VIEWPOINT

Balancing the Risks and Benefits of Benzodiazepines

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In September 2020, the US Food and Drug Administration (FDA) announced an anticipated update to the boxed warning on all benzodiazepines to explicitly "address the serious risks of abuse, addiction, physical dependence, and withdrawal reactions" among this class of medications.[1] The current boxed warning for benzodiazepines (eg, alprazolam, lorazepam, clonazepam, diazepam) highlights only the risks of coadministration of opioids and benzodiazepines. Benzodiazepines are prescribed for multiple indications, most notably generalized anxiety disorder, panic, social phobia, insomnia, and seizure prophylaxis and rescue.

In addition to the revised boxed warning, the FDA is also modifying the detailed prescribing information. The new prescribing information advises physicians to warn patients of the risks of benzodiazepines; assess patients' risk of abuse, misuse, and addiction; use caution when coprescribing benzodiazepines with opioids; seek the lowest effective dose for the shortest treatment duration possible and taper off benzodiazepines slowly; consider alternate therapies; and follow up with patients who are prescribed benzodiazepines frequently.[1]

This increased caution regarding benzodiazepine use is warranted; fewer benzodiazepine prescriptions are needed. However, when considered without an appropriate patient-centered context, this enhanced warning statement might lead to fewer appropriate prescriptions and unintended consequences. This Viewpoint reviews the relative benefits and risks of benzodiazepines, discusses potential consequences of the FDA amendments, and describes a potential approach for the rational prescribing of benzodiazepines.

> The challenge for physicians is simultaneously considering the risks of benzodiazepines while selectively and cautiously using benzodiazepines when clinically appropriate.

Risks and Benefits of Benzodiazepines

Based on an analysis of nationally representative survey data from 86 186 adults in 2015 and 2016, an estimated 30.6 million reported past-year use of benzodiazepines, 17% of whom reported benzodiazepine misuse, defined as use "without a prescription, in greater amounts or more often than prescribed, longer than prescribed, or any other use other than as prescribed."[2] Rates of benzodiazepine misuse were highest among younger respondents; 51% of respondents aged 18 to 25 years reported misuse compared with 4% of those aged 65 years or older.[2] As summarized in the FDA's Drug Safety Communication,[1] in 2019 alone, an estimated 92 million benzodiazepine prescriptions were filled, and in 2018, nearly half of patients who filled an oral benzodiazepine prescription took the medication for 2 or more months.

The risks of drug overdose deaths involving benzodiazepines are significantly augmented when benzodiazepines are combined with other sedating medications and drugs, most notably opioids. For instance, among US women aged 30 to 64 years, the rate of benzodiazepine-related deaths increased from approximately 0.5 per 100 000 population in 1999 to nearly 5 per 100 000 population in 2017; however, these data did not distinguish benzodiazepine monotherapy from coadministration with other medications.[3] Notably, from 1993 to 2014, the national rate per 100 000 outpatient visits including combined use of benzodiazepines and opioids increased from 9.8 to 62.5,[4] and between September 2016 and December 2017 an estimated nearly 2 million adults in the US were coprescribed opioids and benzodiazepines.[5] This pattern may in part contribute to the recent increase in benzodiazepine-related deaths.

Prolonged benzodiazepine use may also lead to abuse, dependence, and tolerance, leading to misuse, dose escalations, and withdrawal reactions. In the most recent available Treatment Episode Data Set, in 2017 among 2 005 395 admissions to publicly funded substance abuse treatment programs, 17% identified benzodiazepines as secondary or tertiary drugs of abuse, whereas only 1% identified benzodiazepines as their primary drug of abuse.[1] In contrast, few published reports have addressed benzodiazepine withdrawal and dependence, although the few studies that do exist suggest that women, older patients, patients with mental health conditions, and patients prescribed antidepressants may be at higher risk of using benzodiazepines at higher doses for longer periods. In Danish cohorts of 113 incident and 992 prevalent users of benzodiazepines for at least 6 months, there was no significant increase in benzodiazepine dose in either group at 2-year follow-up.[6]

The risks of benzodiazepine misuse among adolescents are of particular concern. According to a 2018 survey that included approximately 29 600 high school students, an estimated 3.9% of US 10th- and 12th-grade students reported nonmedical benzodiazepine use.[7] Adolescents are at risk of developing substance use disorders that may persist through early and late adulthood; use of benzodiazepines in this vulnerable population deserves special attention.

There is uncertainty regarding the association of benzodiazepine use and subsequent risk of dementia. A recent cohort study among 235 465 Danish adults with an affective disorder (including depressive and bipolar disorders) revealed no association between

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benzodiazepine use and later development of dementia.[8] Conversely, in a nested case-control analysis of this same cohort, lower benzodiazepine use was associated with risk of dementia but higher use was not, suggesting the possibility of a potential protective relationship with benzodiazepine use.[8]

Furthermore, benzodiazepines are effective for treating various forms of anxiety. A meta-analysis of 58 trials (sample size range, 9-229; mean, 72.5; median, 60) that compared benzodiazepines with placebo for anxiety disorders demonstrated that benzodiazepines were more effective than placebo in trials of patients with higher baseline anxiety severity scores and among studies with shorter treatment durations.[9] To date, no published meta-analyses have compared benzodiazepines with selective serotonin reuptake inhibitors for anxiety.

