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Long-term consequences of benzodiazepine-induced neurological dysfunction: A survey

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Abstract

Background

Acute benzodiazepine withdrawal has been described, but literature regarding the benzodiazepine-induced neurological injury that may result in enduring symptoms and life consequences is scant.

Objective

We conducted an internet survey of current and former benzodiazepine users and asked about their symptoms and adverse life events attributed to benzodiazepine use.

Methods

This is a secondary analysis of the largest survey ever conducted with 1,207 benzodiazepine users from benzodiazepine support groups and health/wellness sites who completed the survey. Respondents included those still taking benzodiazepines (n = 136), tapering (n = 294), or fully discontinued (n = 763).

Results

The survey asked about 23 specific symptoms and more than half of the respondents who experienced low energy, distractedness, memory loss, nervousness, anxiety, and other symptoms stated that these symptoms lasted a year or longer. These symptoms were often reported as *de novo* and distinct from the symptoms for which the benzodiazepines were originally prescribed. A subset of respondents stated that symptoms persisted even after benzodiazepines had been discontinued for a year or more. Adverse life consequences were reported by many respondents as well.

Limitations

This was a self-selected internet survey with no control group. No independent psychiatric diagnoses could be made in participants.

Conclusions

Many prolonged symptoms subsequent to benzodiazepine use and discontinuation (benzodiazepine-induced neurological dysfunction) have been shown in a large survey of

benzodiazepine users. Benzodiazepine-induced neurological dysfunction (BIND) has been proposed as a term to describe symptoms and associated adverse life consequences that may emerge during benzodiazepine use, tapering, and continue after benzodiazepine discontinuation. Not all people who take benzodiazepines will develop BIND and risk factors for BIND remain to be elucidated. Further pathogenic and clinical study of BIND is needed.

Introduction

Acute benzodiazepine withdrawal and its effective treatment are well known and have been described in the literature [1–4]. However, symptoms that persisted for months or even years after complete benzodiazepine discontinuation were observed decades ago [5, 6]. Prior to our survey, the largest study of this phenomenon, in which 50 subjects were examined, was carried out in 1987 and noted that symptoms in some patients persisted for months to years [7, 8]. Since then, clinical recognition of this condition, treatment strategies to address it, and a fundamental mechanistic understanding of how it differs from acute withdrawal remain confounded.

The nature of protracted withdrawal symptoms leads to a variety of interpretations, including the commonly held belief that they merely represent the return of the original symptoms for which the benzodiazepines were originally prescribed. However, if symptoms appeared *de novo* during and after benzodiazepine cessation, they may be attributed to a different or unrelated cause than that for which a benzodiazepine was actually prescribed. These protracted symptoms and other sequelae associated with the use, tapering, and discontinuation of benzodiazepines may be a distinct clinical entity.

The lack of descriptive nomenclature for enduring symptoms associated with benzodiazepine use limits both the clinical identification of this condition and informed discussion of risk with patients. Inadequate terminology such as “withdrawal,” “subacute withdrawal,” “protracted withdrawal,” “post-acute withdrawal syndrome” (PAWS), rebound, and other terms without clear definitions appear in the scant literature about prolonged symptoms after benzodiazepine discontinuation. The focus on specific symptoms and in comparison to acute withdrawal symptoms from other substances, such as alcohol or opioids, implies that benzodiazepine

withdrawal follows a well-defined acute trajectory which resolves over a relatively short period of time. These findings and the results of our earlier reports [9, 10] conflict with some of the literature [11].

To the best of our knowledge, this online survey is the largest ever conducted among benzodiazepine users. Its objective was to better describe and quantify the life consequences associated with these prolonged symptoms. It described constellations of benzodiazepine-induced and sometimes *de novo* symptoms, many of which lasted beyond a year and which were often accompanied by adverse life consequences.

Our objective was to better describe and quantify the life consequences associated with these prolonged symptoms.

Methods and materials

This study represents a secondary analysis of the results from an internet survey published previously [9]. It was approved by the Vanderbilt University Institutional Review Board (IRB) #20052, and did not require written informed consent because it was conducted as an anonymous survey that began with a question which recorded each respondent's consent for participation.

A medical statistician produced the initial results of this survey utilizing SAS Software. Subsequent data analysis was performed in greater detail by an experienced data scientist who imported the survey data into a custom SQL Server data model. Customized queries were employed to obtain correlations among the data. In particular, this analysis examined conditions for which benzodiazepines were prescribed and compared them to protracted symptoms reported by patients who were tapering or had discontinued benzodiazepine use. Adverse life consequences experienced by benzodiazepine patients, as reported in the survey, were also correlated to protracted symptoms. The complete survey form appears in S1 Appendix. The questions and multiple-choice answers used in the survey were derived from a subset of a longer list of benzodiazepine-associated symptoms report by Ashton [12] and Wright [1].

All analyses were delivered via a structured reporting process and validated against the original SAS reports. The survey was made available online through websites and internet benzodiazepine support groups and general health and wellness groups.

Results

A total of 1,207 respondents finished the survey although not all respondents gave an answer to every question and some questions allowed for multiple answers. Respondents to the survey might have been taking their full dose of benzodiazepines, engaged in the process of tapering off benzodiazepines, or had fully discontinued benzodiazepines. Respondents were asked to select among 23 symptoms they may have experienced and to indicate the duration of each symptom (see S1 Appendix). Of all respondents, 88.1% reported having anxiety, nervousness, or fear; 86.9% sleep disturbances; 86.2% low energy levels; and 85.3% difficulty focusing or distractedness. Some respondents reported these symptoms occurring following complete cessation of benzodiazepines and for long-term durations of months or years. In fact, 76.6% of all affirmative answers on symptom questions reported symptom durations to be months or "one year or longer." The most frequently reported symptoms lasting one year or more appear in Table 1.

Table 1. Of those who reported the following symptoms shown in the table, over half of respondents stated the symptom lasted ≥ 1 year.

