

ORIGINAL ARTICLE

Clinical Experience with Baclofen in the Management of Alcohol-Dependent Patients with Psychiatric Comorbidity: A Selected Case Series

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Abstract — **Aims:** To illustrate the potential indications for, and adverse effects of, baclofen pharmacotherapy for alcohol dependence in patients with co-existing psychiatric illness. **Methods:** Audit of the files of alcohol-dependent patients treated for comorbid non-psychotic psychiatric illness in a specialist detoxification unit with integrated outpatient treatment. Files were selected of patients who had been offered treatment with baclofen because other alcohol pharmacotherapies had previously been unsuccessful in preventing relapse or were contraindicated. **Results:** Of the 21 selected patients, 13 attended for outpatient treatment, with follow-up periods ranging from 4 days to 27 months, and the outcomes could be rated. Prescribed baclofen doses ranged from 30 to 275 mg daily. Common side effects at lower doses included tiredness and sedation; one patient on 120 mg/day developed reversible severe back pain, and a patient taking up to 275 mg/day developed somnolence, dizziness and incontinence. Seven patients maintained significant periods of abstinence, and one patient reduced daily consumption to non-problematic levels. Two patients consumed an overdose of other central nervous system (CNS) depressants, while taking baclofen in the first week of treatment, were briefly unwell, were given emergency monitoring, but made a full recovery. **Conclusion:** While more than half the patients reported significant reduction in alcohol use, it is not possible to draw definite conclusions about the effectiveness of baclofen, given that it was combined with other psychiatric and alcohol treatments, and because there was no control or comparison group. We recommend caution when offering baclofen to patients with a history of recurrent overdosing or a history of other substance misuse. When prescribing in conjunction with other medications with CNS depressant action, close monitoring is recommended at initiation and during dose escalation.

INTRODUCTION

The gamma-aminobutyric acid (GABA)-B receptor agonist, baclofen, is a muscle relaxant introduced in the 1960s for the treatment of muscle spasticity due to spinal cord injury, multiple sclerosis and cerebral injuries resulting in spasticity (Dario and Tomei, 2004; Leo and Baer, 2005). Recent randomized controlled trials (RCT's) have also found baclofen to be effective in treating patients with alcohol dependence (Addolorato *et al.*, 2002, 2007, 2011). The anti-craving and anti-reward effects of baclofen appear to relate to its agonist effect on GABA-B receptors in the ventral tegmental area, which are reported to control the activity of mesolimbic dopamine neurons, one of the major pathways in the regulation of the reinforcing properties of drugs of addiction (Addolorato *et al.*, 2002; Colombo *et al.*, 2004).

The Addolorato studies found doses of 10 mg three times daily (tds) to be effective and well-tolerated, even in patients with significant liver disease. Addolorato *et al.* (2011) also found provisional evidence of a dose–response effect, with the effect of baclofen 20 mg tds being greater than baclofen 10 mg tds. Individual case reports (Ameisen, 2005; Bucknam, 2007) have documented reduction and suppression of cravings for alcohol with much higher doses of baclofen, up to 270 mg daily, but such high doses have not been systematically studied.

A meta-analysis by Bouza *et al.* (2004) outlines the effectiveness of naltrexone and acamprosate as adjuvant treatments for alcohol dependence in adults, with a moderate effect size. Both drugs are safe and reasonably well-tolerated, although high levels of non-compliance with treatment are common. However, most studies select medically stable

patients with no other comorbidities or dependencies. At the same time, the literature indicates that comorbid psychiatric disorders are common with alcohol dependence (Regier *et al.*, 1990; Kessler *et al.*, 1994) and these disorders often predict a poorer prognosis and a shorter time to relapse into drinking (Rounsaville *et al.*, 1987; O'Sullivan *et al.*, 1988; Murphy *et al.*, 1992; Cornelius *et al.*, 2003).

