

Baclofen in the Management of Inhalant Withdrawal: A Case Series

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Introduction: Abuse of inhalants and solvents is a significant public health problem. There is no specific treatment for inhalant withdrawal.

Objective: To study the effect of baclofen in treating craving and withdrawal symptoms in patients with inhalant dependence.

Case Reports: Case studies of 3 young male patients with DSM-IV diagnoses of inhalant dependence treated in an inpatient setting with baclofen are presented. All patients had nonspecific withdrawal symptoms in the form of irritability, insomnia, and craving. Baclofen was given in doses up to 50 mg/day and was continued throughout the period of hospitalization.

Discussion: All patients reported significant reduction in withdrawal symptoms within 48 hours of treatment and were free of symptoms for the duration of their hospital stay. One patient continued the medication as an outpatient and has remained abstinent to date. Baclofen was well tolerated by all patients. Our results suggest that baclofen may be an effective treatment modality in this patient population. These effects are possibly due to the agonistic action of baclofen at γ -aminobutyric acid B receptors in the ventral tegmental area.

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The abuse of volatile substances—inhalants or solvents—is a significant public health problem. Data from the National Comorbidity Survey¹ reveal that the aggregate prevalence of inhalant and other controlled substance abuse is as high as 7.5% in adults. There is also evidence of a trend toward increased use among adolescents in the last 2 decades.² Abuse of volatile substances is associated with significant psychiatric comorbidity, especially with externalizing disorders,³ as well as medical morbidity² and an increased risk for the use of other sub-

stances.⁴ Such abuse is also common in developing countries such as India. Although exact prevalence figures are not available, reports suggest that the problem is of considerable magnitude.^{5,6}

Although the exact mechanism by which inhalants exert their effects on the central nervous system is unknown, it is postulated that they, like ethanol, benzodiazepines, and general anesthetics, may hyperpolarize neurons by acting at γ -aminobutyric acid A (GABA_A) receptors.² For example, 1,1,1-trichloroethane, the principal component of typewriter correction fluid, reversibly enhances GABA_A receptor-mediated synaptic currents in rat hippocampal slices.⁷

The withdrawal syndrome that follows abstinence from inhalants, unlike that of other substances of abuse with GABAergic mechanisms such as ethanol and benzodiazepines, is nonspecific and has not been included in the DSM-IV as a separate entity.² Symptoms include irritability, dysphoria, sleep disturbance, headache, dry mouth, and lacrimation beginning within 24 hours of abstinence and lasting for several days.⁵ There is no definitive treatment for this syndrome, although benzodiazepines have been proposed for this purpose.²

The GABA receptor is the major inhibitory neurotransmitter in the brain and generates both fast and slow inhibitory synaptic activity in many types of neurons. There are 2 major types of GABA receptors—GABA_A and GABA_B—that mediate GABA neurotransmission. The GABA_A (ionotropic) receptors mediate the majority of fast inhibitory synaptic transmission in the mammalian central nervous system.^{8,9} Studies suggest that the behavioral and cognitive effects of ethanol may be mediated via an allosteric potentiation of the postsynaptic GABA_A receptors that mediate fast synaptic inhibition in the mammalian central nervous system. The GABA_B (metabotropic) receptors mediate the slow synaptic inhibitory response of GABA transmission.¹⁰ Most GABAergic synapses contain both presynaptic and postsynaptic GABA_B receptors. Presynaptic GABA_B receptors function as autoreceptors, and their activation inhibits GABA_A inhibitory postsynaptic potentials (IPSCs), whereas postsynaptic GABA_B receptors are primarily coupled to the activation of a potassium channel.¹¹ Although ethanol has little direct

effect on the GABA_B receptor response,^{12,13} blockade of the GABA_B receptor has been shown to increase ethanol potentiation of the GABA_A response.¹⁴