Symptom	Symptom persisted ≥ 1 year
Low energy	59.9%
Difficulty focusing, distractedness	58.3%
Memory loss	57.5%
Nervous, anxiety	57.0%
Sleep disturbances	56.4%
Sensitivity to sights and sounds	54.3%
Digestive issues	52.2%
Symptoms triggered by food or drink	52.0%
Muscle weakness	51.2%
Body aches and pains	50.7%

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The symptoms reported in Table 1 occurred across all respondents, regardless of taper status and cause for original prescription of the benzodiazepine. When groups were separated into those still taking benzodiazepines at full dose (11.3%), those tapering (24.4%), and those who had completely discontinued benzodiazepines (63.2%), results showed that respondents who were taking the full-dose at the time of the survey reported experiencing the fewest symptoms, with modest differences between tapering and discontinued respondents. The survey queried respondents about the conditions or situation for which the benzodiazepines were prescribed. The most common reasons for prescriptions were situational anxiety (43.7%), insomnia (40.3%), panic attacks (39.9%), depression (33.0%), and generalized anxiety disorder

(23.7%). However, the prolonged symptoms after benzodiazepine use, tapering, or cessation frequently did not match the reason for which the benzodiazepines were originally prescribed. See Table 2.

Table 2. Proportion of respondents who experienced a protracted symptom for which the benzodiazepines were not originally prescribed.

Reason for the original benzodiazepine prescription	Proportion of respondents (n = 1,207) who reported this symptom but were not prescribed for it
Situational anxiety/anxiety	55.6%
Insomnia	57.5%
Digestive, stomach/gut issues	75.8%
Restlessness	95.3%
Muscle spasms	88.8%
Pain, nerve spasms	88.1%

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More than half of all respondents (54.7%) experienced 17 or more symptoms of the 23 listed; and over 40% of these stated the symptoms as lasting “one year or longer.”

In addition to enduring symptoms associated with benzodiazepines, many respondents reported that adverse consequences had occurred in multiple areas of their life (see Table 3). Over 90% of respondents attributed one or more general adverse life consequences to benzodiazepine use. A large majority of respondents (79.3%) reported six to 13 general life consequences, and 53.2% of respondents reported eight or more specific life consequences, all

of which they attributed to benzodiazepine use.On average, each respondent had 8.1 of the 16 adverse life consequences. Over 90% of respondents attributed one or more general adverse life consequences to benzodiazepine use. These included adverse effect on work life, fun and recreation, ability to take care of home and other, ability to drive or walk, social interactions or friendships, and relationships with spouse or family. More specific adverse life consequences were also reported (see Table 3) and were associated with a higher average frequency of symptoms than the overall survey population, 19/23 versus 15/23 symptoms, respectively. A subpopulation of respondents (n = 225, 18.6%) stated that none of these specific negative life consequences applied to them and, on average, reported their symptom duration in days or weeks rather than months or years; in other words, they experienced acute withdrawal symptoms.

Table 3. Specific life consequences correlated to symptoms attributed to benzodiazepine use.

A total of 23 symptoms could be selected in the survey. For all life consequences, the average duration of reported symptoms was >1 year.

Specific Adverse life consequences	Total reporting (% of total)	Average number of symptoms in this group
Significantly affected marriage, other relationships	686 (56.8%)	18.2
Suicidal thoughts or attempted suicide	657 (54.4%)	18.3
Lost a job, fired, became unable to work	585 (46.8%)	18.5
Experienced significant increase in medical costs	494 (40.9%)	18.5
Loss of wages or lower wages in a reduced job capacity	394 (32.6%)	18.4
Lost savings or retirement funds	322 (26.7%)	19.1
Violent thoughts or actual violence against others	284 (23.5%)	19.3
Lost a home	152 (12.6%)	19.2
Lost a business, if business owner	101 (8.4%)	18.4
Lost child custody	31 (2.6%)	20.9

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Those respondents taking a full dose of benzodiazepine tended to the lowest rates of adverse life consequences. See Table 4.

Table 4. Adverse life consequences of those on full dose benzodiazepine therapy, those tapering, and those who had completely discontinued benzodiazepines.

Totals represent the number of respondents who answered this question in the affirmative and the percentages indicate the proportion of the specific population who reported those consequences.

Life consequences	Total (%) n = 1,207	Full dose n = 136	Tapering n = 294	Discontinued n = 763
To what extent has your condition affected your work or personal life? How severely did this problem affect you? (Respondents could answer on a scale of 1 to 6, where 1 was "not at all" and 6 was "enormous problem.") Response rates are for those who stated ≥ 2.				
Work life	1000 (82.9%)	90 (66.2%)	258 (87.8%)	650 (85.2%)
Fun, recreation, hobbies	1072 (88.8%)	98 (72.1%)	280 (95.2%)	692 (90.7%)
Ability to care for home, others	1031 (85.4%)	91 (66.9%)	271 (92.2%)	667 (87.4%)
Ability to drive or walk	921 (76.3%)	77 (56.6%)	233 (79.3%)	610 (79.9%)
Social interaction, friendships	1042 (86.3%)	92 (67.6%)	275 (93.5%)	673 (88.2%)
Relationships with spouse, family	1023 (84.8%)	88 (64.7%)	272 (92.5%)	661 (86.6%)

Specifically, have any of these been consequences of your benzodiazepine use or withdrawal?				
Significantly affected marriage, other relationships	686 (56.8%)	63 (46.3%)	165 (56.1%)	456 (59.8%)
Suicidal thoughts or attempted suicide	657 (54.4%)	50 (36.8%)	176 (59.9%)	430 (56.4%)
Lost a job, fired, became unable to work	565 (46.8%)	52 (38.2%)	147 (50.0%)	365 (47.8%)
Experienced significant increase in medical costs	494 (40.9%)	39 (28.7%)	134 (45.6%)	320 (41.9%)
Loss of wages or lower wages in reduced job capacity	394 (32.6%)	31 (22.8%)	97 (33.0%)	265 (34.7%)
Lost savings or retirement funds	322 (26.7%)	19 (14.0%)	78 (26.5%)	223 (29.2%)
Violent thoughts or actual violence against others	284 (23.5%)	24 (17.6%)	76 (25.9%)	184 (24.1%)
Lost a home	152 (12.6%)	13 (9.6%)	39 (13.3%)	99 (13.0%)
Lost a business, if business owner	101 (8.4%)	11 (8.1%)	24 (8.2%)	65 (8.5%)
Lost child custody	31 (2.6%)	5 (3.7%)	5 (1.7%)	21 (2.8%)

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Note that there were 1,207 respondents but only 1,193 respondents answered these questions.