No studies have yet investigated the potential effectiveness and safety of baclofen in improving drinking outcomes in patients with comorbid psychiatric disorders. Preliminary reports have indicated its potential usefulness in improving psychiatric symptoms, with reports of baclofen improving panic symptoms, Post-traumatic stress disorder and state anxiety (Breslow *et al.*, 1989; Krupitsky *et al.*, 1993; Addolorato *et al.*, 2002; Drake *et al.*, 2003; Ameisen, 2005). Agabio *et al.* (2007) reported almost complete suppression of alcohol use in an alcohol-dependent patient with schizophrenia, on 75 mg of baclofen daily.

In this paper, the authors summarize their clinical experience with the use of baclofen in a selected group of patients with alcohol dependence and comorbid non-psychotic mental illness, through retrospective file audit. Tolerability and safety of this medication in a group of complex patients on other psychotropic medication were of particular interest.

PATIENTS AND METHODS

All patients described in this case series required admission to a 15-bed inpatient withdrawal ('detoxification') unit, which provides a Statewide service for patients with a comprehensive range of substance use disorders.

In 2008, pharmacotherapy options for alcohol dependence prescribed after withdrawal included acamprosate, naltrexone and disulfiram. Patients were discharged on one or more of these medications as part of a comprehensive aftercare programme, including counselling, rehabilitation, medical review and recovery groups.

In 2009, baclofen was introduced as an alternative pharmacotherapy for patients reluctant to use or unable to afford disulfiram (not subsidized in Australia), and with limited response or contraindications to the use of other pharmacotherapies. Pregnant patients and those with a history of epilepsy were excluded from baclofen treatment. Precautions taken to limit the risks of intoxication, suicide attempts and/or adverse side effects included provision of limited medication supplies at discharge (weekly pharmacy dispensing), initiating treatment with low doses, gradually titrating the dose upwards and regular outpatient monitoring.

Baclofen was initiated once the patient had undergone alcohol withdrawal, usually 3 or more days after the last drink. The dose prescribed was 5 mg tds for 3 days, then 10 mg tds as the usual maintenance dose. The final stabilization dose of baclofen prescribed was at the discretion of the treating clinician, based on clinical response including side effects. Adverse reactions to baclofen were recorded, including reasons for discontinuation of treatment. All patients were offered a comprehensive treatment programme after withdrawal, including individual counselling and medical review. Patients were also encouraged to attend Alcoholics Anonymous (AA) and rehabilitation.

Of the 541 admissions to the unit in 2009, 288 were for patients with alcohol dependence (Fig. 1). Of these 288 admissions, 126 patients had one or more non-psychotic comorbid mental health disorders, in the form of depressive disorder, anxiety disorder/s and bipolar disorder.

Of these 126 patients, (a) 57 had no previous treatment with alcohol pharmacotherapy, and selected acamprosate, naltrexone, disulfiram or no treatment, with General Practitioner review after discharge; (b) 18 patients had had prior pharmacotherapy and selected one of these options with General Practitioner review; (c) 30 patients were inaccessible for follow up (lived outside the local catchment area, were transferred to rehabilitation centres or refused follow up); (d) 21 patients had prior unsuccessful treatment with and/or contraindications to standard alcohol pharmacotherapy, had received a range of other alcohol treatment modalities, were on concurrent psychotropic medication, were available for clinic follow up and provided informed consent for treatment with baclofen. These patients were provided with detailed information about baclofen, including the risks and benefits, and recent studies of baclofen in alcohol dependence. Four of these patients had other coexisting substance use disorder/s, including two on opioid substitution treatment.

The following demographic and clinic data were collected: age, gender, severity and duration of alcohol dependence, baseline alcohol use, previous treatments, alcohol-related problems, comorbid medical and psychiatric conditions, other substance use disorders, psychotropic medication, psychosocial and forensic history, duration of follow up and alcohol consumption at follow up.

