Role of Benzodiazepines in Anxiety Disorders

20

Richard Balon and Vladan Starcevic

Introduction

Benzodiazepines (BZs) have been used for treatment of anxiety and anxiety disorders for over half of a century. The first BZ, chlordiazepoxide, was synthesized by Leo Sternbach in the mid-1950s, and the first reports of its clinical use were published in 1960 (e.g., 1). Sternbach subsequently fairly quickly discovered several other BZs, such as diazepam, clonazepam, flurazepam, nitrazepam, and flunitrazepam. In addition to antipsychotics, antidepressants, and stimulants, psychiatry's armamentarium was thus enriched by a new group of medications that were effective and easy to use, acted quickly, had no unpleasant side effects, and made anxious people feel better.

BZs started to be widely used by physicians not just because of their ability to quickly alleviate anxiety but also for their anticonvulsants, hypnotic, muscle-relaxing, and sedative properties. BZs became one of the most prescribed classes of psychotropic medications [2]. For instance, in 2008, approximately 5.2% of US adults aged 18–80 years used BZs [2], and there were 85 million BZ prescriptions issued in 2007 for outpatients with anxiety and mood disorders [3]. Psychiatrists have been historically apprehensive about BZ abuse potential, withdrawal effects, and possible side effects associated with long-term use. Thus, BZs have been more frequently prescribed by primary care physicians. With the arrival of selective serotonin reuptake inhibitors (SSRIs) during the 1990s and their subsequent approval for use in anxiety disorders, the use of BZs by psychiatrists has become even more

R. Balon (✉)
Department of Psychiatry and Behavioral Neurosciences and Anesthesiology, Wayne State University, Detroit, MI, USA
e-mail: rbalon@wayne.edu

V. Starcevic
Discipline of Psychiatry, Nepean Clinical School, Sydney Medical School, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia

Y.-K. Kim (ed.), *Anxiety Disorders*, Advances in Experimental Medicine and Biology 1191, https://doi.org/10.1007/978-981-32-9705-0_20

limited. SSRIs and other antidepressants (ADs) became a preferable pharmacological choice for treatment of anxiety disorders among psychiatrists, with their use being promoted in various practice guidelines.

Interestingly, as Rickels [3] pointed out, "no evidence for the superiority of the newer ADs over BZs, both in terms of efficacy or safety, exists for either short-term or long-term treatment. BZ toxicity, adverse events, and withdrawal symptoms, not better efficacy, are usually cited in support of the use of ADs over BZs in anxiety disorders. Yet ADs are not better tolerated than BZs and they also cause withdrawal symptoms." In a systematic review and meta-analysis, Offidani and colleagues [4] demonstrated that treatment with BZs resulted in comparable or greater improvements and fewer adverse events in patients suffering from generalized anxiety disorder or panic disorder and that BZs were more effective in reducing panic attacks than tricyclic antidepressants.

BZs are clearly useful, efficacious, and effective medications for the treatment of anxiety disorders. As within the framework of this book, we are rethinking anxiety disorders, and the time has come to rethink the role of BZs in the treatment of these disorders. For the purpose of this book, we are discussing the use of BZs in anxiety disorders in terms of the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) [5]. Thus, we will focus mostly on the use of BZs in panic disorder, generalized anxiety disorder, agoraphobia, social anxiety disorder, specific phobia, and anxiety disorder due to another medical condition. However, we would like to acknowledge that BZs are effective in many other disorders, such as trauma- and stressor-related disorders, obsessive-compulsive and related disorders, sleep disorders, and anxious depression and as adjunctive treatment for anxiety within the frame of mood, psychotic, and other disorders.

Benzodiazepines: Basic Pharmacology and Classification

Mechanism of Action

All BZs have a similar structure: their molecules include a 1,4 benzodiazepine ring, but they differ by the rest of the molecule (2-keto; 3-hydroxy, 7-nitro, triazolo, and imidazo benzodiazepines).

The mechanism of action of BZs involves the potentiation of gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the central nervous system (CNS). BZs bind to the BZ receptors which are a part of the GABA-A-benzodiazepine receptor complex connected to the chloride channel. The GABA-A receptor is basically a chloride channel regulated by GABA binding. GABA "opens" the chloride channels by binding to these receptors and thus inhibits neuronal excitability by the influx of chlorine ions into the cell, which helps to stabilize the membrane potential close to the resting level. GABA actually works on the GABA-A receptor alone. While GABA binds to the receptor, the opening and closing of the chloride channel occurs more frequently, which results in inhibition. However, when BZs bind to this receptor complex, the GABA-A receptor is allosterically modulated, and the action

of GABA is potentiated with the greater influx of chloride ions into the cell (BZs alone, without GABA, cannot influence chloride flow). It is important to note that the GABA-A receptor has several subunits (α_1, α_2, and α_3 and several more). Receptors with different subunits seem to regulate different activities – e.g., α_1 is more implicated in sedative-hypnotic activity, while α_2 is more involved in anxiolytic activity. The distribution of these receptors in the CNS also varies (e.g., α_1 can be found mostly in the cortex and cerebellum, while α_2 is more prominent in the cortex, limbic system, and spinal cord and α_3 in the periphery). Most BZs bind to all three subunits, though BZs binding mainly to the α_1 subunit have also been developed (halazepam, quazepam).