A total of 763 respondents reported they had discontinued benzodiazepines, of whom 426

stated they had been off benzodiazepines for a year or more. Adverse life consequences reported by those who had discontinued benzodiazepines for a year or more were deemed severe or worse by 55.9% to 83.6% of respondents. See Table 5.

Table 5. Respondents who had completely discontinued benzodiazepines for at least one year at the time of the survey (n = 426) rated the severity of life consequences on a scale of 1 to 6, with 6 the most severe.

Life Consequences	Not at all a problem, mild problem, or moderate problem (1, 2, 3)	Severe, quite severe, or enormous problem (4, 5, 6)
To what extent has your condition affected your work or personal life? How severely did this problem affect you? (Respondents could answer on a scale of 1 to 6, where 1 was "not at all" and 6 was "enormous problem.") Response rates are for those who stated ≥ 2.		
Fun, recreation, hobbies	70 (16.4%)	356 (83.6%)
Work life	88 (20.7%)	338 (79.3%)
Social interaction, friendships	99 (23.2%)	327 (76.8%)
Ability to take care of home, others	117 (27.5%)	309 (72.5%)
Relationships with spouse, family	133 (31.2%)	293 (68.8%)
Ability to drive or walk	188 (44.1%)	238 (55.9%)

Discussion

This analysis presents survey evidence that enduring symptoms along with adverse life consequences emerged *de novo* with benzodiazepine use. Although protracted symptoms following discontinuation of benzodiazepine use have been reported previously [9, 13, 14], it has generally been tacitly assumed that these symptoms were withdrawal phenomena that would resolve with time. This study reveals something entirely different: that new, and often persistent, symptoms induced by the use of benzodiazepines may emerge while using, tapering, or after discontinuing these medications. In fact, a subset of respondents who had completely discontinued benzodiazepines, including those who had ceased taking benzodiazepines for a year or more, continued to experience enduring life consequences.

This analysis showed ≥ 17 symptoms of ≥ 1 year's duration post-discontinuation were reported by over 40% of respondents. This is not the first report that benzodiazepine "withdrawal" symptoms persist long after drug discontinuation. As far back as 1981, Hallström and Lader found elevated Hamilton anxiety scores several months after patients had withdrawn from benzodiazepines [5]. Smith and Wesson observed that symptoms following withdrawal from low-dose benzodiazepines typically took six to 12 months to subside completely [6]. In 1987, Ashton, whose study of 50 patients had been to our knowledge the largest study of prolonged benzodiazepine sequelae before our survey, noted symptoms lasting more than a year post-withdrawal [7]. Ashton also wrote that "…all patients had a variety of anxiety/depressive symptoms on presentation, and these had been gradually increased over the years despite continuous benzodiazepine use" [7]. A four-week, double-blind, placebo-controlled diazepam withdrawal study also showed elevated post-withdrawal symptoms [15]. Eight weeks after the end of withdrawal, mean scores for headache, dizziness, depression, tinnitus, paresthesia, and motor symptoms remained higher than pre-withdrawal scores; other symptoms had declined but few had disappeared [15]. A case series (n = 104) is discussed as part of the unpublished report that precipitated the 2020 benzodiazepine-class FDA boxed warning. In this report, of the patients who reported withdrawal, the mean duration of withdrawal was 9.5 months [16]. Prolonged symptoms after benzodiazepine discontinuation have been reported elsewhere, ranging from anxiety, insomnia, nightmares, and deficits in memory or concentration [17]. While few formal studies have examined enduring benzodiazepine symptoms, there are thousands of accounts online from individuals who report

prolonged and distressing symptoms even after complete drug discontinuation [18].

The occurrence of adverse life consequences associated with benzodiazepines has not been thoroughly studied. Although efforts were made, statistical correlations between specific life consequences reported in our study and symptoms could not be drawn, but it appears based on available data from the respondents in the survey that enduring symptoms may have played an important role in damaging life consequences they experienced. This study shows that over 80% of respondents identified more than five serious life consequences which they attributed to benzodiazepine use. To the best of our knowledge, this is the first study to explore adverse life consequences associated with these enduring symptoms, of which many were neurocognitive. A meta-analysis of cognitive effects found that long-term benzodiazepine users were more impaired in all cognitive categories than the controls [19, 20]. This supports our findings, because several life consequences reported in our survey are likely related to impaired cognitive functioning. This would align with recently published findings from Europe where neuropsychological evaluation of cognition in 92 long-term benzodiazepine patients found 20.7% could be categorized as having cognitive impairment across all domains, with processing speed and sustained attention the worst-performing domains [21].

The term benzodiazepine-induced neurological dysfunction and its acronym BIND was coined as an effort by a separately convened work group of experts to provide a name for this condition that may serve both clinicians and the patients who suffer from this condition. See S2 Appendix. BIND serves as a clinically serviceable name for the enduring neurological sequelae of benzodiazepine use and would reify this condition for healthcare professionals. Patients in our survey sometimes wrote in comments that they felt like healthcare professionals did not take them seriously or frankly challenged or disbelieved their long-lasting symptoms [9]. Recognizing this condition with a specific medically accepted term may encourage more professional compassion, better treatment, and future research. Any medical condition with many vague or overlapping names or without a name can too easily be misdiagnosed or dismissed as insignificant or nonexistent. A name would reify this clinical entity. Practical, evidence-based, safe and effective approaches are urgently needed for benzodiazepine deprescribing and managing the enduring neurological sequelae of benzodiazepine use. The name BIND is an important first step in this direction. Thus, BIND describes a constellation of functionally limiting neurologic symptoms (both physical and psychological) that are the

consequence of neuroadaptation and/or neurotoxicty resulting from benzodiazepine exposure.

