EXPERT REVIEWS

The reappraisal of benzodiazepines in the treatment of anxiety and related disorders

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Benzodiazepines (BDZs) continue to be shrouded in controversy, mainly because of dependence associated with their long-term use and some of their side effects. Despite treatment recommendations favoring newer antidepressants, BDZs are still commonly prescribed for anxiety and related disorders. Recent studies have demonstrated that long-term use of BDZs for these conditions can be effective and safe and that BDZs can be combined with psychological therapy and antidepressants to produce optimal outcomes. Such findings, along with a failure to convincingly demonstrate the overall superiority of alternative pharmacotherapy for anxiety and related disorders, have given an impetus to a reconsideration of the role of BDZs. This article reviews BDZs and other pharmacotherapy options for anxiety and related disorders and suggests that treatment guidelines should acknowledge that BDZs can be used as first-line, long-term pharmacological treatment for panic disorder, generalized anxiety disorder and social anxiety disorder.

There is an ongoing controversy about the use of benzodiazepines (BDZs) for anxiety and related disorders (e.g., posttraumatic stress disorder [PTSD]). While most treatment guidelines [1–3] suggest that BDZs should generally be avoided or only used short-term, surveys of the practicing psychiatrists and other physicians and data about medication prescriptions in various countries indicate that BDZs continue to be frequently prescribed and often for long-term use.

Much of the controversy about BDZs appears to be a product of the clashes between their bitter opponents and those who dare challenge the current orthodoxy about the essentially harmful nature of BDZs. A part of the problem is a different perspective by different clinicians. For example, addiction specialists or clinicians working in settings for the treatment of substance use disorders tend to take a 'harsh' stand on long-term use of BDZs and readily perceive them as 'addictive' because they see many addicts who also abuse BDZs; in contrast, clinicians working primarily with non-addicted patients with anxiety and related disorders may be more willing to see the 'good side' of BDZs. Some protagonists in this dispute have been involved as a consequence of their realization that the alternatives to BDZs (e.g., antidepressants) have not delivered what they had promised initially. Therefore, it is timely to re-examine the data and evidence pertaining to BDZs, which is the purpose of the present article.

A number of recent editorials, commentaries, debate articles and reviews have called for BDZs to be revisited [4,5], reconsidered [6–8] or reappraised [9]. Some discuss the 'art' of long-term use of BDZs in anxiety disorders [10], while others consider the reasons for the ongoing popularity of BDZs [11,12] or suggest that BDZs have a future despite previous recommendations to minimize their use or abandon them [6,13,14]. Most of these publications focus on anxiety disorders [5–7,10–14], but others discuss the role of BDZs more generally [4,8,9].

Their conclusions are not the same, as some publications continue to find more harm than benefit associated with BDZs [4,9], some remain cautious about BDZs but seem to be relatively open to reconsidering their authors' generally unfavorable views on BDZs based on the new data [8,11], and others suggest that the time has come to reassess BDZs, especially their role in anxiety and related disorders [5–7,10,13,14].

This tendency to 'have another look' at BDZs may be a result of the findings from various countries that these medications continue to be frequently prescribed and some recent studies of BDZs in anxiety and related disorders. Yet another factor might have contributed to a renewed interest in BDZs: an increased tendency to prescribe for anxiety and insomnia medications such as second-generation antipsychotics, which may represent a less safe option than BDZs. All these are discussed in the text below.

Use of BDZs in the 21st century

BDZs are still frequently prescribed around the world. Recent studies from England [15], The Netherlands [16] and Australia [17,18] confirm this trend, although the findings are slightly different. The pattern of prescribing or using BDZs in England from 1998 to 2010, in Australia between 2000 and 2011, and in The Netherlands from 1992 to 2002 (among people aged 55–64) was generally stable [15–17]. One study found a modest overall decline in the amount of BDZs dispensed in Australia between 1992 and 2011 [18]. Studies from The Netherlands [16] and Canada [19] reported that long-term BDZ use was particularly common.

When it comes to the anxiety disorders, it was estimated that 55–94% of patients in the USA with these conditions were treated with BDZs [20]. Other studies also suggest that BDZs remain the most commonly used medications for anxiety disorders in the USA [21,22]. Frequent use of BDZs has also been reported in several European countries, with these medications being prescribed for anxiety as well as various other disorders, including depression [23,24].

A number of reasons can account for an ongoing tendency to prescribe BDZs for anxiety and related disorders [10]. They include the consistent and reliable effectiveness of BDZs in terms of alleviating the overall experience of anxiety, tension and various physical symptoms of anxiety, their quick onset of therapeutic action, possibility of administering BDZs on an 'as-needed' (pm) basis and their relatively good tolerability. It has been suggested that the apparent popularity of BDZs is also due to the problems with newer antidepressants (selective serotonin reuptake inhibitors [SSRIs] and serotonin and noradrenaline reuptake inhibitors [SNRIs]) in the treatment of anxiety and related disorders, including their inconsistent or unreliable effectiveness, delayed onset of action and unpredictable or intolerable side effects [10].

