Resolving the Paradox of Long-Term Benzodiazepine Treatment:

Toward Evidence-Based Practice Guidelines

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

The published literature presents two starkly different pictures of long-term benzodiazepine treatment, a paradox that is rarely discussed and has never been resolved. One view stems from patients trying to withdraw from long-term use. Reports of discontinuation programs emphasize the difficulty for many of stopping and staying off these medications, with an overall average of about one-third of participants unable to fulfill their intention to do so.[1] Beginning with the work of Ashton,[2] anecdotal reports of patients' adverse experiences with benzodiazepines, not only in withdrawal, but also when continuing to take them long-term, often paint a grim picture. Phenomena described during both continuing use and taper include a wide variety of somatic symptoms, uncontrollable crying or anger, anorexia, fearfulness, agoraphobia, and hallucinations. Patients may describe global impairment in functioning: "I lost my corporate job after 20 years… due to low-dose benzodiazepines. This drug destroyed my entire health, personality, and quality of life."[3]

The view that substantial proportions of long-term benzodiazepine users derive little benefit from these medications, or are made worse by them, and only continue to take them because of the difficulty of withdrawing, is central to the description of such patients as "dependent" and underlies the admonition in treatment guidelines that benzodiazepines are safe and effective only for short-term use.[4] Consistent with this picture, investigations of acute withdrawal phenomena have described long-term benzodiazepine users as having high levels of anxiety and depression at entry into the study, which decrease upon successful taper.[5,6] However, there are no systematic studies of chronic, persistent withdrawal syndromes or devastating effects associated with long-term benzodiazepine use.[7]

A markedly different view comes from investigations of benzodiazepine efficacy and tolerability, in which maintenance treatment is stable and unproblematic. Anxiety disorder patients who improve acutely on benzodiazepines have been followed for up to 3 years with both naturalistic and double-blind studies; none have found patients to escalate dose or lose therapeutic effect.[8] While they would be expected to incur added risk of cognitive or coordination deficits if still taking these medications into the geriatric period, the long-term follow-up treatment literature does not describe such patients as developing the earlier adverse reactions suggested by the withdrawal literature. Recent reviews have found that the withdrawal phenomena of benzodiazepines are similar to, and no more severe than, those of antidepressants[7,9,10] and that benzodiazepines' tolerability is markedly better than that of antidepressants when used to treat anxiety disorders.[11,12]

Parenthetically, there is a third group of benzodiazepine users—polysubstance abusers who use these medications adjunctively with, eg, opioids or cocaine to enhance a high or mitigate unwanted aspects of consumption.[13] Although often conflated with prescription benzodiazepine users, such people are distinct in the goals, patterns, and consequences of use.

There is consensus about the acute anxiolytic efficacy of benzodiazepines. But we need to know more about how to identify those at risk for adverse long-term outcomes and to understand the nature of such outcomes. Although we are limited by lack of systematic studies, the extant literature offers potentially important hints. Differences between populations and treatment histories in withdrawal studies versus clinical trials may help to understand the disparate pictures of long-term benzodiazepine treatment that they present. However, to our knowledge, these differences have never been discussed in the published literature.

In the treatment literature, study participants are screened to meet criteria for carefully defined anxiety disorders and are treated by psychiatrists according to specified protocols. Participants in discontinuation studies are typically vaguely described, and many, if not most, had been treated by primary care physicians. Reasons for their extended treatment often include such questionable indications as depression, insomnia, situational anxiety, psychosis, or somatic symptoms; withdrawal cohorts also typically include subsets of patients who have no stated diagnosis or specific indications.[2,3] Additionally, such studies are devoid of information about participants' prior courses of and responses to treatment. Potential predictive factors are undefined and

unexplored. The reasons for patients' wish to stop benzodiazepines are also unclear; some had been advised to discontinue simply because of their long-term use, and others had had previous unsuccessful attempts to withdraw, while in some studies the issue of motivation is unaddressed.

What aspects of these cohorts might put people at increased risk for severe adverse experiences taking and withdrawing from benzodiazepines? An unknown, but probably small, proportion may be exquisitely sensitive physiologically to benzodiazepines and their withdrawal, leading them to seek help from organized withdrawal trials. A likely larger group are diagnostically undefined study subjects who had sought to dampen dysphoria secondary to life stresses and difficulties, a goal for which benzodiazepines are poorly suited. Such patients typically manifest maladaptive personality traits, which have been found to predict more severe withdrawal in short-term protocols.[14,15] Treatment situations in which patients are not informed about target symptoms and limitations of their medication, not carefully assessed for response, and not referred to non-medical therapies for help in coping, when needed, are at high risk to feel dependent on medication and to attribute to it physical and psychological effects outside of those inherent in the pharmacology. The power of such response expectancies has been well demonstrated,[16] including in short-term withdrawal studies, where a subset of patients who believed they had been tapered but actually had continued on their maintenance benzodiazepine doses experienced subjective withdrawal symptoms.[14]

Psychiatry has never had evidence-based benzodiazepine prescribing guidelines. Following their introduction, benzodiazepines were loosely prescribed for anxiety-related complaints, often with no clear indications, contraindications, or criteria for discontinuation. As the liabilities of benzodiazepines came to light, the idea gained ascendancy that they should never be used as drugs of first choice or for long-term treatment. This retrenchment bears little relation to the extensive evidence about benzodiazepine safety, efficacy, and tolerability.[8,17]

We are limited by lack of systematic studies of long-term adverse effects of benzodiazepines. There is consensus that elderly patients taking them are at increased risk of sedation, cognitive impairment, and falls, limiting their use and requiring close monitoring in this population.[18] At the same time, fears that benzodiazepines convey risk of developing dementia have not been confirmed.[19] An important focus for further studies would be patients in primary care settings who are prescribed benzodiazepines to moderate distress stemming from life stressors. However, we do have considerable evidence about well-monitored treatment for patients with diagnosed anxiety disorders. Neither ignoring the risks of inappropriate prescribing nor ignoring the evidence about appropriate therapeutic use constitutes best practice. As suggested in a recent study of long-term benzodiazepine treatment, revision of current prescribing guidelines may be timely.[20] Adopting working guidelines that are consistent with the extant evidence would be prudent and in the best interests of our patients. We propose the following:

1. Benzodiazepines may be appropriate for both acute treatment and long-term maintenance for well-characterized *DSM* anxiety disorders, particularly panic disorder, social anxiety disorder, generalized anxiety disorder, and disorders with mixed features.
2. Treatment should be continued only when there is a clear and sustained benefit from the medication, at stable doses.
3. Patients should be educated at the outset about the targets, limitations, and goals of benzodiazepine therapy and the possible need for psychotherapy to address cognitive distortions and avoidant behaviors associated with anxiety. Prescribers should be prepared to administer or refer for such treatments when symptoms or functional impairments persist despite medication treatment.
4. A reasonable goal for medication in treating generalized anxiety disorder is to reduce anxiety to a level where it allows the patient to use non-medical means, including cognitive and behavioral strategies, to improve their coping skills.
5. Benzodiazepines prescribed for anxiety or insomnia secondary to life stressors should be closely monitored. Patients with difficulties or perceived need for medication persisting beyond weeks should be reassessed by a psychiatrist.
6. Tapering off benzodiazepines should be done for reasons specific to the individual patient and agreed to by the patient. Tapers should be flexible, collaborative, and supportive.

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

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

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