BIND also includes disturbing life consequences. Unlike other reports about benzodiazepine use and discontinuation, our survey took into account both symptoms and adverse life events, such as financial loss, termination of employment, and other devasting events. The subset of patients who used benzodiazepines and developed BIND experience a bewildering, sometimes severe, set of prolonged effects that have gone largely unrecognized by the medical profession [22]. The mechanisms underlying these prolonged effects have not been elucidated but are likely different from the mechanisms of acute withdrawal, which are well understood [1].

There are only a few studies of low or very low quality evaluating the safety and effectiverness of pharmacological interventions to help manage the symptoms of chronic benzodiazepine use and none of these interventions have been shown consistently to be effective across significant portions of those affected [23]. Since benzodiazepine users are a heterogeneous population, it is unlikely there is a one-size-fits-all approach to tapering and discontinuation [24].

Over 30 million Americans report past-year use of benzodiazepines and this population is heterogenous. It includes old and young, fit and frail, and all demographic groups. Many of these benzodiazepine users are at elevated risk for BIND, which may go undiagnosed. Even when BIND is diagnosed, treatment protocols are lacking. While most benzodiazepine users do not develop BIND, the risk factors for BIND are not known. Since benzodiazepines are among the most frequently prescribed drugs in the United States, treatments for BIND represent an urgent unmet medical need [25]. This warrants greater and more in-depth research.

Our survey was concluded prior to the outbreak of the pandemic, and it is not known how the lockdowns and COVID-19 affected substance use disorders in general or the use of benzodiazepines in particular [26]. According, there is also limited research on how the pandemic impacted benzodiazepine use patterns and the effect that the emergence of so-called “designer benzodiazepines” have had. This is a very complex topic because data on use must be disentangled from prevailing trends and tendencies in drug use patterns that may have been unrelated to the pandemic.

A growing concern is that individuals being tapered or deprescribed benzodiazepines too abruptly might turn to what is available to them, including alcohol, opioids, central nervous system depressants, and, of increasing concern are “designer benzodiazepines,” such as diclazepam, conazolam, and nitrazolam; phenazepam and etizolam have been licensed as medical agents in some countries but not in the United States or Western Europe [27]. Over two dozen distinct “designer benzodiazepines” have been identified and many can be purchased online [28]. From the very limited available evidence, it appears that the use of designer benzodiazepines typically occurs in polysubstance abuse rather than in physician-prescribed benzodiazepine prescribing [29]. Our survey did not ask about these products; however, 90.4% of our respondents reported they definitely or mostly took benzodiazepines as prescribed.

Our study has several limitations. It is based on a self-selected group of respondents who were recruited primarily through benzodiazepine support group websites and may not be representative of all benzodiazepine users. There was no control group. It was a multiple-choice survey and although write-in information was accepted, our results are based entirely on responses from multiple-choice questions. The survey was anonymous and there was no access to the respondents’ medical records to confirm their benzodiazepine use or status. The symptoms included in the multiple-choice survey were a subset of symptoms provided by Ashton [12] and Wright [1], and does not necessarily reflect the complete range of symptoms experienced by respondents. Since this was a survey, we were unable to determine whether respondents met criteria for a formal psychiatric disorder that contains the symptoms. No exclusion criteria were used for old age, comorbidities, or substance use disorder. Respondents were not asked if they were taking or tapering from other sedating or non-benzodiazepine hypnotic drugs. No questions were asked that might have allowed baseline symptoms to be compared with symptoms at other points in the trajectory of benzodiazepine use.

Conclusions

While acute benzodiazepine withdrawal is well described in the literature, there is far less known about the often distressing and enduring symptoms which impair life functioning in those who have discontinued or are in the process of discontinuing benzodiazepines. We propose the term benzodiazepine-induced neurological dysfunction (BIND) for this

constellation of symptoms. Our survey shows that for some benzodiazepine users, these symptoms are severe, life altering, and not infrequent. A significant subpopulation of respondents with BIND reported multiple and severe symptoms, many of which were not the symptoms for which the benzodiazepines were originally prescribed. The mechanisms of BIND, its clinical course, risk factors, and treatment modalities warrant further study.

Supporting information

S1 Appendix. Is the survey in its entirety.

(DOCX)

Click here for additional data file. (219.5KB, docx)

S2 Appendix. Describes the efforts of the benzodiazepine nosology workgroup.

(DOCX)

Click here for additional data file. (21.3KB, docx)

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Data Availability

The data are held in a public repository: https://osf.io/cewgb/ DOI 10.17605/OSF.IO/CEWGB

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References

1. Wright S. Benzodiazepine Withdrawal: Clinical Aspects. In: Peppin J, Pergolizzi J Jr., Raffa R, Wright S, editors. The Benzodizapines Crisis: The Ramifications of an Over-Used Drug Class. New York, New York: Oxford University Press; 2020. p. 117–48. [Google Scholar]

2. Lader M. Benzodiazepines revisited—will we ever learn? Addiction (Abingdon, England). 2011;106(12):2086–109. doi: 10.1111/j.1360-0443.2011.03563.x [DOI] [PubMed] [Google Scholar]

3. Hood SD, Norman A, Hince DA, Melichar JK, Hulse GK. Benzodiazepine dependence and its treatment with low dose flumazenil. Br J Clin Pharmacol. 2014;77(2):285–94. doi: 10.1111/bcp.12023 [DOI] [PMC free article] [PubMed] [Google Scholar]

4. Quaglio G, Pattaro C, Gerra G, Mathewson S, Verbanck P, Des Jarlais DC, et al. High dose benzodiazepine dependence: description of 29 patients treated with flumazenil infusion and stabilised with clonazepam. Psychiatry Res. 2012;198(3):457–62. doi: 10.1016/j.psychres.2012.02.008 [DOI] [PubMed] [Google Scholar]