As far as pharmacokinetics of BZs is concerned, BZs differ in their speed of absorption from the gastrointestinal tract, which also determines the speed of their action (diazepam is absorbed more quickly than some others). BZs are highly lipophilic, which helps crossing the blood-brain barrier. They differ in their lipophilicity, though, and drugs that are more lipophilic (e.g., diazepam) have quicker onset of action.

BZs also differ in their half-life, existence of metabolites (e.g., oxazepam has none, while diazepam has several, e.g., desmethyldiazepam), duration of action, and metabolism. BZs are metabolized in the liver through two principal pathways [6], microsomal oxidation or glucuronide conjugation, followed by excretion through the kidneys. The glucuronide conjugation is considered less susceptible to and impaired by various disease processes and medication than oxidation, and thus BZs metabolized through glucuronide conjugation are considered safer in some subpopulations (e.g., elderly). Some BZs are prodrugs, i.e., they are not active, but their metabolites are.

Classification

There are various ways to classify BZs: according to their structure, pharmacokinetics (half-life), pathway of metabolism, and intensity of hypnotic-sedative effect. We list the best known examples in each classification, as the list of all BZs is beyond the scope of this chapter. There are well over 60 BZs with hundreds of brand names available around the world. Most BZs are indicated for treatment of anxiety, but some (estazolam, flurazepam, quazepam, temazepam, and triazolam) are also indicated (in the USA) for insomnia (among other indications).

A. *Classification based on structure.*
   2-Keto benzodiazepines: chlordiazepoxide, clorazepate, diazepam, flurazepam, halazepam, prazepam.
   3-Hydroxybenzodiazepines: lorazepam, lormetazepam, oxazepam, temazepam.
   7-Nitro benzodiazepines: clonazepam, flunitrazepam, nimetazepam, nitrazepam.
   Triazolo benzodiazepines: adinazolam, alprazolam, estazolam, triazolam.
   Imidazo benzodiazepines: climazolam, loprazolam, midazolam

B. *Classification based on pharmacokinetics.*
   1. Benzodiazepines with short half-life: midazolam, oxazepam, triazolam.
   2. Benzodiazepines with intermediate half-life: alprazolam, bromazepam, estazolam, lorazepam, lormetazepam, temazepam.
   3. Benzodiazepines with long half-life: chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, flurazepam, halazepam, medazepam, prazepam, quazepam

C. *Classification based on metabolism.*
   1. By oxidation: alprazolam, bromazepam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, midazolam, prazepam, quazepam, triazolam, and others.
   2. 2. By glucuronide conjugation: lorazepam, lormetazepam, oxazepam, and temazepam only

D. *Classification based on relative intensity of sedative-hypnotic effect.*

Some benzodiazepines, such as alprazolam, clonazepam, clorazepate, diazepam, and oxazepam, have a fairly low sedative-hypnotic effect, while this effect is much more pronounced with other benzodiazepines, such as flurazepam, midazolam, nitrazepam, and triazolam.

Evidence of Efficacy of Benzodiazepines in Anxiety Disorders

BZs arrived during the 1960s when the regulatory rules, clinical trials, and diagnostic system were different from those of today. The three anxiety disorder diagnoses used before 1980 (arrival of DSM-III [7]) were anxiety neurosis, phobic neurosis, and obsessive-compulsive neurosis. The delineation of panic disorder, agoraphobia with and without panic attacks, and generalized anxiety disorder came with DSM-III [7] during the time when most BZs (with the main exception of alprazolam) were already a part of the psychiatric armamentarium and frequently out of patent. For obvious reasons, the pharmaceutical industry had not much interest in investing in the evaluation of many BZs in "new" indications delineated in DSM-III. Further changes in the classification of anxiety disorders were introduced in DSM-III-R [8]. Thus, BZ registration trials for use in diagnostic categories developed since the DSM-III have not been conducted, except for alprazolam for panic disorder. Nevertheless, there exist data from clinical trials supporting the use of BZs in anxiety disorders.

Panic Disorder with and Without Agoraphobia

The first trial examining BZs in this indication compared diazepam and propranolol in 21 patients with panic disorder and agoraphobia [9]. Panic attacks and phobic symptoms responded to diazepam, but not to propranolol.

The strongest evidence for efficacy of BZs in anxiety disorders comes from evaluation of alprazolam in panic disorder. Alprazolam arrived during the late 1980s and was examined in a number of clinical trials. Ballenger and colleagues [10, 11] studied alprazolam in a placebo-controlled, 8-week, flexible dose trial of 526 patients (481 completed 3 weeks of treatment) with agoraphobia with panic attacks and panic disorder. Alprazolam was significantly more effective than placebo in improving spontaneous and situational panic attacks, phobic fears, avoidance behavior, anxiety, and secondary disability already at week 1. At week 4, 83% of patients on alprazolam vs. 43% of patients on placebo were moderately improved or better; and 50% of alprazolam recipients vs. 28% of placebo recipients were free of panic attacks. Alprazolam was well tolerated, and 84% of alprazolam patients vs. 50% of placebo patients completed the study. In an interesting report [12] analyzing the data from this study [10, 11], the authors examined Donald Klein's theory [13] that the initial event in panic disorder is an unexpected panic attack followed by anticipatory anxiety and agoraphobia. Their finding [12] that panic attacks remitted before phobias seems to indirectly support Klein's theory [13].

