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Enduring neurological sequelae of benzodiazepine use: an Internet survey

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Abstract

Introduction: Benzodiazepine tapering and cessation has been associated with diverse symptom constellations of varying duration. Although described in the literature decades ago, the mechanistic underpinnings of enduring symptoms that can last months or years have not yet been elucidated.

Objective: This secondary analysis of the results from an Internet survey sought to better understand the acute and protracted withdrawal symptoms associated with benzodiazepine use and discontinuation.

Methods: An online survey ($n = 1207$) was used to gather information about benzodiazepine use, including withdrawal syndrome and protracted symptoms.

Results: The mean number of withdrawal symptoms reported by a respondent in this survey was 15 out of 23 symptoms. Six percent of respondents reported having all 23 listed symptoms. A cluster of least-frequently reported symptoms (whole-body trembling, hallucinations, seizures) were also the symptoms most frequently reported as lasting only days or weeks, that is, short-duration symptoms. Symptoms of nervousness/anxiety/fear, sleep disturbances, low energy, and difficulty focusing/distractedness were experienced by the majority of respondents (⩾85%) and, along with memory loss, were the symptoms of longest duration. Prolonged symptoms of anxiety and insomnia occurred in many who have discontinued benzodiazepines, including over 50% who were not originally prescribed benzodiazepines for that indication. It remains unclear if these symptoms might be caused by neuroadaptive and/or neurotoxic changes induced by benzodiazepine exposure. In this way, benzodiazepine withdrawal may have acute and long-term symptoms attributable to different underlying mechanisms, which is the case with alcohol withdrawal.

Conclusions: These findings tentatively support the notion that symptoms which are acute but transient during benzodiazepine tapering and discontinuation may be distinct in their nature and duration from the enduring symptoms experienced by many benzodiazepine users.

Keywords: benzodiazepines, benzodiazepine-induced neurological dysfunction, benzodiazepine taper, benzodiazepine withdrawal, neuroadaptation, neurotoxicity, persistent withdrawal, post-acute withdrawal, protracted withdrawal, withdrawal syndrome

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Introduction

Discontinuation of benzodiazepine use, whether accomplished by abrupt cessation or tapering the dose over time, has been associated with diverse symptom constellations of varying duration described in the literature.[1] In 1982, MacKinnon and Parker remarked that while benzodiazepine withdrawal syndrome was more likely to occur in those taking higher doses of benzodiazepines for longer periods of time, they commented that these symptoms were sometimes observed in people who took even brief courses at recommended dosages.[2] Common clinical belief has held that benzodiazepine withdrawal is relatively short lived,[3,4] and can be effectively treated with pharmacologically similar medication.[5] However, Ashton[6,7]

described clinical experiences with what she called 'protracted withdrawal symptoms', which sometimes lasted for years after benzodiazepines were fully discontinued. Prolonged benzodiazepine withdrawal syndrome was described in 1990 and reported to be a distinct and iatrogenic condition and not an affective disturbance.[8]

These protracted symptoms have not been well studied, and they may be the result of changes in brain function.[7] While acute withdrawal occurs in the immediate period following drug discontinuation and is well documented in the literature,[4,9] long-term symptoms have not been as well described.[10] In September 2020, the Food and Drug Administration (FDA) updated its 'boxed warning' on benzodiazepine labeling to include the risks of benzodiazepine abuse, misuse, addiction, physical dependence, and withdrawal reactions; this warning applied to all medications in the class.[11] The updated labeling described protracted withdrawal symptoms that can last 12 months or more. Furthermore, the new labeling recommends that a gradual taper be used if the drug is to be discontinued but does not provide more specific guidance.[11,12]

The aim of this study was to perform a secondary analysis of the results from an Internet survey of 1207 benzodiazepine users to determine the relationship, if any, among 23 symptoms reported by the respondents[13] and to characterize and better understand the time course of symptom constellations and determine whether there was indeed evidence for these two phases (acute versus protracted) of discontinuation.

Methods and materials

This is a secondary analysis of the results of an Internet survey about benzodiazepine-associated symptoms published earlier.[13] The survey recruited a convenience sample of respondents from 16 Internet sites related to benzodiazepines, mental health, and general health. A link to the survey was offered on some Facebook pages and Reddit threads as well with the goal of collecting the largest sample possible. Samples were collected at three different times in October 2018, November 2018, and January 2019.

