Journal of Behavioral and Cognitive Therapy 35 (2025) 100533

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REVIEW ARTICLE

A narrative review of strategies for discontinuing long-term benzodiazepine use and methodological recommendations: Is a success rate of only one in three patients sufficient?

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AbbreviationsBI, Brief intervention; BZs, Benzodiazepines and Z-drugs; CBT, Cognitive Behavioral Therapy; RCT, Randomized Controlled Trial; TAU, Treatment As Usual; TP, Taper program; SM, Substitution Medication; SNRI, Serotonin Noradrenaline Reuptake Inhibitors; SSRI, Selective Serotonin Reuptake Inhibitors; SRD, Substance-related disorder; WL, Waiting List

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https://doi.org/10.1016/j.jbct.2025.100533

Received 7 August 2024; received in revised form 14 April 2025; accepted 14 May 2025
Available online 13 June 2025

KEYWORDS
Benzodiazepine withdrawal;
Z-drug withdrawal;
Taper program;
Cognitive behavioral therapy;
Brief intervention

Abstract
Benzodiazepines (BZs) are psychotropic medications mainly prescribed for insomnia and anxiety. They can cause dependence, leading to decades of use. As such, there is debate grounded in confusion between substance abuse and fear of dependence in some patients. Clinical practice and evidence-based reviews agree that BZ dependence is difficult to treat: without support, only 7% of misusers manage to stop taking them. Analyzing randomized control trials (RCTs), this review examines three main interventions for BZ withdrawal: brief intervention (BI), substitution medication (SM) and cognitive-behavioral therapy (CBT). Post-intervention abstinence rates suggest that BIs can be compared to a simple taper program (TP), requiring low patient involvement, and may enable one in three patients to discontinue BZ use. However, this strategy should be considered with caution: outcomes could be adversely affected by the presence of a psychiatric disorder, a factor not controlled in these studies, nor are long-term results evaluated. Furthermore, can we consider that treating one in three patients is sufficient? CBT proved highly effective, enabling three in four patients attempting to abstain to successfully discontinue use, including patients with insomnia or anxiety. The SM approach showed no superiority over placebo effects. Moreover, abstinence rates being only measured over the very short term, no recommendations can be made regarding their use. This review concludes that there is a major methodological discrepancy between these approaches, BI and SM studies presenting substantially lower methodological quality in comparison to CBT studies. The present article proposes methodological recommendations for the study of BZ withdrawal methods.

Introduction

BZs are effective in the short-term treatment of anxiety (Bandelow et al., 2015; Slee et al., 2019; Stahl, 2002) and insomnia (Buscemi et al., 2007; Morgan, 2021). They are also effective in alcohol withdrawal and catatonia (Dubovsky & Marshall, 2022). BZs could also be a therapeutic option in anxious depression (Benasi et al., 2018) and in anxiety symptomatology associated with gastrointestinal illness. Although their side effects (Balon et al., 2015) are minor compared to other drugs (e.g. barbiturates), several governmental health authorities do not recommend their long-term use (the French national agency for drug safety (Agence Nationale de Sécurité du Médicament, 2017); the French federal office of public health, (Office fédéral de la santé publique, 2022), the United Kingdom's Department of Health (Ajayi, 2008)).

The long-term prescription and use of benzodiazepines have been criticized for over 40 years (Janhsen et al., 2015) due to their numerous side effects (Baldwin et al., 2013; Federico et al., 2017; Guaiana & Barbui, 2016): In the short term, the use of hypnotics increases daytime drowsiness and the risk of road accidents (Gustavsen et al., 2008). Adverse effects associated with benzodiazepines include muscle weakness, loss of coordination and balance, dizziness, confusion, speech difficulties, problems in forming new memories, and even total anterograde amnesia (Campagne, 2007). Moreover, physiological tolerance to these substances develops rapidly, leading to both physical and psychological dependence, which contributes to chronic use. Long-term use may result in impaired sleep physiology (reduced deep slow-wave sleep), learning and concentration difficulties (especially at high doses: reduced attentional resources and impaired verbal and visuospatial memory, working memory, and executive functions) (Federico et al., 2017). Spontaneous withdrawal attempts can lead to withdrawal syndrome, characterized by a resurgence of insomnia or anxiety, irritability, headaches, muscle and stomach pain, sensory hypersensitivity, significant weight loss, and seizures. These symptoms often lead users to resume medication. Among the elderly, a particularly vulnerable population, prolonged benzodiazepine use is known to increase the risk of falls and hip fractures, road accidents, cognitive decline, and mortality (Marra et al., 2015; Morin et al., 2004; Reeve et al., 2017). Long-term benzodiazepine use also raises the risk of developing a neurodegenerative disease, although the underlying physiological mechanisms are still debated (Marra et al., 2015; Pariente et al., 2016). Benzodiazepines also present an increased mortality risk when combined with opioids (FDA, 2016). Recent research has emphasized additional

health concerns linked to benzodiazepine use, such as dementia, cancer, pneumonia, suicidality, and complex persistent dependence (Brandt et al., 2024).