As the efficacy of alprazolam in panic disorder and agoraphobia with panic attacks was established, a question was raised whether alprazolam is unique among antianxiety agents as to its efficacy. Thus, alprazolam was also compared to several other medications. In a double-blind, placebo-controlled study of 55 patients with panic disorder and agoraphobia with panic attacks, alprazolam was superior to propranolol [14]. Two trials [15, 16] found lorazepam as effective as alprazolam in this indication. Some interesting observations regarding the doses were made: in one study [15], the mean dose of lorazepam was 7 mg vs. 3 mg alprazolam daily; in the other study [16], the dose of lorazepam required for antipanic efficacy was twice that of alprazolam, a ration that was considered consistent with the relative potency of these drugs for generalized anxiety. In another study [17], clonazepam was found to be similarly effective to alprazolam in the treatment of panic disorder.

As it became clear that BZs are probably all effective in the treatment of panic disorder and agoraphobia with panic attacks, the question remained whether BZs are similarly effective as antidepressants in this indication. In a large multicenter, double-blind, placebo-controlled study of 1168 panic disorder patients comparing alprazolam and imipramine, improvement with alprazolam occurred by week 1 and 2 while with imipramine by week 4. By the end of week 8, the effects of both medications were similar and superior to placebo [18]. In a 6-month maintenance treatment study [19] comparing alprazolam with imipramine or placebo, all patients who completed the maintenance phase were panic free, both medications produced significant panic relief, but imipramine was associated with poorer patient acceptance.

Interestingly, as pointed out by Offidani and colleagues [4], there have not been many comparisons of efficacy of BZs and SSRIs. In a series of reports [20–22], Nardi and colleagues compared clonazepam and paroxetine in patients with panic disorder with and without agoraphobia. The first report [20] from a randomized, open-label, naturalistic 8-week study of 63 patients on clonazepam (target dose 2 mg) and 57 patients on paroxetine (target dose 40 mg) demonstrated the efficacy

of both medications, with clonazepam performing better on several measures of panic and anxiety and being better tolerated. The second report [21], a 3-year follow-up of the same cohort of patients (47 on clonazepam and 37 on paroxetine), showed that both medications remained effective in reducing the frequency of panic attacks and anxiety, with clonazepam showing a small but significantly better improvement on the Clinical Global Impressions improvement rating. After 3 years, treatment was discontinued in patients who had achieved remission. The last report [22] focused on relapse rate in these patients with follow-up at years 1, 2, 3, 4, 5, and 6 after treatment discontinuation. Cumulative relapse rate in 85 patients who completed follow-up was 50% at year 1 and 89.4% at year 6. One-year relapse rates were lower in patients previously treated with clonazepam than in those previously treated with paroxetine, and low 6-year relapse rates were associated with high anxiety rating scores before treatment and previous treatment with clonazepam.

BZs are clearly effective and efficacious in treatment of panic disorder with or without agoraphobia, are well tolerated, and it seems that they are suitable for a long treatment in this indication, too.

Generalized Anxiety Disorder

BZs have been used in treatment of symptomatology akin to symptomatology of generalized anxiety disorder (GAD) (e.g., 1) since their inception. Similar to panic disorder, double-blind, placebo-controlled, mostly short-term trials examining their efficacy started to appear during the 1980s. In 1982, Chouinard and colleagues [23] reported on the efficacy of alprazolam in GAD and panic disorder in a small double-blind study. Alprazolam up to 3 mg/day was effective in both disorders. Interestingly, Elie and Lamontagne [24] found that both alprazolam (average dose 2 mg/day) and diazepam (average dose 15.8 mg/day) were effective in GAD, with diazepam being more effective than alprazolam in the reduction of several symptoms of anxiety and depression.

Several other BZs were tested in GAD. Two placebo-controlled studies [25, 26] demonstrated the efficacy of lorazepam in GAD, one in comparison with bromazepam (both equally effective) [25] and another one [26] finding both oral and sublingual forms of lorazepam effective in GAD. Bromazepam was also found equally helpful in GAD as chlorprothixene [27]. Etizolam displayed anxiolytic activity equivalent to those of alprazolam and bromazepam and possessed a more antidepressant effect than alprazolam or bromazepam [28]. The long-acting chlordesmethyldiazepam was a more effective therapy for GAD than lorazepam in a trial by Berlin and colleagues [29]. Finally, adinazolam-SR was superior to placebo in the treatment of GAD in another trial [30].

To further explore their usefulness and place among antianxiety medications, BZs were compared to other drugs with anxiolytic properties. As mentioned, bromazepam and chlorprothixene were equally effective in a multicenter study of 245 GAD patients in a general practice [27]. Two studies [31, 32] compared diazepam and one [33] alprazolam to modest doses of buspirone. Diazepam [32] and

alprazolam [33] produced a more rapid improvement, but BZs were equally effective at the endpoints. One of these studies [31] suggested that buspirone may be particularly indicated for anxious patients with depression. In an interesting study by Rickels and colleagues [34], abercanil (anxioselective β-carboline) and diazepam provided more symptom relief than placebo at the end of week 1; however, only diazepam differed from placebo at week 6.

Similar to panic disorder, not many trials compared BZs in GAD to antidepressants. Rickels and colleagues [35] compared diazepam to imipramine and trazodone in a placebo-controlled trial of 230 GAD patients (depression and panic disorder were excluded). At the end of week 8, moderate to marked improvement was reported by 73% of patients treated with imipramine, 69% of patients treated with trazodone, 66% patients treated with diazepam, and only 47% of patients on placebo. Imipramine (max 143 mg/day) had somewhat better anxiolytic efficacy than diazepam (22 mg/day). Only two studies [36, 37] provided any data on comparisons of BZs and newer antidepressants. There were no differences in response rate between venlafaxine XR, diazepam, and placebo in one of these studies [36], and both lorazepam and paroxetine were significantly better than placebo, with lorazepam separating from placebo earlier in the other one [37].