The authors of this survey used both the scientific literature and lived experiences of those in the online benzodiazepine support communities to generate a list of 23 symptoms that were used in the survey.[6,14] Initial survey results were produced by a medical statistician utilizing SAS Software. An experienced data scientist performed the detailed analysis by importing the data into a customized data model on the SQL Server platform. Chi-Square Goodness of Fit Test and customized queries were utilized to evaluate the findings and determine the time course of symptom constellations and whether there was indeed evidence for these two phases of discontinuation. All analyses were delivered via a structured reporting process and validated against the original SAS reports.

Results

A total of 1207 respondents completed the original survey,[13] although not all of them answered every question and some questions allowed one respondent to offer more than one answer. The survey was started by 1682 individuals (IP addresses were verified to avoid duplication) and 1207 submitted it electronically. These 1207 'finishers' were the study population, although not all of them answered every question. Respondents were 71% female, 26% male, and 2% who preferred not to state their gender identity or stated it as 'other'. The complete survey appears in Appendix I.

The majority of finished respondents (52.4%) had taken only one type of benzodiazepine. Of the finished respondents in this survey, 40.4% tapered off the benzodiazepine over a period of time (days, weeks, months, years), while 22.8% reported they stopped the medication abruptly or 'cold turkey'. Thus, 63.2% of respondents had fully discontinued benzodiazepines at the time of the survey. The majority of those who tapered or quit benzodiazepines (97.2%) reported consequences. At the time of the survey, 35.7% had not taken any benzodiazepines in the past year. About a quarter of respondents (24.4%) were in the process of tapering off benzodiazepines at the time of the survey. A large number of withdrawal symptoms were reported and are summarized in Table 1. Note that of the 23 symptoms included, 20 of them were experienced to some degree by more than half of respondents. See Figure 1.

Respondents reported experiencing on average 15 of the 23 symptoms listed in the survey and 6% reported having all of them. The three least frequently reported symptoms (whole body trembling

Table 1. Respondents were asked if they had experienced a specific symptom and for how long (days, weeks, months, over a year). Included in this table were only the 63.2% of all respondents who had completely discontinued benzodiazepine use. The 'Experienced' column provides the number and percentage of those who have discontinued benzodiazepines and who had experienced that specific symptom ($n = 763$). The short-term and long-term columns report the duration of these symptoms with percentages reflecting the proportion of those respondents who reported that symptom. Short-term symptoms resolved in days or weeks, while long-term symptoms resolved in months or a year or more.

Symptom	Experienced		Short-term		Long-term	
	n	%	Days	Weeks	Months	⩾1 year
Anxiety, nervousness	689	90.3%	5.1%	8.4%	28.4%	58.1%
Sleep disturbances	677	88.7%	5.5%	8.1%	29.0%	57.5%
Cognitive/focus	665	87.2%	6.6%	8.0%	27.7%	57.7%
Low energy	665	87.2%	5.6%	8.1%	26.9%	59.4%
Sense sensitivity	627	82.2%	5.7%	10.7%	29.8%	53.7%
Memory	595	78.0%	8.1%	6.7%	28.9%	56.3%
Digestive problems	580	76.0%	9.5%	11.4%	27.9%	51.2%
Trembling limbs, skin	575	75.4%	9.0%	10.4%	31.0%	49.6%
Balance problems	567	74.3%	9.7%	12.9%	34.2%	43.2%
Head pain, pressure	563	73.8%	8.3%	11.2%	30.9%	49.6%
Muscle weakness	558	73.1%	6.3%	10.8%	31.4%	51.6%
Crying/anger	555	72.7%	10.1%	15.3%	36.0%	38.6%
Difficulty driving or walking	553	72.5%	7.8%	12.1%	32.4%	47.7%
Pain/ache/burning	541	70.9%	6.7%	9.6%	31.2%	52.5%
Food or drink triggered	540	70.8%	7.2%	9.6%	30.0%	53.1%
Heart rhythm, blood pressure	513	67.2%	8.2%	10.7%	34.5%	46.6%
Muscle spasms	508	66.6%	11.0%	12.4%	30.3%	46.3%
Loss of appetite	495	64.9%	13.7%	21.0%	35.4%	29.9%
Akathisia	447	58.6%	12.5%	15.2%	36.0%	36.2%
Difficulty breathing or swallowing	433	56.7%	13.4%	15.9%	32.3%	38.3%
Whole body trembling uncontrollably	395	51.8%	19.7%	21.5%	32.7%	26.1%
Hallucinations	271	35.5%	28.8%	21.8%	29.9%	19.6%
Seizures	165	21.6%	41.2%	15.2%	21.2%	22.4%

