Adv Ther (2022) 39:1871–1880
https://doi.org/10.1007/s12325-022-02055-y

COMMENTARY

Surviving Benzodiazepines: A Patient's and Clinician's Perspectives

Carrie M. Silvernail · Steven L. Wright

Received: September 15, 2021 / Accepted: January 20, 2022 / Published online: March 3, 2022

ABSTRACT

Although benzodiazepines have been used for 6 decades, many questions remain unanswered by research. The lived experiences of those adversely affected long term can provide insights into how these agents might be more thoughtfully prescribed. Here, perspectives of one such experience encompassing benzodiazepine initiation, ongoing use with adverse consequences and difficult discontinuation are presented through the eyes of an affected individual and a clinician. This experience highlights the importance of limited initiation and duration of use (2–4 weeks) as well as a supported, slow tapering process led by patients. Because researched evidence about deprescribing benzodiazepines is insufficient and because individual experiences vary so widely, it is the patient's expertise—that of her or his lived experience—that should assume a primary role in determining the course and pace of discontinuing these medications.

Keywords: Benzodiazepine; Benzodiazepine receptor agonist; Withdrawal; Tapering

> Pain isn't real unless you get somebody to believe in it.
> If someone doesn't believe in it, It is just madness or hysteria.
> Naomi Wolf, The Beauty Myth

Key Summary Points

Benzodiazepines should be reserved for when function is impaired.
Physiologic dependence is expected when benzodiazepines are used for more than a month.
Benzodiazepine prescribing should be limited to 2–4 weeks.
Benzodiazepines should be discontinued by tapering if used for a month or more.
Benzodiazepine tapering should be slow, anticipating 12–18 months or more for completion.
Benzodiazepine tapering should be patient-led, relying on patients' responses.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-022-02055-y.

C. M. Silvernail · S. L. Wright (✉)
Alliance for Benzodiazepine Best Practices, 3221 NE 30th Ave, Portland, OR 97212, USA
e-mail: sleighwright@gmail.com

INTRODUCTION

Sixty years ago, Hollister was the first to identify withdrawal symptoms associated with chlordiazepoxide (Librium®) discontinuation [1]. Just one year after this, the first marketed benzodiazepine (BZD) became available for use. Decades later, 13 other BZDs have been approved by the US Food and Drug Administration (FDA); unfortunately, there is still much that is not understood. Prevalence of discontinuation symptoms in research ranges from 20 to 100%, dependent on a number of measurement variables [2–5]. Ashton estimated 10–15% of long-term users develop a "post-withdrawal syndrome" [6], and other literature suggests 15–44% have protracted symptoms of at least moderate severity [7]. Although investigations have significant methodologic limitations and are uncertain, the FDA has recently required a class-wide boxed warning for BZDs emphasizing the risk of physiologic dependence.

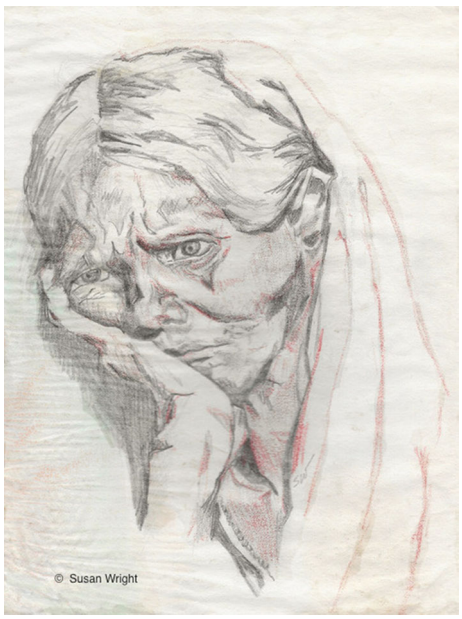
Clinically, symptom attribution to discontinuation, relapse or rebound of the underlying medical condition or a new condition can be difficult [8]. Dramatic symptom fluctuations are not infrequent during withdrawal [8–10], but might be misconstrued simply as a somatic symptom disorder. Presentations may seem unrelated to what is currently understood about neurophysiologic adaptation. Practitioners might associate unusual psychologic and physical complaints (Table 1) with alternative diagnoses [8]. Finally, patients in withdrawal present differently—sometimes dramatically so; therefore, it is difficult for medical providers to see commonalities associated with BZD cessation.