5. Hallstrom C, Lader M. Benzodiazepine withdrawal phenomena. Int Pharmacopsychiatry. 1981;16(4):235–44. doi: 10.1159/000468500 [DOI] [PubMed] [Google Scholar]

6. Smith DE, Wesson DR. Benzodiazepine dependency syndromes. J Psychoactive Drugs. 1983;15(1–2):85–95. doi: 10.1080/02791072.1983.10472127 [DOI] [PubMed] [Google Scholar]

7. Ashton H. Benzodiazepine withdrawal: outcome in 50 patients. Br J Addict. 1987;82(6):665–71. doi: 10.1111/j.1360-0443.1987.tb01529.x [DOI] [PubMed]

[Google Scholar]

8. Lugoboni F, Quaglio G. Exploring the dark side of the moon: the treatment of benzodiazepine tolerance. Br J Clin Pharmacol. 2014;77(2):239–41. doi: 10.1111/bcp.12148 [DOI] [PMC free article] [PubMed] [Google Scholar]

9. Finlayson A, Macoubrie J, Huff C, Foster D, Martin P. Experiences with benzodiazepine use, tapering, and discontinuation: an Internet survey. Ther Adv Psychopharmacol. 2022;2:1–10. [DOI] [PMC free article] [PubMed] [Google Scholar]

10. Huff C, Finlayson A, Foster D, Martin P. Enduring neurological sequelae of benzodiazepine use: an Internet survey. Ther Adv Psychopharmacol. 2022;12:1–9. [DOI] [PMC free article] [PubMed] [Google Scholar]

11. Cosci F, Chouinard G. Acute and Persistent Withdrawal Syndromes Following Discontinuation of Psychotropic Medications. Psychother Psychosom. 2020;89(5):283–306. doi: 10.1159/000506868 [DOI] [PubMed] [Google Scholar]

12. Ashton H. The diagnosis and management of benzodiazepine dependence. Curr Opin Psychiatry. 2005;18(3):249–55. doi: 10.1097/01.yco.0000165594.60434.84 [DOI] [PubMed] [Google Scholar]

13. Ashton H. Protracted withdrawal syndromes from benzodiazepines. J Subst Abuse Treat. 1991;8(1–2):19–28. doi: 10.1016/0740-5472(91)90023-4 [DOI] [PubMed] [Google Scholar]

14. Fixsen AM, Ridge D. Stories of Hell and Healing: Internet Users' Construction of Benzodiazepine Distress and Withdrawal. Qual Health Res. 2017;27(13):2030–41. doi: 10.1177/1049732317728053 [DOI] [PubMed] [Google Scholar]

15. Ashton CH, Rawlins MD, Tyrer SP. A double-blind placebo-controlled study of buspirone in diazepam withdrawal in chronic benzodiazepine users. Br J Psychiatry. 1990;157:232–8. doi: 10.1192/bjp.157.2.232 [DOI] [PubMed] [Google Scholar]

16. Food and Drug Administration. Integrated drug utilization, epidemiology, and

pharmacovigilance review: Benzodiazepine use, misuse, abuse, dependence, withdrawal, morbidity, and mortality Rockville, Maryland: Food and Drug Administration; 2020 [Available from: https://www.benzoinfo.com/wp-content/uploads/2020/11/Benzodiazepine-Information-Coalition-FOIA-FDA-.pdf/.

17. Authier N, Balayssac D, Sautereau M, Zangarelli A, Courty P, Somogyi AA, et al. Benzodiazepine dependence: focus on withdrawal syndrome. Ann Pharm Fr. 2009;67(6):408–13. doi: 10.1016/j.pharma.2009.07.001 [DOI] [PubMed] [Google Scholar]

18. Huff C. Response to Acute and Persistent Withdrawal Syndromes following Discontinuation of Psychotropic Medications by Cosci et al. (2020). Psychother Psychosom. 2021;90(3):207–8. [DOI] [PubMed] [Google Scholar]

19. Barker MJ, Greenwood KM, Jackson M, Crowe SF. Cognitive effects of long-term benzodiazepine use: a meta-analysis. CNS drugs. 2004;18(1):37–48. doi: 10.2165/00023210-200418010-00004 [DOI] [PubMed] [Google Scholar]

20. Crowe SF, Stranks EK. The Residual Medium and Long-term Cognitive Effects of Benzodiazepine Use: An Updated Meta-analysis. Archives Clin Neuropsychol. 2018;33(7):901–11. doi: 10.1093/arclin/acx120 [DOI] [PubMed] [Google Scholar]

21. Zetsen SPG, Schellekens AFA, Paling EP, Kan CC, Kessels RPC. Cognitive Functioning in Long-Term Benzodiazepine Users. Eur Addict Res. 2022;28(5):377–81. doi: 10.1159/000525988 [DOI] [PubMed] [Google Scholar]

22. Dubovsky SL, Marshall D. Benzodiazepines Remain Important Therapeutic Options in Psychiatric Practice. Psychother Psychosom. 2022;91(5):307–34. doi: 10.1159/000524400 [DOI] [PubMed] [Google Scholar]

23. Baandrup L, Ebdrup BH, Rasmussen J, Lindschou J, Gluud C, Glenthøj BY. Pharmacological interventions for benzodiazepine discontinuation in chronic benzodiazepine users. Cochrane Database Syst Rev. 2018;3(3):Cd011481. doi: 10.1002/14651858.CD011481.pub2 [DOI] [PMC free article] [PubMed] [Google Scholar]

24. Brett J, Murnion B. Management of benzodiazepine misuse and dependence. Aust Prescr. 2015;38(5):152–5. doi: 10.18773/austprescr.2015.055 [DOI] [PMC free article] [PubMed] [Google Scholar]

25. Maust DT, Lin LA, Blow FC. Benzodiazepine Use and Misuse Among Adults in the United States. Psychiatr Serv. 2019;70(2):97–106. doi: 10.1176/appi.ps.201800321 [DOI] [PMC free article] [PubMed] [Google Scholar]

