



Baclofen: a new drug for the treatment of alcohol dependence

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SUMMARY

Recent preclinical and clinical studies have suggested that baclofen, the prototypic γ -aminobutyric acid B (GABA_B) receptor agonist, is a promising pharmacological compound for use in the treatment of alcohol dependence. In particular, baclofen has been found to suppress symptoms of alcohol withdrawal syndrome with an efficacy comparable with that of the 'gold standard' diazepam. Moreover, baclofen has proven effective in the prevention of relapse due to its ability to reduce alcohol intake and craving in

alcoholic patients. Baclofen proved to be manageable, producing no significant side effects and displaying no addictive properties. The efficacy of the drug in the management of both alcohol withdrawal syndrome and relapse prevention should entail a vastly simplified pharmacotherapy of alcohol dependence.

Keywords: Baclofen; γ -aminobutyric acid B receptor; alcohol dependence; craving; relapse prevention; alcohol withdrawal syndrome; delirium tremens

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INTRODUCTION

Approximately 4% of the global burden of disease can be attributed to alcohol consumption (1). Alcohol dependence (also termed alcoholism) constitutes the most serious alcohol use disorder (AUD), affecting nearly 14% of the general population (2). In addition to alcohol dependence, unhealthy alcohol consumption includes other AUDs such as alcohol abuse and the less severe – but more frequent – heavy drinking (3). The high prevalence rate of unhealthy alcohol consumption highlights the importance of this issue for public health and socioeconomic impact (1).

Consequently, the availability of an appropriate treatment for AUDs is of critical importance in public health issues. Among the currently available strategies, pharmacological approaches are thought to represent an effective instrument not only for the treatment of alcohol-related emergencies, such as alcohol intoxication and alcohol withdrawal syndrome (AWS), but also for management of relapse prevention, in this case complementing psychosocial interventions (4).

Over the last few years, many potentially useful drugs for the treatment of alcohol dependence have been tested both in preclinical and clinical studies. Among the latter,

the prototypic γ -aminobutyric acid B (GABA_B) receptor agonist, baclofen, is apparently characterised by a favourable profile. Baclofen is at present used to control spasticity (5). Recent preclinical studies and clinical data have shown that baclofen may be effective in the treatment of alcohol dependence, both in AWS and in relapse prevention. These data are summarised and discussed in the present review.

PRECLINICAL DATA

The 'anti-alcohol' profile of baclofen has been characterised using multiple experimental procedures intended to model different aspects of the human disease. Specifically, non-sedative doses of baclofen – as well as other GABA_B receptor full agonists and positive allosteric modulators – have been found to suppress: (a) acquisition of alcohol drinking behaviour in alcohol-preferring rats exposed to the choice between two bottles containing an alcohol solution and water, respectively (6); (b) daily alcohol intake in alcohol-experienced rats (i.e. rats in which the consumption of pharmacologically relevant doses of alcohol was already established before baclofen administration, representing a model of the 'active drinking' phase of human alcoholism) tested under the two-bottle choice regimen (7,8); (c) extra-amount of alcohol consumed by alcohol-preferring rats after a period of alcohol abstinence (model of the loss of control over alcohol and the episodes of alcohol relapse of human alcoholics) (9); (d) increase in alcohol intake induced in alcohol-preferring rats by the administration of opioids and cannabinoids (10); (e) oral self-administration of alcohol in

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rats trained to press a lever to gain access to alcohol (11–15); (f) motivational properties of alcohol in rats, measured by the extinction responding procedure, i.e. the maximal amount of 'work' that rats trained to lever-press for alcohol are willing to perform to obtain alcohol (a validated experimental model of craving for alcohol) (16); (g) development of tolerance to the motor-incoordinating effects of alcohol in mice tested on a rotating drum (17); (h) severity of different signs of AWS in rats made physically dependent on alcohol (8); (i) alcohol-induced stimulation of locomotor activity (i.e. the animal correlate of alcohol's euphorogenic properties) in mice (18–20).

With regard to the possible mechanism of action by which baclofen exerts its reducing effect on alcohol consumption and alcohol's motivational and reinforcing properties, a recent preliminary microdialysis experiment demonstrated that baclofen suppressed alcohol-stimulated dopamine release in the shell of the nucleus accumbens of rats (21). Different lines of experimental evidence suggest that mesolimbic dopamine neurons are involved in the mediation of alcohol intake and reinforcement [see (22)]. Interestingly, GABA_B receptors are located in the ventral tegmental area (the area where mesolimbic dopamine neurons originate), both on the cell body of dopamine neurons and on the terminals of glutamatergic afferent neurons (23). Their activation by GABA_B receptor agonists may exert an inhibitory action on the dopamine neurons (24,25): the possible mechanism through which baclofen suppresses alcohol-stimulated dopamine release and, in turn, dopamine-mediated, alcohol-reinforced and -motivated behaviours. Finally, with regard to baclofen efficacy on AWS, it has been hypothesised that baclofen-induced activation of GABA_B receptors might counterbalance AWS-associated, enhanced function of NMDA-mediated glutamate excitatory neurotransmission, resulting in an attenuation of alcohol withdrawal symptomatology (8).

