, as mentioned in the report, I think my stuttering had a lot to do with finding the right words when speaking Dutch. Also, anxiety and nervousness played a key role, especially on my first few weeks visiting my physician at The Home Clinic. Detoxification was also the cause for anxiety and nervousness, which slowly ceased as my baclofen dosage increased. At present I do not have any problems with stuttering.

Learning points

- ▶ High-dose baclofen is a non-registered but promising treatment of alcohol dependence (AD). However, currently there is only one study demonstrating the efficacy of a high dose of baclofen in the treatment of AD, with no indication of a clear dose–response effect,<sup>17 19</sup> and one study with negative findings, which suggests that baclofen might only work on certain subgroups.<sup>18 20</sup>
- ▶ Based on this case study, baclofen might have beneficial effects on stuttering either through muscle relaxation, reduction of anxiety, or indirect dopaminergic inhibition.
- ▶ Further research is warranted using larger samples and placebo-controlled studies.

always accompanied with alcohol use and the cessation of stuttering followed a decrease in alcohol use, it cannot be excluded that stuttering was caused by excessive alcohol use and just quitting drinking helped overcome stuttering instead of baclofen. To disentangle alcohol use and stuttering, it would be of great importance to study the effect of baclofen in participants who stutter without drinking problems.

**Contributors** EB, PB, WvdB and RW contributed to the planning, conception and design of the work, as well as to the acquisition and the interpretation of data. EB, PB, WvdB and RW contributed of the drafting of the work and revising it critically for important intellectual content. The submitted version is approved by EB, PB, WvdB and RW, and all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Competing interests** I serve as an investigator of a trial of ecopipam in stuttering which is not related to this case report.

**Patient consent** Obtained.

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