26. Jager J, Keyes KM. Is substance use changing because of the COVID-19 pandemic? Conceptual and methodological considerations to delineating the impact of the COVID-19 pandemic on substance use and disorder. Addiction (Abingdon, England). 2021;116(6):1301–3. doi: 10.1111/add.15414 [DOI] [PMC free article] [PubMed] [Google Scholar]

27. Moosmann B, Auwärter V. Designer Benzodiazepines: Another Class of New Psychoactive Substances. Handb Exp Pharmacol. 2018;252:383–410. doi: 10.1007/164_2018_154 [DOI] [PubMed] [Google Scholar]

28. Orsolini L, Corkery JM, Chiappini S, Guirguis A, Vento A, De Berardis D, et al. 'New/Designer Benzodiazepines': An Analysis of the Literature and Psychonauts' Trip Reports. Curr Neuropharmacol. 2020;18(9):809–37. doi: 10.2174/1570159X18666200110121333 [DOI] [PMC free article] [PubMed] [Google Scholar]

29. Kriikku P, Wilhelm L, Rintatalo J, Hurme J, Kramer J, Ojanperä I. Phenazepam abuse in Finland: findings from apprehended drivers, post-mortem cases and police confiscations. Forensic Sci Int. 2012;220(1–3):111–7. doi: 10.1016/j.forsciint.2012.02.006 [DOI] [PubMed] [Google Scholar]

PLoS One. doi: 10.1371/journal.pone.0285584.r001

Decision Letter 0

Simona Zaami

Transfer Alert

This paper was transferred from another journal. As a result, its full editorial history (including decision letters, peer reviews and author responses) may not be present.

14 Mar 2023

PONE-D-23-04336Long-term Consequences of Benzodiazepine-Induced Neurological Dysfunction: A SurveyPLOS ONE

Dear Dr. Ritvo,

Thank you for submitting your manuscript to PLOS ONE. After careful consideration, we feel that it has merit but does not fully meet PLOS ONE's publication criteria as it currently stands. Therefore, we invite you to submit a revised version of the manuscript that addresses the points raised during the review process.

Please submit your revised manuscript by Apr 27 2023 11:59PM. If you will need more time than this to complete your revisions, please reply to this message or contact the journal office at plosone@plos.org. When you're ready to submit your revision, log on to https://www.editorialmanager.com/pone/ and select the 'Submissions Needing Revision' folder to locate your manuscript file.

Please include the following items when submitting your revised manuscript:

- A rebuttal letter that responds to each point raised by the academic editor and

reviewer(s). You should upload this letter as a separate file labeled 'Response to Reviewers'.

- A marked-up copy of your manuscript that highlights changes made to the original version. You should upload this as a separate file labeled 'Revised Manuscript with Track Changes'.
- An unmarked version of your revised paper without tracked changes. You should upload this as a separate file labeled 'Manuscript'.

If you would like to make changes to your financial disclosure, please include your updated statement in your cover letter. Guidelines for resubmitting your figure files are available below the reviewer comments at the end of this letter.

If applicable, we recommend that you deposit your laboratory protocols in protocols.io to enhance the reproducibility of your results. Protocols.io assigns your protocol its own identifier (DOI) so that it can be cited independently in the future. For instructions see: https://journals.plos.org/plosone/s/submission-guidelines#loc-laboratory-protocols. Additionally, PLOS ONE offers an option for publishing peer-reviewed Lab Protocol articles, which describe protocols hosted on protocols.io. Read more information on sharing protocols at https://plos.org/protocols?utm_medium=editorial-email&utm_source=authorletters&utm_campaign=protocols.

We look forward to receiving your revised manuscript.

Kind regards,

Simona Zaami

Academic Editor

PLOS ONE

Journal Requirements:

When submitting your revision, we need you to address these additional requirements.

1. Please ensure that your manuscript meets PLOS ONE's style requirements, including those for file naming. The PLOS ONE style templates can be found at

https://journals.plos.org/plosone/s/file?id=wjVg/PLOSOne_formatting_sample_main_body.pdf and

https://journals.plos.org/plosone/s/file?id=ba62/PLOSOne_formatting_sample_title_authors_affiliations.pdf

2. Thank you for stating the following in the Competing Interests section:

"I have read the journal's policy and the authors of this manuscript have the following competing interests: Alexis Ritvo is contracted as the medical director for the national non-profit the Alliance for Benzodiazepine Best Practices. Alexis Ritvo and D Foster volunteer as co-chairs for the Benzodiazepine Action Work Group with the Colorado Consortium for Prescription Drug Abuse Prevention. D Foster is also the founder and owner of Easing Anxiety. Christy Huff is a director with the Benzodiazepine Information Coalition. Bernie Sanders is president of the Alliance for Benzodiazepine Best Practices. "

Please confirm that this does not alter your adherence to all PLOS ONE policies on sharing data and materials, by including the following statement: "This does not alter our adherence to PLOS ONE policies on sharing data and materials." (as detailed online in our guide for authors http://journals.plos.org/plosone/s/competing-interests). If there are restrictions on sharing of data and/or materials, please state these. Please note that we cannot proceed with consideration of your article until this information has been declared.

Please include your updated Competing Interests statement in your cover letter; we will change the online submission form on your behalf.

3. We note that you have stated that you will provide repository information for your data at

acceptance. Should your manuscript be accepted for publication, we will hold it until you provide the relevant accession numbers or DOIs necessary to access your data. If you wish to make changes to your Data Availability statement, please describe these changes in your cover letter and we will update your Data Availability statement to reflect the information you provide.

4. Please include your full ethics statement in the 'Methods' section of your manuscript file. In your statement, please include the full name of the IRB or ethics committee who approved or waived your study, as well as whether or not you obtained informed written or verbal consent. If consent was waived for your study, please include this information in your statement as well.