CLINICAL DATA

Alcohol Withdrawal Syndrome

Alcohol withdrawal syndrome is a life-threatening condition affecting alcohol-dependent patients on discontinuation or decrease of their alcohol consumption (26). Symptoms usually develop within 6–24 h of the last drink (27) and include – in light to moderate forms – the presence of raised blood pressure and pulse rate, tremor, hyperreflexia, irritability, anxiety and depression. These symptoms may progress to more severe forms including seizures and delirium, coma, cardiac arrest and death, occurring in 5–10% of patients (28–31). The main objectives of the clinical management of AWS are to minimise the severity of symptoms, prevent the occurrence of more severe withdrawal manifesta-

tions, such as seizures and delirium, and facilitate admission of the patient into a treatment programme in an attempt to achieve and maintain long-term abstinence from alcohol (32). Clinical evaluation of AWS symptoms can be performed by several scales, such as the Withdrawal Syndrome Scale for alcohol and related psychoactive drugs (33) and the Clinical Institute Withdrawal Assessment for Alcohol-revised scale (CIWA-Ar) (34). In particular, the latter represents a scoring system for the quantitative evaluation of the physical symptoms of withdrawal syndrome; only subjects with a CIWA-Ar score >10 points (defined as moderate or severe AWS) require pharmacological treatment for AWS.

In addition to the administration of fluids, thiamine and electrolytes, benzodiazepines (e.g. diazepam 100–120 mg/day; chlordiazepoxide 300–500 mg/day) currently represent the drugs of choice in the treatment of AWS (35,36). However, benzodiazepines display addictive properties which constitute a major limitation to their use in subjects affected by AUDs (36,37). Thus, the discovery of potentially useful and manageable drugs for the treatment of AWS is of considerable practical importance.

With regard to the potential use of baclofen in AWS, a first open clinical study showed how baclofen rapidly suppressed symptoms of severe AWS (38). Specifically, five patients with a CIWA-Ar score higher than 20 were treated with baclofen (10 mg orally administered every 8 h). A rapid decrease of the CIWA-Ar score and a marked improvement in AWS symptoms were observed shortly after baclofen administration in all patients. In particular, a rapid decrease in several withdrawal symptoms, such as anxiety and agitation, was observed. These data are of interest as a rapid improvement of patient's distress may facilitate her/his transition into a long-term rehabilitation programme (32).

Subsequently, the successful treatment of a case of severe AWS complicated by delirium tremens (DT) with baclofen has been reported (39). AWS and DT symptoms were rapidly suppressed by the oral administration of baclofen 25 mg every 8 h for the first 3 days, subsequently tapering the dose to 10 mg every 8 h. Following drug discontinuation, AWS and DT symptoms did not recur.

The efficacy of baclofen in the treatment of AWS has recently been compared with that of the 'gold standard' diazepam in a randomised study that enrolled 37 alcohol-dependent patients with AWS (40). Baclofen ($n = 18$; 30 mg/day for 10 consecutive days) and diazepam ($n = 19$; 0.5–0.75 mg/kg/day for six consecutive days, tapering the dose by 25% daily from day 7 to day 10) significantly decreased both total CIWA-Ar score (Figure 1) and CIWA-Ar subscales for sweating, tremors, anxiety and agitation, with no significant differences between the two treatments, suggesting that the efficacy of baclofen in treatment of AWS was comparable with that of diazepam.

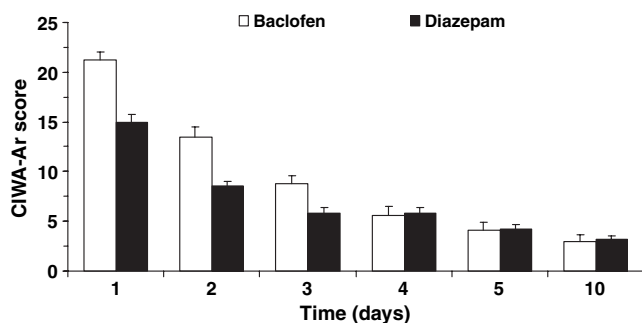


Figure 1 Score of the Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) scale in patients treated for 10 consecutive days with baclofen or diazepam. CIWA-Ar administration occurred once a day, on days 1, 2, 3, 4, 5 and 10, immediately before the first daily administration of drugs (scoring of day 1 acting as baseline). Reprinted from: Addolorato et al. (40), © 2006 Elsevier, with kind permission from Excerpta Medica, Inc.