Given the adverse effects of these products, health authorities recommend prescribing them at the lowest possible doses and for the shortest duration and advise against the use of benzodiazepines beyond 12 weeks, or 4 weeks for benzodiazepines and related substances prescribed for sleep. These time frames include the dosage reduction period, which helps prevent the onset of withdrawal syndrome. Epidemiological studies highlight that these usage recommendations are rarely followed. Since dependence can occur as early as the first month of consumption (de las Cuevas et al., 2003), the majority of users exceed the legally prescribed duration (Kurko et al., 2015). It is estimated that between 2% and 5% of the general population abuse benzodiazepines (use beyond the scope of the medical prescription) or consume them for more than 6 months (Kurko et al., 2015; Neutel, 2005; Olfson et al., 2015). Abuse is defined as the use of benzodiazepines without a prescription, at higher doses or frequencies than prescribed, or for recreational rather than medical purposes. The number of prescriptions issued has increased exponentially over the past 20 years (G et al., 2019). This misuse affected 2.2% of the U.S. population in 2012, representing over 7 million people (Votaw et al., 2019). The number of people receiving at least one benzodiazepine prescription per year increased by 67% between 1996 and 2013 in the U.S., and the average dose of benzodiazepines prescribed tripled during this period. Benzodiazepine overdose deaths have increased by over 400%, and emergency room visits related to benzodiazepine prescriptions increased by more than 300% between 2004 and 2011 (Bachhuber et al., 2016). The proportion of drivers involved in accidents who have consumed benzodiazepines has steadily increased over the past 10 years (Orriols et al., 2019).

The major issue with long-term benzodiazepine use is the high level of dependence these substances induce (Ashton, 1994; Owen & Tyrer, 1983). In order to follow deprescription recommendations (Grandjean et al., 2021; Guaiana & Barbui, 2016; Haute Autorité de Santé - HAS, 2017; Pollmann et al., 2015; Pottie et al., 2018; Ribeiro & Schlindwein, 2021), it is essential to analyze the effectiveness and feasibility of large-scale treatments for benzodiazepine dependence. Various withdrawal interventions have been tested over the past thirty years. These include brief intervention (BI), medication substitution (SM) and cognitive behavioral therapy (CBT). Which are most effective? The aim of this article is to review these three types of intervention in adults having used BZs for more than one month, as this is the maximum duration recommended for hypnotic use recommended by the French national agency for drug safety (Agence Nationale de Sécurité du Médicament, 2017); the French federal office of public health, (Office fédéral de la santé publique, 2022); and the United Kingdom's Department of Health (Ajayi, 2008; Olfson et al., 2015), and there is currently no consensus on a definition of long-term use (Kurko et al., 2015). The empirical design implemented consisted of randomized controlled trials (RCTs), which provided the percentage of participants who successfully abstained (i.e., stopped taking BZs) for each withdrawal intervention studied. A critical analysis of RCT methodologies, inclusion criteria and withdrawal program procedures was conducted for each article.

Brief interventions

According to Mugunthan et al. (2011), minimal intervention in BZ withdrawal can be defined as the use of self-help information, a letter signed by the physician, or a short consultation with a general practitioner explaining, among other things, possible side effects and how to reduce or stop consuming these substances.

The different types of brief intervention

Written material

Many studies proposed a BI in the form of a letter encouraging patients to reduce or even discontinue using BZs, and/or an educational brochure. The degree of customization and the depth of this type of material varied from study to study. The letter, sent by the general practitioner, sometimes explained the risks of BZ use and ask the participant to reduce or stop usage, offering brief advice (Cormack et al., 1994; Heather et al., 2004; Morgan et al., 2002). The brochures provided detailed information sometimes covering known problems with long-term use, potential treatment alternatives, and in some instances a gradual withdrawal protocol (Kuntz et al., 2019; Martin et al., 2018; Tannenbaum et al., 2014). Nevertheless, this type of intervention was rarely limited to written material, as they often offered participants the opportunity to discuss with the physician or pharmacist. They were therefore not strictly controlled (Cormack et al., 1994; Heather et al., 2004; Tannenbaum et al., 2014). One study also stated that the material was either sent or physically handed over – and therefore potentially discussed with the patient, and that a communication from the pharmacist was sent to the physician with proposed alternatives to BZs. In effect, it is not known what was discussed between the physician and participant (Martin et al., 2018).

Interview with a healthcare professional

An interview with a healthcare professional was also considered a BI. This sometimes consisted in an explanation about insomnia and the risks associated with prolonged BZ treatment (Kosto et al., 2023). It could also involve an initial interview followed by one or more short follow-up interviews. The first interview might have focused on the withdrawal program and/or explanations of the properties of BZs, treatment of symptoms and causes, or risks. Follow-up sessions focused on assessing withdrawal symptoms and providing psychological support and motivational interviewing (Belleville et al., 2007; Vicens et al., 2006).

Mixed method

Most of the studies selected consisted of brief interventions combining a letter and/or brochure with an interview with a healthcare professional. Some offered a single interview and a brochure and/or letter (Bashir et al., 1994; Heather et al., 2004; Kosto et al., 2023; Kuntz et al., 2019), some proposed several consultations accompanied by one or more letters or brochures. (Bashir et al., 1994; Heather et al., 2004; Kuntz et al., 2019) and others offered several consultations accompanied by one or more letters or brochures (Belleville et al., 2007; Ten Wolde et al., 2008; Vicens et al., 2014).