uncontrollably, hallucinations, and whole or partial body seizures) were also the three symptoms with the greatest proportion of respondents experiencing them for days or weeks. The majority of those who discontinued benzodiazepines reported experiencing the same four symptoms: (1) nervousness, anxiety, fear; (2) sleep disturbances; (3) difficulty focusing, distractedness; and (4) low energy. See Figure 1.

Symptom duration in the survey was described in terms of days or weeks (short-term symptoms) and

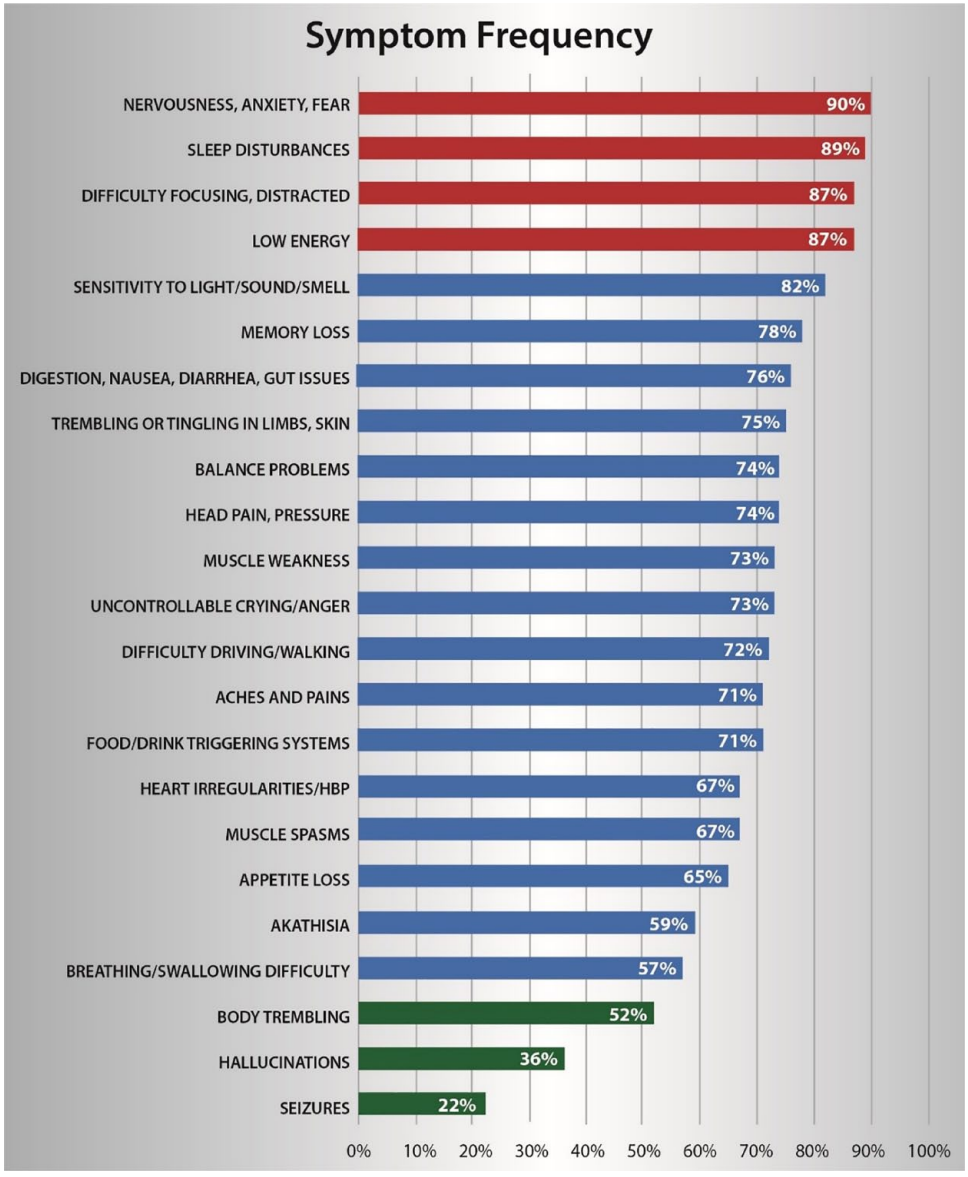

Figure 1. Most respondents who had discontinued benzodiazepines (n=763) reported multiple symptoms from the 23 symptom choices on the survey, and they were typically of long duration. The four symptoms in red were reported by over 85% of respondents. The least frequently reported symptoms appear below in green; of the respondents who experienced these symptoms $>$ 40% found them to be of short duration (days, weeks).

months or $\geqslant$ 1 year (long-term symptoms). Early symptoms of short duration were primarily whole-body trembling, hallucinations, and seizures, which are symptoms associated with acute withdrawal. The first 20 most frequent of the reported symptoms in Figure 1 were the more enduring.

Ten symptoms emerged as being particularly long-lasting with over 50% of respondents endorsing having these symptoms stating that they persisted for a year or longer. Those symptoms of longest duration, reported as lasting 1 year or longer, were cognitive symptoms (difficulty focusing, memory loss), anxiety and agitation (nervousness and sleep disturbances), hypersensitivity (sensitivity to sights and sounds, body aches and pains), digestion (digestive issues, symptoms triggered by food or drink), and fatigue (low energy and muscle weakness).

Among the respondents who reported anxiety as an enduring symptom after discontinuation of benzodiazepines (1063/1207), 55.6% were not prescribed the benzodiazepines for anxiety. Likewise, of the 1049/1207 respondents who reported long-lasting insomnia as a symptom, 57.5% were not originally prescribed benzodiazepines for insomnia.

Discussion

Respondents in this survey reported experiencing on average 15 of the 23 symptoms queried, and 76.6% of all respondents (those taking full dose, those tapering, and those who discontinued benzodiazepines) who reported symptoms reported them to be of long duration (months or years). This conflicts with older reports in the literature stating that benzodiazepine withdrawal symptoms typically resolved within 28 days[15–17] or that withdrawal tends to be associated with mild, self-limiting symptoms, particularly in people taking low doses.[3]

