Benzodiazepines as Special Risk Medications

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The finding by Olfson et al[1] that benzodiazepine prescribing to older adults has declined during the period 2018–2022 is surely good news, since, as the authors point out, people in this age group are the most vulnerable to the adverse effects of these medications and to the situation of polypharmacy in which they are often prescribed. While they cite the risks of "prescriptions of benzodiazepines and other CNS depressants," their focus is clearly on benzodiazepines specifically, reflecting the prevalent view that they are special risk medications that require a special level of concern.[2] At the same time, as the report highlights, benzodiazepine prescriptions have risen substantially in recent decades, raising the question of how much prescribers have been appropriately using their therapeutic benefits vs inappropriately neglecting their risks.

It is widely accepted that benzodiazepines are effective anxiolytic agents, comparable to antidepressants for patients with diagnosed anxiety disorders, and that they have more favorable side-effect profiles.[3–5] However, the widespread perceptions of them as prone to tolerance, dose escalation, abuse, dependence, difficult withdrawal, and lethality in overdose have perpetuated guidelines that warn against their use as first-line or long-term maintenance medications.[2] What does the extant evidence base actually tell us about these issues?

In the more than 6 decades since diazepam was introduced, scientific study of benzodiazepines has produced solid knowledge of them, although some important questions remain unanswered. Despite their persistent reputation of losing therapeutic effectiveness over time, all systematic study of this possibility has found that over 90% of patients prescribed long-term benzodiazepines for anxiety do not develop tolerance and do not escalate their dose.[6] However, sedating effects tend to diminish over weeks to months, making long-term benzodiazepine treatment of insomnia problematic, except when the insomnia is secondary to chronic anxiety.[7]

Benzodiazepines do not have the defining features of primary drugs of abuse; it is difficult to induce animals to work to self-administer them, and they do not produce euphoria or cravings in humans.[8–10] However, because they blunt affect and work quickly,[3] they are susceptible to being abused, usually by established polysubstance abusers, to enhance the high or mitigate unwanted effects of primary substances.[11] Olfson et al note that "prescribed benzodiazepines are associated with an increased risk of developing substance use problems or disorders relative to untreated controls and patients receiving comparator medications."[1] While the risk of such outcomes is likely real, they have been found to occur in only a small proportion of patients. In the study quoted by Olfson et al,[1] approximately 5% of patients prescribed benzodiazepines for anxiety and mood disorders had developed substance abuse after 14-year follow-up.[12] Other evidence is broadly consistent with this number.[13,14] Only about 6% of adverse substance-related events presenting to emergency services have been found to be due to ingestion of benzodiazepines alone, rather than as a component of polydrug use.[15]

The potential for withdrawal syndromes associated with benzodiazepines was initially minimized, but their prevalence and severity now tend to be exaggerated. The majority of patients discontinuing long-term benzodiazepines have no more than minor difficulty,[16] although we are still unable to draw precise conclusions about the epidemiology of more severe withdrawal syndromes. Formal withdrawal programs report that about two-thirds of patients complete their tapers,[17] but long-term abstinence rates vary widely, from a low of 13% to a high of 73%.[18] Because this literature generally neglects reasons for the original prescription, treatment histories, and reasons for discontinuing, it tells us little about the risk factors for having severe or persistent withdrawal symptoms, some of which likely represent return of untreated anxiety rather than true withdrawal. Other important factors affecting withdrawal outcome, usually unaccounted for, include the degree of working alliance between patient and prescriber,[19] the presence of personality pathology,[20] and patients' expectations.[21]

Most benzodiazepines have LD50s in the thousands and are among the safest medications when taken alone.[22] However, as respiratory depressants, they are potentially dangerous in combination with other such medications. Over 90% of reported "benzodiazepine-related" overdose deaths, for example, have occurred in people using them along with opioids or other drugs.[23] Similarly, they must be used with caution in patients with underlying respiratory disorders, such as sleep apnea or chronic obstructive pulmonary disease.[24]

Common, well-established adverse effects of benzodiazepines are those related to their sedating properties and their impact on coordination and cognition: increased falls associated

with use for anxiety and insomnia in older adults[25]; use proximate to the time of driving associated with increased accident risk, and much more so when the driver concurrently uses alcohol[26]; and cognitive decrements, especially in processing speed and new learning of nonverbal material, found on formal testing even in younger patients taking benzodiazepines.[27] However, except for those with increased vulnerability, such as older patients, people usually do not notice cognitive changes and are not functionally impaired by them.[27] Reports associating use of benzodiazepines with risk for dementia have been disconfirmed by subsequent studies with more rigorous methodology.[3]

In sum, the scientific evidence base tells us that, for the majority of nongeriatric adults, benzodiazepines are well-tolerated, safe, and effective for acute and maintenance treatment of anxiety disorders. The small proportion of patients who abuse them or escalate their doses are likely to have multiple psychiatric diagnoses or histories of substance abuse[28–30] and merit special caution in prescribing. All patients should be educated about possible withdrawal symptoms at the outset of treatment, and clinicians should appreciate the importance of attaining agreement about the need for withdrawal and of use of flexible, collaborative taper procedures.[19,31] An anecdotal literature suggests that patients who report severe adverse effects while taking benzodiazepines may be at high risk of problematic withdrawal [32]; therefore, prescribers should not continue trials when patients fail to manifest prompt, clear improvement.

Although it has historically been underappreciated, antidepressants come with liabilities that are similar to those of benzodiazepines. They convey risk for memory impairment,[5] falls,[33] and driving accidents,[26] and they have withdrawal syndromes that are similar to those of benzodiazepines.[34,35] They also come with small but well-demonstrated risks of blood dyscrasias[36] and potentially dangerous cardiac arrhythmias[37] not shared by benzodiazepines. Conversely, antidepressants have little or no liability for misuse or abuse. Gabapentin, commonly used for anxiety, and quetiapine, commonly used for insomnia, however, have known street value and abuse potential.[38,39] Neuroleptics used for insomnia may have adverse metabolic effects that are not observed with benzodiazepines.[40]

Their immediate onset of action and favorable side-effect profile, and their effectiveness in some patients who do not respond well to other types of medication, are legitimate reasons why benzodiazepines might be drugs of choice, both acutely and for maintenance treatment. In ambiguous cases, where the diagnosis might be either primary depression with anxiety or a primary anxiety disorder with dysphoria, an initial trial of benzodiazepines can often clarify the situation within the first week of treatment, saving the patient from possible months of inconclusive antidepressant trials.

Rather than being uniquely risky, benzodiazepines are comparable in overall risk level to other medications used for the same indications, with some risks in common and some unique to each medication class. Despite their immediate onset of action, they are not a "quick fix" for any disorder and, like other drugs, must be prescribed in the context of thorough evaluation and careful monitoring of therapeutic and adverse effects. If psychiatry can move away from both cavalier prescription of benzodiazepines and reflexive rejection of them to evidence-based therapeutic use, our patients will be major beneficiaries.

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