

## Review Article

# Baclofen-Induced Manic Symptoms: Case Report and Systematic Review

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**Background:** The gamma-aminobutyric acid type B receptor agonist baclofen is approved for spasticity and is used off-label for diverse types of addictive disorders, notably alcohol dependence. Baclofen may induce numerous neuropsychiatric adverse drug reactions, including behavioral disinhibition. However, this precise adverse drug reaction has never been assessed using either a validated causality algorithm or a scale for manic symptoms. **Methods:** We report a case of a 49-year-old male patient who exhibited *de novo* mania during treatment with baclofen for alcohol dependence. Symptoms were evaluated using the Young Mania Rating Scale, and the causality of baclofen was determined using the Naranjo algorithm. This case was also compared with other cases of baclofen-induced

mania through a systematic literature review. **Results:** Mr. X, taking 180 mg/d of baclofen, presented with mania and scored 24 of 44 on the Young Mania Rating Scale, and the imputability of baclofen was “probable” using the Naranjo algorithm (8 of 13). In addition, 4 other cases of baclofen-induced mania were reported in the literature; 3 cases had a bipolar I disorder history. Baclofen-induced manic symptoms occurred mostly during the dose-escalation phase. **Conclusion:** Baclofen-induced manic symptoms may appear in patients with or without bipolar disorder. Particular attention is required during the dose-increase phase and in patients with a history of mood disorders.

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## INTRODUCTION

Baclofen is a gamma-aminobutyric acid type B (GABA-B) receptor agonist that has been approved in the treatment of spasticity for more than 35 years.<sup>1</sup> Recently, baclofen has also emerged as a promising treatment for alcohol dependence.<sup>2</sup> Although the most notable findings have concerned low-dose baclofen, i.e., 30 mg/d for abstinence maintenance,<sup>3</sup> a growing off-label practice has arisen, consisting of prescribing very high doses of baclofen (HDB), i.e., more than 100 mg/d and sometimes up to 400 mg/d, with the aim of reducing and controlling alcohol consumption.<sup>4–7</sup> Historically, this HDB-prescribing practice essentially emerged in France, following the singular history of a French cardiologist, Olivier Ameisen, who had alcohol consumption problem and claimed he had become

indifferent to alcohol craving because of HDB.<sup>8</sup> Ameisen wrote a best-selling book that disseminated the practice of HDB among French physicians.<sup>6,9</sup> Currently, running trials in France aim to better

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determine the true efficacy and safety of HDB in patients with alcohol-use disorder (AUD). Until then, HDB remains a widespread but entirely empirical prescribing practice. Recently, published case series and cohort studies on HDB efficacy have provided a low level of evidence in support of the use of HDB. Moreover, numerous safety concerns have emerged since 2011, notably in the case of baclofen intoxication.<sup>10,11</sup> In both its approved and off-label indications, baclofen has been reported to induce numerous specific adverse drug reactions, including dose-dependent drowsiness,<sup>12</sup> seizure vulnerability,<sup>13,14</sup> and the risk for triggering specific pharmacologic withdrawal syndrome.<sup>13,15</sup> To date, the harm-benefit balance of HDB in AUD remains unclear.<sup>16</sup>

Baclofen has been previously reported in neurologic indications for inducing behavioral disinhibition and mania-like symptoms. In this article, we report a new case that was carefully assessed for mood symptoms and that was, for the first time, also assessed with a validated imputability tool. In addition, we conducted a systematic review of other cases reported in the international literature to elucidate the clinical characteristics and etiopathogenesis of baclofen-induced mood disturbances.

## METHODS

First, we report the follow-up of a 49-year-old white male with alcohol dependence in whom DSM-IV-TR criteria (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision) for mania developed under HDB. We assessed the time course of symptoms using the Young Mania Rating Scale, which is an 11-item clinician-rated scale designed to assess severity of manic symptoms and is widely used in research and clinical practice.<sup>17</sup> Additionally, the imputability of baclofen treatment was evaluated using the Naranjo algorithm,<sup>18</sup> which is one of the most used and validated tools for determining the causality of adverse drug reaction.<sup>19</sup>

In August 2013, we conducted a systematic review of baclofen-induced elevated mood disturbances. Articles were obtained from the PubMed electronic database. The literature search was performed using the following Mesh heading: “baclofen” and (“mania” or “hypomania” or “bipolar” or “manic” or

“disinhibition”). We also used the related-articles function of the PubMed database and the reference list of retained studies. We included only data published in English and in peer-reviewed journals.

## RESULTS

### Case Description

Mr. X, a 49-year-old white male, presented with no prior somatic or psychiatric history except for alcohol dependence. Mr. X's lack of psychiatric history was confirmed by his spouse. He reported a 20-year history of problematic alcohol consumption, with an average daily drinking range of 150–200 g of alcohol. Baclofen was introduced to reduce alcohol consumption. Baclofen was introduced slowly to reduce the occurrence of adverse effects related to baclofen drowsiness.<sup>20</sup> After 5 months of baclofen use, we observed no effect on Mr. X's level of alcohol consumption. As the treatment was well tolerated, we continued with a progressive dose increase. Suddenly, after Mr. X reached the dose of 180 mg/d, we were alerted by his family. Within a week, he experienced a state of behavioral disinhibition with inflated self-esteem, decreased need for sleep by approximately 3 hours per night, increased loquacity, flight of ideas, and distractibility. Although he was married, he had subscribed to an adult dating website and was planning to meet new sexual partners. Finally, during the same period, he had been caught stealing books from a library. We quickly confirmed that he appeared to meet criteria for a manic episode and he scored 24 of 60 on the Young Mania Rating Scale.

Because Mr. X had no history of mood disorder and based on previous literature reports, we immediately identified baclofen as the possible mania-inducing agent. To avoid the baclofen-specific withdrawal syndrome, which can occur if baclofen is stopped too quickly, we tapered his treatment over 5 days. To reduce harm, we proposed that Mr. X be committed to the hospital. However, his family refused and preferred that he stay at home and be regularly re-evaluated by our team. We prescribed 20 mg/d of olanzapine and 150 mg/d of oxazepam but he never took these prescriptions. Nevertheless, the Young Mania Rating Scale score decreased to 10 of 60

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