Taper program

Taper programs were varied and could be adapted to the specific characteristics of the participant. Four studies out of the 10 provided no information on either the methods of reducing consumption nor the interval between each reduction (Bashir et al., 1994; Cormack et al., 1994; Kuntz et al., 2019; Ten Wolde et al., 2008).

Results of brief interventions

Seven studies out of 10 reported a significantly higher BI success rate than the control group (shown in Fig. 1). Control groups which received no advice achieved between 5% and 15% success, with an average of 8%, with the notable exception of one group which achieved a 26% success rate (Kuntz et al., 2019). Studies comparing different types of interventions did not identify one type of brief intervention as being more effective than another. They were also difficult to compare due to the different methodologies employed. On average, BIs reported a success rate of 36%. Only three studies provided follow-up data beyond 6 months, with abstinence rates ranging from 25% to 45% in the BI group (Vicens et al., 2006; Wolde et al., 2008). Two of these reported abstinence rates maintained at 6 and 12 months (Vicens et al., 2006, 2014). One study with a 10-year follow-up reported abstinence rates falling to 7% with the intervention being a written letter from the physician (de Gier et al., 2011).

Substitution medication

SMs are the most extensively studied interventions for BZ withdrawal (Pollmann et al., 2015). Several types of substances have been proposed for this purpose, such as anticonvulsants, antidepressants, antihypertensives, antiemetics, antihistamines, anxiolytics, muscle relaxants, BZ antagonists, long-half-life BZs, herbal substances and melatonin (Fluyau et al., 2018).

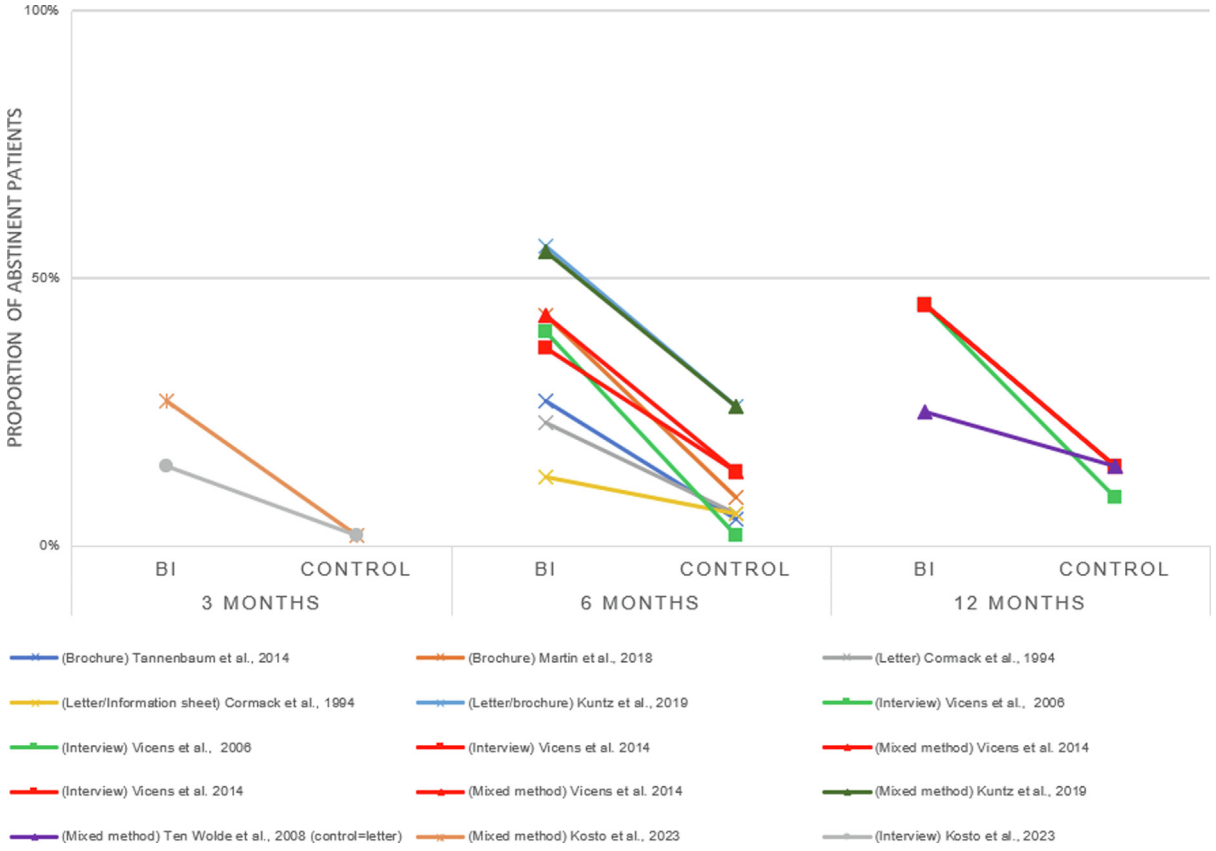

Fig. 1 Proportion of RCT participants abstaining from BZ use after a brief intervention (BI) was significantly superior to a control group.