The major finding of this study was that the majority of survey respondents experienced multiple, distressing symptoms associated with benzodiazepine exposure lasting months to years after benzodiazepine discontinuation and these symptoms may not simply have been the re-emergence of symptoms for which the benzodiazepines were originally prescribed. Respondents reported experiencing symptoms that greatly differed from the symptoms for which they were originally prescribed benzodiazepines. An analysis of symptom frequency and duration found that the least frequent symptoms were also those of shortest duration. The issue that emerges is how these protracted symptoms might differ from the acute symptoms. While acute withdrawal symptoms from benzodiazepines are well-known, long-term symptoms remain less well described in the literature.[4]

Acute withdrawal symptoms after benzodiazepine discontinuation have been well described in the literature and are dependent on the rates of drug elimination from the body. For short-acting benzodiazepines, acute withdrawal lasts for approximately 10 days as the residual drug is eliminated. Longer-acting benzodiazepines with longer half-lives and active metabolites require additional time to clear the body, perhaps as long as 28 days.[3] These long-term symptoms have not been thoroughly elucidated. This study documents these protracted symptoms, which can persist for months or years after benzodiazepine cessation, suggesting the possibility that they may be due to a neurological injury. Furthermore, these symptoms may emerge due to tolerance, a form of neuroadaptation, even as the drug is still being taken and can lead to increased dose requirements. While these enduring symptoms of benzodiazepine use have been called protracted withdrawal syndrome, they are not true withdrawal symptoms. A systematic review and meta-analysis reported neurocognitive dysfunction as a consequence of long-term benzodiazepine use that persists even after drug discontinuation.[18] Historically, the condition went by many different names, some of which, such as 'protracted withdrawal', 'post-acute withdrawal syndrome or PAWS', and 'benzodiazepine withdrawal syndrome' introduced more confusion than clarity.[7,15,19]