Patients are often caught up in these diagnostic dilemmas that can result in an array of off-target treatments. They may find themselves in the position of trying to convince their prescribers of the reality of their symptoms and then of the relationship of their symptoms with BZD discontinuation. While it is true patients can be mistaken, it is also true their expertise includes at least their own lived experience. Since the research base provides insufficient guidance, patient expertise is central to diagnostic and management decision-making in the context of BZD cessation.

Table 1 Selected benzodiazepine discontinuation symptoms that can be misdiagnosed

Suicidality
Derealization
Depersonalization
Delusions, illusions, hallucinations
Anxiety severity beyond original baseline
Auditory alterations, loss, hyperacusis, tinnitus
Alteration or hypersensitivity of taste, smell, vision, speech
Cutaneous sensory alterations
Sense of motion
"Brain zaps"
Pain

Carrie Silvernail is one of many who experienced such challenges. Let's listen to her account.



A PATIENT'S PERSPECTIVE

In 2008, I was a busy 55-year-old mother, wife and nurse. I sought care from my physician for episodes of tachycardia, arrhythmias and back pain. He quickly diagnosed generalized anxiety disorder and lower back pain and prescribed 0.25 mg of alprazolam and ibuprofen as needed along with exercise for stress reduction and pain. I took this seriously and upped my current yoga practice. I also began exercises for back pain and studied meditation while making changes to my already healthy diet. I was aware of the dependency potential with benzodiazepine use, so I sparingly used alprazolam. I would cut the dose in quarters and take the least amount possible. I never exceeded the prescribed dosage. I did not dose more than a few times a week and often would go months with no use. Adopting this prescribed protocol helped reduce but did not resolve the symptoms. I returned to my primary care provider (PCP) requesting a cardiac evaluation and was diagnosed with atrial fibrillation (AF). I was prescribed diltiazem hydrochloride 180 mg per day and was told I could continue the alprazolam to manage any anxiety associated with AF and pain. Again, I used the drug infrequently while continuing the lifestyle modifications I had adopted.

In 2011, I developed acute pelvic pain and intense periods of anxiety and panic. I had soaking night sweats, insomnia, tinnitus, dizziness and paresthesia. These symptoms intensified over the next few months, and I sought advice from my PCP, who referred me to neurology and gynecology for evaluation. All of my labs, pelvic ultrasound, lumbar and pelvic MRIs were within normal limits.

My mental health was suffering with these debilitating symptoms, and I was seeing a psychologist for supportive care. My PCP suggested I start alprazolam full time to treat the intense anxiety and panic. She also suggested the addition of gabapentin for pain. I began taking 0.25 mg of alprazolam three times a day (TID) and gabapentin 600 mg TID. My gynecologist added 5 mg of diazepam vaginally to treat the pelvic pain. Desperate for relief, I agreed to the treatment plan hoping it would get me through this intense period.

Initially, the symptoms decreased, but I continued to feel very unwell with fatigue, insomnia, anxiety, hyperacusis and moderate myalgia. I became unable to safely work, drive or care for myself or family. I took medical leave and eventually early retirement. After a few weeks, symptoms increased with greater intensity, and I developed a new terrifying symptom: suicidal ideation. I consulted my PCP and was told to up my dose of alprazolam. When I questioned the possibility that my symptoms were unwanted effects of the drugs, I was told they were not related and that I needed to up my dose of alprazolam or she could not help me.

I began researching the effects of benzodiazepines and found literature that supported my worsening condition. I read the Ashton Manual [6] and other works by Dr. Heather Ashton and learned about benzodiazepine dependency and tapering. I found online support groups where others were experiencing the same or similar symptoms after using benzodiazepines. I was able to construct a new supportive health care team which included an internal medicine physician, naturopath, acupuncturist, psychologist, physical/massage therapists and pharmacists. With help from the team and my husband, I began to taper gabapentin. When this was complete, I tapered alprazolam and lastly the diazepam. Tapering the benzodiazepines took a total of 38 months. Even at this slow taper rate, symptoms were intense and affected every bodily system. I had over 100 physical and mental symptoms and was often bed or couch bound. It was a grueling experience that had enormous impacts on my family, professional and social life.

I saw multiple medical doctors who told me that my symptoms were unrelated to benzodiazepine use. I persisted, trying to find a health care provider who was willing to listen to my story and learn about benzodiazepine dependency. I am fortunate to live in a city where a variety of health care professionals are available. None of the team of providers that I eventually assembled were benzodiazepine experts, but they were willing to listen to me, read the

resources and support my efforts. After our initial consultation, my new medical doctor said it best, "First, I believe you. Second, how can I best support you?" The care provided by my medical team and the support from family and friends were a critical piece of my recovery.