Prevention of Relapse

After achieving relief from AWS, the main objective in the clinical management of alcohol dependence is to move patients into a treatment programme aimed at promoting alcohol abstinence and relapse prevention. These programmes are usually based on psychological and social interventions, but should also provide for specific pharmacological treatment. Indeed, although psychosocial treatments result in a reduction of alcohol consumption and maintenance of abstinence in some patients, up to 70% of patients treated by means of psychosocial therapy alone resume alcohol drinking within a year (41). Pharmacotherapy should be considered as a tool to increase the efficacy of psychosocial treatments, and high priority should be given to investigations testing novel and potentially effective medications (42).

Over the last few years, considerable emphasis has been placed on 'craving', defined as an uncontrollable desire to take a substance, a desire which, if not satisfied, provokes physical and psychological suffering, often accompanied by asthenia, anorexia, anxiety, insomnia, aggressiveness and depression. Craving is now considered as a core symptom of the disease and has become a critical target for potential pharmacotherapies (43).

Several GABAergic compounds seem to be promising anti-craving drugs (44). Among these medications, baclofen is of potential interest. A first pilot open-label study performed in alcoholic patients showed how the oral administration of baclofen at a dose of 15 mg/day for the first 3 days and 30 mg/day for a subsequent 27 days, fractioned in three times per day, was capable of reducing alcohol intake and craving for alcohol (45). After the obtaining of these initial data, the efficacy of baclofen was evaluated in a double-blind randomised controlled study, which enrolled

39 alcohol-dependent patients randomly divided into two groups of $n = 19-20$ (46).

The study results indicated that the percentage of dropouts was lower in the baclofen group respect to the placebo group; a significantly higher percentage of patients achieving and maintaining abstinence throughout the experimental period were found in the baclofen group compared with subjects treated with placebo. Baclofen was effective in reducing daily alcohol intake within the first week of treatment (Figure 2). In patients who continued to drink, baclofen was still effective in reducing daily alcohol consumption. Cumulative abstinence duration (CAD) was significantly higher in baclofen- than placebo-treated patients. Score of Obsessive Compulsive Drinking Scale (OCDS), a widely used scale for measuring craving (47), was constantly lower in baclofen than placebo group. A significant effectiveness of baclofen in reducing both compulsive and obsessive components of craving was also found (Figure 3).

More recently, a further open-label study confirmed the effects of the 12-week administration of the drug in reducing alcohol intake and craving (48). The drug (30 mg/day) was administered to 12 patients undergoing four sessions of motivational enhancement therapy. A significant reduction in the number of drinks per drinking day and heavy drinking days was found. Significant decreases in anxiety and craving were also recorded.

Finally, a self-case report has recently been published by a physician with a long history of alcohol dependence, who achieved and maintained complete alcohol abstinence using remarkably high doses of baclofen (49). It is noteworthy how no drug (including naltrexone and acamprosate) taken previous to baclofen had exerted any beneficial effect. *Vice versa*, baclofen produced immediate relief of the physician's dependence on alcohol (49).

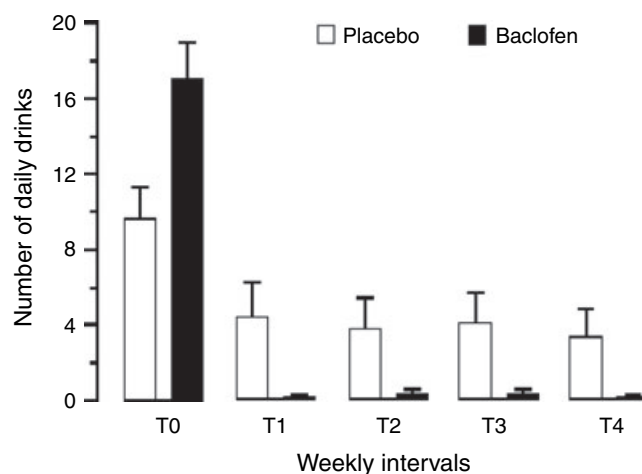


Figure 2 Number of daily drinks in baclofen and placebo groups at T0 (baseline) and over the four weekly visits (T1-T4). Reprinted from Addolorato et al. (46), © 2002 Oxford University Press, with kind permission from Oxford University Press