A recent meta-analytic review [38] of BZs, SSRIs, and serotonin-norepinephrine reuptake inhibitors (SNRIs) of 54 articles reporting the results of 56 studies on the use of these medications in GAD concluded that "the most common forms of pharmacotherapy for adult GAD are moderately effective, with BZs being the most effective drugs." Reinhold and Rickels [39] also wrote that "Evaluation of the literature suggests consistent, reliable efficacy of BZs in improving the central features of GAD – both the psychiatric and somatic. BZs elicit an earlier response than the ADs and provided that a response occurs by the eight week, it tends to be sustained throughout the length of treatment."

Social Anxiety Disorder (Social Phobia)

Two observations [40, 41] noted a positive response to alprazolam in a small number of patients with social phobia. Subsequently, two reports [42, 43] described a positive response to clonazepam in small groups of patients suffering from social phobia.

Clonazepam was found effective in relieving anxiety, phobic avoidance, and social phobic symptoms in 23 patients with social phobia in a study comparing clonazepam to no treatment [44]. Finally, in a double-blind, placebo-controlled trial of clonazepam in 75 outpatients with social phobia, clonazepam was found significantly more effective than placebo. Response rates were 78.3% for clonazepam and 20% for placebo [45].

Clonazepam was also compared to other treatments for social phobia. Patients treated either with clonazepam or cognitive-behavioral group therapy improved significantly, and the differences between treatment conditions were absent, except for improvement with clonazepam on several measures at week 12 in a study by Otto

and colleagues [46]. A small study by Seedat and Stein [47] with a complicated design found a trend favoring the combination of clonazepam and paroxetine over paroxetine/placebo group. Global outcome measures also favored the combination of clonazepam with paroxetine over paroxetine alone.

Clonazepam thus seems to be a suitable, effective, and well-tolerated treatment for social phobia.

Other Anxiety Disorders

Alprazolam in combination with house calls was described as helpful in a small placebo-controlled study of 12 patients with agoraphobia [48]. Intranasal midazolam was effective in claustrophobia induced by MR imaging in a randomized, placebo-controlled study of 54 patients scheduled for MR imaging [49]. BZs are frequently used in fear of flying, but no study have been done in this indication.

Dependence and Withdrawal Symptoms

BZ dependence is arguably the most controversial aspect of the use of these pharmacological agents. To a large extent, this is due to the negative connotations of the concept of dependence. In addition, this concept has often been confused with the notions of abuse and addiction.

BZ dependence is a physical or pharmacological dependence that denotes a physiological adaptation to the presence of BZs that is required to maintain their use [50]. As such, dependence develops in all patients who use BZs long-term, even after only a few months. It does not reflect pathology and is similar to dependence that develops during administration of other drugs. The usual manifestations of dependence, including BZ dependence, are tolerance and/or withdrawal symptoms. Thus, tolerance and withdrawal symptoms are regarded as an "evidence of normal adaptation" [51] to a long-term substance use.

Tolerance refers to a need for greater amounts of the substance to achieve desired effect or a markedly decreased effect if the substance continues to be administered in the same dose. Tolerance does occur when BZs are abused, and there have been reports of tolerance to the therapeutic (anxiolytic) effects of BZs. However, a convincing evidence now exists that tolerance to the anxiolytic effects of BZs usually does not develop during long treatment of anxiety disorders, especially panic disorder [21, 52–56]. Consequently, escalation of doses of BZs and loss of their therapeutic benefit are rarely seen when patients with anxiety disorders use BZs long-term for therapeutic reasons – as anxiolytic agents – and in the absence of other substance abuse issues.

The main implication of BZ dependence is the likelihood of the withdrawal symptoms if BZs are ceased abruptly after long-term use. These withdrawal symptoms are common, although not inevitable. One early study reported that withdrawal problems occurred in only 40% of those who took BZs regularly [57]. BZ

withdrawal often resembles a recurrence of an anxiety disorder and consists of various nonspecific symptoms such as restlessness, irritability, insomnia, feelings of weakness or fatigue, numbness or tingling sensations, nausea, stomach cramps, flu-like symptoms, muscle cramps, involuntary movements, and unsteady gait. The relatively specific BZ withdrawal symptoms include hypersensitivity to various stimuli, perceptual disturbances, "metallic taste," distorted body image, depersonalization and derealization, confusion, ringing in the ears, and a sense that things are moving as if being on a boat. Although unpleasant and distressing, BZ withdrawal symptoms are rarely serious or life-threatening (e.g., seizures). They usually last from several days to 4 weeks but can last longer. Withdrawal symptoms may abate without specific treatment and usually produce no long-lasting consequences.

Withdrawal symptoms should be distinguished from rebound symptoms upon BZ cessation. The latter represent an exacerbation of the primary condition, usually anxiety disorder, for which BZs were originally prescribed. Rebound symptoms may be more severe than those experienced before the medication was commenced. Given the manifestations of BZ withdrawal, it may be difficult to make a distinction between the withdrawal and rebound symptoms in clinical practice. However, their implications are very different, as rebound symptoms call for BZs to be reinstated and perhaps for another treatment modality to be added.