Another explanation for the frequent use of BDZs is that the medical practitioners may prefer to follow their own 'mindlines' (i.e., internalized guidelines) rather than the official guidelines [11]. As these 'mindlines' are usually based on clinical experience, the popularity of BDZs may reflect a tension or a conflict between experience-based clinical practice and evidence-based recommendations. If so, it behooves us to try to ascertain whether the clinicians 'have it wrong' or whether the authors of clinical guidelines may be too removed from the reality of clinical practice.

Recent studies of BDZs in anxiety & related disorders

In recent years, several studies have challenged the notions that BDZs should be considered the second- or third-rank pharmacotherapy choice for anxiety disorders, that they may not be as efficacious as antidepressants in the short- and long-term treatment of anxiety disorders, that their role in the treatment of anxiety disorders is very limited and that they are likely to reduce therapeutic effects if combined with techniques of cognitive-behavioral therapy (CBT) such as exposure.

A systematic review and meta-analysis comparing BDZs with antidepressants in anxiety disorders found that there was no evidence to support the primacy given to antidepressants [25]. This pertains particularly to tricyclic antidepressants, as they were found to be both less efficacious and less well tolerated than BDZs in treating panic disorder. Likewise, no advantage for tricyclic antidepressants over BDZs was found in the treatment of generalized anxiety disorder (GAD). Offidani et al. [25] noted that only a few studies compared BDZs with newer antidepressants (paroxetine and venlafaxine), with the findings suggesting no difference in efficacy (or potentially greater efficacy of BDZs) and better tolerability of BDZs. These results thus provide support to a previous suggestion that a shift from BDZs to SSRIs as the preferred treatment for anxiety disorders was premature because it occurred without an adequate demonstration of the comparative advantage of the SSRIs [26]. This shift may have occurred as a result of an influence of the pharmaceutical industry at the time when SSRIs were developed and promoted [5,6] or exaggeration of the issues of dependence, abuse and side effects associated with BDZs [5,6]. According to Healy (p. 170 [27]), 'If the addiction card had not been played, Prozac would probably not have been the phenomenon it was in the West'.

Studies by Nardi et al. [28–30] demonstrated that although clonazepam and paroxetine were both efficacious in the short-term (8 weeks) and long-term (3 years) treatment of panic disorder, clonazepam was associated with greater clinical improvement and faster onset of action during the short-term treatment and better tolerability in the course of short-term and long-term treatment. An important finding of the long-term treatment study [30] is a confirmation of previous reports and observations that tolerance develops to the sedative, but not to the antipanic effects of clonazepam, resulting in maintenance of efficacy and fewer problems with drowsiness and memory/concentration. In contrast, side effects of paroxetine (e.g., sexual dysfunction and weight gain) persisted over the long-term treatment.

One study randomized patients with social anxiety disorder (SAD) who failed to respond to the initial, 10-week treatment

with sertraline to a 12-week treatment with sertraline plus clonazepam (up to 3 mg/day), sertraline plus placebo or venlafaxine [31]. Patients treated with the combination of sertraline and clonazepam generally fared better than the patients in the other two groups, although not all differences in the efficacy parameters were statistically significant. In addition, patients who received clonazepam had fewer side effects, confirming that BDZs are generally better tolerated than antidepressants. The findings of this study were interpreted as supporting the common clinical practice of combining antidepressants and BDZs in the treatment of anxiety disorders [14]; however, this combination seems to be frequently used at the *beginning* of treatment and not only for cases resistant to the initial treatment with antidepressants. In fact, a body of literature supports the use of this combination for quick alleviation of distress and panic symptoms and for producing an earlier response in the treatment of panic disorder [32,33] and for achieving a better outcome in the treatment of SAD [34]. Finally, given the high rate (68%) of non-responders to monotherapy with sertraline in the study and evidence that clonazepam alone is efficacious in the treatment of SAD [35], it is reasonable to raise questions about the appropriateness of monotherapy with sertraline as first-line pharmacotherapy for SAD and the omission to use clonazepam alone in at least some SAD patients from the very beginning of treatment.

It has been a long-standing assumption that BDZs interfere with CBT and that they should generally be avoided in patients with anxiety disorders undergoing CBT [36], although the evidence supporting this assumption has been equivocal [37–39]. Various mechanisms have been postulated to explain this interference, including passivity and reduced motivation for participation in CBT by using BDZs, use of BDZs as 'safety devices', attribution of treatment gains to BDZs rather than to CBT, and interference of BDZs with learning that occurs during CBT ('state-dependent learning') and the consequently impaired extinction of fear. However, these mechanisms have not been clearly supported by research [40]. In this context, it is important to highlight a study demonstrating that patients with PTSD who underwent prolonged exposure therapy had a similar outcome regardless of whether or not they took BDZs [41]. The authors suggested that 'prolonged exposure psychotherapy is robust enough that even PTSD patients who are taking BDZs can often benefit from it' (p. 1242), implying that all or most of the benefit is to be attributed to prolonged exposure, with BDZs having an inherent tendency to interfere with it. Instead, these findings may also be interpreted as suggesting that in a subset of PTSD patients, BDZs actually facilitated prolonged exposure, thus producing results comparable to those in PTSD patients who perhaps did not need BDZs to cope with their symptoms or help them undergo prolonged exposure.

Are second-generation antipsychotics an alternative to BDZs for anxiety disorders?

