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Benzodiazepine Safety and Tapering

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Benzodiazepines are commonly prescribed for a variety of mental health conditions. The Food and Drug Administration (FDA) labeled indications vary based on each specific benzodiazepine and include seizures, alcohol withdrawal, insomnia, panic disorder, anxiety, and adjunctive treatment of muscle spasms. They are also often used off-label for schizophrenia, depression, acute stress disorders, bipolar disorder, or agitation. In the United States, use of benzodiazepines has continued to increase, and it is estimated that over 7% of clinician visits are associated with prescription of a benzodiazepine.[1] However, despite common use, there is little evidence on efficacy and safety of long-term benzodiazepine use. This article briefly reviews evidence on safety of long-term use, describes interventions to deprescribe benzodiazepines, and provides resources for clinicians interested in tapering strategies.

Evidence and Guidance Against Long-term Use

There are limited controlled data available on long-term use of benzodiazepines, but many adverse events have been documented with long-term use. Controlled studies evaluating efficacy of benzodiazepines in mental health conditions were on average only 1 to 10 weeks in duration.[2] Similarly, there is little evidence of long-term benefit or evidence that benzodiazepines improve quality of life or function when used as a muscle relaxant for chronic pain.[3] Current guidelines from multiple societies recommend against use of benzodiazepines or recommend only short-term use for acute symptoms. For example, in patients with chronic low back pain, the Veterans Administration and Department of Defense (VA/DOD) guidelines recommend strongly against the use of chronic benzodiazepines as a muscle relaxant.[4] Only non-benzodiazepines muscle relaxants are recommended for short-term, acute pain.[4] Guidelines from National Institute for Health and Care Excellence (NICE) also recommend against use of benzodiazepines for muscle spasticity in patients with cerebral palsy, and only recommend diazepam as a third line agent in patients with spasticity due to multiple sclerosis.[5,6] Recent guidelines from the VA/DOD for post-traumatic stress disorder (PTSD) and acute stress reactions have a strong recommendation against the use of benzodiazepines (as monotherapy or combination therapy) for treatment of PTSD due to the lack of evidence supporting efficacy and known risks associated with treatment.[7] Similarly, guidelines from NICE for treatment of generalized anxiety disorder recommend against benzodiazepines except for short-term use during crisis.[8] For treatment of insomnia, first-line treatments include non-pharmacological modalities such as cognitive behavioral therapy.[9,10] Because insomnia often occurs as a result of other comorbid conditions, pharmacological treatment should address the underlying cause of insomnia. Pharmacotherapy (including benzodiazepines) is recommended only with intermittent dosing or short-term use (≤ 4 weeks) and only when first-line options have failed.[9,10] In the Oregon Health Plan (OHP), short-term use of zolpidem is the preferred sedative product for insomnia.

Safety Concerns with Benzodiazepines

Safety concerns with long-term benzodiazepines include risk for overdose, psychiatric instability, cognitive impairment, complications with pregnancy, and dependence or abuse. All benzodiazepines have a boxed warning for concomitant use with opioids.[11] Concomitant use can result in profound sedation, respiratory depression, coma and death. Evidence assessing the magnitude of risk associated with concomitant opioid and benzodiazepine prescribing is primarily based on observational data.[2] In 2 large retrospective cohort studies (n=5540), co-prescribing of these medications was associated with increased risk of drug-related deaths (adjusted hazard ratio [HR] 1.4; 95% CI 1.2 to 1.7 and HR 4.35; 95% CI 1.32 to 14.30).[2,12,13] Similarly, in 5 case series examining methadone overdose deaths (n=1127), blood toxicology was positive for both benzodiazepines and methadone in 36 to 67% of deaths.[2] Due to the retrospective nature of these data, the exact magnitude of risk associated with concomitant benzodiazepine and opioid administration is unclear. However, trends in combined opioid and benzodiazepine overdose remain of concern. Estimates from the National Institute on Drug Abuse indicate approximately 23% of opioid overdose deaths also tested positive for benzodiazepines.[14] Due to concerns associated with over-sedation, guidelines from both the Centers for Disease Control and 2016 Oregon Guidelines developed by the Chronic Pain Taskforce recommend against use of concomitant benzodiazepines and opioids (or other sedatives) whenever possible.[15,16] For patients on long-term therapy with both opioids and benzodiazepines, consider sequential tapers. Because rapid benzodiazepine tapers may be associated with more rebound anxiety or withdrawal symptoms, it is reasonable to consider an opioid taper first.[15]

Other adverse effects associated with benzodiazepine use include psychiatric or paradoxical reactions. Adverse events reported in postmarketing studies include acute hyperexcited states, irritability, aggression, hallucinations, psychoses, and sleep disturbances, and may occur more frequently in children or elderly patients.[17-19] Cognitive and memory impairment is another significant concern with long-term benzodiazepine use, and negative cognitive effects may persist for up to 6 months after discontinuation of the benzodiazepine.[9] Use of benzodiazepines has also been associated with emergence or worsening of pre-existing depression in postmarketing studies; use in patients with primary depressive disorder or psychosis is not recommended.[17] While rare, use of benzodiazepines (and other antiepileptic drugs) may be associated with an increased incidence of suicidal thoughts or behavior. In an analysis of 27,863 patients treated with 11 antiepileptic drugs including clonazepam, the estimated incidence of suicidal thoughts and behavior was approximately twice as high as placebo treated patients (0.43% vs. 0.24%; RR 1.8, 95% CI 1.2 to 2.7).[18] The estimated risk was similar upon comparison of clonazepam to other antiepileptic drugs.[18]