RESULTS

Eight of the 21 patients were lost to clinic follow up. Five of these patients transferred to their General Practitioner or a residential rehabilitation service for follow up, while a further three patients offered clinic follow up did not attend appointments.

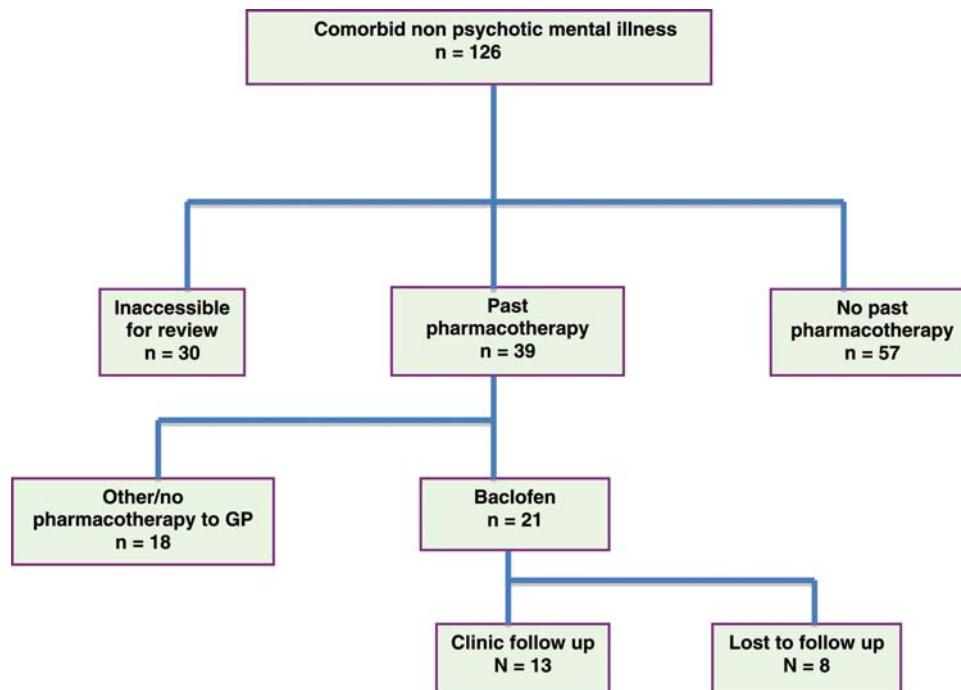


Fig. 1. Diagram on selection of alcohol-dependent patients for baclofen treatment.

Thirteen patients attended for comprehensive outpatient care (Table 1), with a mean age of 49 years (range 41–62 years). Ten patients were male and three female. The mean duration of alcohol dependence was 15 years (range 2–32 years). Baseline daily alcohol consumption ranged from 110 to 400 g daily. Thirteen patients had a depressive disorder and eight of those also had a co-existing anxiety disorder (including Post-traumatic Stress Disorder, Generalized Anxiety Disorder, Social Anxiety Disorder, Panic Disorder). Nine patients reported significant suicidal ideation prior to treatment. Patients were on a range of psychotropic medications, as outlined in Table 1.

Follow-up periods ranged from 4 days to 27 months, with two patients relapsing immediately after discharge, both non-compliant with baclofen. Alcohol consumption during follow up is outlined for each patient in Table 1, indicating total number of drinking days for the follow-up period, as well as amounts of alcohol consumed during those drinking days. The term 'relapse' is used to indicate a return to drinking at pre-treatment levels.

Baclofen doses prescribed by the clinic ranged from 30 to 275 mg daily, administered in three divided doses. Of note, patient 5's General Practitioner independently reduced the baclofen dose to 10 mg daily, adding naltrexone 50 mg daily.