In addition to showing that the number of prescriptions for BDZs has been steady or decreased slightly over the past 10–15 years, studies from England and Australia have reported an exponential increase in the utilization of the second-generation antipsychotic drugs [15,17]. A review of pharmaco-epidemiological studies from the USA, Canada, Europe and Australia also showed a large increase in the use of the second-generation antipsychotics [42]. This increase could not be attributed solely to the utilization of these medications for schizophrenia and bipolar disorder, and they were often prescribed for non-psychotic disorders [42]. In some studies, use of the second-generation antipsychotics in lower doses accounted for high prescription rates [15]. This low-dose use has often been 'off-label' and/or for conditions like anxiety and related disorders.

There has been a particularly prominent increase in prescribing second-generation antipsychotics with sedative properties such as olanzapine and quetiapine [15,17]. In New Zealand, quetiapine seems to be prescribed frequently and off-label by general practitioners [43]. Two articles reported a decreased use of BDZs (from 36.7 to 30.6%) among the veterans with PTSD in the USA between 1999 and 2009, along with the largest increase for low-dose quetiapine in the number of prescriptions filled [44,45]. While there was little comment about the appropriateness of this off-label use of quetiapine, a concern was expressed that the frequency of BDZ use among PTSD patients was still above 30%, prompting one of the commentators to state ironically that this implied that 'we are in the midst of a public health crisis as a result of benzodiazepine use' (p. 304 [46]).

There is good evidence that quetiapine is efficacious for GAD [47,48] and in some countries (e.g., Australia), quetiapine has been approved by the regulatory authorities for the treatment of GAD. It is unknown whether quetiapine is also effective for other anxiety and related disorders. The popularity of off-label use of quetiapine for 'anxiety' or 'distress' has been attributed to its calming effects [49]; it has been argued that calming effects may temporarily help people feel less troubled by their anxiety, although these effects are not always necessary to produce the desired decrease in anxiety [49]. If so, is quetiapine going to replace BDZs in the treatment of anxiety disorders?

The findings of the studies referred to above suggest that quetiapine may be used instead of BDZs, probably to avoid dependence issues associated with BDZs. This is not the first time that sedating or calming medications have been used instead of BDZs for the same reason: examples include tricyclic antidepressants (e.g., amitriptyline), other antidepressants such as trazodone and mirtazapine and some first-generation antipsychotics (e.g., thioridazine and trifluoperazine). Perhaps quetiapine has become more popular in recent times both because of its aggressive marketing and because clinicians have been under an ongoing pressure to avoid prescribing BDZs as a result of dependence-related issues. With quetiapine, however, there are two caveats. First, it is unknown whether quetiapine has any advantage over BDZs in treating anxiety and related disorders, and studies that would directly compare the efficacy of BDZs

and quetiapine in various anxiety and related disorders are urgently needed. Second, there is a question of safety, as quetiapine has been associated with serious side effects such as weight gain and metabolic syndrome, even in lower doses that are typically used for anxiety, distress and insomnia. A recent study has found that some second-generation antipsychotics (olanzapine and aripiprazole) are associated with insulin resistance independent of weight gain, increase in food intake and presence of a mental disorder [50]. Moreover, discontinuation of second-generation antipsychotics has been associated with the withdrawal and rebound symptoms [51]. Without firmly establishing that quetiapine is at least as efficacious and as safe as BDZs, there should be no haste to replace the latter with the former.

Are there any changes in treatment guidelines regarding BDZ use for anxiety & related disorders?

In view of the converging data suggesting the greater role for BDZs in the treatment of anxiety and related disorders than that accorded to them in the previous guidelines, one might expect this to be acknowledged in the new guidelines. So far, this is occurring minimally, as demonstrated by the recent documents produced by the leading members of the Psychopharmacology Special Interest Group of the Royal College of Psychiatrists and the British Association for Psychopharmacology [8], the British Association for Psychopharmacology [52] and the Canadian Anxiety Guidelines Initiative Group [53].

In the recommendations produced by Baldwin et al. (p. 971 [8]), the main changes pertain to long-term BDZ use. These authors acknowledge that many clinicians have been 'dissatisfied with previous guidance that benzodiazepines should be used for short-term treatment only and no longer than four weeks'. They then go on to state that 'if treatment courses lasting longer than four weeks are required, this should not necessarily be regarded as a deviation from good clinical practice', but such treatment should be used 'if the alternative to benzodiazepine treatment … proves to have little benefit' and 'provided the patient periodically attempts to slowly reduce the dosage at regular intervals and tries to stop altogether when or if possible'. These statements carry a strong implication that long-term treatment with BDZs should really be avoided; such a treatment might be acceptable only as the last resort because of the risks associated with it.

