

Withdrawal: Another Danger of Diversion

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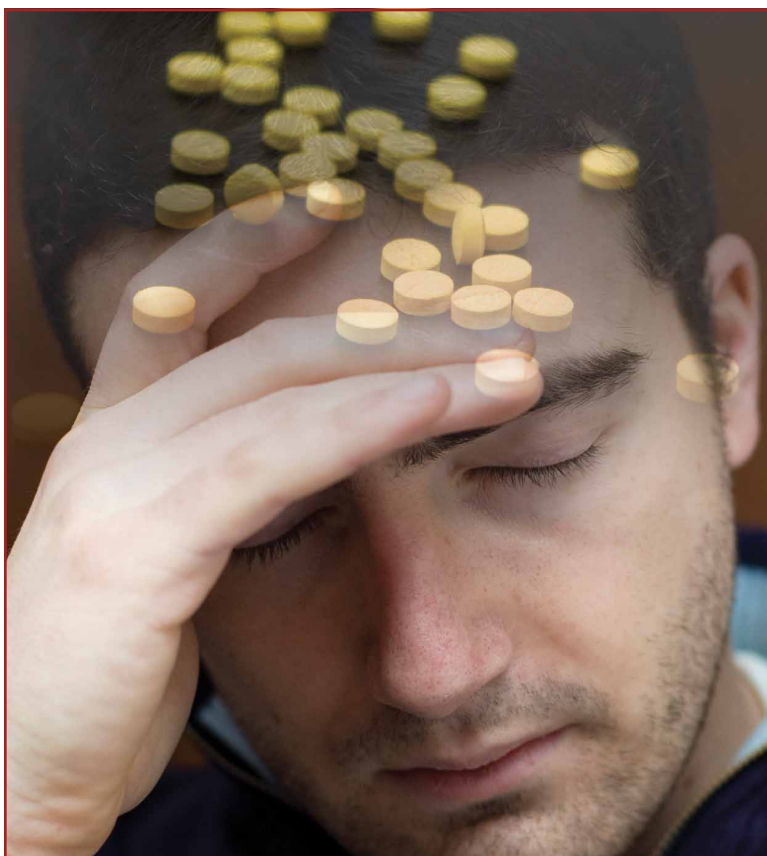
A 34-year-old man with a history of substance abuse presented for evaluation after experiencing a witnessed seizure.

Case

A 34-year-old man with a history of poly-substance abuse presented to the ED after he had a seizure during his regular methadone-treatment program meeting. While at the clinic, attendees witnessed the patient experience a loss of consciousness accompanied by generalized shaking movements of his extremities, which lasted for several minutes.

Upon arrival in the ED, the patient stated that he had a mild headache; he was otherwise asymptomatic. Initial vital signs were: blood pressure, 126/80 mm Hg; heart rate, 82 beats/minute; respiratory rate, 16 breaths/minute; and temperature, 97.3°F. Oxygen saturation was 98% on room air, and a finger-stick glucose test was 140 mg/dL.

Physical examination revealed a small right-sided parietal hematoma. The patient had no tremors and his neurological examination, including mental status, was normal. When reviewing the patient's medical history and medications in the health record, it was noted that the patient had a prescription for alprazolam for an anxiety disorder. On further questioning, the



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patient admitted that he had sold his last alprazolam prescription and had not been taking the drug for the past week.

What characterizes the benzodiazepine withdrawal syndrome?

Benzodiazepines (BZDs) are a commonly prescribed class of sedative-hypnotic medications that have an expansive number of clinical indications for use. Through their agonism at the γ -aminobutyric acid (GABA)-chloride channel complex, BZDs hyperpolarize neurons and reduce their excitability. As with other GABAergic agents, BZDs are associated with the development of physiological dependence and tolerance, and the need for an escalating dose over time is expected.