Inhibition of GABA_B receptor function enhances ethanol-mediated potentiation of distal GABA_A IPSCs in inbred long-sleep but not in inbred short-sleep mice.¹⁵ Inbred long-sleep and short-sleep lines of mice differ markedly in their genetic sensitivity to alcohol, and long-sleep mice derive far greater reinforcement from ethanol.¹⁶

Baclofen, a selective GABA_B receptor agonist, has long been used for the treatment of spasticity in a variety of neurologic conditions. Baclofen has been shown to be effective in animal models of alcohol dependence.^{17,18} Human studies suggest that baclofen reduces craving and alcohol intake in patients with alcohol dependence^{19,20} and is effective in suppressing alcohol withdrawal,²¹ including delirium tremens.²² There is preliminary evidence that baclofen may also be of use in the treatment of cocaine dependence.²³ These varied effects may be due to the agonistic action of baclofen at GABA_B receptors in the ventral tegmental area. These receptors control the activity of the mesolimbic dopamine pathway, which is the final common pathway for the reinforcing effects of substances of abuse.²⁴

On the basis of the above findings, we hypothesized that baclofen might be beneficial in treating the symptoms of inhalant withdrawal as well as in reducing craving. We report 3 patients for whom baclofen was found to be effective who presented to the Deaddiction Centre (National Institute of Mental Health and Neurosciences, Bangalore, India) for treatment.

CASE REPORTS

Case 1

Mr. A, a 21-year-old man, presented with a history of inhalant and nicotine dependence (DSM-IV criteria) for the last 7 years. At the time of the current admission, he was sniffing 5 to 8 bottles of typewriter correction fluid per day. He and his caretakers both described symptoms of craving, irritability, mood swings, dysphoria, and aggression that occurred during periods of abstinence. He had comorbid sensorineural deafness of uncertain etiology. No family history could be collected. He had been admitted 2 years before for the same complaints but was not given any medications at that time and had relapsed immediately after discharge.

In view of his severe withdrawal symptoms, which had triggered his relapse, the patient was given baclofen 10 mg/day after written informed consent was obtained. This dose was slowly increased to 50 mg/day over the next week. Mr. A reported feeling significantly better within 48 hours of admission and was essentially asymptomatic by the end of 1 week. This improvement was

maintained until he was discharged. Keeping in mind his past relapse, we decided to continue treatment with baclofen 50 mg/day on an outpatient basis to reduce craving. In view of persisting mild depressive symptoms, escitalopram 5 mg/day was added to his regimen. Mr. A has been adherent to medications, attends regular follow-ups, and has remained abstinent to date.

Case 2

Mr. B, a male adolescent aged 17 years, presented with a 2-year history of inhalant and nicotine dependence (DSM-IV criteria). He reported symptoms of intense craving, irritability, insomnia, anorexia, and anger whenever he tried to abstain from inhalants and at presentation was sniffing up to 300 mL of glue per day. Family history was positive for nicotine dependence in a first-degree relative. There was no history of abuse of any other substances.

After obtaining consent from the patient and his parents, Mr. B was treated with baclofen 10 mg/day, which was titrated upward to 50 mg/day over the next week. He reported significant improvement in craving after 48 hours. Craving was absent at the end of 10 days, and insomnia and anorexia also improved. At the time of discharge, Mr. B did not report any craving for inhalants.

Case 3

Mr. C, a 20-year-old man, presented with a history of abuse of multiple substances. He met DSM-IV criteria for inhalant and nicotine dependence. He reported occasional use of cannabis, not amounting to dependence, and satisfied criteria for adult attention-deficit/hyperactivity disorder and dissocial personality disorder. There was no history of comorbid alcohol dependence or abuse. Mr. C had faced social and legal problems as a result of his substance use. There was a family history of delusional disorder in a first-degree relative and bipolar affective disorder with inhalant abuse in another first-degree relative. At presentation, he had been huffing 3 to 4 boxes of correction fluid per day for the last 4 years. He reported withdrawal symptoms in the form of irritability, insomnia, anger outbursts, and craving for inhalant.