Patients who may have an increased risk for adverse events include elderly patients, patients who are pregnant, and those with concomitant respiratory disease or substance use disorders. Increased instability and sedation have been documented in patients over 65 years of age and Beer's Criteria recommends against use in this population.[20] Decreased clearance of benzodiazepines can occur in patients with impaired renal or hepatic function, and if treatment is necessary for these patients, the lowest effective dose for the shortest duration should be used.[17-19,21] In particular, benzodiazepines with active metabolites and longer duration of effect (e.g., diazepam and chlordiazepoxide) may be associated with increased drug accumulation or adverse effects in the elderly and should be avoided.[20] Risk of respiratory depression is also increased in patients with severe respiratory insufficiency such as chronic obstructive pulmonary disease (COPD) or sleep apnea syndrome, and benzodiazepines should only be prescribed when absolutely necessary for this population.[17-19] Benzodiazepines may also potentially cause fetal harm and congenital abnormalities during the first trimester, and while there are no well controlled studies in humans, congenital malformations have been documented in animal studies. Benzodiazepines should be avoided whenever possible or used with caution after an evaluation of risks and benefits of therapy in women who are pregnant or intending to become pregnant. Additionally, regular use in late pregnancy may increase the risk of withdrawal symptoms and complications for the infant after birth.[19] Symptoms such as hypothermia, muscle flaccidity, respiratory depression or apnea, and difficulty feeding have been documented in neonates born to mothers using benzodiazepines.[17,18,21] Benzodiazepines are classified by the Drug Enforcement Agency (DEA) as schedule IV substances and have been associated with abuse, misuse, and dependence.[17,19] Caution and monitoring are advised if prescribing benzodiazepines to patients with substance use disorders because of an increased predisposition to habituation and dependence. In Oregon, benzodiazepines are reported to the statewide prescription drug monitoring program (PDMP), and evaluation of the PDMP is recommended before prescribing for every patient.[22]

Risks with Benzodiazepine Withdrawal

Because of documented risks associated with benzodiazepine therapy and the lack of long-term efficacy data, periodic reassessment to evaluate ongoing need for therapy and current risks with treatment is recommended for all patients prescribed long-term benzodiazepines. If risks of therapy outweigh benefits, gradual dose reduction is recommended for patients on established long-term therapy. Benzodiazepines are associated with physical dependence and discontinuation (particularly abrupt discontinuation) may be associated with significant adverse effects including rebound, withdrawal, and symptom recurrence.[19,21] Rebound symptoms refer to the recurrence of symptoms at a greater severity than observed at baseline. The exact incidence of withdrawal or rebound symptoms with benzodiazepine discontinuation is unclear, and more frequent symptoms may occur in patients prescribed higher doses or longer-term therapy.[19,21] For example, discontinuation symptoms occurred more frequently or with greater severity in patients prescribed more than 4 mg/day of alprazolam or prescribed diazepam for longer periods.[19,21]

In a clinical trial evaluating alprazolam discontinuation in 63 patients with panic disorder, common withdrawal symptoms included heightened sensory perception, impaired concentration, and muscle cramps.[21] Severe withdrawal symptoms with benzodiazepines can include seizures, though the exact incidence of severe symptoms is unclear. Of the 1980 patients treated with alprazolam during clinical trials, seizures were observed in 8 patients after drug discontinuation (5 of which occurred after abrupt dose reduction or discontinuation).[21] The risk of seizures with alprazolam appear to be greatest in the 24 to 72 hours after discontinuation.[21] Similar withdrawal symptoms have been documented in post-marketing studies of other benzodiazepines, but there is little data comparing incidence or severity of withdrawal symptoms between agents.

Benzodiazepine Taper Strategies

In patients prescribed benzodiazepines for mental health conditions or insomnia, gradual dose reduction can significantly decrease risk of withdrawal symptoms. However, there is little evidence available on the optimal duration or rate of tapering and no evidence which indicates a single tapering strategy may be more successful than another. Guidelines from the VA/DOD provide the following recommendations for patients with sedative hypnotic use disorder stabilization and withdrawal:[23]

- Gradual taper the original benzodiazepine OR
- Substitute a longer-acting benzodiazepine (diazepam or chlordiazepoxide) then taper OR
- Substitute phenobarbital for the addicting agent and taper gradually

