

# Concerns About Long-Term Benzodiazepine Treatment and the State of the Evidence:

## Reply to Sigler et al

**To the Editor:** We thank Sigler et al<sup>1</sup> for their interest in the questions about benzodiazepines raised in our recent commentary.<sup>2</sup> The issues flagged in their letter are a sample of the variety of concerns raised about these medications and the differing degrees to which the extant evidence base addresses them.

While some earlier reports suggested a link between benzodiazepine use and dementia, others found none; more recent studies, with arguably more definitive methodology, failed to confirm the relationship. Dubovsky and Marshall<sup>3</sup> have summarized this literature. While benzodiazepines have not been proven to cause dementia, future research may modify the present picture.

The evidence base that we described as finding long-term benzodiazepine use to be “stable and unproblematic” consists of at least 7 naturalistic follow-up studies,<sup>4–10</sup> 2 double-blind controlled studies,<sup>11,12</sup> 1 small survey study,<sup>13</sup> and more recently, a large national register-based study.<sup>14</sup> While not as extensive as the topic deserves, these reports are unanimous in finding dose stability and consistent benefits for patients taking benzodiazepines for up to 3 years; we have found no systematic research contradicting these findings, and none has been brought to our attention. Sigler et al correctly point out that prescribing guidelines typically caution against long-term use of benzodiazepines, but such recommendations ignore, rather than reflect the extant evidence.

Finally, there are patients who have had severe and/or persistent adverse effects associated with both taking and withdrawing from long-term benzodiazepines. Such outcomes have been the subject of essentially no systematic research,<sup>15</sup> and they appear in adverse effect surveys and anecdotally in the withdrawal literature.<sup>16,17</sup> We therefore have no basis for understanding the risk factors and mechanisms for such adverse experiences, or the reasons why the efficacy and tolerability literature contains little sign of them.

The question should not be which of these pictures are correct, but which is a likely outcome for whom, under what conditions of treatment and withdrawal. For example, while the withdrawal literature suggests that up to one-third of patients are unable to complete a taper,<sup>17</sup> Nardi and others have successfully tapered patients who are personally motivated to come off their medication, using a slow taper, without major difficulty.<sup>18,19</sup> There is substantial support for long-term benzodiazepines as safe, effective antianxiety medications for patients with diagnosed anxiety disorders, as well as reason for concern that they may be harmful to other, as yet poorly defined patient groups. Understanding the past treatment and withdrawal histories of people with long-term adverse outcomes to benzodiazepine use would be an important focus of future research.

## References

1. Sigler B, Silvernail B, Ritvo AD, et al. Evidence-based benzodiazepine practice guidelines are needed. *J Clin Psychiatry*. 2024;85(2):241r15306.
2. Silberman E, Nardi AE, Starcevic V, et al. Resolving the paradox of long-term benzodiazepine treatment: toward evidence-based practice guidelines. *J Clin Psychiatry*. 2023;84(6):23com14959.
3. Dubovsky SL, Marshall D. Benzodiazepines remain important therapeutic options in psychiatric practice. *Psychother Psychosom*. 2022;91(5):307–334.
4. Rickels K, Case WG, Downing RW, et al. Long-term diazepam therapy and clinical outcome. *JAMA*. 1983;250(6):767–771.
5. Nagy LM, Krystal JH, Woods SW, et al. Clinical and medication outcome after short-term alprazolam and behavioral group treatment in panic disorder. 2.5 year naturalistic follow-up study. *Arch Gen Psychiatry*. 1989;46(11):993–999.
6. Pollack MH, Otto MW, Tesar GE, et al. Long-term outcome after acute treatment with alprazolam or clonazepam for panic disorder. *J Clin Psychopharmacol*. 1993;13(4):257–263.
7. Worthington JJ III, Pollack MH, Otto MW, et al. Long-term experience with clonazepam in patients with a primary diagnosis of panic disorder. *Psychopharmacol Bull*. 1998;34(2):199–205.
8. Soumerai SB, Simoni-Wastila L, Singer C, et al. Lack of relationship between long-term use of benzodiazepines and escalation to high dosages. *Psychiatr Serv*. 2003;54(7):1006–1011.
9. Khan A, Joyce P, Jones AV. Benzodiazepine withdrawal syndromes. *N Z Med J*. 1980;92(665):94–96.
10. Sheehan DV. Benzodiazepines in panic disorder and agoraphobia. *J Affect Disord*. 1987;13(2):169–181.
11. Schweizer E, Rickels K, Weiss S, et al. Maintenance drug treatment of panic disorder. I. Results of a