Side effects ranged from mild and transient at lower doses to more problematic at higher doses. The most common side effects were tiredness and sedation. Several patients reported a gradual reduction in anxiety as a positive side effect. One patient developed severe back pain at doses of 120 mg and above, despite no evident spinal pathology. The pain resolved completely with cessation of the drug, and was only mild in nature when baclofen was reinstated. The other patient noted increased tiredness and somnolence, with occasional bedwetting and dizziness at 275 mg of baclofen, and at times he felt close to fainting. These symptoms settled on doses of 200–250 mg, with limited return of cravings. This patient is described in detail below.

Two patients experienced an overdose of other central nervous system (CNS) depressants in combination with baclofen in the first week of treatment, both requiring emergency review, with full recovery. One of these cases is described in detail later.

Case 1

Mr A (Patient 2, Table 1), a 44-year-old single man, had a 16 year history of alcohol dependence, drinking 150–300 g of alcohol daily. A previous 6-months period of abstinence was associated with severe alcohol cravings. Acamprosate had been ineffective. Psychiatric history included depression with chronic suicidality, and panic attacks with agoraphobia. Mr A could not attend AA due to disabling panic attacks when he left the house. While Mr A reported a reduction in cravings and alcohol consumption on baclofen 175 mg daily, drinking continued at 150 g daily. Baclofen dose was gradually titrated to 275 mg daily with weekly reviews, at which point all cravings for alcohol were suppressed, despite exposure to previous drinking cues. At this dose, Mr A experienced increased tiredness, somnolence with occasional bedwetting and dizziness, which led him to feel he might faint. He was able to maintain abstinence on lower doses of

baclofen, but found that cue-related cravings were more evident with baclofen doses below 200 mg daily. Ongoing major depression and severe panic attacks required treatment with mianserin and alprazolam as well as cognitive therapy. Mr A has been abstinent from alcohol for 16 months.

Case 2

Mr B (Patient 12, Table 1), a 47-year-old male beneficiary, presented with a 7-year history of alcohol dependence, drinking 240 g of alcohol daily at presentation. Mr B had multiple previous detoxification and rehabilitation admissions, as well as unsuccessful treatment with acamprosate. Mr B had a history of chronic opioid dependence successfully managed with methadone then buprenorphine, and was Hepatitis C positive. At presentation, he was injecting methamphetamine fortnightly and was abstinent from illicit opioids for many years. Psychiatric history included borderline and antisocial personality disorder, and he was on venlafaxine XR 225 mg daily. Chronic suicidal ideation had resulted in multiple suicide attempts, but none recently. Mr B was stabilized on baclofen 10 mg tds. He reported acute anxiolytic effects at this dose, rapidly escalating the dose in the first week of treatment, without consultation. After taking 80 mg of baclofen over 90 min in combination with prescribed buprenorphine and venlafaxine, as well as diazepam he had at home (dose unknown), he became sweaty, dizzy, ataxic and disoriented. He collapsed briefly and required emergency department admission overnight, with full recovery. Mr B denied this was a deliberate overdose, denied alcohol use and said he escalated the dose for its anxiolytic effects. Daily doses of baclofen were arranged through a pharmacy. He reported no alcohol use when on baclofen, because of the reduction in his anxiety. Mr B disengaged from treatment after further requests to increase the dose were refused, obtaining baclofen from a different doctor and pharmacy. Within a month he was hospitalized for alcohol withdrawal.

DISCUSSION

There is a growing literature assessing the safety and effectiveness of naltrexone and acamprosate in comorbid psychiatric conditions. Petrakis *et al.* (2005) randomized 178 patients with major depression to treatment with disulfiram, naltrexone, placebo and a combination of disulfiram/naltrexone. All groups showed high rates of abstinence, with the active medication groups showing greater improvement, but no advantage for the combination group. Pettinati *et al.* (2010), in a double blind placebo-controlled trial, found that depressed alcohol-dependent patients had higher rates of abstinence and more resolution of depressive symptoms with a combination of sertraline and naltrexone. Latt *et al.* (2002) noted a significant improvement in depression scores during alcohol dependence treatment in both naltrexone and placebo groups. However, a significantly greater number of patients in the naltrexone group had Beck Depression Inventory scores exceeding 20 at 3 months. The authors advised ongoing monitoring of depression in alcohol-dependent patients in treatment with naltrexone.