On July 17, 2015, I took my last small dose of diazepam. Today, 6 years later, I am better but still struggle with the effects from benzodiazepine exposure. Most frequently, dizziness, generalized pain, muscle stiffness, fatigue, paresthesia, tinnitus, exercise intolerance and hyperacusis are present. These vary in intensity and can be very limiting. I continue with healthy lifestyle practices and manage the remaining symptoms as best I can. My life was greatly changed by the use of this commonly prescribed class of medication. I feel fortunate to have found my way through tapering and the long recovery period. Had I known of the possible long-term effects of their use, I would not have filled the prescriptions.

Fig. 1 Carrie M. Silvernail, *RN* retired

A CLINICIAN'S PERSPECTIVE

Carrie's experience with benzodiazepines and with medical providers is not at all uncommon. As a family physician and addictionist for more than 3 decades, I had thought BZDs were well understood, easy to use, relatively benign, generally beneficial for long-term use and a nuisance to stop. That perspective changed, however, at a conference in 2017, where a panel of benzodiazepine survivors like Carrie shared their personal narratives (Fig. 1).

"Stories" and "challenges" do not begin to express the extent and severity of their articulated experiences. Despite the wide variety of BZD accounts, there was consistency. There was unanimity about failed efforts to have medical providers understand and validate their conditions, much less provide effective professional assistance. There was credibility: each had a good understanding of these medications, including physiologic dependence, which had played out into nightmare discontinuation scenarios. BZDs were not discarded outright, but rather a more nuanced and narrower role was suggested, differing significantly from the received "knowledge" I as a prescriber had been taught.

Carrie, as did these other survivors, reported that BZDs were initiated by prescribers without providing sufficient (if any) informed consent and without offering alternative options [11, 12]. First-line indications for BZD use are actually quite limited (Table 2). Yet, they are most frequently prescribed for non-first-line indications like insomnia and anxiety when cognitive behavioral therapy (CBT) with a more favorable risk/benefit profile is preferred [13, 14].

Even more, CBT benefit can extend a year or more after completion of treatment [15, 16] in contrast to BZD efficacy, which may fade over time [11, 17–19]. Loss of significant initial improvement can prompt increased dosing that may be ineffective as well. In fact, it appears some individuals may experience worsening anxiety due to these medications themselves [11, 20].

Paradoxical anxiogenesis is among a number of BZD-related adverse effects that may be misdiagnosed as unrelated to those agents [8, 11] (Table 3). If a causal nexus between such symptoms and BZD use goes unrecognized, misdirected treatment and cascading

Table 2 First-line indications for benzodiazepines. Short-Term Use: 2-4 Weeks

Benzodiazepine withdrawal
Alcohol withdrawal
Crisis anxiety
Anesthesia
Status epilepticus
Stiff person syndrome
Burning mouth syndrome
Certain acute movement disorders

Table 3 Selected benzodiazepine adverse reactions that can be misdiagnosed. List not comprehensive

Paradoxical worsening anxiety
Paradoxical akathisia, agitation
Paradoxical irritability, hostility, aggressiveness, homicidal ideation
Paradoxical disinhibition, emotional lability, bizarre behavior
Interdose withdrawal symptoms, kindling
Dysthymia, depression, suicidality
Delusions, illusions, hallucinations
Anhedonia
Mania
Psychomotor impairment, accidents, injuries
Movement abnormalities, "pseudoseizures"
Abdominal distress, nausea, vomiting, constipation
Sensory alterations: sound, taste, touch, sight
Sense of motion, dysequilibrium
Vasomotor disturbances
Pain

polypharmacy can ensue. When Carrie, for example, reported suicidal ideation to her PCP, she was told that it was unrelated to alprazolam and was directed to increase the dosage even though research shows BZDs are associated with suicidality [21].

Addiction and physiologic dependence are also serious adverse reactions related to exposure to BZDs and other substances. The former is an involuntary brain disease involving the reward system, which is behaviorally defined and diagnosed by compulsive use, loss of control and continued use despite negative consequences [22]. Addiction involves the non-medical use (NMU) of a substance, though BZD NMU more often occurs voluntarily and unprompted by the craving that characterizes addiction. BZD NMU is not unusual, whereby the user intends to amplify or ameliorate the effects of or withdrawal from other addiction-prone substances [8, 23]. BZD addiction or use disorder per se is a subset of NMU but is seen infrequently [8, 22]. Indeed, the vast majority of those struggling with BZDs are not addicted to them, and for them traditional addiction treatment approaches are unsuccessful [8, 11].