The most recent 'evidence-based' pharmacological treatment guidelines from the British Association for Psychopharmacology (p. 412 [52]) make similar recommendations, stating that 'benzodiazepines will usually be reserved for the further treatment of patients who have not responded to at least three previous treatments (such as after non-response to both an SSRI and an SNRI and a psychological intervention)', but noting that 'concerns about potential problems in long-term use should not prevent their use in patients with persistent, severe, distressing, and impairing anxiety symptoms, when other treatments have proved ineffective'. The Canadian clinical practice guidelines (p. 7 [53]) appear somewhat stricter about BDZ use

by stating that 'benzodiazepines may be useful as adjunctive therapy early in treatment, particularly for acute anxiety or agitation, to help patients in times of acute crises, or while waiting for onset of adequate efficacy of SSRIs or other antidepressants. Due to concerns about possible dependency, sedation, cognitive impairment, and other side effects, benzodiazepines should usually be restricted to short term use'. The British guidelines (p. 412 [52]) provide the highest strength of recommendation to their assertion that BDZs 'can be effective in many patients with anxiety disorders', suggesting that in terms of efficacy, there is no difference between BDZs and newer antidepressants such as SSRIs and SNRIs. Similarly, the Canadian guidelines accord BDZs the highest 'strength of evidence' for the pharmacotherapy of panic disorder, SAD and GAD, but consider BDZs a second-line option for these disorders. If the efficacy of BDZs, SSRIs and SNRIs is approximately the same, the implication is that long-term use of SSRIs and SNRIs is much safer than that of BDZs. What evidence do the authors of the British guidelines provide for this claim?

The British guidelines (p. 411, 412 [52]) mention that BDZs 'can cause troublesome sedation and cognitive impairment… and tolerance and dependence can occur (especially in predisposed patients)'. With regards to SSRIs, these guidelines state that they have 'potentially troublesome adverse effects, including initial increased nervousness, insomnia, nausea and sexual dysfunction', that they 'may interact with some other psychotropic drugs and treatment for physical illness', and that 'when stopped abruptly, and even when tapered slowly, SSRIs can produce a discontinuation syndrome characterized by dizziness, insomnia and flu-like symptoms'. With respect to SNRIs, the British guidelines note that 'duloxetine and venlafaxine may be less well tolerated than the SSRIs', that they have both been 'associated with discontinuation symptoms after abrupt withdrawal', that 'venlafaxine is sometimes associated with an increase in blood pressure' and that 'it is recommended that duloxetine is avoided in patients with known liver disease and patients considered to be at risk of hepatic dysfunction'.

Comparing the side effects of BDZs with those of the SSRIs and SNRIs, it is hard to understand why the long-term treatment with SSRIs and SNRIs is considered much safer than the long-term treatment with BDZs. It appears that the authors of both the British and Canadian guidelines give more weight to problems associated with the use of BDZs than to problems arising in the course of treatment with SSRIs and SNRIs. In doing so, they seem to ignore evidence that BDZs are often better tolerated than SSRIs and SNRIs [21,25,28–31,54], further overestimating the problems arising in the course of treatment with BDZs and underestimating the problems occurring during the treatment with SSRIs and SNRIs. Perhaps it would be unrealistic to expect any recommendations to favor BDZs, considering that BDZs are unflatteringly referred to in the literature as 'the lesser evil' [55] or a 'necessary evil' [56]. In the text below, the specific problems associated with the use of BDZs, SSRIs and SNRIs are addressed in some detail.

Sedation, cognitive impairment & related problems with BDZs

Sedation is the most common side effect of BDZs. It is usually dose-dependent and patients experiencing it can decrease the dose if sedation is prominent or persistent; alternatively, patients can remain on the same dose and wait for a few days or up to 1–2 weeks until they have become used to that particular dose and sedation no longer poses a problem [57]. In other words, tolerance usually develops to the sedative effects of BDZs [30] and patients who initially felt slowed down, tired, drowsy or even sleepy, usually do not complain of these side effects if they remain on the same dose. In practical terms, this means that sedation may be an issue at the very beginning of treatment with BDZs or immediately after the dose has been increased, and these are the times when patients need to be cautious. Remaining on the same dose for longer periods of time is usually not associated with the symptoms of sedation.

Impairment of motor coordination and interference with psychomotor performance are side effects of BDZs closely related to sedation and the above suggestions about managing sedation also apply to addressing these problems. Also, an additional dose of a BDZ should not be taken prior to driving or operating machines. Although impairment of coordination may affect driving skills [58] or skills needed for other complex tasks, some studies failed to relate long-term BDZ use to psychomotor impairment [59]. Moreover, no dose or serum level of a BDZ has been clearly associated with impairment of a driving ability [60], and calls to limit prescriptions for BDZs because of their possible interference with driving have not been widely supported.

Cognitive changes (e.g., alterations in visuospatial ability, speed of processing and verbal learning) associated with chronic administration of BDZs have been a source of controversy because of the conflicting findings and a failure to take into account the potential confounding factors. Anterograde amnesia occurs relatively frequently and refers to a difficulty remembering what happened in the period of up to several hours *after* a BDZ has been taken; in most cases, memory can still be retrieved, although with some effort. A review of the literature found that a long-term use of BDZs had a negative effect on various aspects of cognitive functioning (p. 13 [61]), although 'the clinical impact of cognitive changes may be insignificant in most patients in terms of daily functioning', suggesting only subtle alterations. A study in the elderly reported that chronic BDZ use was associated with poorer cognitive performance, but not with an accelerated cognitive decline with age [62]. One brain imaging study [63] did not find brain abnormalities in patients undergoing long-term treatment with BDZs.