An effort should be made to prevent and alleviate BZ withdrawal symptoms. The key consideration in this regard is engaging patients in the treatment planning and decision-making process. This increases the chances of the right timing for BZ cessation, so that it is suggested only when patients are ready for it, i.e., able to cope with anxiety or distress without relying on medication and feeling relatively comfortable when facing the symptoms [58]. Coercion of any kind, including a threat to stop prescribing BZs if the patient is unwilling to discontinue them or pressuring patients to complete taper within a rigidly set time limit, is likely to lead to more difficulties and should be avoided.

Once a decision has been made to discontinue BZs after long-term treatment, this should be done gradually and in an individualized manner, discussing and negotiating with patients the rate of taper that they feel comfortable with. This rate can be changed during the taper, depending on patients' response to a decreasing dose of the medication and level of discomfort. As a result, the duration of taper varies substantially – between several weeks and more than 12 months. BZs with a shorter half-life (e.g., alprazolam) are generally more likely to be associated with more intense withdrawal symptoms than BZs with a longer half-life (e.g., clonazepam). Techniques of CBT can also facilitate the taper.

Considering the nature and the course of BZ withdrawal symptoms, it is somewhat paradoxical that there is such a widespread fear of them. Several reasons can account for it. The first has to do with sheer ignorance and misinformation. Secondly, there are terminological issues and inherently negative connotations of the term "withdrawal symptoms" and the accompanying sinister expectations. Moreover, media have tended to portray BZ withdrawal symptoms in a negative, sensationalist manner. Still another reason is a deliberate exaggeration of the severity and consequences of BZ withdrawal. This has occurred because of the conflict of interest,

when promoting the alleged or real advantages of alternative pharmacotherapy (e.g., SSRIs) or psychological treatment (e.g., CBT). The fear of BZ withdrawal symptoms motivates some patients to continue taking BZs even when they do not seem to benefit from treatment. Such patients are often hypervigilant about any bodily changes and likely to misinterpret minor symptoms during minimal dose reductions as signs of withdrawal, which reinforces the erroneous notion that they are "addicted" to BZs and that they will never be able to cease them. These considerations underscore a need for proper education of both BZ users and BZ prescribers.

The characteristics of BZ dependence that develops in the context of long-term treatment, especially its occurrence even with relatively low doses of the medication and the combination of little or no tolerance with the likelihood of withdrawal symptoms upon abrupt discontinuation, have led to various terms in an effort to describe what may be relatively specific for BZ dependence and how it differs from dependence that is encountered in the context of drug abuse or addiction. These terms include "therapeutic dose dependence" [59, 60], "therapeutic dependence" [61, 62], "nonaddictive dependence" [63], "low-dose iatrogenic dependence" [64], and "low-dose dependence" [65].

"Psychological dependence" is a term that has been used somewhat loosely with reference to BZ dependence. This phenomenon has no basis in the pharmacological properties of BZs and is not a part of the physiological adaptation to the presence of BZs. It is not a form of BZ abuse and does not suggest addiction. Due to its propensity to be misused or misinterpreted, it should best be avoided. One of its manifestations is "talisman dependence," which denotes a need to constantly carry tablets of BZs and have them close at hand in case the person needs the medication. This is a safety behavior that should best be addressed during psychological therapy of the underlying condition (usually an anxiety disorder). "Last dose dependence" is another form of "psychological dependence," which refers to an inability to complete the hitherto successful BZ taper. This suggests an overreliance on medication and may mean that the patient is not quite ready for medication cessation.

An approach to BZ dependence should be rational, without appealing to its possible emotional connotations. Consequently, BZ dependence should neither be overestimated nor trivialized and needs to be approached like any other pharmacotherapy-related issue. A statement made by Dell'Osso et al. [66] reflects this position succinctly: "Dependence is neither a valid reason to continue prescribing nor a sufficient reason, on its own, to refuse to prescribe BZs."

Abuse and Addiction

Substance abuse is no longer an official diagnosis in the DSM system. Although there are various definitions of substance abuse, they all have in common two elements: [1] a pattern of excessive, indiscriminate or inappropriate substance use and [2] various negative consequences of such substance use. These consequences pertain to physical and mental health problems, difficulties in terms of social or

interpersonal functioning, and/or legal issues. Features that are often associated with substance abuse include craving (intense or abnormal desire or longing for the substance), unnecessarily prolonged use, dose escalation, and tolerance.

BZs are often considered to have a high abuse potential, but this is true only in the context of other substance abuse. The mood-modulating and/or euphoria-like effects of BZs in such a context are the main reason for craving and BZ abuse. Consequently, these agents can be used as "downers" or mild euphoriants, usually in combination with other drugs or while abstaining from them.

Patients who are prescribed BZs for their anxiety disorder rarely abuse them in the absence of other substance abuse issues. This is related to the findings that neither craving for BZs nor BZ-induced euphoria have been consistently reported in anxiety disorder patients taking BZs long-term. In this context, it is important to emphasize that interpreting as euphoria a BZ-induced relief from anxiety, tension, distress, and/or misery among patients with anxiety disorders and the subsequent "good" and "calming" feeling is erroneous.

In 1990, the American Psychiatric Association Task Force Report on benzodiazepine dependency concluded that "BZs … are not widely abused drugs. When abuse does occur, it is almost always among persons who are also actively abusing alcohol, opiates, or other sedative hypnotics. In these people, diazepam and alprazolam – the most commonly used benzodiazepines – are the most abused benzodiazepines." [67]. This report also noted that cocaine abusers use BZs to ease the "crash" of the rapid decline in euphoria. This assessment continues to be relevant and is a concise summary of what is known about BZ abuse.

