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Commentary

Does baclofen have antidepressant qualities?



Le baclofen a-t-il des qualités antidépresseurs ?

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Enclosed to this Encéphale issue, Drs Rivollier and Masson published a new case report of baclofen-induced manic symptoms (BIMS). This article adds up to five previously published cases of BIMS [1–5]. Triggering hypomania or mania is a common side effect among all the drugs exhibiting antidepressant properties [6,7]. This thus raises the question of whether baclofen might possess a therapeutic potential for depression.

Baclofen is a gamma amino-butyric acid type B (GABA-B) receptor agonist that was approved in the treatment of spasticity in the 1970s [8]. It has also recently emerged as a promising treatment for alcohol dependence [9]. In this later indication, a growing practice has arisen consisting of prescribing very high doses of baclofen (HDB), i.e., more than 100 mg per day and sometimes up to 400 mg per day, with the aim of reducing and controlling alcohol consumption [10]. These very HDB prescriptions have been reported to be the most likely to induce BIMS [1]. This might suggest that the putative antidepressant effect of baclofen could also be dose-related.

Pre-clinical studies also found that baclofen can produce the characteristic behavioural effects usually observed with other antidepressant drugs. Indeed, baclofen (0.25 mg/kg) decreased immobility time in animals during the forced swimming test (FST), which is considered to reflect antidepressant properties [11]. Furthermore, it has also been demonstrated in humans and animal models that baclofen can promote excitability and seizure generation with a concentration-dependent effect [12]. Interestingly, this is a core property shared with other antidepressant drugs such as tricyclic antidepressants [12].

The mechanisms through which baclofen may have antidepressant or switching properties remain unclear. It has been observed that baclofen has a complex and indefinite action on both the dopaminergic and serotonergic systems [1] that are also involved in the efficacy of antidepressant drugs [6,7]. Indeed, GABA-B receptor agonists accelerate noradrenaline turnover by changing the firing rate of GABA neurons without changing postsynaptic receptor density and diminish serotonin liberation by up-regulating serotonin (5HT₂) receptors [13].

These various arguments may support the possibility of testing baclofen in future human studies as a novel antidepressant agent. If

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this antidepressant efficacy is confirmed in future studies, it needs to be emphasized that the HDB prescription in this antidepressant indication should be balanced with numerous safety concerns, notably baclofen intoxication [14,15]. Furthermore, baclofen has been reported to induce numerous specific neuropsychiatric adverse drug reactions, including dose-dependent drowsiness [16], seizure vulnerability [17,18], and the risk of triggering specific pharmacological withdrawal syndrome [19,20]. In the particular case of patients with bipolar disorders, the use of high dosages of baclofen requires particular attention and should not be prescribed without a mood stabilizer. Moreover, the safety issues that may occur with HDB have recently appeared to be more sustained among patients with borderline personality disorder [21] which has sometimes been considered to belong to the same disorder spectrum as bipolar disorder [22].

Despite these tolerability features, the practice of using HDB for alcohol dependence seems to have generated a large enthusiasm in France not only among psychiatrists but also general practitioners and addiction specialists [23,24]. Before initiating specific clinical trials for assessing the antidepressant properties of baclofen, it could be a first step to investigate whether the depression scores improve along baclofen treatment in patients with alcohol dependence, independently or not of the alcohol outcome. Previous studies have already shown that anxiety was decreased by low dose baclofen among such patients which appeared to directly affect the drinking outcome [25].

Baclofen is a surprising psychotropic molecule whose therapeutic prospects in the psychiatric field have surely not yet been totally explored. If the initial use of baclofen for alcohol dependence was made by the team of Giovanni Addolorato in Italy [26], French clinicians were the first to use HDB in clinical practice following the personal account of Olivier Ameisen [27]. Consequently, France has been accumulating empirical and scientific experiences on HDB. It is to be wished that the possible HDB effect on depression be investigated by a French team.

Authors' contributions

P.A. Geoffroy and B. Rolland participated in the manuscript redaction and approved the final version of the manuscript.

Disclosure of interest

P.A. Geoffroy declares that he has no competing interest.

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