Although introduced into clinical practice in the 1960s, the potential for dependence and a withdrawal syndrome was not appreciated until the early 1980s. This clinical syndrome can manifest with a wide variety of findings, most commonly with what are termed “rebound effects” or “rebound hyperexcitability.” These effects include anxiety, insomnia or sleep disturbance, tremulousness, irritability, sweating, psychomotor agitation, difficulty in concentration, nausea, weight loss, palpitations, headache, muscular pain and stiffness, or generalized weakness.² More severe manifestations include delirium, seizures, or psychosis. Often, these symptoms and signs may be confused with the very manifestations that prompted the initial use of the BZD, a reemergence of which can exacerbate the withdrawal syndrome.

When does benzodiazepine withdrawal occur?

The exact time course of BZD withdrawal can vary considerably and, unlike alcohol withdrawal (which occurs from a single compound, ethanol), can be difficult to characterize. The onset of withdrawal symptoms is dependent on a number of factors, including the half-life of the BZD

involved. For example, delayed onset withdrawal symptoms of up to 3 weeks after cessation of the medication are described with long-acting BZDs such as chlorthalidone and diazepam. Conversely, symptoms may present as early as 24 to 48 hours after abrupt termination of BZDs with shorter half-lives, alprazolam and lorazepam. This variable time of onset differs considerably from other withdrawal syndromes, notably ethanol withdrawal. While both syndromes correlate to the individual patient’s severity of dependence, alcohol withdrawal follows a more predictable time course.

Some authors distinguish a rebound syndrome from a true withdrawal syndrome, the former of which is self-limited in nature and the result of cessation of treatment for the primary disease process. In this model, rebound symptoms begin 1 to 4 days after the abrupt cessation or dose reduction of the BZD, and are relatively short-lived, lasting 2 to 3 days.²

What is the appropriate treatment for benzodiazepine withdrawal?

The standard therapy for almost all withdrawal syndromes is reinstatement of the causal agent. A number of non-BZD-based treatment strategies have been investigated, and all have met with limited success. Of these, anticonvulsant drugs such as carbamazepine and valproic acid were initially considered promising based on case reports and small case series.⁴ These medications ultimately proved ineffective in randomized, placebo-controlled studies.⁵ β -Adrenergic antagonists, such as propranolol, have been studied as a method to normalize a patient’s vital signs but also proved nonbeneficial in managing withdrawal.^{5,6}

The safest and most effective management approach for patients with BZD withdrawal is reinstatement of the BZD followed by a prolonged and gradual tapering until cessation, if that is desired.^{1,2,5,6} While all BZDs share structural and mechanistic similarities, there are subtle variations within

this class that can affect their pharmacologic effects. These structural differences may result in incomplete cross-tolerance, which may lead to inadequate mitigation of the withdrawal syndrome. For example, previous reports suggest that alprazolam and clonazepam are structurally unique and bind to the BZD receptor with higher affinity than other BZDs. Therefore, while in general any BZD can be used to treat withdrawal from another BZD, it is recommended to treat withdrawal from these two agents with the implicated BZD.

There are, however, limitations to this approach. Namely, some BZDs are only available in oral formulations (eg, alprazolam and clonazepam) or the BZD of choice may not be readily available or on formulary within a given institution. In a patient with a severe withdrawal syndrome where it is not feasible or potentially harmful to administer an oral medication, it is reasonable to provide parenteral (preferably intravenous [IV]) BZD therapy. The optimal approach is to start with a small “standard” dose and titrate to effect while monitoring for adverse effects (eg, oversedation, ventilatory depression). Redosing should be triggered by symptoms or signs, and not performed in a timed or standing-order fashion. If this approach proves ineffective and withdrawal symptoms persist despite adequate BZD therapy, a direct GABA ago-

nist such as propofol is a sensible alternative or adjuvant treatment. This may sound similar to the management of patients with ethanol withdrawal; indeed, this approach is essentially the same, with the exception of the more drawn-out time course.

Case Conclusion

After arrival in the ED, the patient received diazepam 10 mg IV and was subsequently admitted to the hospital for further evaluation. During his hospitalization, the patient was re-started on his usual dose of oral alprazolam. No further withdrawal syndrome was observed, and he was discharged on hospital day 2 with a plan to slowly taper his alprazolam dose with his outpatient psychiatrist.

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