Like the term "abuse," the term "addiction" does not relate to an official DSM diagnosis and has also suffered from too many definitions and a tendency to be equated with dependence. In recent times, the emphasis in the conceptualization of addiction has shifted from substances to behaviors. Thus, one influential approach to the definition of addiction [68, 69] focuses on "behavioral engagement" and posits that the core features of addiction include an urge or a craving that immediately precedes behavioral engagement, poor self-control over behavioral engagement, continued behavioral engagement despite its adverse consequences, and "compulsive" behavioral engagement, which refers to a continued use of the substance to avoid withdrawal symptoms. This approach is very much in line with other definitions that consider impairment in behavioral control (over substance use) and related inability to consistently abstain the key components of addiction [70].

In view of the above definitions, it is clear that addiction and dependence must not be considered interchangeable terms. Moreover, dependence can exist without addiction [71], and this is perhaps nowhere more evident than with BZs [72]. Therefore, a response to the frequently posed question of whether patients dependent on BDZs are inevitably addicted must not be an affirmative one. As already noted and in contrast to substance addiction, BZ dependence is not characterized by craving and an all-encompassing preoccupation with BZs, and there is no compulsive or uncontrolled, drug-seeking behavior. Tolerance and adverse health and/or social consequences are usually not associated with BZ dependence, whereas they are a part of substance addiction. Withdrawal upon abrupt cessation is the only

feature that BZ dependence and substance addiction have in common, although withdrawal symptoms are not inevitable as part of BZ dependence. All these considerations mandate avoidance of the term "addiction" in the context of therapeutic BZ use and dependence.

Adverse Effects

While BZs are generally well tolerated and their adverse effects are relatively rarely a reason for discontinuation, they do produce adverse effects that may limit their utility. The most common adverse effect of BZs is sedation – a general mental and motoric slowing down. Sedation is dose-dependent and is often experienced and described as a difficulty remaining focused or feeling tired, drowsy, or sleepy. While sedative effects of BZs are desirable when these agents are used as hypnotics, they can be problematic or even impairing during the day, when patients wish to remain awake and alert. Sedation is not directly related to anxiolytic properties of BZs, but there is a common perception that sedative drugs of any kind also have antianxiety effects.

Sedation usually occurs when the medication is commenced or after its dose has been increased, and patients taking BZs need to be warned about this. It is advisable to avoid driving, operating machinery, or performing other complex tasks at that time, at least until patients adapt themselves to the medication or its higher dose. This adaptation usually occurs after several days because tolerance to sedative effects of BZs tends to develop rapidly. Therefore, the dose of the medication usually does not need to be reduced if sedation occurs, and avoiding activities in which sedation might be troublesome or dangerous is all that needs to be done in that situation. Additional doses of BZs prior to driving or performing complex tasks should be avoided. Patients who are on a constant dose of a BZ for longer periods of time usually do not experience sedation, but they should remain cautious because their driving ability can still be affected. In case of severe sedation or a need to perform activities that might be affected adversely by BZ-induced sedation, the dose of a BZ medication can be decreased, or the medication can be discontinued.

An impaired psychomotor performance is a related and common adverse effect of BZs. Besides its impact on activities that require complex psychomotor coordination, this adverse effect has been implicated in the falls and fractures among the elderly. Due to the propensity of BDZs to cause sedation and psychomotor impairment, the usual recommendation is to avoid their long-term administration to the elderly and frail patients. This recommendation pertains particularly to BZs with a long half-life (e.g., diazepam) because of their slower metabolism and tendency to accumulate in the body. Consequently, BZs with a shorter half-life (e.g., lorazepam) are preferred for use in this population. Some guidelines consider use of any BZs in the elderly risky, regardless of their duration of action and half-life. If BZs are used in the elderly, this should be done with the lowest possible dose, generally avoiding increases in dosing. Moreover, a need for administration of BZs to the elderly should be frequently reassessed.

Many elderly patients are resistant to a suggestion to cease BZs or at least decrease their use substantially. This occurs for various reasons, including the effectiveness of BZs for treating insomnia, anxiety, or distress, long-term use, and fear of a "life without BZs" and fear of the withdrawal symptoms. Also, some elderly patients find the calming and soothing effects of BZs more important than any BZ-induced cognitive problems [73]. In these situations, it is crucial to carefully weigh the risks and benefits of BZ use and have appropriate discussions with patients.

The assessment of the risk of BZ use in old age in terms of falls and fractures may be confounded by various other factors, including a concomitant or sequential use of other medications (e.g., antidepressants or antipsychotics) that have been associated even more strongly with this adverse effect [74]. Therefore, attribution of the risk solely or mainly to BZs may be misleading [75], and all the relevant risk factors need to be taken into consideration.

Another problem with use of BZs in the elderly is their association with cognitive impairment. The cognitive effects of BZs in the elderly include problems with concentration, decreased speed of processing and verbal learning, and alterations in visuospatial ability. Reports of the effects of BZs on memory in the elderly have been conflicting, with studies finding memory difficulties of varying magnitude that were both reversible and irreversible, with some of them persisting after BZ cessation [76]. The clinical significance of these cognitive effects has been controversial and seems to vary from one person to another; some reports suggest that daily functioning is not significantly affected by the cognitive effects of chronic BDZ use [77]. Anterograde amnesia (difficulty recalling events that occurred during the period of several hours after taking a BZ medication) is common with use of BZs and is seen in patients of all ages. Although BZs have been linked with dementia, a direct causal relationship between BZ use and development of dementia has not been demonstrated.