Taper program and substitution medication method of consumption

The TPs offered and the associated method of SM use were highly heterogeneous. Certain TPs were abrupt (immediate interruption of BZ use), with direct substitution with a BZ-type SM or placebo, over a one-week period (Petrovic et al., 1999; Petrovic et al., 2002). One study offered substitution with another BZ during the TP, but over 3 to 4 weeks with a gradual reduction in SM (Lemoine et al., 2006). Other studies used 4 to 8 weeks of TP without a stabilization phase, with the SM taken between 1 to 3 weeks before, during, and for 4 weeks after the TP (Schweizer et al., 1995), (Schweizer et al., 1991), or during the TP and for 5 weeks afterwards (Tyrer et al., 1996), or during the TP only (Lähteenmäki et al., 2014). Other TPs included a stabilization phase of 2 to 4 weeks beforehand, and the SM was taken between 1 and 4 weeks beforehand, during, and then for 3 to 6 weeks after the TP (Vissers et al., 2007; Rickels et al., 1999, 2000; Rynn et al., 2003).

The different types of substitution medication

Melatonin

Three studies assessed the effectiveness of using melatonin in BZ withdrawal (Lähteenmäki et al., 2014; Puustinen et al., 2018; Vissers et al., 2007). They compared a group of participants taking melatonin and another taking a placebo during the BZ tapering program. The daily dose administered ranged between 2 mg to 5 mg, taken before bedtime. Melatonin was taken during withdrawal (Lähteenmäki et al., 2014; Puustinen et al., 2018), or during withdrawal and for 6 weeks post-withdrawal (Vissers et al., 2007). The results showed that taking melatonin did not contribute to a higher rate of successful BZ withdrawal than taking a placebo.

Antidepressants

Bearing in mind that they might be a treatment for an associated disorder, several antidepressants were assessed across the selected studies: trazodone (Petrovic et al., 1999; Rickels et al., 1999), imipramine (Rickels et al., 2000; Rynn et al., 2003) and dothiepin (Tyrer et al., 1996). These substances were taken either as direct substitutes for the usual BZ (Petrovic et al., 1999), in parallel before, during and after BZ withdrawal (Rickels et al., 1999, 2000; Rynn et al., 2003), or during and after withdrawal (Tyrer et al., 1996). The study by Rickels et al. (2000) is the only one which shows better performance of imipramine over placebo at 3-month follow-up.

Other benzodiazepines

Some authors (Lemoine et al., 2006; Petrovic et al., 1999; Petrovic et al., 2002) studied groups in which lormetazepam or bromazepam were substituted for the habitually taken BZs. Lormetazepam, a common BZ, was given at a low dose of 1 mg daily before bedtime for one week (Petrovic et al., 1999; Petrovic et al., 2002). Lemoine et al. (2006) used bromazepam, being a BZ commonly used in BZ withdrawal. They adapted the daily dose of bromazepam to the patients' usual consumption, giving them between 2 and 4 capsules of 1.5 mg per day. Substitution with the usual BZ was conducted for 2 weeks at these doses, then reduced by 50% for 2 weeks before bromazepam was replaced by a placebo.

Only one study, by Petrovic et al. (Petrovic et al., 2002) showed a positive result for lormetazepam versus placebo in BZ discontinuation. However, measurements were only taken at 30 days follow-up.

Other pharmaceutical treatments

Other pharmaceutical treatments based on anxiolytics (Rynn et al., 2003), antiepileptics (Rickels et al., 1999; Schweizer et al., 1991), antipsychotics (Lemoine et al., 2006) or hormones (Schweizer et al., 1995) were tested. Among these, sodium valproate (Rickels et al., 1999) and carbamazepine (Rickels et al., 1999) performed better than placebo in BZ withdrawal. However, in the Schweizer et al. study (Rickels et al., 1999), measures were taken only 5 weeks after withdrawal, and carbamazepine discontinuation was initiated between 2 and 4 weeks after BZ withdrawal, rather than at the same time. Rickels et al. (1999) took measurements at 5 weeks after withdrawal, but these were not considered herein, as the SM had been consumed up to that point. Although sodium valproate showed a positive result at 3 months post-withdrawal, this result was biased by antidepressant use among 55% of patients.

Results of substitution medication

Of the 12 articles retained, only 4 studies reported a significant result at follow-up suggesting superiority of Substitution Medication over placebo for BZ discontinuation (shown in Fig. 2). On average, SM accompanied by TP led to an abstinence rate of 84%. The placebo + TP condition yielded an average success rate of 50%. However, these results are all very short-term, since no follow-up data beyond 3 months was collected, leading to an absence of evidence of sustained effect over time. Furthermore, none of these results could be replicated in further studies for the same pharmaceutical treatment.

Cognitive behavioral therapies

Unlike brief interventions, CBTs target not only the problem of BZ dependency, but also the cause of substance use (Chapoutot et al., 2021). They can specifically address reasons for use, such as insomnia (Rossman, 2019) or anxiety disorders, including panic disorders (Takeshima et al., 2021).

