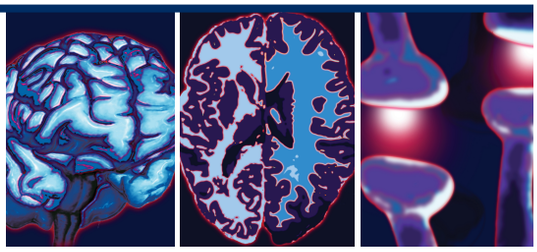
EDITORIAL



Benzodiazepines: tackling the symptoms of withdrawal

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"With such high levels of prescription it is not surprising that benzodiazepine dependence is common; cutting across all socioeconomic levels."

Benzodiazepines (BZDs) are compounds that are still widely used as anxiolytics and hypnotics because of their low cost and low toxicity. They have also been mainly used to prevent the symptoms of alcohol withdrawal. Globally, BZDs remain one of the most prescribed medications, especially in the primary care setting [1].

The adverse effects of these drugs have been extensively documented and their effectiveness is being increasingly questioned. Despite repeated recommendations to limit BZDs to short-term use (2–4 weeks), doctors worldwide are still prescribing them for months or years. With such high levels of prescription it is not surprising that BZD dependence is common; cutting across all socioeconomic levels. Their use continues to excite controversy; many countries have drawn their attention to the risks of dependence. To avoid any risk of dependence it would be necessary to select patients presenting with anxiety without mood disorders or hysteria. Various arguments have been developed to explain their continuous use [2]:

- Resurgence of anxiety after withdrawal;
- Unpleasant withdrawal effects;
- Fear of withdrawal;
- No clear treatment duration told by the physician to the patient;
- Sociological phenomenon.

Are there predisposing factors to dependence? Indeed, if one considers that not all patients receiving BZDs become dependent, even though the treatment is of short duration, the patient vulnerability to develop dependency must be considered. Unfortunately, this is often not the case. Views differ from expert to expert and from country to country as to the extent of the problem, or even whether long-term BZD use actually constitutes a problem [2].

The prevalence of withdrawal syndromes or symptoms that may arise when BZDs are abruptly stopped, has been estimated

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to be between 0 and 100% according to studies [3]. Approximately 40% of patients who have received BZDs for at least 6 months present with some withdrawal syndromes after abrupt treatment interruption. The most frequently observed withdrawal symptoms are tremors, confusion, anxiety and insomnia. Severe symptoms such as convulsions and psychotic reactions can occur, as well as a substantial increase in blood pressure or an increased risk of myocardial ischemia. Few withdrawal studies have been conducted in elderly subjects. As compared with young adults, elderly subjects present less severe withdrawal symptoms, however, psychotic withdrawal symptoms might be more significant.

Withdrawal symptoms may be linked to hyperactivities of the noradrenergic, serotonergic and cholinergic systems whose activities have previously been inhibited by the chronic administration of BZDs. In elderly subjects, plasma BZD levels decrease at a lower rate as compared with younger adults, which may explain the fact that withdrawal symptoms are less severe [4].

Given the high morbidity/mortality risk associated with BZD use, especially in elderly populations, the benefit of BZD use in those populations is not clear. Cumming and Le Couteur stated that older subjects should be rarely prescribed with BZDs and that, in those already taking with BZDs, these treatments should be interrupted under appropriate supervision, mainly during hospitalization [5].

Pharmacokinetic factors, such as half-life duration, can play a role in withdrawal syndromes after abrupt BZD cessation. Indeed, BZDs with a short half-life may carry a higher risk of withdrawal symptoms. Short or intermediate half-life BZDs may be associated with withdrawal symptoms 24–36 h after interruption, while long half-life BZDs may be associated with withdrawal symptoms only 1 week after cessation and the relationship between the symptoms, and BZD withdrawal is not always established. The use of long-term treatment, especially with high BZD doses, may increase the risk as well.

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Clinical factors (i.e., premorbid personality disorders and especially passive, dependent personality traits, previous alcohol use or a low education level) may also play an important role in the risk of occurrence of withdrawal symptoms and may increase the severity of symptoms.