Physiologic dependence, on the other hand, is an expected and very common response that may occur with as little as 1–2 weeks of BZD exposure [24] and/or at therapeutic, normal or low BZD dosages [25]. It is due to neurophysiologic adaptations of at least the gamma-aminobutryic acid receptor subtype A ($GABA_A$), glutaminergic, adenosine A_{2A} and translocator protein receptor systems and the hypothalamic-pituitary-adrenal axis. Though only hypothetical, its pathophysiology may involve a biochemical cascade that generates toxic oxygen species, which then may become propagated and perpetuated through interacting pernicious feedback cycles in susceptible individuals who end up experiencing protracted withdrawal states[26].

BZD physiologic dependence may be evident as tolerance or the loss of effect with repeated exposure [8, 27]. Principally, though, it is distinguished by symptoms that emerge with discontinuation or dosage reduction [2–8]. A withdrawal picture may also be present in the absence of dose decrements due to developing tolerance in the context of waning BZD blood (brain) levels prior to the next scheduled dose: interdose withdrawal [8, 28]. Although many

withdrawal symptoms are well recognized, there are those that go unrecognized (Table 1), particularly when they fluctuate dramatically in the absence of any change in environmental stressors [8]. This becomes a real challenge for patient and prescriber alike.

Fundamental and critical to addressing physiologic dependence and BZD cessation is a very slow tapering process [4–6, 8]. For Carrie, this required 38 months. For some, discontinuation can proceed fairly rapidly (weeks), but this cannot be predicted. For many, a brisk tapering trajectory results in a severe adverse course, so it cannot be recommended at the outset. Rather, a gradual initial pace is advised, one that anticipates at least 12–18 months to complete [8]. A fixed schedule is ill-advised, as patient responses vary so widely. In addition, as tapering proceeds, patient tolerability requires slowing its rate in a nonlinear, hyperbolic fashion [8, 29].

After tapering is initiated, its pace should be adjusted up or down depending on the patient's response. This calls for the expertise of both prescriber and patient through shared decision-making. Prescriber expertise includes understanding and outlining BZD pharmacology, the deprescribing process, its anticipated flexible course and informed consent. As tapering proceeds, however, it is the patient's expertise—her/his actual response to sequential BZD dose reductions—that assumes an ascendant role. This somewhat upends the shared decision-making model as it is usually practiced, whereby although shared, ongoing medical management choices tend to tilt toward reliance upon the provider's expertise. Reliance upon the patient's expertise, however, is the more dependable pathway to successful BZD cessation, as indeed Carrie discovered.

Aside from a clear recommendation for slow tapering [4–6, 8], published research offers only limited guidance to aid BZD discontinuation. Self-management, nutritional approaches and many plausible modalities have not been examined. CBT, though, does appear to have value [30]. Published investigations suggest potential roles for adjunctive medications [31–33] (Table 4), but their value is uncertain because of mixed results, flawed research methodology and the lack of long-term outcomes including the likely need for tapering certain adjuncts themselves [8]. No confident recommendation regarding any of these agents, therefore, can be made.

Table 4 Potential adjunctive medications for benzodiazepine tapering

Carbamazepine	Valproic acid
Pregabalin	Gabapentin
Paroxetine	Imipramine
Trazodone	Magnesium
Oxcarbazepine	Flumazenil

Ultimately, Carrie achieved significant success through a supportive network of medical providers, family and peer survivors. Because she originally found that her prescribers had insufficient BZD knowledge and even discredited her, she, like tens of thousands of others, sought out support and guidance in online communities. It was there she ascertained a pathway that led to favorable outcomes: information and practical approaches she had not previously found in traditional medicine sources. She was subsequently able to find medical providers willing to listen and employ a reasonable BZD discontinuation course.

The plight faced by Carrie and a cohort of BZD survivors has received scant attention in the literature. Traditional studies to date have not been sufficiently informative nor have they employed observation periods of the months and years needed to identify the extent and severity of difficulties, which are far more common [6–8] than appreciated by many medical providers. In fact, only two published [11, 34] and two unpublished [35, 36] qualitative surveys of long-term BZD-affected individuals have been identified. Together, these studies identify themes consistent with Carrie's account: disabling symptoms lasting months or years and prescribers often untrained to provide effective assistance.

Although some published studies on managing BZD use have value, practitioners have made inferences beyond study parameters.