These protracted symptoms do not occur in all benzodiazepine patients,[12] but have a reported incidence between 15% and 44% among those taking these drugs on a regular rather than an as-needed (PRN) basis.[20] Considering that benzodiazepines are among the most frequently prescribed medications in the world with an estimated 92 million prescriptions dispensed in the United States in 2019,[21] those who experience these enduring consequences represent a substantial population. The US Preventive Services Task Force, appointed by the Department of Health and Human Services, has recently recommended that physicians screen all patients under age 65, including children, for anxiety.[22] This has the potential to increase benzodiazepine prescribing. Furthermore, although benzodiazepines are generally indicated for short-term use only (<4 weeks), they are frequently prescribed for longer-term use, extending over the course of many months or years.[23]

Acute benzodiazepine withdrawal might be compared to acute alcohol withdrawal, where an abrupt and marked decrease or cessation of alcohol consumption by heavy drinkers can result in a range of mild to moderate symptoms, such as tremors, anxiety, irritability, agitation, but may also occasion severe symptoms, such as hallucinations, seizures, and delirium tremens.[24] Alcohol consumption influences inhibitory and excitatory neurotransmission in the central nervous system, particularly enhancing gamma-aminobutyric acid (GABA) function and inhibiting glutamate systems.[25,26] Benzodiazepines and alcohol are cross-tolerant,[27] and benzodiazepines are typically used to treat acute alcohol withdrawal as they affect the same neuronal systems.[24] Acute benzodiazepine withdrawal symptoms, like acute alcohol withdrawal symptoms, can be life-threatening.[28] The severity of acute symptoms associated with alcohol withdrawal increases in dose-dependent fashion,[24] but it has not yet been established whether this is the case with benzodiazepines. The fact that alcohol withdrawal exhibits certain similarities to benzodiazepines in terms of mechanisms by no

means suggests that detoxification protocols for these two substances should be the same. Alcohol and benzodiazepines both seem to exhibit an initial acute withdrawal syndrome followed by more prolonged and often different symptoms in a subset of individuals.

The protracted withdrawal syndrome from alcohol and alcohol-associated neurotoxicity are well described in the literature.[29–31] It is plausible to hypothesize that the same may be true for long-term consequences of benzodiazepine exposure, although the underlying mechanisms may not be the same. Of course, mechanistic understanding of the enduring benzodiazepine-associated symptoms remains to be elucidated, and it is not known why some patients develop more severe or more protracted symptoms than others or why some patients experience very few effects beyond the acute withdrawal phase. At one time, personality traits were implicated as exacerbating benzodiazepine withdrawal, but this notion has been largely refuted.[32] It has been speculated that benzodiazepine withdrawal can be correlated with duration of use as well as the type, formulation, and dose of the benzodiazepine, but these ideas are more suggestive than conclusive.[33] There is a regrettable paucity of scientific investigations into the possible neuroadaptive and/or neurotoxic changes induced by benzodiazepine use and research may shed light on these prolonged benzodiazepine-associated symptoms.

The literature speculates that a cascade of neuronal responses to benzodiazepine cessation might lead to chronic illness.[34] A hypothesis, based on the observation that discontinuation of benzodiazepines elevates peroxynitrite levels potentiating L-type voltage-gated calcium channels, has been put forth. As benzodiazepine withdrawal continues, an abundance of *N*-methyl-D-aspartate (NMDA) receptor activity, combined with the heightened activity of the L-type voltage-gated calcium channels, increases the influx of calcium ions into the cells and triggers elevated nitric oxide (NO) synthesis. The increased production of NO leads to sustained high levels of peroxynitrite. This can launch a self-perpetuating feedback loop that may reduce GABA function, causing prolonged symptoms.[34] It is hypothesized that this pathway could be a common link in several other disorders with overlapping symptomatology.[35] The long-term use of diazepam in a murine study was reported to alter the synaptic plasticity of the dendritic spines of the neurons by way of the mitochondrial 18 kDa translocator protein, potentially explaining its association with cognitive decline.[36] Further study is needed to understand both acute and chronic toxicity of benzodiazepines and the associated residual clinical symptoms as well as the basis of the heterogeneity of responses among individuals.

The authors consider it important to note that current best practices in benzodiazepine use and discontinuation[9,37] supports the Ashton manual[6] that advocates a slow, patient-led taper to mitigate withdrawal symptoms. The FDA added warnings to benzodiazepine labeling to taper slowly.[38] Further study is needed to produce the evidence on which to base an effective benzodiazepine tapering protocol; at the moment, the consensus is that a slow, gradual taper in small increments is preferred.