The optimal rate and type of taper strategy may vary between patients and should be tailored based on patient experience and current benzodiazepine dose. In clinical studies of clonazepam, patients with short-term use for treatment of panic disorder (6-9 weeks) were tapered over 7 weeks with dose reductions of 0.125 mg twice daily every 3 days until the drug was completely withdrawn.[18] While there is no evidence to accurately estimate the risk of withdrawal symptoms in patients on long-term benzodiazepine use, more gradual tapers may be required for patients on higher doses or those with longer use. Because early withdrawal symptoms are often better tolerated than later withdrawal symptoms, taper strategies may begin with a more rapid early dose reduction followed by a slower taper.[23] For patients on low dose benzodiazepines, an initial reduction of up to 20% weekly may be initially considered with more gradual reductions over time.[15,23] Patients on higher doses of benzodiazepines (e.g., those approaching the FDA-approved maximum daily dose) will likely require a longer taper period over 2 to 6 months.[23] One common taper strategy in patients on high dose benzodiazepines is a weekly 25% dose reduction over 2 weeks until 50% of the dose remains then further reduction by 1/8 (~12%) every week.[23] Because rebound or withdrawal symptoms may occur with rapid dose reduction, periodic monitoring is recommended with adjustments to slow the taper plan if needed.[23]

Transitioning to a longer-acting benzodiazepine is another strategy which is intended to minimize fluctuations in drug levels over time. The approximate equivalent doses of common benzodiazepines are shown in **Table. 1**. Both chlordiazepoxide and diazepam have active metabolites with extended half-lives, and use of these agents may provide more consistent drug levels, and potentially fewer withdrawal symptoms, as the patient is tapered.[23] However, both diazepam and chlordiazepoxide are excreted in the urine, and this strategy may not be an optimal choice for elderly patients or those with renal impairment due to an increased risk of drug accumulation.

Table 1. Common Benzodiazepine Conversions[23]

Drug	Approximate Equivalent Dose	Time to Peak plasma level (hours)	Half-life (in hours for parent drug)	Metabolic activity (maximal half-life in hours)
Alprazolam	1 mg	1-2	12 ± 2	Inactive
Chlordiazepoxide	25 mg	1-4	10 ± 4	Active (up to 120 hours)
Clonazepam	1 mg	1-4	23 ± 5	Inactive
Diazepam	10 mg	2-4	43 ± 13	Active (up to 120 hours)
Lorazepam	2 mg	1-2	14 ± 5	Inactive
Phenobarbital	30 mg	1+	53-140	Inactive

Substitution therapies have been used to try to mitigate withdrawal symptoms and facilitate deprescribing, but benefit with these therapies remains unclear. Guidelines from the VA/DOD suggest offering pharmacological substitution with phenobarbital as an option to facilitate discontinuation of benzodiazepines based on low quality evidence.[23] The daily benzodiazepine dose is converted to a phenobarbital equivalent and divided into 3 doses per day for two days.[23] Beginning on day 3, phenobarbital is reduced by 30 mg per day.[23] Other drugs studied for benzodiazepine discontinuation included valproate, pregabalin, tricyclic antidepressants, paroxetine, carbamazepine and flumazenil. [24] Evidence for these therapies is overall insufficient to low quality due to small sample sizes of available studies (n=18 to 144), notable risk of bias, and significant heterogeneity which limits confidence in any findings.[24]

Patient education and cognitive behavioral therapy are recommended in conjunction with benzodiazepine tapers and have demonstrated improved success with complete benzodiazepine discontinuation compared to tapering alone.[15,23] In a Cochrane review of tapering strategies for benzodiazepines (n=575), use of cognitive behavioral therapy in addition to a tapering regimen resulted in a higher rate of successful discontinuation at 2-3 months follow-up compared to a taper alone (58.9% vs. 41.5%; ARR 17.4%; RR 1.51, 95% CI 1.15 to 1.98; moderate quality evidence).[25] While the long-term effects of cognitive behavioral therapy on benzodiazepine use are less clear, use in the short-term may help patients develop positive behaviors and coping strategies during the taper process.[25]

Additional Resources

Multiple resources are available for both providers and pharmacists to assist with developing taper plans and discussing tapering with patients.

- Clinician resources and clinical pearls from the VA/DOD for tapering benzodiazepines in patients where risks outweigh benefits (e.g., patients with PTSD)[26]
- The Canadian Family Physicians guidelines for tapering patients using benzodiazepines for insomnia[27]
- The College of Psychiatric and Neurologic Pharmacists toolkit for tapering benzodiazepines[28]

OHP Policy

In the OHP, most benzodiazepines (with the exception of clonazepam) are paid for by fee-for-service rather than coordinated care organizations. Due to the lack of long-term efficacy and known safety concerns, a prior authorization is required for use of benzodiazepines beyond 4 weeks. Requests for treatment of mental health conditions must document trial or failure of first-line treatment options and rationale to support long-term use. Use for PTSD or use

in combination with other sedating medications is not recommended. For patients in which the risks of therapy outweigh the benefits, providers should consider a taper plan for their patient.

> For OHP patients starting benzodiazepine treatment, prior authorization is required for durations of more than 4 weeks.

More information on these treatment options, along with other therapeutic reviews, can be found on the Oregon Health Plan fee-for-service searchable preferred drug list at http://www.orpdl.org/drugs/.

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