Taper program

Some taper program included a stabilization phase beforehand (Morin et al., 2004; Spiegel et al., 1994) or required patients to maintain stable BZ use prior to intervention,

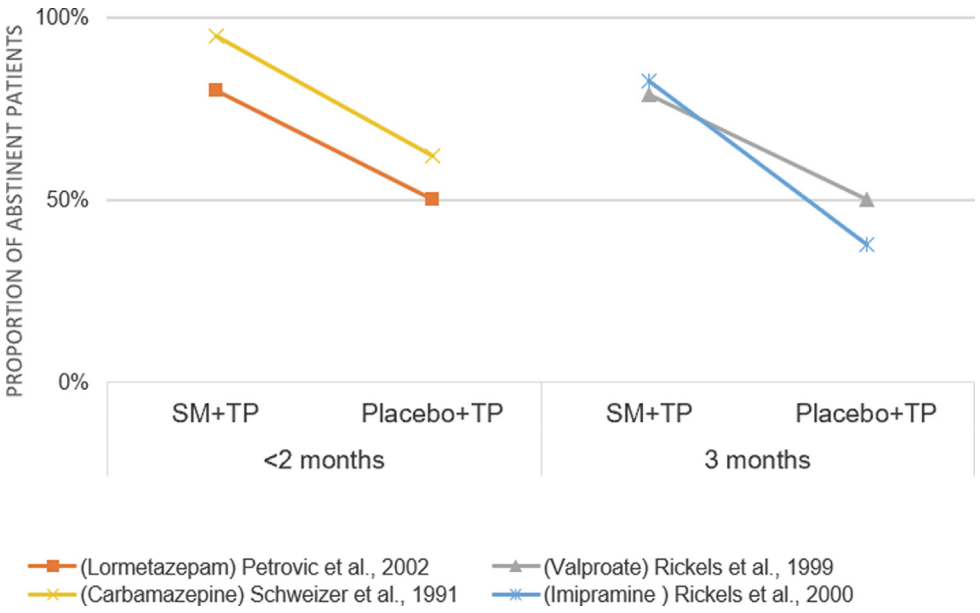

Fig. 2 Proportion of RCT participants abstaining following a SM + TP intervention significantly superior to a Placebo + TP group.

which was part of the inclusion criteria (Gosselin et al., 2006a). Another study transferred all participants not using diazepam to an equivalent dose of this BZ (Voshaar et al., 2003). Substitution for diazepam is based on the assumption that BZs with long half-lives induce less intense withdrawal syndromes than those with short half-lives (Ashton, 1994). Moreover, a comparison of experimental groups of patients taking the same BZs is methodologically more reliable. The duration of TP ranged between 4 to 16 weeks, depending on the study. Stages and intervals of consumption reduction varied, depending in particular on the initial dose, the molecule and/or the patient's motivation.

Different types of CBT

The studies offered between 5 and 12 individual or group CBT sessions, ranging from 45 to 120 min per session. Some studies included 1 to 3 post-taper ''booster" sessions (Baillargeon et al., 2003; Otto et al., 2010). Psychotherapy specifically targeted participants with panic disorder (Otto et al., 1993, 2010; Spiegel et al., 1994), insomnia (Baillargeon et al., 2003; Lichstein et al., 2013; Morin et al., 2004) or generalized anxiety disorder (GAD) (Gosselin et al., 2006a). Only one study targeted long-term BZ users, with no intervention specifically targeting the disorder for which the BZ had been prescribed (Voshaar et al., 2003). The taper program starts either at the same time as CBT, in the middle of CBT, or at the end (See Table S3 in supplementary data).

Most protocols included a disorder-specific informational or psycho-educational component and a cognitive restructuring component. CBT designed for panic disorder also included interoceptive exposure, and CBT for GAD included cognitive and situational exposure. CBT for insomnia included behavioral instructions aimed at regulating sleep (sleep restriction and stimulus control).

CBT results

Fig. 3 presents the 6 studies which demonstrated the advantage of CBT over TP alone, with an average success rate of 71% versus 33% for BZ withdrawal. We could identify one type of CBT intervention as being more effective than another, as the interventions were disorder-specific: CBT which does not target a specific disorder does not appear to be effective (Voshaar et al., 2003).

CBT reported a high abstinence rate, with an average of three out of four people successfully discontinuing BZ use. The withdrawal program alone enabled one person in three to stop use. Only half of the studies provided follow-up data beyond 6 months. Results appeared to be maintained over time in three studies (Baillargeon et al., 2003; Gosselin et al., 2006a; Spiegel et al., 1994), while weakening in the study of Morin et al. (Morin et al., 2004).

Discussion

Effectiveness of interventions

Despite the recommendations of the health authorities, several observational studies have shown that BZs are used chronically: in the United States, this concerns 2.7% of elderly people (nearly one third of the overall chronic BZ-use population) (Olfson et al., 2015); in British Columbia, approximately 8.4% of the population used a benzodiazepine in 2006, of whom 3.5% had prescriptions for more than 100 days (Cunningham et al., 2010); in Australia, 15 to 42% of all older adults use BZs long-term (Reeve et al., 2017); the misuse of BZs concerns approximately 2% of the general adult population and 13.5% of users in France (Agence Nationale de Sécurité du Médicament, 2017). The aim of this study was to compare different interventions for the treatment of BZ depen-