A potentially important finding in the survey was that a disproportionate number of respondents had taken clonazepam, either as monotherapy or together with other benzodiazepines. This was surprising because clonazepam is not the most frequently prescribed benzodiazepine in the United States. In 2019, there were 2.3 million Americans taking clonazepam compared to 3.9 million taking alprazolam and 2.8 million taking lorazepam.[39] The percentage for alprazolam prescribing according to these figures from 2019 is 70% higher than that of clonazepam, and yet clonazepam usage in this survey is 27% higher than alprazolam. These findings mirror claims by benzodiazepine support groups that patients who have taken clonazepam appear to have a higher incidence of enduring symptoms than those who took other benzodiazepines, although little if any research has been published on this topic. Another possible explanation is that until recently, clinicians tended to switch the most severe benzodiazepine users to long-acting clonazepam for detoxification rather than simply tapering the first drug; this is no longer considered the treatment of choice.[40] Age may also play a role. A study in mice found that chronic diazepam exposure had an adverse effect on memory retrieval performance in middle-aged but not young mice.[41] This warrants further study.

One important question that often arises in this context is whether some of the symptoms that emerge after discontinuation might be the recurrence of the original condition for which the benzodiazepines were prescribed.[8] Rebound symptoms are reported in the literature.[42] It

must be noted that when respondents were asked about withdrawal and discontinuation symptoms, many of these symptoms did not match their stated indications. Respondents attributed these symptoms to their benzodiazepine use and/or discontinuation. In most cases, it is not possible to determine if these were de novo symptoms, although some respondents said they were experiencing new conditions they had not had previously. Although many respondents reported well-known benzodiazepine indications such as nervousness, anxiety, and insomnia, these symptoms after benzodiazepine discontinuation greatly differed in character from the symptoms for which they were originally prescribed benzodiazepines.

This study has certain limitations. It was an Internet survey and was thus self-selected and without a control group. Respondents were asked in some cases to recall symptoms, and spontaneous recall is subject to error. The survey was anonymous, so responses could not be verified against the medical records of respondents. The symptoms included in the multiple-choice survey were a subset of a longer list of benzodiazepine-associated symptoms reported by Ashton[6] and Wright[9] and it should not be assumed that this survey reported the full range or extent of symptoms experienced by respondents. Respondents were not excluded if they had significant comorbid conditions, if they were elderly, if they had substance use disorders, or if they were taking or tapering from other sedating or non-benzodiazepine hypnotic agents. There was no question to compare baseline symptoms with symptoms at other points in the benzodiazepine experience, for instance, symptoms before initiating treatment or during the taper. Finally, our survey was composed of a self-selected group of respondents who were motivated to participate in this benzodiazepine survey and may not be representative of all benzodiazepine users.

Conclusions

Benzodiazepines are taken by millions of people around the world and many who prescribe and those who receive benzodiazepine therapy do so with the belief that the drugs are safe, effective, and helpful. The first survey by the authors reported that a subset of patients who were prescribed benzodiazepines experienced a perplexing array of symptoms which may have lasted for months or years after the drugs were fully discontinued and may be different from the symptoms for which the benzodiazepine was originally prescribed. Evidence tentatively suggests that early and late symptoms occurring following benzodiazepine use may be attributable to different mechanisms. The transition from acute withdrawal to protracted symptoms may have some overlap and lack clear delineation. While acute withdrawal may be related to the removal of the drug from the receptor sites in the brain, these enduring symptoms may well have an incompletely elucidated mechanism based on neurotoxicity and/or neuroplastic changes associated with benzodiazepine use. Moreover, these effects are not fully understood nor widely appreciated. If these symptoms are mechanistically disparate, early and late symptoms of benzodiazepine withdrawal might possibly have been conflated in previous studies. Further research is needed into the protracted neurological dysfunctions associated with benzodiazepine use along with greater training for clinicians in benzodiazepine prescribing and deprescribing.

Declarations

Ethics approval and consent to participate

This was approved by the Vanderbilt University Institutional Review Board (IRB) #200521. The IRB did not require written informed consent because the survey was anonymous. The first question of the survey (see Appendix I) also asked for patient consent and explained the survey.

Consent for publication

We are not using any patient-specific information. The table and figure in this article are original.