Excessive sedation and psychomotor impairments may make the elderly more prone to falls and fractures. As with many other medications, the elderly should generally use BDZs with caution and at the lowest possible dose. Hip fracture rates in the elderly were not found to be necessarily associated with BDZ use [64], and the risk of falls in the elderly is not only associated with BDZs, but also with antidepressants and antipsychotic drugs [65]. Therefore, it does not follow that the elderly are at an especially high risk of falls solely because of using BDZs. Many elderly patients are unwilling to cease BDZs because they perceive it as unnecessary and arduous and because it would deprive them of the highly valued soothing properties of BDZs [66,67].

Disinhibition, which refers to irritability, anger or behavior that is inappropriate, 'out of character' or aggressive, is not a common side effect of BDZs [68]. Still, individuals with emotionally unstable personalities, immaturity, impulse control problems, brain damage and substance misuse may be more likely to exhibit disinhibition, and BDZs should generally be avoided in people with these characteristics.

Tolerance, dependence & withdrawal symptoms with BDZs

Although there are occasional reports of patients with anxiety disorders who increase the dose of BDZs to continue experiencing the initial anti-anxiety effect or who experience a loss of therapeutic benefit with the continuing treatment with BDZs, a body of evidence shows that the vast majority of patients with anxiety disorders do not have a tendency to increase the dose during long-term treatment with BDZs [30,69–72]. Therefore, tolerance to anxiolytic effects of BDZs usually does not occur in the course of long-term treatment. When patients increase the dose of BDZs, this usually appears in the context of other substance misuse.

Patients with anxiety disorders who are treated continuously with BDZs for several weeks develop dependence, which has been referred to as therapeutic dose dependence [73,74], therapeutic dependence [75,76], low-dose iatrogenic dependence [4] and low-dose dependence [12]. Non-addictive dependence is another term applicable to BDZ dependence, as it is characterized by the symptoms of withdrawal upon abrupt discontinuation and no tolerance [77]. This dependence is a consequence of the physiological adaptation at the receptor level to the continuous use of BDZs [78]; it is therefore pharmacological or physical in nature and does not denote abuse, drug-seeking or lack of benefit [79]. More than two decades ago, it was noted for BDZs that 'physical dependence at therapeutic dose levels is not a major clinical problem' (p. 260 [73]). BDZ dependence has been clearly distinguished from BDZ abuse (i.e., a pattern of indiscriminate use, associated with harmful behavior and often with a tendency to increase the dose) and addiction to other substances [10]. The main implication of therapeutic dependence is that people using BDZs for a long time should not cease them abruptly because of the likelihood of experiencing withdrawal symptoms.

Withdrawal symptoms occurring after an abrupt cessation of long-term BDZ use are not inevitable; such problems were reported in approximately 40% of individuals taking BDZs regularly [80,81] and they were more likely in people with personality disorders, especially those with passive-dependent personality traits [82,83]. However, concerns about the withdrawal, occurrence of some withdrawal symptoms during BDZ taper

and reluctance to discontinue BDZs are much more common. The BDZ withdrawal syndrome is often portrayed in an exaggerated manner [5,6] and as dangerous; it is therefore dreaded by both patients and physicians. In fact, some patients continue taking BDZs only to avoid withdrawal. This intensifies their fear that they will not be able to stop the medication and reinforces the notion that BDZs are 'addictive'. Withdrawal symptoms are rarely life-threatening, do not last very long (from several days to 2–3 weeks), usually leave no consequences and often disappear without treatment. Still, the BDZ withdrawal syndrome should neither be overestimated nor trivialized [10], with the likelihood of the occurrence of withdrawal symptoms minimized through a gradual and individualized tapering schedule before ceasing the medication; this approach should be used particularly with shorter-acting BDZs such as alprazolam, because they are more likely to be associated with the withdrawal symptoms. It is also important that patients feel ready for BDZ discontinuation, which means that they feel capable of coping with the anxiety without having to continuously rely on the medication [10]. Patients should never be coerced to cease BDZs, and setting the strict time limits for discontinuation is usually not helpful.

Discontinuation symptoms & side effects associated with the SSRIs & SNRIs

When SSRIs and SNRIs were licensed for anxiety disorders, they were touted as safer than BDZs, especially as they were marketed as a 'non-addictive' treatment alternative [27]. This is ironic, as SSRIs and SNRIs have both been associated with the withdrawal symptoms and withdrawal syndrome, euphemistically called 'discontinuation symptoms' and 'discontinuation syndrome' [84–86]. When the BDZ withdrawal symptoms were systematically compared with the SSRI discontinuation symptoms, they were found to be very similar, which led to a proposal to abolish this seemingly artificial distinction between 'withdrawal' and 'discontinuation' [87]. However, the terms 'sedative, hypnotic or anxiolytic withdrawal' (which includes the BDZ withdrawal syndrome) and 'antidepressant discontinuation syndrome' have been incorporated into the DSM-5 [88], suggesting that they are different conditions. This is also emphasized in the DSM-5 by classifying sedative, hypnotic or anxiolytic withdrawal among substance-related and addictive disorders, whereas antidepressant discontinuation syndrome is placed in the group of 'medication-induced movement disorders and other adverse effects of medication'. Moreover, the DSM-5 stipulates that 'unlike withdrawal syndromes associated with opioids, alcohol and other substances of abuse', the symptoms of antidepressant discontinuation syndrome 'tend to be vague and variable', suggesting that a listing of its diagnostic criteria is not possible (p. 713, [88]). Such a statement runs contrary to the conclusions of the Nielsen et al. study (p. 713, [87]). Finally, the DSM-5 states arbitrarily and prematurely that 'the antidepressant discontinuation syndrome is based solely on pharmacological factors and is not related to the reinforcing effects of an antidepressant' (p. 713, [88]).