Potential Unintended Consequences of an Enhanced Boxed Warning

In the context of this revised warning, physicians may restrict their use of benzodiazepines, in some cases without appropriate regard for patient-specific needs and risks factors that could predispose specific patients to adverse effects of benzodiazepines. Absent this contextual information, physicians might inappropriately withhold benzodiazepine therapy, thereby leading to poorly treated anxiety disorders and insomnia, as well as precipitation of withdrawal among patients already using benzodiazepines. There are currently no US guidelines that specifically address use of benzodiazepines; however, the practice guideline from the American Psychiatric Association includes benzodiazepines among first-line pharmacologic treatment strategies for panic disorder.[10]

Many patients with anxiety disorders may benefit from antidepressants or various forms of psychotherapy (most notably cognitive behavior therapy); however, a significant number of patients will derive inadequate symptom relief from these modalities or may have limited access to psychotherapeutic treatments. Likewise, patients with residual and impairing anxiety or insomnia may use alcohol, cannabinoids, or illicit substances that not only have little to no evidence of efficacy for anxiety and insomnia but also may worsen these symptoms with long-term use. The risks of developing substance use disorders with these nonprescribed substances is likely higher than with use of benzodiazepines, especially given that use of these substances is not medically regulated.

Toward the Rational Use of Benzodiazepines

The challenge for physicians is simultaneously considering the risks of benzodiazepines while selectively and cautiously using benzodiazepines when clinically appropriate. Ideally, physicians will seek a balance between overprescribing of benzodiazepines to patients at risk and underuse of these effective medications when indicated.

As the FDA recommends, patients should be carefully screened for risk factors before initiating benzodiazepines, including substance use disorders, a history of misuse of prescribed medications, cognitive impairment, older age and risk of falls, and concomitant use of opioids. Physicians should consider alternate pharmacological and behavioral strategies before using benzodiazepines whenever possible and appropriately engage patients in a discussion regarding the risks and benefits of benzodiazepines. Among patients already prescribed a benzodiazepine, physicians should regularly reevaluate their use of benzodiazepines, aiming for the lowest effective dose. Following the behavioral change model of advise, assess, and address, patients should be informed of the risks of benzodiazepines, assessed for their willingness and perceived ability to decrease their use, and offered a tailored plan to gradually taper their dose while monitoring for recurrent symptoms and withdrawal.

Like all medications, benzodiazepines have the potential for both harm and benefit. Physicians should help patients weigh these factors and develop a treatment plan that is safe and effective as well as flexible and responsive to changing circumstances. The newly enhanced boxed warning appropriately highlights the real risks posed by benzodiazepines; it is up to physicians to judiciously act on but not overreact to this information.

ARTICLE INFORMATION

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REFERENCES

1. US Food and Drug Administration. FDA requiring Boxed Warning updated to improve safe use of benzodiazepine drug class. Published September 23, 2020. Accessed October 11, 2020. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requiring-boxed-warning-updated-improve-safe-use-benzodiazepine-drug-class

2. 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

3. VanHouten JP, Rudd RA, Ballesteros MF, Mack KA. Drug overdose deaths among women aged 30-64 years—United States, 1999-2017. *MMWR Morb Mortal Wkly Rep*. 2019;68(1):1-5. doi:10.15585/mmwr.mm6801a1

4. Hirschtritt ME, Delucchi KL, Olfson M. Outpatient, combined use of opioid and benzodiazepine medications in the United States, 1993-2014. *Prev Med Rep*. 2017;9:49-54. doi:10.1016/j.pmedr.2017.12.010

5. Zhang VS, Olfson M, King M. Opioid and benzodiazepine coprescribing in the United States before and after US Food and Drug Administration boxed warning. *JAMA Psychiatry*. 2019;76(11):1208-1210. doi:10.1001/jamapsychiatry.2019.2563

6. Willems IAT, Gorgels WJMJ, Oude Voshaar RC, Mulder J, Lucassen PLBJ. Tolerance to benzodiazepines among long-term users in primary care. *Fam Pract*. 2013;30(4):404-410. doi:10.1093/fampra/cmt010

7. Johnston LD, Miech RA, O'Malley PM, Bachman JG, Schulenberg JE, Patrick ME. *Monitoring the Future National Survey Results on Drug Use 1975-2018: Overview, Key Findings on Adolescent Drug Use*. University of Michigan Institute for Social Research; 2019. Accessed October 20, 2020. https://files.eric.ed.gov/fulltext/ED594190.pdf

8. Osler M, Jørgensen MB. Associations of benzodiazepines, z-drugs, and other anxiolytics with subsequent dementia in patients with affective disorders: a nationwide cohort and nested case-control study. *Am J Psychiatry*. 2020;177(6):497-505. doi:10.1176/appi.ajp.2019.19030315

9. Gale C, Glue P, Guaiana G, Coverdale J, McMurdo M, Wilkinson S. Influence of covariates on heterogeneity in Hamilton Anxiety Scale ratings in placebo-controlled trials of benzodiazepines in generalized anxiety disorder: systematic review and meta-analysis. *J Psychopharmacol*. 2019;33(5):543-547. doi:10.1177/0269881118822146

10. Work Group on Panic Disorder. *Practice Guideline for the Treatment of Patients With Panic Disorders*. American Psychiatric Association; 2010. Accessed October 20, 2020. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/panicdisorder.pdf