Author Contributions

Christy Huff: Conceptualization; Methodology; Project administration; Writing – review & editing.

A. J. Reid Finlayson: Conceptualization; Writing – review & editing.

D.E. Foster: Formal analysis; Writing – review & editing.

Peter R. Martin: Methodology; Writing – review & editing.

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Availability of data and materials

The data are available upon request to D. E. Foster, foster@denmp.com.

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Supplemental material

Supplemental material for this article is available online.

References

1. Hollister LE, Motzenbecker FP and Degan RO. Withdrawal reactions from chlordiazepoxide ('Librium'). *Psychopharmacologia* 1961; 2: 63–68.
2. MacKinnon GL and Parker WA. Benzodiazepine withdrawal syndrome: a literature review and evaluation. *Am J Drug Alcohol Abuse* 1982; 9: 19–33.
3. Busto U, Sellers EM, Naranjo CA, *et al.* Withdrawal reaction after long-term therapeutic use of benzodiazepines. *N Engl J Med* 1986; 315: 854–859.
4. Martin P and Patel S. Pharmacology of drugs of abuse. In: Golan D, Armstrong E and Armstrong A (eds) *Principles of pharmacology: the pathophysiologic basis of drug therapy*. 4th ed. Philadelphia, PA: Wolters Kluwer Health, 2017, pp. 308–334.
5. Martin PR, Bhushan CM, Kapur BM, *et al.* Intravenous phenobarbital therapy in barbiturate and other hypnosedative withdrawal reactions: a kinetic approach. *Clin Pharmacol Ther* 1979; 26: 256–264.
6. Ashton H. The diagnosis and management of benzodiazepine dependence. *Curr Opin Psychiatry* 2005; 18: 249–255.
7. Ashton H. Protracted withdrawal syndromes from benzodiazepines. *J Subst Abuse Treat* 1991; 8: 19–28.
8. Higgitt A, Fonagy P, Toone B, *et al.* The prolonged benzodiazepine withdrawal syndrome: anxiety or hysteria? *Acta Psychiatr Scand* 1990; 82: 165–168.
9. Wright S. Benzodiazepine withdrawal: clinical aspects. In: Peppin J, Pergolizzi J Jr, Raffa R, *et al.* (eds) *The benzodizapeines crisis: the ramifications of an over-used drug class*. New York: Oxford University Press, 2020, pp. 117–148.
10. Schweizer E and Rickels K. Benzodiazepine dependence and withdrawal: a review of the syndrome and its clinical management. *Acta Psychiatr Scand Suppl* 1998; 393: 95–101.
11. Food Drug Administration. FDA drug safety communication, https://www.fda.gov/media/142368/download (2020, accessed 29 March 2022).
12. Pergolizzi JV Jr, LeQuang JA and Raffa RB. Benzodiazepines: thinking outside the black box. *J Clin Pharm Ther* 2020; 46: 554–559.
13. Reid Finlayson AJ, Macoubrie J, Huff C, *et al.* Experiences with benzodiazepine use, tapering, and discontinuation: an internet survey. *Ther Adv Psychopharmacol* 2022; 12: 20451253221082386–20451253221082310.
14. Kobayashi M, Okajima I, Narisawa H, *et al.* Development of a new benzodiazepine hypnotics withdrawal symptom scale. *Sleep Biol* 2018; 16: 263–271.
15. Pétursson H. The benzodiazepine withdrawal syndrome. *Addiction* 1994; 89: 1455–1459.
16. Owen RT and Tyrer P. Benzodiazepine dependence. A review of the evidence. *Drugs* 1983; 25: 385–398.