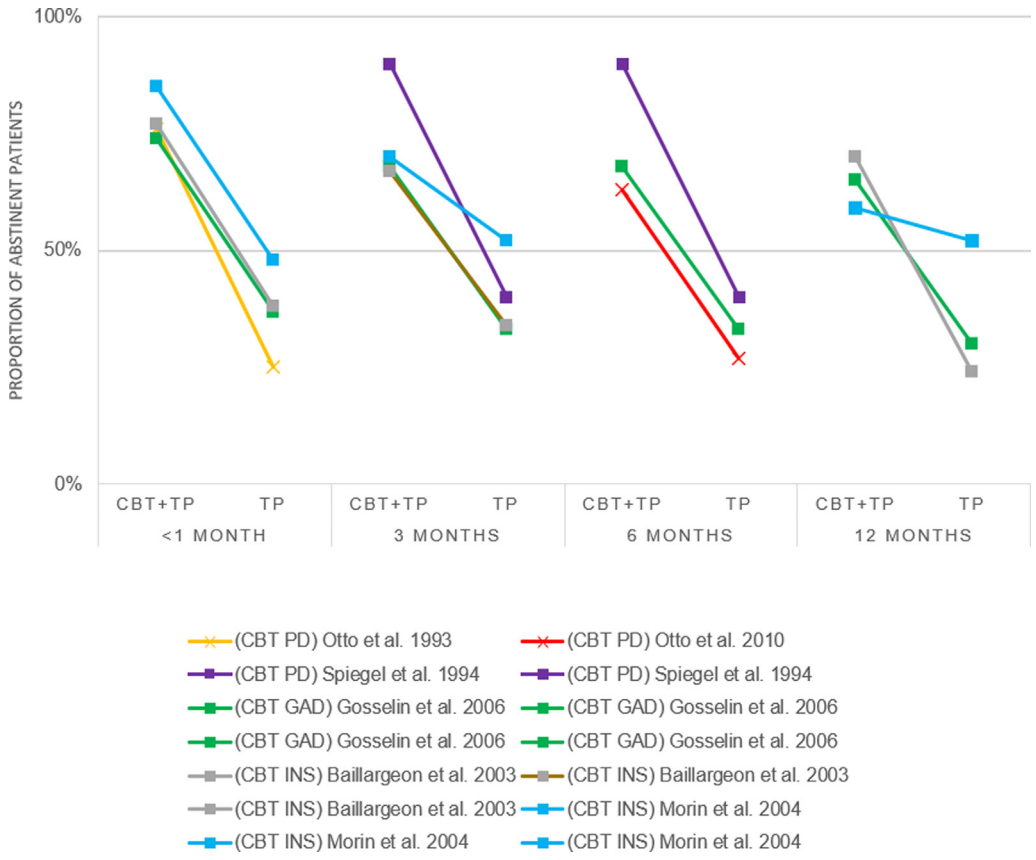

Fig. 3 The proportion of RCT participants abstaining following a CBT + TP intervention is significantly higher than a TP alone group.

dency and to identify the most effective in terms of abstinence. We compared the three types of interventions that are most widely studied scientifically and most frequently cited in reviews and recommendations. We excluded non-evidence-based interventions (such as alternative medicine).

Brief interventions

An analysis of the current literature revealed that brief interventions can lead to abstinence in around one in three participants, compared to one in ten participants without intervention. Given the low cost of this type of intervention, the efficacy of BIs therefore seems attractive. However, the small sample sizes studied, methodological weaknesses of control groups (motivational bias, pygmalion effect) and the diversity of methods employed mean that it is not possible to draw any conclusions on the most effective BI, nor its benefits beyond 12 months, as few studies included longer-term follow-up data. Furthermore, as these studies targeted more BZ users without mental disorders, the generalizability of these results to a population with psychiatric disorders, which are often long-term users, has not been established. Many reviews conclude that BIs triple the number of abstinent patients. Considering that the number of patients who manage to wean themselves off benzodiazepines is very low (7%), tripling a low ratio does not yield a high proportion of patients. Indeed, we experience a contrast between what is reported in some articles (which present benzodiazepine withdrawal as being easy with BIs) and our meetings with clinicians in our sleep training courses, who mostly agree that withdrawal is difficult for the majority of their patients and that they often fail. Nevertheless, the low cost of BIs in terms of time and money are highly advantageous and should be considered an essential first step in the treatment of benzodiazepine dependence.

Pharmaceutical treatments

The largest number of studies in the literature concern interventions using SM. However, very few show SM to be more effective than placebo or another molecule, and in these rare cases, observed results were very short-term. Currently, no pharmacological treatment is recognized as being effective in treating BZ addiction (Grandjean et al., 2021). Generalization of results appears therefore hazardous, especially as most studies (22 out of 27) show no advantage of SM over placebo. Moreover, placebo conditions show notable short-term success rates. In these studies, placebo resulted in 27% more abstinence compared

with the TP condition. However, the lack of long-term follow-up in these studies means that no conclusions can be reliably drawn. Finally, we note that a strategy often used in studies or in routine care, which consists of substituting the BZ with another BZ having a longer half-life, such as diazepam, has not yet been sufficiently proven, and it is based solely on clinical experience. Furthermore, unlike BZs with short-lived rebound effects, withdrawal from other psychotropic medications (selective serotonin reuptake inhibitors — SSRIs (Fava et al., 2015), serotonin noradrenaline reuptake inhibitors — SNRIs (Fava et al., 2018), or antipsychotics (Cerovecki et al., 2013)) can cause persistent post-withdrawal disorders. This fact discourages the use of substituted medication for BZ withdrawal (Cosci & Chouinard, 2020). In addition, some authors claim that substituting BZs with SSRIs and SNRIs might serve an important commercial purpose or raise methodological difficulties in comparing substances of which we must be mindful (Cosci et al., 2015; Offidani et al., 2013).