Regardless of the exact mechanism responsible for the antidepressant discontinuation syndrome, it is now considered good clinical practice to gradually decrease the dose of SSRIs (and SNRIs) before their cessation in a manner analogous to the BDZ taper. Moreover, SSRIs with a shorter half-life (e.g., paroxetine) seem more likely to be associated with the discontinuation symptoms than SSRIs with a longer half-life (e.g., fluoxetine), just like BDZs with a shorter half-life (e.g., alprazolam) are more likely to be associated with the withdrawal symptoms than BDZs with a longer half-life (e.g., clonazepam).

The fact that the discontinuation symptoms occur with SSRIs and SNRIs does not mean that these agents are 'addictive' [89], but by the same token, the occurrence of the withdrawal symptoms with BDZs should not be taken as evidence that BDZs are 'addictive'. Likewise, although BDZs can be abused, whereas 'SSRIs and other antidepressants do not have abuse potential' (p. 911 [89]), this does not necessarily represent an advantage of the SSRIs over BDZs in the treatment of anxiety and related disorders. This is because BDZ abuse among anxiety disorder patients is rare in the absence of current or past substance use problems [90,91].

At the beginning of treatment with SSRIs and SNRIs, side effects are common and include nausea, vomiting, diarrhea other gastrointestinal disturbances, headache, dizziness and insomnia. In addition, agitation, restlessness and increased anxiety ('jitteriness syndrome' or 'activation syndrome') often occur when commencing SSRIs or SNRIs at their usual antidepressant dosage in patients with panic disorder or those with prominent physical symptoms of anxiety. All these symptoms usually abate with continued pharmacotherapy, but they can be quite severe and lead to a premature discontinuation of SSRIs or SNRIs in a substantial proportion of patients, for example, in those with panic disorder [54]. It is now recommended to commence treatment of patients with anxiety disorders in lower doses to avoid 'jitteriness syndrome'. Still, some anxious patients describe the initial side effects of SSRIs and SNRIs as the 'worst-ever experience'. Because the occurrence of these symptoms is unpredictable, patients should be well informed about them in a non-alarming manner before commencing treatment.

Unfortunately, numerous side effects may occur in the course of long-term treatment with SSRIs [92]. Arguably, the most troublesome and the most frequent of these are various problems with sexual functioning. After sexual dysfunction, when the seriousness, frequency and evidence for problems associated with long-term use of SSRIs are taken into account [92], the following is their ranking: hyponatremia, risks during pregnancy, sleep disturbance, emergent suicidal ideation, osteoporosis with the risk of fractures, bleeding (e.g., upper gastrointestinal bleeding), cardiovascular abnormalities, extrapyramidal symptoms, apathy/amotivation and weight gain. In addition, use of antidepressants in vulnerable patients, especially those who are young, may be associated with a switch to mania or hypomania [93]. These problems, as well as the potential for drug interactions with certain SSRIs, have led some to view BDZs as much safer than antidepressants in the long-term

treatment of anxiety disorders [25,94]. As already noted, SNRIs may be even less well tolerated than SSRIs, their side-effect profile is otherwise similar to that of the SSRIs and they may have additional side effects. A recent review has suggested that use of antidepressants for anxiety disorders should be reduced unless there is a co-occurring major depressive disorder or other treatments have failed [95].

Safe long-term use of BDZs for anxiety & related disorders

Despite our best efforts to treat people with anxiety and related disorders quickly and effectively, it is likely that there will always be patients with these conditions who need long-term pharmacological treatment. This does not necessarily mean that our pharmacological and psychological treatments are inadequate and is a consequence of various disorder- and personality-related factors. After all, many anxiety and related disorders tend to run a chronic course and short-term treatments for chronic conditions are often insufficient.

When encountering a patient who needs long-term pharmacological treatment, a medication that has a greater likelihood of producing optimal outcomes should be chosen. This does not have to be a single drug, and clinicians should not put themselves in an 'either-or' situation. For example, a patient with GAD who has responded well to a BDZ, but who also has a history of depressive episodes and currently presents with depressive symptoms, would probably do well with a combination of a BDZ and an antidepressant. This underscores a well-known clinical dictum that treatment decisions largely depend on the individual circumstances of each patient.

This article has reviewed evidence that BDZs can be used safely in the long-term treatment of anxiety and related disorders and concludes, in agreement with other authors [5,6,14], that BDZs should be considered for such use. BDZs are not inferior to newer antidepressants such as SSRIs and SNRIs, and the choice of medication depends on patient preference and particular clinical situations and considerations shown in TABLE 1. Clinicians should be flexible in their judgment and decision-making and realize that all recommendations are relative and that idiosyncratic personal circumstances may ultimately play a more important role. Good examples are general suggestions that BDZs should be avoided in individuals with a history of substance use problems and that BDZs may be preferred if the patient has a history of sexual dysfunction during the previous course of treatment with antidepressants. Treatment with BDZs may still be justified in some individuals who misused alcohol or illicit drugs in the past [96], while the SSRI-induced sexual dysfunction may trouble some patients far less than their previously SSRI-responsive disabling anxiety, in which case it would be appropriate to recommence treatment with an SSRI, after discussing this with such patients.

