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Baclofen in the short-term maintenance treatment of benzodiazepine dependence

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ABSTRACT

Benzodiazepine (BZD) dependence is a significant public health problem. Apart from the long-term tapering doses of BZD, no other drugs are available for the maintenance treatment of BZD dependence. Baclofen has been used in alcohol and other drug dependence as long-term anti-craving agent. Since alcohol and BZD act through the GABA receptor, we attempted to study the effect of Baclofen as maintenance treatment in a series of five cases with BZD dependence.

Key words: Anti-craving, baclofen, benzodiazepines, dependence, gamma-aminobutyric acid B, maintenance

Introduction

Studies have shown prevalence of long-term benzodiazepine (BZD) use in general population as 2-7.5%.^[1] 15-44% chronic users experience withdrawal symptoms on discontinuation.^[2] Continued BZD use is associated with cognitive side-effects, injuries and accidents and legal complications.^[3]

Current treatments for chronic BZD use and dependence can be categorized as: (a) Gradual tapering of the same BZD, (b) substituting a short-acting agent with a long-acting BZD and slow taper of the same and (c) using specific medication during detoxification and continuing during maintenance phase. A number of medications have been tried for long-term maintenance like anti-depressants, anti-epileptics and Azapirones with no clear evidence of efficacy.^[4]

Baclofen, a stereo-selective Gamma-aminobutyric acid B (GABA-B) receptor agonist had been used in preclinical and clinical studies as anti-craving agent in cocaine, heroin, alcohol, volatile solvent and nicotine

dependence.^[5,6] As both alcohol and BZD are CNS depressants acting through GABA-A receptors^[7] and baclofen is effective in alcohol dependence as an anti-craving agent,^[8] we hypothesized that Baclofen might be beneficial in BZD dependence and present a case series where baclofen was found to be effective.

Case Reports

Case 1

A 45-year male presented with 12 years history of BZD dependence (ICD 10) with average daily intake was 40 mg of Nitrazepam. Withdrawal symptoms were evaluated on Clinical Institute Withdrawal Assessment for Benzodiazepines (CIWA-B)^[9] with a score of 29, indicating moderate withdrawal and significant craving on subjective evaluation. Nitrazepam was tapered and stopped over 3 weeks. He was then started on baclofen 20 mg/day in two divided doses, increased to 30 mg/day after 2 days. His CIWA-B score was 13 after 15 days on baclofen and there was a significant reduction in craving. He remained abstinent from BZD for 6 months and was lost to follow up.

Case 2

A 25-year male presented with BZD and barbiturate dependence for 1 year (ICD 10). For the last 3 months he was taking Nitrazepam 30 mg and Phenobarbitone 180 mg/day. He scored 14 on CIWA B at admission. After admission Nitrazepam and Phenobarbitone were tapered off in 3 weeks and he was then started on

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baclofen 20 mg/day in two divided doses, increased to 40 mg/day after 2 days. After 3 weeks on baclofen his CIWA B score was 0 and no craving for both drugs. He remained abstinent for a follow-up period of a year while on the same dose of baclofen.

Case 3

A 50-year male presented with alcohol and BZD dependence and substance-induced depressive disorder (ICD-10) was taking 100 mg per day of diazepam, which he was unable to stop on account of severe withdrawal. Diazepam was tapered and stopped over 3 weeks. Baclofen was started at 20 mg/day and was increased to 40 mg/day over 1 week. He was also treated with Mirtazapine 15 mg/day for alcohol depression. He reported significant reduction in craving and withdrawal symptoms over the next 3 weeks. His depression remitted within a month after starting treatment and he continues to remain abstinent from BZD and alcohol for almost a year.

Case 4

A 39-year male presented with BZD dependence (ICD-10) for 10 years was taking 10 mg of Alprazolam per day and had severe withdrawal on attempted abstinence. At admission, he was started on 50 mg/day of diazepam based on response on evaluation of withdrawals (CIWA-B), which was tapered and stopped over 3 weeks. He was then started on baclofen 20 mg/day and increased to 40 mg/day over 1 week. He is remaining abstinent on follow-up for a year.

Case 5

A 40-year-old man with BZD dependence for the last 4 years, was taking 100 mg/day of Nitrazepam, which was tapered and stopped over 3 weeks. He was started on baclofen 20 mg/day, increased to 40 mg/day over 1 week. He reported no withdrawal over the next 3 weeks of hospital stay. He has remained abstinent for over 6 months while on the same dose of baclofen.

Informed consent was obtained from all patients before starting baclofen. All patients tolerated baclofen well and did not report any side effects on clinical evaluation.

Discussion

There are multiple mechanisms which might explain baclofen's efficacy for BZD dependence.

- Pre-synaptic GABA-B heteroreceptor activation is shown to decrease excitatory neurotransmitter release. This may explain its efficacy in decreasing withdrawal symptoms^[8]

- GABA-B receptors are located pre-synaptically on dopamine (DA) neurons in ventral-tegmental area (VTA) and post-synaptically on glutamate synapses. Activation of these receptors decreases DA discharge at multiple sites like nucleus accumbens and amygdala. This may explain decreased drug-seeking, reinforcing effects and reinstatement effects^[6]
- Another mechanism of action involves GABA-B agonist, which blocks alcohol-induced potentiation of GABAA transmission, and therefore may regulate behavioral sensitivity to ethanol and BZDs.^[10]

There are certain limitations to our study. As it's a preliminary report there is no control group. Assessment of craving was done based on subjective report. Further, all patients were managed in an inpatient setting which may have influenced the selection and outcome.

Our findings provide preliminary support for the use of baclofen in the short-term management of craving and withdrawal in patients with BZD dependence. Larger controlled trials are required before it can be routinely recommended in BZD dependence.

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