The cognitive and motor impairment associated with BZ use becomes more prominent in the context of alcohol consumption. Therefore, alcohol should generally be avoided during treatment with BZs and especially after taking the BZ medication.

BZ use has been associated with irritability, disinhibition, "out of character" or inappropriate behavior, anger, and aggression, but the frequency of these adverse effects varies considerably. One systematic review has confirmed this association to be "moderate" [78], but the circumstances under which aggressive behavior follows BZ use and the underlying mechanisms remain unclear. It is often assumed that these behavioral and emotional adverse effects of BZs are more likely in individuals with severe and emotionally unstable (i.e., borderline) personality disorders, impulse control disorders, emotional or intellectual immaturity, neurodevelopmental disorders, brain damage, and substance abuse. Evidence for such associations is inconclusive, but BZs may need to be avoided in the presence of these conditions.

Positioning Benzodiazepines in the Treatment of Anxiety Disorders

Treatment Guidelines, Benzodiazepines, and Antidepressants

Virtually all clinical practice and treatment guidelines consider BZs as second- or third-line pharmacotherapy in the treatment of anxiety disorders (i.e., panic disorder, generalized anxiety disorder, and social anxiety disorder), with SSRIs and less often SNRIs being considered the pharmacological treatment of choice. Long-term treatment with BZs is generally not recommended or may be reserved for severely ill and functionally impaired patients who failed to respond to several other treatments. Only a brief use of BZs in selected circumstances is deemed appropriate by most guidelines. It has been argued that these recommendations are not based on good evidence, that they are misleading because of exaggerating the dangers of BZs and downplaying the risks with SSRIs and SNRIs, and that they are too restrictive, depriving patients of a valuable treatment option [79–83]. Therefore, a reappraisal of BDZs and their adequate positioning in the treatment of anxiety disorders are essential.

The first issue concerns the efficacy of BZs for anxiety disorders. Treatment guidelines often assume or suggest that BZs are either less effective than SSRIs and SNRIs or equally effective, at best. However, very few studies directly comparing BZs with SSRIs or SNRIs have been conducted. In one such study, clonazepam was compared with paroxetine in the treatment of panic disorder; a greater clinical improvement with clonazepam and its faster onset of action were reported during short-term treatment [21, 56], whereas treatment with clonazepam predicted a lower relapse rate after long-term treatment [22]. One systematic review and meta-analysis comparing BDZs with antidepressants (though mainly tricyclic antidepressants) for anxiety disorders found no support for the primacy given to antidepressants on the grounds of efficacy [4]. A meta-analysis of the efficacy of medications for generalized anxiety disorder reported significantly greater effect sizes (Hedges' *g*) for BZs (0.497) than for SNRIs (0.357) and SSRIs (0.325) [38]. Although more studies that directly compare BZs with SSRIs and SNRIs are needed, current evidence does not support the notion that SSRIs and SNRIs are more efficacious than BZs, especially for panic disorder and generalized anxiety disorder.

With regard to adverse effects, BZs appear to be better tolerated than SSRIs and SNRIs in the treatment of anxiety disorders [4, 84–86]. Thus, clonazepam was better tolerated than paroxetine over the course of both short-term and long-term treatment of panic disorder [21, 56]. Numerous reports suggest that early adverse effects of SSRIs and SNRIs during the treatment of anxiety disorders, especially increased anxiety and agitation, insomnia, headache, dizziness, and gastrointestinal symptoms, lead to a premature discontinuation of these agents. Adverse effects of SSRIs and SNRIs that may be more prominent in the long run, especially sexual dysfunction, also contribute to their poor tolerability.

There is abundant evidence that the cessation of SSRIs and SNRIs is associated with the withdrawal symptoms [87, 88] and that, in this respect, SSRIs and SNRIs

do not differ significantly from BDZs [89]. For reasons that have much more to do with marketing and commercial interests than science, withdrawal symptoms that occur with SSRIs and SNRIs have been labelled as "discontinuation symptoms." This terminological ploy, along with conflicts of interest and a generally negative attitude toward BZs, has contributed to a biased portrayal in the treatment guidelines of the importance and magnitude of the withdrawal symptoms caused by the cessation of antidepressants [90]. As a result, treatment guidelines tend to minimize these withdrawal symptoms and make them look less severe and less clinically important than the BZ withdrawal symptoms.

Considering the comparative efficacy and tolerability data, there is no reason to deny BZs the status of the first-line pharmacotherapy for anxiety disorders. In addition, BZs have a significant advantage over antidepressants in terms of their quick onset of action. This is particularly important in an acute clinical setting, crisis situation, and whenever there is a need to quickly alleviate distress, restlessness, agitation, autonomic hyperarousal, muscle tension, and other symptoms of anxiety or panic. The fast onset of action of BZs remains one of the key reasons for their ongoing popularity among both patients and prescribers. This feature of BZs also allows them to be used on an "as needed" (PRN) basis. Such use of BZs is sometimes frowned upon by clinicians and researchers, especially when it is interpreted as a safety behavior, but many patients prefer to use BZs in this manner rather than take them continuously and for longer periods of time.