Behavioral and cognitive therapies

CBT interventions, on the other hand, target populations with insomnia or anxiety disorders. They demonstrate significant results, with three in four participants succeeding not only in withdrawing from BZ use, but also in remaining abstinent over the long term. They have the advantage of offering treatment of the disorder underlying drug use alongside a TP. This dual therapeutic focus enhances the chances of withdrawal while preventing relapse. It can be argued that, by treating the underlying cause of BZ use, they reduce the need for BZs. CBT interventions that do not target the disorder underlying the BZ use, only the addiction itself, do not appear to offer any added value (Voshaar et al., 2003). This may indicate that it is because participants are armed against the rebound effects of insomnia or anxiety that 80% of CBT interventions show effectiveness and long-term sustainability. CBT interventions can be criticized for their higher financial cost and need for greater patient involvement, but this disadvantage must be balanced against the excessive duration of BZ use and the failure rates of other methods. Comparing like with like, CBT + TP are 8 times more effective than the TAU conditions of BI, and therefore more than twice as effective as BIs. Compared with studies of short interventions, the efficacy of which is compared with no treatment, CBT studies show powerful results while comparing them, not with no treatment, but with regular monitoring of a withdrawal program (i.e. a larger therapeutic arsenal than a short intervention). Furthermore, CBT studies have a much more robust methodology than studies of other types of intervention. The effectiveness of CBT can be explained not only by the fact that participants are more motivated than with other approaches. Indeed, Gosselin et al (2006) found that CBTs obtained 3 times more drug-free participants than comparable intervention conditions such as Non-Specific Therapy control (Borkovec & Nau, 1972).

When should withdrawal be suggested?

The French Department of Health decision tree is available in the public domain (Haute Autorité de Santé, 2007). Withdrawal must be assessed on a case-by-case approach, with knowledge of treatment alternatives, the benefits and disadvantages of taking BZs in a given case, in a collaborative assessment between patient and prescriber, the patient's motivations and the ultimate reason for taking them (in some cases, BZs are the only and ultimate treatment for the patient's disorder and should not be stopped). A diagnosis and prognosis of the pathology that led to the use of BZs must be established. In the case of persistent pathologies, a list of resources and treatment alternatives must be carried out before proposing withdrawal.

Which interventions should be used?

Step 1: BIs seem to be an effective strategy for certain patients. Given their low cost (sending a letter), it seems reasonable to introduce them initially. Step 2: In the event of failure at the end of 3 months, a TP supervised by the prescriber (with or without a substitute substance) could be conducted over 6 months. Step 3: If this second strategy fails, CBT should be proposed. Long-term follow-up is necessary whatever the approach.

Limitations

This review could be criticized for not being a *meta*-analysis, but it would be impossible to conduct such a study on the subject, given that the control conditions are different in all three approaches (TAU, TP, Placebo). Comparison of effect sizes is therefore impossible, although our findings corroborate a previous attempt (Gould et al., 2014). It is therefore arguably essential to harmonize methodologies in this field of research. Given the prevalence of benzodiazepine dependence, the use of CBT is limited by the availability of trained therapists. A potential research avenue would be to either condense the effectiveness of CBT into a few sessions (for example, studies have shown that a ''Single-Shot" session of CBT-I (Ellis et al., 2015) is effective for treating insomnia) or to optimize brief interventions by teaching core CBT techniques (such as sleep restriction and stimulus control for insomnia or graded in vivo exposure for anxiety).

Methodological proposition

We found that the methodologies of the interventions examined were not always consistent, even within the same intervention category. Inconsistencies were also found in the withdrawal protocols for the different types of intervention, but also within the same category of intervention. This is why, in order to facilitate comparison and profiling of the effectiveness of proposed interventions for BZ discontinuation, we propose a number of specific recommendations (see Table 1), in addition to the methodological recommendations for randomized controlled trials (Hopewell et al., 2022).

The first step would be to adopt a common measure of abstinence, defined as self-reported non-consumption of BZs for at least 3 months. Studies show that the self-reported result of BZ withdrawal almost always corresponds

to the result of blood tests, urine tests or prescription monitoring (Rickels et al., 1999; Voshaar et al., 2003).

There is also no consensus on the notion of long-term use, with some authors proposing 1 month, others 3, 6 or even 12 months of BZ use to meet this definition. However, most of the studies mentioning long-term or chronic users in their inclusion criteria cited at least 6 months' use. We suggest that this term be qualified by proposing that a duration of use of between 1 and 6 months corresponds to short-term use, between 6 and 12 months to medium-term use, and over 12 months to long-term use, and that a duration of use of over 10 years corresponds to very long-term use, as BZ-dependent people often use them for decades.