5. Please include captions for your Supporting Information files at the end of your manuscript, and update any in-text citations to match accordingly. Please see our Supporting Information guidelines for more information: http://journals.plos.org/plosone/s/supporting-information.

6. We note that you have referenced (unpublished on page 13) which has currently not yet been accepted for publication. Please remove this from your References and amend this to state in the body of your manuscript: (ie "Bewick et al. [Unpublished]") as detailed online in our guide for authors

http://journals.plos.org/plosone/s/submission-guidelines#loc-reference-style

Additional Editor Comments:

Dear Authors,

Thanks for your submission to Plos One.

I am hereby requesting that you amend their manuscript according to both reviewers' comments and suggestions.

Best regards,

Prof. Simona Zaami

[Note: HTML markup is below. Please do not edit.]

Reviewers' comments:

Reviewer's Responses to Questions

Comments to the Author

1. Is the manuscript technically sound, and do the data support the conclusions?

The manuscript must describe a technically sound piece of scientific research with data that supports the conclusions. Experiments must have been conducted rigorously, with appropriate controls, replication, and sample sizes. The conclusions must be drawn appropriately based on the data presented.

Reviewer #1: Yes

Reviewer #2: Yes

****

2. Has the statistical analysis been performed appropriately and rigorously?

Reviewer #1: Yes

Reviewer #2: Yes

****

3. Have the authors made all data underlying the findings in their manuscript fully available?

The PLOS Data policy requires authors to make all data underlying the findings described in their manuscript fully available without restriction, with rare exception (please refer to the Data Availability Statement in the manuscript PDF file). The data should be provided as part of the manuscript or its supporting information, or deposited to a public repository. For example, in addition to summary statistics, the data points behind means, medians and variance measures should be available. If there are restrictions on publicly sharing data—e.g. participant privacy or use of data from a third party—those must be specified.

Reviewer #1: Yes

Reviewer #2: Yes

****

4. Is the manuscript presented in an intelligible fashion and written in standard English?

PLOS ONE does not copyedit accepted manuscripts, so the language in submitted articles must be clear, correct, and unambiguous. Any typographical or grammatical errors should be corrected at revision, so please note any specific errors here.

Reviewer #1: Yes

Reviewer #2: Yes

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5. Review Comments to the Author

Please use the space provided to explain your answers to the questions above. You may also include additional comments for the author, including concerns about dual publication, research ethics, or publication ethics. (Please upload your review as an attachment if it exceeds 20,000 characters)

Reviewer #1: It was my pleasure to review the manuscript Long-term Consequences of Benzodiazepine-Induced Neurological Dysfunction: A

Survey.

The article revolves around a sound and painstaking analysis of 1,207 benzodiazepine users from benzodiazepine support groups and health/wellness sites.

The article is quite informative and cogently enunciated in its most relevant findings, which are ultimately a worthy research contribution likely to appeal to a rather broad readership of mental health professionals and addiction specialists. Shedding a light on the underlying factors determining or contributing to neurological repercussions from BDZ use is essential for forensic medicine and public health as well, given the far-reaching implications thereof.

In that regard, I feel that the article does not go far enough, and does not fully succeed in making the most out of its data analysis.

More depth needs to be added to the Discussion, also mentioning "substitute" BDZ substances and the threat they pose in terms of detection and control, in addition to the psychiatric implications.

Thereference pool should be enhanced, consider the following:

PMID: 32144953.

PMID: 29543325

PMID: 31799633.

PMID: 36041417.

The article is clear and straightforward overall, and the tables are meaningful and well conceived.

Making it more comprehensive will add to its relevance and improve balance and development.

Sincerely.

Reviewer #2: Dear Authors,

I have read and mostly appreciated your article titled Long-term Consequences of Benzodiazepine-Induced Neurological Dysfunction: A

Survey, in which the distinctive features and complex dynamics at the heart of BIND have been expounded upon quite effectively and in a scientifically sound fashion.

The article has qualities and strengths which make it a praiseworthy scientific research contribution. It has considerable elements of novelty, relevance and thorougness as far as its stated objective is. The methodology is sound, as far as I could determine.

The one area in which the article falls short is the limited scope in terms of mentioning and elaborating on factors such as screening and detection and policies and measures aimed at mitigating the spread of BDZs with an eye on designer drugs, i.e. replacements to BDZs and other substances of abuse.

Briefly addressing such elements of discussion would certainly contribute to making the article more comprehensive and well-rounded, which would be advisable in light of the uniquely

consequential issues arising fron BDZs abuse. It is also worth mentioning the impact of the COVID-19 pandemic on abuse dynamics overall. Too many sources are older than five years.

The following sources ought to be drawn upon and cited as well:

Zaami S, Graziano S, Tittarelli R, Beck R, Marinelli E. BDZs, Designer BDZs and Z-drugs: Pharmacology and Misuse Insights. Curr Pharm Des. 2022;28(15):1221-1229. doi: 10.2174/1381612827666210917145636.

Moosmann B, Auwärter V. Designer Benzodiazepines: Another Class of New Psychoactive Substances. Handb Exp Pharmacol. 2018;252:383-410. doi: 10.1007/164_2018_154.

Lo Faro AF, Venanzi B, Pilli G, Ripani U, Basile G, Pichini S, Busardò FP. Ultra-high-performance liquid chromatography-tandem mass spectrometry assay for quantifying THC, CBD and their metabolites in hair. Application to patients treated with medical cannabis. J Pharm Biomed Anal. 2022 Aug 5;217:114841. doi: 10.1016/j.jpba.2022.114841.

Negro F, Di Trana A, Marinelli S. The effects of the COVID-19 pandemic on the use of the performance-enhancing drugs. Acta Biomed. 2022 Jan 19;92(6):e2021401. doi: 10.23750/abm.v92i6.12377.

Mannocchi G, Di Trana A, Tini A, Zaami S, Gottardi M, Pichini S, Busardò FP. Development and validation of fast UHPLC-MS/MS screening method for 87 NPS and 32 other drugs of abuse in hair and nails: application to real cases. Anal Bioanal Chem. 2020 Aug;412(21):5125-5145. doi: 10.1007/s00216-020-02462-6.

