Commentary

Exploring the dark side of the moon: the treatment of benzodiazepine tolerance

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Introduction

The use of benzodiazepines (BZDs) has a history of more than 50 years. The first BZD, chlordiazepoxide, was approved in 1960, primarily to treat anxiety and insomnia.

The 1960s saw a rapid diffusion of the use of this drug, followed soon by the still popular diazepam and, gradually, by several others. As early as the 1970s diazepam became the best-selling drug in the UK and the USA [1]. Soon after its introduction, however, reports of BZD tolerance and dependency emerged. BZD tolerance has been reported as early as 1961 [2], but this and other reports during the 1960s and 1970s were obscured by the enthusiastic easy management in the use of these barbiturates replacement drugs. Many countries now have recommendations for a short term use of BZD (2–4 weeks) [1]. Unfortunately these recommendations are largely disregarded by patients and doctors themselves. Misuse of BZD can cause deficits in learning, attention, memory, depression and injurious falls, traffic and other accidents [3].

Overall, the prevalence of long term use in the general population is approximately 2–7.5%, with estimates for long term use among BZD users ranging from 25% to 76% [4]. The problem of use of BZDs is also related to the use of high doses [5–7]. A cross-sectional study with 520 000 patents, estimated that 1.6% used BZDs in very high doses, exceeding the maximal recommended daily dose more than two-fold [8]. Surveys from France, Germany, Italy and the UK showed that 3.9% and 3.2% of current hypnotic and anxiolytic users have been taking a dose higher than the recommended therapeutic range [9]. Few studies evaluated the quality of life in long term users and even less among patients who use BZD at high doses.

BZD withdrawal management

The risk of dependence after long term use has been described, as reflected in the appearance of a series of symptoms when the drug is abruptly withdrawn. Between

15–44% of chronic BZD users experience protracted moderate to severe withdrawal symptoms upon cessation, including emergent anxiety and depressive symptoms [10]. In some cases withdrawal syndrome can lead to serious events such as (potentially lethal) seizures [1, 11].

The discomfort experienced by patients stopping long term BZD use led to the development of treatment strategies for discontinuing these medications. The common management of BZD withdrawal syndrome includes, either individually or in combination (i) a gradual tapering of the drug, (ii) switching to an equivalent dose of a long half-life BZD before tapering withdrawal and (iii) adding medications prior to detoxification and continuing these medications after discontinuation. For high dose BZD users with personality disorder and/or co-dependency on alcohol and illicit drugs, there is an increasing use of substitution treatment (with a slow onset of action BZD such as clonazepam), with an approach similar to methadone substitution in heroin users [12, 13].

Flumazenil and the management of benzodiazepine withdrawal

A potential approach of particular pharmacological interest is BZD detoxification using flumazenil (FLU). FLU is commonly used in the treatment of BZD overdose. It is usually considered a BZD antagonist. When compared with placebo bolus infusion of FLU (1 mg in 5 min) produced effects consistent with BZD withdrawal in BZD users. Nonetheless, results of studies in chronic BZD users who have discontinued BZD use suggest that multiple slow bolus infusions of FLU reduce the symptoms of withdrawal [1, 11, 13].

The mechanism of the FLU effect remains not fully elucidated. Chronic high dose consumption of BZD causes allosteric alterations of the sites for BZD, reducing the affinity between the site for BZD and site for GABA in the macromolecular GABA_A complex. FLU acts by removing BZDs from the receptor and probably induces up-regulation of the receptor site for BZDs by resetting (uncoupling) the relationship between the BZD and GABA sites. This could

explain its ability to attenuate withdrawal symptoms after chronic exposure to the drug because it has weak agonistic action on the BZD receptor, now normalized [13]. The first to propose and provide a treatment protocol in an outpatient hospital using an intravenous infusion of FLU, were Gerra *et al.* [14]. Since then, until the report of Hood *et al.*, described in this issue, few studies have been reported in the literature [15]. The recent experience of a subcutaneous infusion of FLU increased patient compliance and made the treatment more 'low risk' for doctors, apparently removing barriers to treatment [16].

Research implications

In spite of its potential benefits, a number of aspects of this therapeutic approach need to be clarified [13]. With respect to the inclusion criteria, questions that could be posed are: what is the minimum diazepam-like BZD dosage threshold for recommending FLU treatment and what is the minimum time of continuous use of BZD beyond which the FLU treatment can be recommended? Should the treatment be used only after tapering detoxification has failed? Should patients with a history of seizures be excluded from the treatment? As regards the treatment, given the potential side effects of the treatment and the difficulty in dosage, FLU case-control studies to optimize dosage, both intravenous and subcutaneous administration, need to be done. At present, the dose used in most of the studies, referred to Gerra's protocol [14], without any clinical rationale. The times of administration and the end point of the treatment should also be better evaluated. Could increasing the times of infusion per day or decreasing the dosage of FLU be suitable strategies? With FLU, it is likely that long term administration will have a beneficial effect. Oral administration (not available on the market) has limited application due to the short half-life of the drug. More studies are needed to determine the drug's safety. Seizure risk is important and remains an unmet issue of this treatment which could limit its use on a larger scale [17]. Related to this aspect, the opportunity to use adjunctive medications needs to be explored further [13].

In recent years the use of partial agonists, such as buprenorphine and varenicline in the treatment of opioid dependencies and smoking dependence, has increased significantly. The diffusion of FLU use in the treatment of BZD dependence is much slower. We hope that the treatment could receive more attention from researchers and clinicians. It must not be forgotten that BZD addiction is the most emblematic form of iatrogenic dependence.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf

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