In the interest of transparency, results should always be reported both for all randomized participants assigned to treatment in an ''intention-to-treat" analysis, and for the sample of participants who completed the clinical trial excluding dropouts, i.e., in a ''per-protocol" analysis. The first method avoids a biased conclusion on the efficacy of an intervention (McCoy, 2017), and the second is interesting because it gives an indication of adherence to treatment. In addition, tests of significance should be provided in both cases, so that we can understand whether the result of one condition can be defined as superior or not to another. If some participants used pharmaceutical or psychotherapeutic treatments other than those tested before the different measurement times, e.g. antidepressants, these should always be reported, and those participants should not be reported as abstainers. Each intervention should be described, and its duration specified in relation to the TP alone. The TP should always mention: 1) whether follow-up sessions are proposed, for how long and how often; 2) whether there is a transfer phase to another molecule, and if so, which one and in what proportion in relation to the base molecule; 3) whether a stabilization phase is planned and for how long; and 4) the steps for reducing the BZ dose percentage down to the theoretical 0%, as well as the duration of each reduction step, indicating whether BZ-free days/nights are planned. The total duration of withdrawal should be indicated, including any margin for flexibility.

Factors known to influence withdrawal success should be controlled and considered in order to compare groups of pre-treatment participants, such as duration of use, level of stress and anxiety, and degree of confidence in ability to discontinue use (Allary et al., 2020; O'Connor et al., 2008). Given that not all BZs are the same, it is necessary to describe and control their half-life (Ashton, 1994; Cosci et al., 2015), dose and diazepam equivalence. Furthermore, it appears that problematic BZ-users present more somatic and psychiatric comorbidities than those with other substance use disorders. Moreover, 40% of problematic BZ users present a psychiatric disorder, hence the importance of diagnosing at inclusion and of treating the underlying disorders (Schmitz, 2016; Tjiong et al., 2020). Moreover, questionnaires assessing degree of dependence and severity of the withdrawal syndrome should be used systematically. In this respect, it should be noted that the most widely used BZ withdrawal questionnaire, the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ), does not assess for the two main withdrawal symptoms of anxiety and rebound insomnia (Tyrer et al., 1990). The Clinical Institute Withdrawal Assessment-Benzodiazepines (CIWA-B) is preferred by the present authors. With regard to molecule half-lives, it would be useful to agree on definitions, which vary from

Table 1 Recommendations of RCTs on BZ withdrawal.

Inclusion Terminology	- Abstinence = discontinuing BZ consumption
	- Short-term user = ≥ 1 month and < 6 months use
	- Medium-term user = ≥ 6 months and < 12 months use
	- Long-term user = ≥ 12 months and < 10 years use
	- Very long-term user = ≥ 10 years use
	- Half-life = ≤12 h, 12 h—40 h average, max >40 h
Study Plan	- Introduce a control condition with a group continuing usual treatment
Description and Interventions	- Description and duration of the intervention
	- For pharmaceutical treatments, an indication of how long they are to be taken in the context of the withdrawal program and the recommended dose.
	- Description of the withdrawal program, including the number, duration and schedule of any follow-up sessions, eventual switch of molecule and stabilization phase, the duration of each step and % of dosage reduction, and the total duration of withdrawal (variable or fixed).
Analysis and measurement	- Abstinence measured by self-reported non-consumption over a period of at least three months
	- Intention-to-Treat and Per-Protocol analyses, incl. significance tests
	- Mention in the results of participants who received an alternative withdrawal treatment than the one provided by the intervention
	- Pre-treatment report of BZ half-life, dose, duration of use, stress and anxiety levels, any mental disorders, and degree of perceived ability to discontinue use
	- Pre- and post-treatment use of a questionnaire assessing degree of dependence
	- Measuring follow-up results for at least 12 months.

one author to another: a long half-life is, for example, over 24 h for Mihic et al. (2017) and over 20 h for Buxeraud and Faure (2019). We propose (2021) the following cut offs: a short half-life of up to 12 h, a medium half-life of 12 h to 40 h and a long half-life of over 40 h.

Finally, it would be useful to take long-term follow-up data of effectiveness at 12 months, and to detail all measurements in the analyses.

Conclusion

Misuse of BZs affects a large proportion of the population, and more particularly people meeting criteria for mental disorders. After numerous failed attempts at withdrawal, patients and physicians alike are often at a loss as to how to face the problem of addiction However, abstinence is possible if the right methods are implemented. In particular, addressing the psychological difficulties underlying BZ use appears a promising way to address BZ dependence, which is often more of a secondary disorder. Much of the literature on withdrawal methods ignores this hierarchy of disorders and tends to present results from the standpoint that it is relatively easy to stop using this type of medication. While this may be true for some people, it is not the case for the majority. It is important not to fall into strict rules of systematic withdrawal without taking into account the clinical reality of each case, given that BZs are prescribed in different contexts and often in support of an inability to try alternatives (such as CBT). Deprescription of benzodiazepines is a systemic issue where the prescriber and the patient agree on the best alternative between the benefits of treating a disease and the associated side effects. We consider that optimizing withdrawal methods is a key to the ''benzodiazepine problem". To achieve this, research on withdrawal must progress.

Funding sources

This work was funded by the Alcea Foundation to which we would like to express our thanks.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was undertaken by the PROSOM association which we thank sincerely.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbct.2025.100533.

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