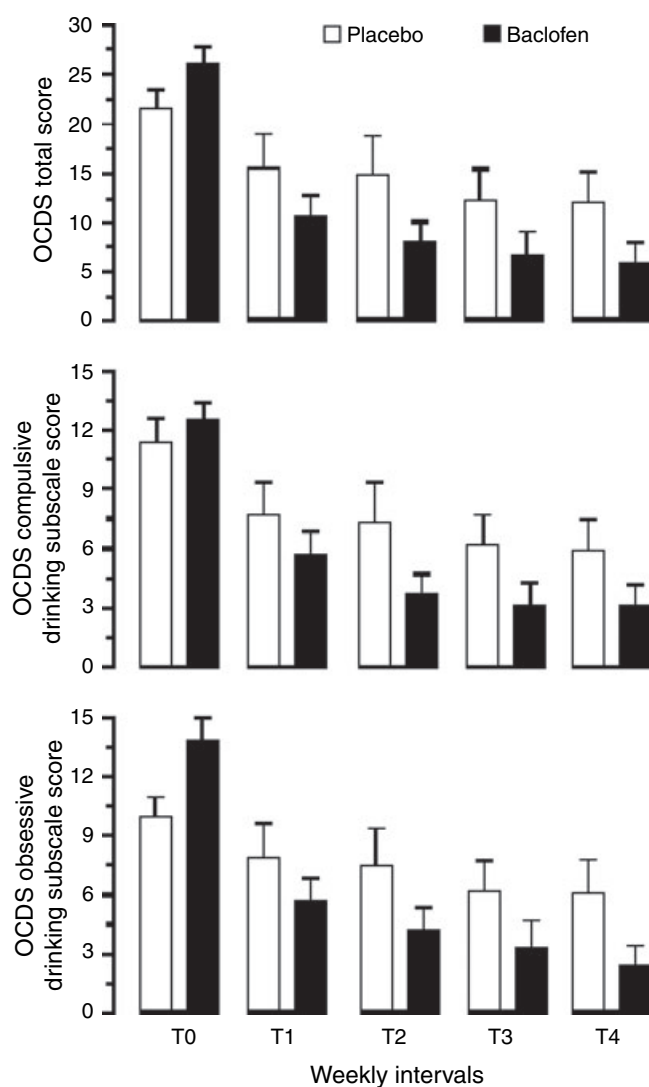


Figure 3 Score of Obsessive Compulsive Drinking Scale (OCDS) total (top panel), OCDS Compulsive Drinking subscale (centre panel) and OCDS Obsessive Drinking subscale (bottom panel) scores in baclofen and placebo groups at T0 (baseline) and over the four weekly visits (T1–T4). Reprinted from Addolorato et al. (46), © 2002 Oxford University Press, with kind permission from Oxford University Press

Manageability and Safety of Baclofen in Alcoholic Patients

Baclofen has been employed for years as a particularly manageable and safe antispasticity drug (5). Likewise, throughout all the abovementioned clinical studies investigating baclofen efficacy in alcohol dependence (38–40,45,46,48), the drug proved to be manageable and did not produce any significant side effect. Specifically, no sedation or respiratory disorders were observed and no systemic or single-organ events leading to drug cessation were reported. The manageability and safety of baclofen in the treatment of alcohol dependence is supported by

the self-case report on the complete and prolonged suppression of alcohol consumption achieved with high doses of baclofen (49).

Tolerability was fair in all baclofen-treated patients included in the above surveys. Interestingly, we recently observed a fair degree of tolerability in patients previously treated with baclofen who subsequently required a new cycle of baclofen for a sudden episode of alcohol craving; none of these patients displayed severe side effects or reported drug-induced sedation and all continued their usual daily activity (this laboratory, unpublished results). These observations might be explained hypothesising the development of cross-tolerance between the sedative effects of alcohol and those of baclofen, which would persist even after long periods of abstinence.

Finally, no patient treated with baclofen reported either drug-induced euphoria or other pleasurable effects or any degree of craving for the drug. On discontinuation of baclofen, no drug withdrawal syndrome and/or side effects due to drug suspension were observed. The absence of addictive properties of baclofen represents a feature of paramount importance for the pharmacological treatment of alcohol addicted patients.

CONCLUSIONS

Baclofen displayed proven efficacy in reducing the main components of craving (obsessive and compulsive), in suppressing alcohol intake and relieving AWS symptoms. Although future studies involving large number of patients should be conducted to confirm the present findings, these observations suggest a possible role for baclofen in the treatment of patients affected by alcohol dependence, also in view of its acknowledged manageability and safety.

From a clinical point of view, it is of interest to note how the use of baclofen expedited the treatment of patients affected by AWS in an outpatient setting. This led to a considerable decrease in treatment costs compared with those incurred in the case of inpatient treatment of AWS.

Finally, the suppressing effects exerted by baclofen on craving for alcohol and drinking during AWS feature baclofen as a promising and unique pharmacotherapy for use in the treatment of alcohol dependence. This drug is of particular interest in view of its efficacy on two major aspects of the disorder, namely AWS and maintenance of abstinence. This specific ability of baclofen is expected to result in a vastly simplified pharmacotherapy of alcohol dependence and higher compliance to treatment.

DISCLOSURES/CONFLICT OF INTEREST

The authors have declared that they have no interests which may be perceived as posing a conflict or bias.

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