17. Busto U and Sellers EM. Pharmacologic aspects of benzodiazepine tolerance and dependence. *J Subst Abuse Treat* 1991; 8: 29–33.
18. Crowe SF and Stranks EK. The residual medium and long-term cognitive effects of benzodiazepine use: an updated meta-analysis. *Arch Clin Neuropsychol* 2018; 33: 901–911.
19. Cosci F and Chouinard G. Persistent postwithdrawal syndrome after benzodiazepine discontinuation. A reply to huff. *Psychother Psychosom* 2021; 90: 209–210.
20. Lugoboni F and Quaglio G. Exploring the dark side of the moon: the treatment of benzodiazepine tolerance. *Br J Clin Pharmacol* 2014; 77: 239–241.
21. Food Drug Administration. FDA requiring labeling changes for benzodiazepines. Boxed warning to be updated to include abuse, addiction and other serious risks. Rockville, MD: Food and Drug Administratin, 2020, https://www.fda.gov/news-events/press-announcements/fda-requiring-labeling-changes-benzodiazepines
22. US Preventive services task force. Screening for anxiety in adults, https://www.uspreventiveservicestaskforce.org/uspstf/draft-update-summary/anxiety-adults-screening (2022, accessed 23 September 2022).
23. Janhsen K, Roser P and Hoffmann K. The problems of long-term treatment with benzodiazepines and related substances. *Dtsch Arztebl Int* 2015; 112: 1–7.
24. Saitz R. Introduction to alcohol withdrawal. *Alcohol Health Res World* 1998; 22: 5–12.
25. Ho IK and Yu S. Effects of barbiturates on GABA system: comparison to alcohol and benzodiazepines. *Keio J Med* 1991; 40: 183–186.
26. Lobo IA and Harris RA. GABA(A) receptors and alcohol. *Pharmacol Biochem Behav* 2008; 90: 90–94.
27. Sachdeva A, Choudhary M and Chandra M. Alcohol withdrawal syndrome: benzodiazepines and beyond. *J Clin Diagn Res* 2015; 9: VE01–VE07.
28. Lann MA and Molina DK. A fatal case of benzodiazepine withdrawal. *Am J Forensic Med Pathol* 2009; 30: 177–179.
29. Martin PR, Singleton CK and Hiller-Sturmhöfel S. The role of thiamine deficiency in alcoholic brain disease. *Alcohol Res Health* 2003; 27: 134–142.
30. Béracochéa D, Mons N and David V. Targeting the glucocorticoid receptors during alcohol withdrawal to reduce protracted neurocognitive disorders. *Front Psychiatry* 2019; 10: 580.
31. Parks MH, Dawant BM, Riddle WR, *et al.* Longitudinal brain metabolic characterization of chronic alcoholics with proton magnetic resonance spectroscopy. *Alcohol Clin Exp Res* 2002; 26: 1368–1380.
32. Tyrer P. Benzodiazepine dependence: a shadowy diagnosis. *Biochem Soc Symp* 1993; 59: 107–119.
33. Wolf B, Grohmann R, Biber D, *et al.* Benzodiazepine abuse and dependence in psychiatric inpatients. *Pharmacopsychiatry* 1989; 22: 54–60.
34. LaCorte S. How chronic administration of benzodiazepines leads to unexplained chronic illnesses: a hypothesis. *Med Hypotheses* 2018; 118: 59–67.
35. Pall ML. Common etiology of posttraumatic stress disorder, fibromyalgia, chronic fatigue syndrome and multiple chemical sensitivity via elevated nitric oxide/peroxynitrite. *Med Hypotheses* 2001; 57: 139–145.
36. Shi Y, Cui M, Ochs K, *et al.* Long-term diazepam treatment enhances microglial spine engulfment and impairs cognitive performance via the mitochondrial 18 kDa translocator protein (TSPO). *Nat Neurosci* 2022; 25: 317–329.
37. Horowitz MA and Taylor D. How to reduce and stop psychiatric medication. *Eur Neuropsychopharmacol* 2022; 55: 4–7.
38. Food Drug Administration. FDA requiring boxed warning updated to improve safe use of benzodiazepine drug class, https://www.fda.gov/drugs/drug-safety-and-availability/fda-requiring-boxed-warning-updated-improve-safe-use-benzodiazepine-drug-class (2020, accessed 3 November 2020).
39. Database CD. The top 200 drugs of 2019, https://clincalc.com/DrugStats/ (2022, accessed 28 January 2022).
40. Soyka M. Treatment of benzodiazepine dependence. *N Engl J Med* 2017; 376: 1147–1157.
41. Furukawa T, Nikaido Y, Shimoyama S, *et al.* Impaired cognitive function and hippocampal changes following chronic diazepam treatment in middle-aged mice. *Front Aging Neurosci* 2021; 13: 777404.
42. Morgan K and Tomeny M. Benzodiazepine withdrawal and rebound insomnia. *Acta Psychiatr Scand* 1989; 80: 297–298.