The effectiveness and safety of naltrexone in patients with bipolar disorder and alcohol dependence have also been

Table 1. Characteristics of alcohol-dependent patients with psychiatric comorbidity on baclofen with clinic follow up

	Age, sex	Baseline daily alcohol	Duration dependence	Concurrent problems	Comorbid diagnoses	Other psycho-tropics	Length follow up	Total drinking days; amount per day (grams)	Daily baclofen dose	Baclofen side effects	Reported effect on alcohol cravings
1	47, F	320 g	7 years	Hypertension	Depression	Fluoxetine 20 mg	18 months	0 days	50–70 mg	Drowsy unless taken with food	Total suppression of cravings
2	44, M	150–300 g	16 years	Homeless	Depression	Mianserin 100 mg	16 months	0 days	150–275 mg	275 mg daily: somnolence, dizziness, bedwetting	275 mg total suppression cravings
				Unemployed	Panic disorder	Alprazolam 2 mg tds					
3	43, M	110 g	9 years	Suicidal ideation Unemployed	Panic disorder	Paroxetine 40 mg	29 weeks	0 days for 23 weeks. Relapse from week 24	30 mg	Forgetful	Reduced craving. Relapse after baclofen ceased
				Gastric ulcer Anaemia Unemployed	Social phobia Depression GAD, depression	Escitalopram 40 mg	15 weeks	0 days	30 mg	Reduced anxiety. Mild headache, tiredness	Not stated
4	62, M	150 g	30 years	Suicidal ideation Suicidal ideation Unemployment	Codeine misuse THC dependence Depression Complex PTSD Chronic Hepatitis C	Paroxetine 20 mg Naltrexone 50 mg	7 weeks	0 days	10–30 mg	Nil reported	Not stated
5	51, M	180–240 g	9 years	Suicidal ideation	Depression	Citalopram 20 mg	23 weeks	6 days: 30–120 g	30–60 mg	Reduced anxiety	Reduced cravings; greater effect at 60 mg
				Drink driving charge Gastritis Unemployment	Depression	Mirtazapine 60–90 mg	27 months	First 12 months: 9 drinking days (45–150 g), second 15 months 0 days	30 mg	Transient sedation, dizziness, 'speed like' effect at initiation	Total suppression of cravings
				Depression Suicide attempt	Opioid dependence Chronic Hepatitis C THC dependence	BPN 4 mg					
6	57, M	300 g	32 years	Suicidal ideation	Depression	Desvenlafaxine 50–100 mg	20 weeks	140 days: 30–40 g	100–150 mg	>120 mg severe back pain; resolved on cessation; mild pain on reinstatement	Marked reduction in cravings
				Repeated ED visits Divorced, homeless	Gambling						
7	41, M	300–400 g	2 years		Depression, Anxiety	Sertraline 50 mg	14 days	Lapse at day 14; 20 g	30 mg	Transient tiredness Improved sleep & anxiety	Reduced cravings
8	47, F	150–200 g	12 years		Depression	Citalopram 60 mg	7 days	Relapsed day after discharge	30 mg	Never took baclofen	
9	50, F	150–200 g	20 years	Suicidal ideation Multiple ED visits Withdrawal seizure	Panic disorder Depression Anxiety	Olanzapine 5 mg Fluoxetine 20 mg	7 days	Relapsed day after discharge	30 mg	Never took baclofen	

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12	47, M	240 g	7 years	Multiple past suicide attempts Unemployed	Borderline, Antisocial PD Depression Opioid dependence Chronic Hepatitis C	Venlafaxine XR 225 mg BPN 32 mg	2 months 0 days for 2 months	30 mg	Acute anxiolytic effect: rapid unapproved dose escalation Polypharmacy overdose	Reduced cravings
13	47, M	200–400 g	8 years	Accidental overdoses Suicidal ideation	Depression GAD, Social phobia	Venlafaxine 150 mg	4 days 4 days: amount unknown	30 mg	Polypharmacy overdose	None