Different studies have reported designs to help clinicians to adequately withdraw BZDs, especially in elderly patients. In particular, Baillargeon *et al.*, using a method based on a combination of cognitive–behavioral therapy and BZD tapering, have concluded that this combination was superior to gradual tapering alone in the management of patients with insomnia and chronic BZD use [6]. Petrovic *et al.* proposed an initial replacement therapy with low-dose BZDs (lormetazepam 1 mg) [7]. This treatment is preferred over a placebo since the latter alternative is associated with worse sleep quality and a lower success rate.

A withdrawal scale [8,9] was used in a study that compared the effects of an abrupt discontinuation of buspirone and lorazepam [10] in patients presenting with generalized anxiety disorder. In this study, it was difficult to differentiate between anxiety and withdrawal symptoms, even when using the Hamilton–Anxiety Rating Scale.

The withdrawal scale for BZDs includes physical tiredness, sleep disruption, migraines, dizziness, orthostatic symptoms, palpitations, tremors, sweating, constipation and micturition problems [8,9].

The management of BZD treatment interruption varies widely. The usual method of withdrawal is slow tapering but it may not completely obviate the problems. Several other options have been described, including gradual tapering of the current BZD, substitution with a longer half-life BZD or treating the symptoms of withdrawal [11]. Psychological interventions, ranging from a simple support through counseling to expert cognitive–behavioral therapy, might be useful in combination with BZD interruption. In any case, treatment interruption is beneficial for the patient. It is followed by improved psychomotor and cognitive functioning, particularly in the elderly [4]. The use of selective serotonin reuptake inhibitors to alleviate anxiety symptoms may also widen the prescriber's therapeutic options and help to reduce BZD use, especially in the long-term and in elderly patients.

There is definitely a need for controlled clinical trials concerning proper management of BZD treatment interruption [12]. Primary care physicians remain the main prescribers of BZDs. It is also particularly important that these physicians are aware of the potential consequences of long-term BZD use in their patients. In addition, in patients already receiving BZD treatments, easy-to-use interventions such as monitoring of prolonged prescriptions with the help of pharmacists and regular assessments of the patient by the primary care physician, pointing out the

prolonged use of BZDs and questioning its utility, may help the patient to reduce or, even better, stop BZD use.

A recent Cochrane review has analyzed eight studies and concluded that carbamazepine has shown modest benefits in reducing BZD withdrawal syndrome severity and in significantly improving outcome after BZD withdrawal [13]. Antidepressants are useful to treat comorbid depressive symptoms that appear before or during withdrawal. This Cochrane analysis confirmed that tapering BZDs is the best strategy to avoid withdrawal syndromes but no clear evidence was shown in regard to the rates and schedules of tapering. The duration of tapering BZDs can vary from weeks to years. The recommendation of this Cochrane review is a duration of less than 6 months. The use of the liquid formulation of diazepam might be useful. Psychological interventions, such as supportive psychotherapy, counseling and group therapy, as well as cognitive–behavioral therapy, in combination with gradual BZD tapering might also be useful. Cognitive–behavioral therapy seems the most effective treatment as the patient receives clear benefits from BZD abstinence.

The subcutaneous infusion was shown to be tissue compatible so the development of a longer acting (i.e., several weeks) depot flumazenil formulation has been explored. This could be useful in the management of both acute and longer term BZD withdrawal sequelae [14].

The cellular mechanisms underlying BZD dependence have not been fully clarified. Several investigators have shown an involvement of mGluRs in the pathophysiology of dependence or withdrawal symptoms. Antagonists of NMDA, non-NMDAs and mGluRs can suppress the behavioral signs of BZD withdrawal in mice and rats [15]. The inhibitory effects of nonselective mGluR ligands on adenylate cyclase activity was reduced in mice that showed signs of BZD withdrawal. The mRNA expression levels of *mGluR2* and *mGluR3* were decreased in the cerebral cortex of mice pretreated with diazepam or alprazolam. Some results suggest that a decrease in the expression of group II mGluRs subunits may be involved in the development of BZD dependence [16].

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