A type of cognitive bias termed extension neglect can result in invalid conclusions derived from studies with small sample sizes and/or short observation periods. Many prescribers are anchored in the false assumption that investigations demonstrating short-term value of BZDs necessarily assure long-term benefit and safety. To generalize that "most" do well with a specific intervention does not address the major challenges faced by a significant minority. Evidence-based research methodology by necessity requires inclusion and exclusion criteria that essentially portrays "typical" patients with characteristics that may not match those of the affected person seeking medical assistance. In addition, some outcomes are truly unknowable because of wide variability of patient treatment response to BZD-related interventions. These factors lead back to the essential principle of individualizing care for those needing and seeking medical help.

CONCLUSIONS

Carrie's account is reflective of many others who struggle with BZDs and have left traditional medical care to seek assistance online from their similarly affected peers. This should be a wake-up call to us all. Their lived experiences are not well depicted in published research but are instructive nonetheless. Common threads include misdirected interventions, such as addiction treatment which focuses on craving, which the majority with physiologic dependence alone do not experience. Arduous withdrawals can ensue despite BZD use just as prescribed, at low dosages, or for short periods of time. Prescribers may erroneously ascribe symptoms to other than BZD withdrawal when those symptoms seem unusual and/or emerge unprompted by external stressors with wild and unpredictable fluctuations ("waves" and "windows"), particularly when disabling symptoms extend months or years beyond complete BZD cessation. Finally, it is simply unacceptable for practitioners to disparage BZD-struggling patients and their experiences in the manner that has been reported.

This is a call for new BZD heuristics, new mental strategies for medical decision-making about prescribing and deprescribing these agents. More than effort-reduction shortcuts to aid time-pressured medical providers, heuristics are essential in clinical practice to render reasonable, though imperfect, management approaches when knowledge of a topic or a patient's neurophysiology is unknown or unknowable as is often true with BZDs. Still, recommendations should be based on what *is* known:

1. BZDs often work well initially.
2. Efficacy can decay and may worsen the conditions intended to treat.
3. Adverse reactions can build over time.
4. Adverse reactions may not be evident until tapering or full cessation is complete.
5. Physiologic dependence is the rule and is worse the longer BZDs are used.
6. True BZD addiction is quite infrequent.
7. Discontinuation can be disabling, especially if tapering proceeds too quickly.
8. Withdrawal symptom, severity, fluctuation and duration vary widely among individuals.

Therefore, derived heuristics or best practices (Table 5) should embrace the principles of limited initiation, limited duration of use and supported patient-led slow tapering when BZDs are used for more than a month.

And all this, to be sure, is predicated on good-faith attention to patients' concerns and

Table 5 Key benzodiazepine best practices

Seek alternative therapies
Limit initiation
Prescribe only if function is limited
Limit duration of use to 2–4 weeks
Discontinue by slow tapering, anticipating 12–18 months to complete
Ensure team-based support throughout discontinuation
Allow the patient to lead and direct the pace of tapering

authentic shared decision-making. While prescriber expertise can advance evidence-based options (when available) and share the unknowns about outcomes, patient expertise is essential since the peculiar and the unpredictable are not unusual during BZD discontinuation. Much is not understood about its dark chemistry that reaches out from mind to body and from body to mind, and so treatment choices rightly become therapeutic trials. Because research is wanting and individual responses vary so widely, deference to patient observations and interpretations is advised. It is the three most important words in any relationship—"Maybe you're right"—which are in order: authentic validation and no discrediting are indicated. Indeed, it is through such shared decisions and effort that success is more likely.

That is what is meant by being benzowise.

And *that* is what is critical because every Carrie counts.

ACKNOWLEDGEMENTS

To all the benzodiazepine survivors who kept courage while we prescribers weren't listening: I am sorry.

Funding. Direct funding for this paper has not been provided. However, Steven L. Wright, MD, was the paid medical consultant for the Alliance for Benzodiazepine Best Practices.

Other Assistance. Carrie M. Silvernail, RN, and Steven L. Wright, MD, are the sole authors for this paper. We appreciated the assistance Bernie Silvernail, the CEO of the Alliance for Benzodiazepine Best Practices who reviewed the manuscript and provided comments.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. As well as co-authorship of this paper, Steven L. Wright, MD, was solely involved the review of the background literature, and reviewed and approved the final version of the manuscript. Carrie M. Silvernail authored the section entitled "A Patient's Perspective" and Steve L. Wright authored the other sections.

Disclosures. Carrie M. Silvernail, RN, is the spouse of the CEO of the Alliance for Benzodiazepine Best Practices. Steven L. Wright, MD, served as medical consultant for the Alliance for Benzodiazepine Best Practices until he fully retired and is a member of the *Advances in Therapy* Editorial Board.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by the authors. Carrie M. Silvernail gives permission for publication of her photograph in this paper.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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