PD, personality disorder; BPN, buprenorphine; GAD, generalized anxiety disorder; ED, emergency department; THC, tetrahydrocannabinol.

assessed in several studies (Salloum *et al.*, 2003; Petrakis *et al.*, 2005; Brown *et al.*, 2006, 2009). All studies found naltrexone to be well-tolerated, with reduced drinking days and alcohol cravings. A recent, open-label pilot study of add-on acamprosate in alcohol-dependent bipolar patients found acamprosate to be safe and well-tolerated with likely efficacy in reducing alcohol consumption (Tolliver *et al.*, 2009).

In comparison, detailed studies investigating the potential effectiveness and safety of baclofen in patients with psychiatric comorbidity are lacking. At the same time, baclofen is potentially an important addition to the armamentarium when treating this patient group, when other alcohol pharmacotherapies are not beneficial or inappropriate.

The patients presented in this case series all had comorbid mental illness treated with psychotropic medication, and would normally be excluded from RCT's, yet are commonly patients encountered in day-to-day practice. While previous studies (Addolorato *et al.*, 2007, 2011; Garbutt *et al.*, 2010) found baclofen to be well-tolerated, the patients were a highly selected group, and more likely to have lower rates of adverse effects than patients with more complex comorbidities. While baclofen was generally well-tolerated in the group of patients we have described here, transient side effects were common—particularly, tiredness and sedation. Two patients experienced problematic side effects at higher doses of 120 and 275 mg.

In the general literature, the incidence of adverse effects with oral baclofen has been reported as 10–75% (Dario and Tomei, 2004), usually with doses greater than 60 mg daily. The most common side effects are sedation or somnolence, weakness, vertigo, nausea, dry mouth and psychological disturbances. Side effects can be minimized by initiating treatment with low doses and gradually titrating the dose upwards. Sedation and unsteadiness are likely to be exacerbated with concurrent alcohol consumption (Rossi, 2010). Baclofen has also been reported to cause impairments of cognitive function—particularly, confusion—in up to 11% of patients in controlled studies (Jones and Lance, 1976; Skausic and Korsgaard, 1977; Sandyk and Gillman, 1984) and this adverse event should be closely monitored for.

The majority of neuropsychiatric effects reported in the literature involve rapid dose reduction or abrupt cessation of baclofen. A review by Leo and Baer (2005) found that such psychiatric symptoms were consistent with delirium, and included hallucinations (auditory, visual, tactile), delusional beliefs, confusion, disorientation, fluctuating level of consciousness, anxiety, agitation and formal thought disorder. These symptoms were associated with autonomic changes, seizures, spasticity and sometimes dyskinesia. Other possible causes for delirium had been eliminated, and the delirium abated rapidly after reinstatement with the usual dose of baclofen. Abrupt cessation of baclofen is more likely to increase the risk of withdrawal delirium, and discontinuation by gradual tapering over several weeks is recommended. Cases reviewed by Leo and Baer (2005) had a minimum of 5 months of treatment with baclofen, and it has been suggested that delirium is unlikely with abrupt cessation after only 1–2 months of exposure (Terrence and Fromm, 1981). Withdrawal delirium did not appear to be dose-dependent,

with a range of doses from 10 to 160 mg daily (mean 70.3 mg/day).

There are also limited reports of adverse psychiatric effects associated with ongoing baclofen use rather than withdrawal. [Dario and Tomei \(2004\)](#) noted rates of depression from 1.7 to 6.2%. Other case reports have noted the development of psychiatric symptoms with complete resolution after baclofen cessation. The psychiatric sequelae include psychotic depression (one case: [Sommer and Petrides, 1992](#)), catatonia (one case: [Pauker and Brown, 1986](#)) and psychosis (two cases: [Roy and Wakefield, 1986](#); [Chawla and Sagar, 2006](#)). One case of acute mania in paranoid schizophrenia has been reported ([Wolf *et al.*, 1982](#)) and one case of mania precipitated by baclofen in a bipolar patient ([Yassa and Iskadar, 1988](#)).