Expert commentary

It is a paradox that more than 50 years since BDZs were introduced, psychiatry remains embroiled in a debate about the advantages and disadvantages of these medications. The main reason for this situation is an approach to BDZs that can be described as 'emotional' and at times laden with conflict of interest and hence irrational and biased. It is not a simple case of 'disliking' BDZs, but rather, a systematic and a seemingly never-ending campaign against them. Unfortunately, the individuals leading this campaign have shaped public and professional opinion and managed to incorporate their views into the official documents such as treatment guidelines.

The main disadvantage of BDZs is that they are habit-forming. While no one denies this, the only question is about the seriousness of dependence and its implications and consequences. Multiple lines of evidence suggest that this problem has been blown out of proportion, with many clinicians being induced to believe that BDZs are inevitably and automatically 'addictive' and that this overshadows and cancels out any advantages that they may have. This atmosphere has almost stifled any dissent and prevented discussion lest the 'defenders' of BDZs are perceived as condoning something that is *a priori* judged as socially and even morally unacceptable.

The reality is that BDZ dependence should be treated just like any other problem that arises as a consequence of medication treatment. Another reality is that a more effective and a better tolerated alternative to BDZs (e.g., antidepressants) for the pharmacotherapy of *all* individuals with anxiety and related disorders has not been developed, despite the efforts of the propaganda to convince us otherwise. This calls for an individualized approach, whereby potential risks and benefits of BDZs and other agents need to be weighed carefully for each patient and considered in a transparent and rational manner. A therapeutic recommendation is to be made on the basis of such consideration and it should also take into account patient needs and preferences.

In case of BDZs, clinical practice has been ahead of treatment guidelines. It is clinical practice that has inspired research challenging the dogmas about BDZs. Owing to this research, we are now in a better position to evaluate the role of BDZs in the treatment of anxiety and related disorders and understand how they can be combined optimally with other medications and psychological treatments such as CBT. While there is certainly a need for more research, treating BDZs as a dangerous, last-resort treatment option for anxiety and related disorders cannot be justified. In fact, it is irresponsible to deny patients access to BDZs as the first-line pharmacotherapy option; if treatment guidelines are to be relevant for clinical practice, they should clearly acknowledge an important role of BDZs in the treatment armamentarium for anxiety and related disorders.

Five-year view

It is likely that BDZs will continue to be used for anxiety and related disorders as long as there are no medications that are superior to them in terms of both effectiveness and tolerability. The endorsement by the official treatment guidelines of BDZs as first-line pharmacotherapy for anxiety and related disorders may not occur soon, and the discrepancy between clinical

Table 1. Factors influencing the choice of benzodiazepines and selective serotonin reuptake inhibitors/ serotonin and noradrenaline reuptake inhibitors in the long-term treatment of anxiety and related disorders.

	Favoring BDZs	Favoring SSRIs/SNRIs
Primary diagnosis of panic disorder and/or agoraphobia	+	+
Primary diagnosis of generalized anxiety disorder	+	+
Primary diagnosis of social anxiety disorder	+	+
Primary diagnosis of obsessive-compulsive disorder		+
Primary diagnosis of posttraumatic stress disorder (use for symptoms such as insomnia and autonomic hyperarousal)	?	+
History of depressive episodes or chronic depression		+
Current moderate to severe depressive symptoms		+
Bipolar disorder or a risk for bipolar disorder	?	
History of substance use disorders or current substance use disorder	?	+
Severe personality disturbance, including features of emotionally unstable personality, prominent dependent traits and immaturity		?
Impulse control problems or brain damage		?
Need for a quick symptomatic relief (e.g., for severe anxiety or panic attacks)	+	
Possibility of administration on an as-needed (prn) basis	+	
Predominance of somatic symptoms of anxiety, especially symptoms of autonomic hyperarousal	+	
Prominent muscle tension	+	?
Prominent sleep disturbance	+	
Predominance of cognitive symptoms of anxiety (e.g., pathological worry)	?	+/?
Predictability of side effects	+	?
General concerns about tolerability	+	?
History of severe side effects to the previously administered SSRIs/SNRIs (e.g., agitation, sexual dysfunction), especially if these effects led to a premature cessation of the medication	+	
Concern about excessive sedation and related problems (e.g., impairment of motor coordination)	?	+
Use in elderly	?	?
Relative safety in overdose, if the medication is taken alone	+	+ (? for SNRIs)

+: Evidence and/or clinical experience favoring the choice; ?: Uncertainty/equivocal evidence about the choice; BDZs: Benzodiazepines; SNRIs: Serotonin and noradrenaline reuptake inhibitors; SSRIs: Selective serotonin reuptake inhibitors.

practice and the official treatment recommendations in terms of the usage of BDZs will probably persist for some time. Ultimately, it will not be possible to ignore what clinicians do or dismiss their prescribing of BDZs as 'bad clinical practice'.