Walton SE, Krotulski AJ, Logan BK. A Forward-Thinking Approach to Addressing the New Synthetic Opioid 2-Benzylbenzimidazole Nitazene Analogs by Liquid Chromatography-Tandem Quadrupole Mass Spectrometry (LC-QQQ-MS). J Anal Toxicol. 2022 Mar 21;46(3):221-231. doi: 10.1093/jat/bkab117.

Napoletano S, Basile G, Lo Faro AF, Negro F. New Psychoactive Substances and receding

COVID-19 pandemic: really going back to "normal"? Acta Biomed. 2022 May 11;93(2):e2022186. doi: 10.23750/abm.v93i2.13008.

The article is overall well-written and coherently assembled. With a few adjustments, I believe it could make for a valuable and meaningful contribution to a highly relevant area of research.

Best regards.

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6. PLOS authors have the option to publish the peer review history of their article (what does this mean?). If published, this will include your full peer review and any attached files.

If you choose “no”, your identity will remain anonymous but your review may still be made public.

Do you want your identity to be public for this peer review? For information about this choice, including consent withdrawal, please see our Privacy Policy .

Reviewer #1: No

Reviewer #2: No

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[NOTE: If reviewer comments were submitted as an attachment file, they will be attached to this email and accessible via the submission site. Please log into your account, locate the manuscript record, and check for the action link "View Attachments". If this link does not appear, there are no attachment files.]

While revising your submission, please upload your figure files to the Preflight Analysis and

Conversion Engine (PACE) digital diagnostic tool, https://pacev2.apexcovantage.com/. PACE helps ensure that figures meet PLOS requirements. To use PACE, you must first register as a user. Registration is free. Then, login and navigate to the UPLOAD tab, where you will find detailed instructions on how to use the tool. If you encounter any issues or have any questions when using PACE, please email PLOS at figures@plos.org. Please note that Supporting Information files do not need this step.

PLoS One. 2023 Jun 29;18(6):e0285584. doi: 10.1371/journal.pone.0285584.r002

Author response to Decision Letter 0

Article notes Copyright and License information

31 Mar 2023

Thank you for the opportunity to revise our manuscript. Please see attached rebuttal letter worksheet for our response to each point raised by the academic editor and reviewers.

Attachment

Submitted filename: *3.24.23_Benzo #3 Rebuttal Letter Worksheet for Peer Review.docx*

Click here for additional data file. (20.4KB, docx)

PLoS One. doi: 10.1371/journal.pone.0285584.r003

Decision Letter 1

Simona Zaami

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27 Apr 2023

Long-term Consequences of Benzodiazepine-Induced Neurological Dysfunction: A Survey

PONE-D-23-04336R1

Dear Dr. Ritvo,

We’re pleased to inform you that your manuscript has been judged scientifically suitable for publication and will be formally accepted for publication once it meets all outstanding technical requirements.

Within one week, you’ll receive an e-mail detailing the required amendments. When these have been addressed, you’ll receive a formal acceptance letter and your manuscript will be scheduled for publication.

An invoice for payment will follow shortly after the formal acceptance. To ensure an efficient process, please log into Editorial Manager at http://www.editorialmanager.com/pone/[redacted], click the 'Update My Information' link at the top of the page, and double check that your user information is up-to-date. If you have any billing related questions, please contact our Author Billing department directly at authorbilling@plos.org.

If your institution or institutions have a press office, please notify them about your upcoming paper to help maximize its impact. If they’ll be preparing press materials, please inform our press team as soon as possible -- no later than 48 hours after receiving the formal acceptance. Your manuscript will remain under strict press embargo until 2 pm Eastern Time on the date of publication. For more information, please contact onepress@plos.org.

Kind regards,

Simona Zaami

Academic Editor

PLOS ONE

Additional Editor Comments (optional):

Dear Authors,

I have gone over the latest version of the manuscript titled Long-term Consequences of Benzodiazepine-Induced Neurological Dysfunction: A Survey, it is my belief that you have mostly succeeded in improving the manuscript by addressing the reviewers' comments, and amend their article accordingly.

I feel that in light of the improvements made, the article is now more comprehensive and well-rounded overall.

It will make for a valuable contribution to a highly relevant field of toxicology research.

Best regards,

Prof. Simona Zaami

PLoS One. doi: 10.1371/journal.pone.0285584.r004

Acceptance letter

Simona Zaami

21 Jun 2023

PONE-D-23-04336R1

Long-term consequences of benzodiazepine-induced neurological dysfunction: A survey

Dear Dr. Ritvo:

I'm pleased to inform you that your manuscript has been deemed suitable for publication in PLOS ONE. Congratulations! Your manuscript is now with our production department.

If your institution or institutions have a press office, please let them know about your upcoming paper now to help maximize its impact. If they'll be preparing press materials, please inform our press team within the next 48 hours. Your manuscript will remain under strict press embargo until 2 pm Eastern Time on the date of publication. For more information please contact onepress@plos.org.

If we can help with anything else, please email us at plosone@plos.org.

Thank you for submitting your work to PLOS ONE and supporting open access.

Kind regards,

PLOS ONE Editorial Office Staff

on behalf of

Dr. Simona Zaami

Academic Editor

PLOS ONE

Associated Data

This section collects any data citations, data availability statements, or supplementary materials included in this article.

Supplementary Materials

S1 Appendix. Is the survey in its entirety.

(DOCX)

Click here for additional data file. (219.5KB, docx)

S2 Appendix. Describes the efforts of the benzodiazepine nosology workgroup.

(DOCX)

Click here for additional data file. (21.3KB, docx)

Attachment

Submitted filename: *3.24.23_Benzo #3 Rebuttal Letter Worksheet for Peer Review.docx*

Click here for additional data file. (20.4KB, docx)

Data Availability Statement

The data are held in a public repository: https://osf.io/cewgb/ DOI 10.17605/OSF.IO/CEWGB