Two of the patients in this series experienced an overdose of baclofen in combination with other CNS depressants in the first week of treatment, despite close monitoring and supervision. One patient with a prior history of accidental overdoses took an excessive amount of promethazine and alcohol as well as the prescribed dose of baclofen (30 mg daily), becoming confused and disoriented. He required monitoring in the emergency department overnight and made a full recovery. He was later re-trialled on baclofen after a period of stabilization, but found it unhelpful in managing cravings for alcohol. The other patient (Mr B described earlier) experienced an acute anxiolytic effect from baclofen, which led him to rapidly escalate the dose without consultation, resulting in an overdose in combination with other CNS depressants. While some of the other patients in this series reported a reduction in anxiety on baclofen, it was gradual in onset, unlike the acute effect Mr B experienced. While baclofen is considered to have limited abuse potential ([Evans and Bisaga, 2009](#)), some cases of baclofen abuse have been reported ([May, 1983](#); [Perry *et al.*, 1998](#); [Nasti and Brakoulias, 2011](#)), and clinicians should be vigilant about the possibility of overuse.

Accidental or deliberate overdose of baclofen can cause profound central nervous system depression, including delirium, coma, respiratory depression, seizures, hypotonia, hypothermia and cardiovascular effects, including bradycardia and hypertension ([Perry *et al.*, 1998](#); [Leung *et al.*, 2006](#); [Wall *et al.*, 2006](#)). [Leung *et al.* \(2006\)](#) found that coma, delirium and seizures occurred only with doses of 200 mg or more in adults. The respiratory depression associated with baclofen overdose may be exacerbated by the concurrent ingestion of alcohol ([Van Dierendonk and Dire, 1999](#)) or other sedatives ([May, 1983](#)). Generally, the prognosis with baclofen overdose seems to be good if adequate supportive care is provided, including mechanical ventilation if necessary, until the patient recovers ([Wall *et al.*, 2006](#)). Some patients with a high risk of self-harm or suicide may be unsuitable for treatment with baclofen. Where baclofen is initiated in such patients, high levels of monitoring and supervision should be available, such as daily dispensing of tablets with regular psychiatric reviews.

Notable in this case series is the variation in doses of baclofen tolerated by patients and reported by patients to be helpful in reducing alcohol cravings and consumption, from 30 mg to 275 mg daily. Neurologists have safely used high doses of baclofen, up to 270 mg daily, to treat spasticity ([Smith *et al.*, 1991](#)) and there are case reports in the literature

of high doses used in alcohol dependence ([Ameisen, 2005](#); [Bucknam, 2007](#)). However, there has been no systematic study of safe and effective doses in patients with psychiatric comorbidity.

We recommend that a risk/benefit analysis be conducted to determine the suitability of patients with psychiatric comorbidity for baclofen treatment. In our opinion, baclofen is not a first-line treatment for relapse prevention in alcohol dependence in patients with psychiatric comorbidity. However, baclofen could be considered when first-line agents are ineffective, poorly tolerated or contraindicated. As already mentioned, we recommend caution when offering it to patients with a history of recurrent overdoses or suicide attempts and patients with other unstable substance use disorders. Care should be taken when combining baclofen with other CNS depressants, and monitoring should be more frequent, particularly early in treatment and during dose escalation.

Limitations of this report include the selected nature of the patient group, and the retrospective audit of clinical data. Furthermore, the lack of a control group, and the initiation of psychiatric medication in conjunction with baclofen as part of a comprehensive treatment programme, obviously restrict the report's potential to comment on the efficacy of baclofen in this context.

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