The amount of evidence needed to revise treatment guidelines is anyone's guess because the 'status' of BDZs in these guidelines is more a consequence of a negative or biased attitude toward them and conflicts of interest of the authors of the guidelines than a matter of evidence. Still, it would be important to conduct randomized studies comparing BDZs with SSRIs (and SNRIs) in the long-term treatment of patients with 'core' anxiety disorders, that is, panic disorder, GAD and SAD.

Another closely related research task involves studying the predictors of the outcome of long-term treatment of these patients with BDZs, SSRIs and SNRIs.

The funding of this kind of research should not be expected to come from the pharmaceutical industry because all BDZs and practically all SSRIs and SNRIs are now generic, and there is no commercial incentive to compare these medications for long-term treatment of anxiety and related disorders. While this presents a good opportunity to conduct such studies in a more objective climate, devoid of commercial interests, it may still be difficult to persuade the funding bodies to sponsor this research.

Any attempts in the future to 'rebrand' or 'reinvent' antidepressants as medications for use in anxiety and related disorders should be met with skepticism because previous attempts to do so have not led to breakthroughs in the pharmacological treatment of anxiety. Moreover, SSRIs and SNRIs have only contributed to further blurring of the boundary between (mild to moderate) depression and anxiety by suggesting that the distinction between the two does not really matter as they both respond to the same type of medication – SSRIs or SNRIs. If indeed there is a boundary between them, the development and discovery of agents for mild-to-moderate depression should be a process separate from the development and discovery of agents for anxiety. If, on the other hand, this boundary is deemed to be artificial, the underlying neurobiological alterations common to both mild-to-moderate depression and anxiety, once they are discovered, should be targeted in the course of new drug development for these disorders.

In the meantime, can the pharmacological treatment of anxiety and related disorders be improved by modifying BDZs so that their effectiveness is retained, while their habit-forming property and side effects are minimized? BDZs exert their effects through GABA$_A$ receptors, which have several subtypes and are located in different parts of the brain. These receptor subtypes are believed to mediate various effects of BDZs, and novel BDZ-like compounds might be developed to target them. For example, such drugs might act selectively on the α-2 subtype and exhibit anxiolytic effects [97], without activating the α-1 subtype, which is deemed to be responsible for sedation, cognitive side effects and dependence [98,99]. Such non-sedating and non-dependence producing BDZ-like anxiolytics, also devoid of cognitive side effects, might represent a significant improvement in the pharmacological treatment of anxiety and related disorders. Unfortunately, the introduction of such medications into clinical practice does not seem to be within reach.

Various other drugs with anti-anxiety properties are being developed around the world, but this process is still in its early stages, with an uncertainty about its outcome. Therefore, BDZs and other currently available anxiolytic medications are here to stay for a number of years. Our immediate task is to optimize their use to the greatest possible benefit of patients with anxiety and related disorders.

Key issues

- Benzodiazepines (BDZs) continue to be frequently prescribed for anxiety and related disorders, and for long-term use in these conditions, despite suggestions by the treatment guidelines to generally reserve these medications for short-term use and for patients who are resistant to newer antidepressants and/or psychological treatments.

- The likely reasons for the ongoing popularity of BDZs include their consistent and reliable effectiveness for the most prominent symptoms of anxiety, relatively good tolerability, quick onset of action, possibility of using them on an 'as-needed' (prn) basis and the realization that newer antidepressants have not been as useful for anxiety and related disorders as they had initially seemed to be.

- BDZs differ in terms of their potential to be associated with problematic use; for example, the longer-acting BDZs (such as clonazepam) are less likely to be implicated in the withdrawal symptoms than the shorter-acting BDZs (such as alprazolam).

- It appears that some second-generation antipsychotics, especially quetiapine, are prescribed for anxiety and related disorders to avoid using BDZs; clinicians should be cautious about this practice, as there is no evidence that quetiapine is at least as safe and effective as long-term use of BDZs.

- BDZs are generally a safe option for long-term treatment of many patients with anxiety and related disorders and may be chosen as the first-line pharmacotherapy for panic disorder, generalized anxiety disorder and social anxiety disorder.

- In the absence of substance use disorders, BDZs are usually not associated with tolerance to their anti-anxiety effects in the course of long-term treatment of anxiety and related disorders, and they are rarely abused by patients with these conditions.

- In the absence of substance use disorders, the risk of addiction to BDZs during long-term treatment of anxiety and related disorders has been exaggerated; the pharmacological dependence that develops when BDZs are used long-term does not denote an all-encompassing preoccupation with and craving for BDZs, compulsive or uncontrollable BDZ-seeking behavior and adverse health and/or social consequences.

- The BDZ withdrawal syndrome is not an inevitable consequence of the long-term BDZ use; while an effort should be made to prevent withdrawal symptoms, it is not good clinical practice to portray the BDZ withdrawal syndrome in a catastrophic manner because it intimidates patients and veers them toward treatment options that are not necessarily safer or more suitable.

- The choice between BDZs and antidepressants in the long-term treatment of anxiety and related disorders should be made on the basis of patient preference and careful consideration of the individual circumstances of each patient.

- Evidence is emerging that combining BDZs with cognitive-behavioral therapy does not necessarily lead to poorer outcome of cognitive-behavioral therapy; more research is needed to ascertain how these treatment modalities can be optimally combined.

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