With the informed consent of the patient, baclofen was initiated at 10 mg/day and gradually increased to 50 mg/day in 3 divided doses. This regimen resulted in a significant decrease in the above symptoms as reported by the patient as well as by his parents and the nursing staff. He was discharged while taking the same medication but soon relapsed and required rehospitalization 8 months later. In view of baclofen's earlier beneficial effect, Mr. C was again given baclofen 40 mg/day, and he subsequently reported a significant decrease in craving. Mr. C remained abstinent from substances for a month but relapsed thereafter.

DISCUSSION

Although inhalant abusers do not always experience significant withdrawal symptoms, it has been recommended that these patients be closely monitored as if they were being treated for alcohol withdrawal. Some authors suggest there is no role for medication in inhalant abuse treatment,²⁵ and there are no studies that have looked at treatment of these symptoms.²

Benzodiazepines have been recommended in the treatment of inhalant withdrawal.² However, there is insufficient evidence regarding their safety and efficacy. In addition, this group of patients may be at a higher risk of developing dependence on benzodiazepines.

Baclofen is a GABAergic medication whose mechanism of action is distinct from that of benzodiazepines, and it does not have reported abuse potential. Baclofen's mechanism of action involves GABA_B agonism that blocks alcohol-induced potentiation of GABA_A transmission and therefore may regulate behavioral sensitivity to ethanol.²⁶ The GABA_A receptor is also a pharmacologic target of inhalant action.²

Available literature shows that patients with alcohol dependence receiving baclofen achieved reduction in intake or abstinence within the first week of treatment and maintained this improvement throughout the treatment period.¹⁹ Baclofen also has a suppressant effect on craving and withdrawal symptoms. A recent study²¹ demonstrated that baclofen is comparable with the "gold standard" benzodiazepine diazepam in terms of safety and efficacy in treating alcohol withdrawal. In addition, case reports suggest that even high doses of baclofen (up to 270 mg/day) given for several weeks are well tolerated, reduce craving for alcohol, and are not associated with a potential for abuse.^{27,28}

On the basis of its efficacy in alcohol-dependent subjects, we hypothesized that baclofen would be a safe and effective alternative to benzodiazepines in the management of inhalant withdrawal and craving. The 3 patients included in this report presented to our center with a primary diagnosis of inhalant dependence. They all described a withdrawal syndrome that was nonspecific; insomnia and irritability were the most common symptoms and caused significant distress to the patients. All 3 patients reported a significant decrease in craving and withdrawal symptoms within 48 hours of starting baclofen. This improvement was maintained throughout the duration of treatment. The medication was well tolerated by all patients.

Certain limitations need to be mentioned. There is no objective scale for the measurement of inhalant withdrawal symptoms, and, therefore, medication titration was based on clinical indicators (patient report and clinician observations), with the final dose being higher than

that tried in previous studies of alcohol withdrawal.²¹ In addition, the presence of comorbid diagnoses in our patients suggests that the improvements seen may not apply to patients with solvent dependence alone. Pre-treatment with baclofen has been shown to reduce, in a dose-dependent manner, the nicotine-, morphine-, and cocaine-evoked dopamine release in the shell of the nucleus accumbens in rodents. This ability of baclofen to modulate the mesolimbic dopaminergic transmission might indicate baclofen as a putative candidate in the pharmacotherapy of polydrug abuse.²⁹ Also, the first patient received concomitant escitalopram, and it is unclear if this contributed to his prolonged abstinence. Finally, the benefits seen with acute baclofen treatment were not sustained in the third case.

Our findings provide preliminary support for the use of baclofen in the management of craving and withdrawal in patients with inhalant dependence and possibly in relapse prevention. However, larger controlled trials are required before baclofen can be widely recommended in the treatment of inhalant dependence.

Drug names: baclofen (Lioresal, Kemstro, and others), diazepam (Valium and others), escitalopram (Lexapro and others).

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