Risks Associated with Long-Term Benzodiazepine Use

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Benzodiazepines and benzodiazepine receptor agonists (e.g., zaleplon [Sonata], zolpidem [Ambien]) are widely used to treat anxiety and insomnia, even though antidepressants are first-line therapy for anxiety disorders based on the evidence.[1] In this issue of *American Family Physician*, Drs. Ramar and Olson review the management of insomnia and other sleep disorders.[2] When benzodiazepines are used to treat insomnia, the effect wears off after a few weeks,[3] and rebound insomnia has been reported with cessation of the drugs. Although patients report enhanced sleep with long-term use, there is no objective evidence to support this. Despite the lack of evidence of effectiveness, alprazolam (Xanax), zolpidem, clonazepam (Klonopin), and lorazepam (Ativan) were the number 1, 2, 6, and 7 most prescribed psychotropics in the United States in 2009, respectively. Approximately 150 million prescriptions for benzodiazepine agonists were issued that year.[4]

Although zaleplon and zolpidem are often described as nonbenzodiazepines, they are chemically similar and both act on benzodiazepine receptors. These drugs are specific for the benzodiazepine 1 receptor. Because of the short half-life (two hours or less), withdrawal after discontinuing these drugs does not occur unless they are abused or taken in high doses for an extended period. As with other potentially addictive drugs, benzodiazepines activate dopamine in mesolimbic projections.[5]

Benzodiazepines can become street drugs obtained from drug dealers or by prescription sharing. According to the National Epidemiologic Survey on Alcohol and Related Conditions, which included 35,000 participants, benzodiazepine prescriptions were associated with nonmedical use (odds ratio = 1.9) and development of benzodiazepine abuse or dependence (odds ratio = 2.6). These results were not associated with an anxiety disorder diagnosis, severity of anxiety disorder, or co-occurring drug use.[6]

Many of the 4 million daily benzodiazepine users in the United States meet the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., criteria for substance dependence.[7] Outpatients on long-term benzodiazepine therapy have the potential for a protracted, uncomfortable withdrawal syndrome that can last for months. Withdrawal symptoms are possible after only one month of daily use.

In addition to abuse and dependence, other major risks associated with benzodiazepine use include the following:

- Cognitive impairment. Benzodiazepines cause acute adverse effects: drowsiness, increased reaction time, ataxia, motor incoordination, and anterograde amnesia. Additionally, a meta-analysis of studies looking at withdrawal from an average of 17 mg per day of diazepam (Valium) found that long-term use led to substantial cognitive decline that did not resolve three months after discontinuation.[8]
- Motor vehicle crashes. The risk of driving while on benzodiazepines is about the same as the risk of driving with a blood alcohol level between 0.050% and 0.079% (an alcohol level greater than 0.08% is illegal in all states).[9]
- Hip fracture. Benzodiazepines increase the risk of hip fracture in older persons by at least 50%.[9] In a study of 43,343 persons, zolpidem increased the risk of hip fracture by 2.55 times in those older than 65 years.[10]

In summary, it is unclear where long-term benzodiazepine use fits into current medical practice. Many patients underestimate the degree of impairment caused by benzodiazepines.[8] Benzodiazepines increase the risk of addiction, withdrawal, cognitive decline, motor vehicle crashes, and hip fracture. The risk of overdose is particularly great when combined with sedative drugs such as opioids or alcohol. For these reasons, if ▶

used, benzodiazepines generally should not be prescribed continuously for more than one month. There are effective alternatives. Psychotherapy and antidepressants are the treatments of choice for anxiety disorders. Short-term medications that can be used for anxiety without risk of addiction include propranolol, anticonvulsants, or major tranquilizers. Finally, insomnia can be treated with trazodone, doxepin, or ramelteon (Rozerem) without risk of rebound insomnia.

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