Choice of Pharmacotherapy for Anxiety Disorders

Medications with calming effects, including BZs, will always have a role in the pharmacological treatment of pathological anxiety because of the perennial human need to alleviate anxiety-associated distress and suffering [91]. Pharmacotherapy versus psychotherapy for anxiety disorders is a forced and false dichotomy, and both clinical practice and research show that a careful, well-planned combination of both modalities can contribute to favorable outcomes. BZs have often been considered unsuitable for combination with psychological interventions, especially CBT, presumably due to their interference with CBT. However, this assumption has not been tested adequately, and there is emerging evidence that BDZs can be combined with CBT safely and effectively [92].

A decision to use BZs or antidepressants as the initial treatment for anxiety disorders depends on several factors. If the key factor is the speed of onset of antianxiety effects, BZs have a clear advantage. Prominent physical symptoms of anxiety and tension may respond more reliably and more consistently to BZs than to antidepressants. Evidence is mixed about the preferential response of cognitive symptoms of anxiety, with a potential advantage of SSRIs in this realm. If the patient has a history of alcohol or other substance abuse, antidepressants are usually preferred over BZs, but this suggestion has been controversial in light of the reports that in such clinical situations, use of BZs may not be as risky [93, 94]. A history of severe adverse effects of the previously administered SSRIs or SNRIs, including sexual

dysfunction, strongly suggests that these medications should be avoided and that BZs may be preferred. The presence of depressive illness or a history of depressive episodes makes SSRIs or SNRIs a logical pharmacotherapy choice, although BZs can be co-administered for their anxiolytic properties or even used as a monotherapy for anxious depression [95]. Anxiety disorders have been associated with a higher risk of suicide, and prescribing medications with a low lethality potential in an overdose constitutes good clinical practice. If used alone, both BZs and SSRIs are relatively safe in an overdose. Unfortunately, overdosing on more than one drug is common, with the outcome depending on the particular combination of pharmacological agents and their quantities.

Combining BZs with SSRIs or SNRIs is common in clinical practice. However, this approach to the pharmacotherapy of anxiety disorders should not be haphazard, and its purpose should be clear. For example, one goal of this combination is to minimize adverse effects of SSRIs and SNRIs, especially at the beginning of treatment. A better tolerability of sertraline and clonazepam than of sertraline alone in the treatment of social anxiety disorder [86] supports such use. Another reason for combining BZs with SSRIs or SNRIs is to avoid waiting for too long for antidepressants to start "working." In other words, a combination of BZs with SSRIs or SNRIs tends to achieve a faster response compared to the response to an antidepressant alone, as demonstrated in panic disorder using various combinations of medications [96, 97]. Finally, there is some evidence that combining SSRIs with BDZs may produce better outcomes than treatment with an SSRI alone [47].

How to Select and Use Benzodiazepines in Anxiety Disorders

The treating physician should carefully evaluate the patient and rule out anxiety disorder due to other illnesses or causes (e.g., excessive intake of caffeine) first. The next management step should be the consideration of an initial trial of non-pharmacological treatment which may include short-term counseling, CBT and other psychotherapies, stress management, exercise, or meditation [98]. The decision to use medication may follow the failure of non-pharmacological treatments or may be the first choice in cases of severe symptomatology or when the availability of effective non-pharmacologic treatments is limited.

As Shader and Greenblatt wrote (99, p 1399–1400), "The ultimate decision to prescribe a benzodiazepine derivative or any other medication should be based on the assessment of the patient's degree of emotional distress and level of functional disability, the potential hazards of nontreatment in relation to the probable success of pharmacologic treatment, and the hazards of the medication." BZs should always be considered as a possible first medication choice considering their efficacy and safety. BZs can offer quick symptomatic relief and, e.g., in GAD, may reduce somatic symptoms and hyperarousal fairly quickly [99, 100]. Substance abuse could, of course, be a limiting factor in selecting BZs.

The decision as to which specific BZ to select may be based on various clinical factors and on BZ characteristics, e.g., their pharmacokinetic properties (short- vs. long half-life; metabolic pathway) and the degree of sedation.

Following the advice of Shader and Greenblatt [98] again, "Approaches to initiating benzodiazepine therapy are based largely on clinical experience. Therapy is initiated with a low dose that is based on patient's age, sex, body size, and medication history, and the dose is increased every few days until therapeutic benefit is achieved or side effects supervene. When side effects are encountered, further increases in the dose should be delayed or the dose should be reduced. Many patients who have drowsiness or other sedative effects soon after the initiation of therapy report that these symptoms diminish with continued therapy" (p 1400). "The duration of benzodiazepine treatment should be tailored to the character of the underlying illness. Patients with intermittent symptoms or symptoms that are triggered by identifiable anxiety-provoking situations are candidates for intermittent therapy. Those with persistent unremitting symptoms may require more continuous treatment, but the appropriate duration of therapy has not been clearly established" [98]. Solid evidence regarding the length of treatment from long-term trials does not exist. It is our clinical experience that treatment could continue indefinitely, though decrease and/or discontinuation of BZs should be attempted from time to time, depending on clinical status.

Conclusion

BZs are effective, efficacious, and safe medications indicated for the treatment of anxiety and anxiety disorders. They may be considered the treatment of choice in a number of patients and preferred to ADs in a number of clinical situations. BZs are quite versatile agents that could be used intermittently, for short-term treatment and for long-term, or even indefinite treatment. It is clearly time to rethink their role in the treatment of anxiety disorders in the upcoming era of personalized medicine and more specifically targeted treatment.

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