- prospective, placebo-controlled comparison of Alprazolam and Imipramine. *Arch Gen Psychiatry*. 1993;50(1):51–60.
12. Nardi AE, Freire RC, Mochcovitch MD, et al. A randomized, naturalistic, parallel-group study for the long-term treatment of panic disorder with clonazepam or paroxetine. *J Clin Psychopharmacol*. 2012;32(1):120–126.
13. Chathanchirayil SJ, Elias A. Long term use of benzodiazepines by patients cared for by primary care physicians in consultation with psychiatrists. *Acta Psychiatr Scand*. 2022;146(2):165–167.
14. Rosenqvist TW, Wium-Anderson MK, Wium Anderson IK, et al. Long-term use of benzodiazepines and benzodiazepine-related drugs: a register-based Danish cohort study on determinants and risk of dose escalation. *Am J Psychiatry*. 2024;181(3):246–254.
15. Cosci F, Chouinard G. Acute and persistent withdrawal syndromes following discontinuation of psychotropic medications. *Psychother Psychosom*. 2020;89(5):283–306.
16. Ashton H. Benzodiazepine withdrawal: outcome in 50 patients. *Br J Addict*. 1987;82(6):665–671.
17. 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.
18. Welsh JW, Tretyak V, McHugh RK, et al. Review: adjunctive pharmacologic approaches for benzodiazepine tapers. *Drug Alcohol Depend*. 2018;189:96–107.
19. Nardi AE, Freire RC, Valença AM, et al. Tapering clonazepam in patients with panic disorder after at least 3 years of treatment. *J Clin Psychopharmacol*. 2010;30(3):290–293.

Edward Silberman, MD  
Antonio E. Nardi, MD, PhD  
Vladan Starcevic, MD, PhD  
Richard Balon, MD  
Fiametta Cosci, MD  
Giovanni A. Fava, MD  
Carl Salzman, MD  
Richard Shader, MD  
Nicoletta Sonino, MD

## Scan Now



Cite and Share  
this article at  
[Psychiatrist.com](https://Psychiatrist.com)

## Article Information

**Published Online:** May 27, 2024.  
<https://doi.org/10.4088/JCP.241r15306a>

© 2024 Physicians Postgraduate Press, Inc.

*J Clin Psychiatry* 2024;85(2):241r15306a

**To Cite:** Silberman E, Nardi AE, Starcevic V, et al. Concerns about long-term benzodiazepine treatment and the state of the evidence: reply to Sigler et al. *J Clin Psychiatry*. 2024;85(2):241r15306a.

**Author Affiliations:** Tufts University School of Medicine, Boston, Massachusetts (Silberman, Shader); Federal University of Rio de Janeiro, Rio de Janeiro, Brazil (Nardi); University of Sydney, Camperdown, Australia (Starcevic); Wayne State University School of Medicine, Detroit, Michigan (Balon); University of Florence, Florence, Italy (Cosci); State University of New York, Buffalo, New York (Fava); Harvard Medical School, Boston, Massachusetts (Salzman); University of Padova, Padua, Italy (Sonino).

**Corresponding Author:** Edward Silberman, MD, Tufts University School of Medicine, 800 Washington St, #1007, Boston, MA 02111 ([edward.silberman@tufts.edu](mailto:edward.silberman@tufts.edu)).

**Relevant Financial Relationships:** The authors had no conflicts of interest in preparing the commentary discussed in this letter.

**Funding/Support:** The authors received no funding for the preparation of this commentary discussed in this letter.

**Additional Information:** The authors are members of the International Task Force on Benzodiazepines.