



## Clinical Review: Recommendations for the Tapering of Benzodiazepines

### Learning Objectives:

- Explain why long-term use of benzodiazepines should be limited
- Describe clinical circumstances when tapering of benzodiazepines should be considered
- Identify clinical and patient-specific factors to consider when designing a benzodiazepine taper
- Recognize signs of withdrawal and when to slow down a benzodiazepine taper

### Key Points:

- Overprescribing of benzodiazepines and co-prescribing benzodiazepines with opioids may lead to serious side effects, including death.
- Limit use of benzodiazepines to the shortest possible duration and utilize gradual discontinuation (tapering) to minimize the risk of withdrawal symptoms.
- Regularly assess the need for benzodiazepine use in patients who take these medications and discuss strategies for discontinuation when the risks outweigh the benefits.
- Consider alternative treatments if benzodiazepines are needed long-term.
- Overall use of benzodiazepines in the Medi-Cal population has decreased steadily over the last five years, with a 50% decrease in Medi-Cal utilizing beneficiaries with at least one paid claim for a benzodiazepine from 2016 to 2020. However, some beneficiaries remain at increased risk for benzodiazepine-related adverse events, including adults of 65 years of age or older that accounted for 3% of the paid claims for benzodiazepines in the Medi-Cal program during 2020.

### Background

Benzodiazepines are gamma-aminobutyric acid (GABA) receptor agonists used to treat a variety of conditions, including generalized anxiety disorder, insomnia, seizures, social phobia, and panic disorder. Benzodiazepines are also used as a premedication before some medical procedures. The long-term use of these medications is not supported by scientific evidence due to the potential for adverse events, dependence, and abuse. Nevertheless, these medications are often overprescribed, and clinicians may encounter patients who have been on benzodiazepines long-term and face the difficulty of discontinuing these medications.<sup>1</sup>

Sedative and depressive effects on the respiratory system are among the more serious risks associated with benzodiazepines. Concurrent use of these medications with other central nervous system and respiratory depressants such as opioids and alcohol increases the likelihood of intentional or unintentional toxicity or overdose, due to synergistic effects on respiration.<sup>2</sup> From January to June 2018, 32.5% of opioid deaths that occurred in the United States involved benzodiazepines.<sup>3</sup> In the 2016 Guideline for Prescribing Opioids for Chronic Pain, the Centers for Disease Control and Prevention (CDC) recommended against co-prescribing opioids and benzodiazepines due to a significant increase in the risk of overdose and contributing to the overdose epidemic.<sup>4</sup> Other potential concerns include psychiatric effects (disinhibition, depression, and others), cognitive impairment, dependence, falls and accidents.<sup>1,2</sup>

In 2020, the U.S. Food and Drug Administration (FDA) announced that the *Boxed Warning* for benzodiazepines will be updated to include the serious risks of abuse, misuse, addiction, physical dependence, and withdrawal reactions.<sup>5</sup>

The FDA recommends that the dosage and duration of each benzodiazepine be limited to the minimum needed to achieve the necessary clinical effect; the nature and degree of response may vary from condition to condition. Discussing an anticipated length of therapy with patients at the time of prescribing may be a helpful strategy for patients. Psychotherapy should be considered for anticipatory anxiety associated with tapering.<sup>2</sup>

For these reasons, it is important to regularly assess the need for benzodiazepine use in patients who take these medications, and to discuss strategies for discontinuation.<sup>6</sup> This is especially important for patients who are more at risk of complications, such as elderly patients, patients with a cognitive disorder or history of traumatic brain injury, those who use opioids and/or amphetamines concurrently with benzodiazepines, and patients with a current (or history of) substance use disorder.<sup>7-9</sup>

Withdrawal symptoms may occur if benzodiazepines are discontinued too rapidly and may pose a challenge to clinicians and patients. The onset of withdrawal symptoms is typically two days after discontinuation of a short-acting benzodiazepine and five days after discontinuation of a long-acting benzodiazepine (**Table 1**).<sup>2</sup> Symptoms in the acute withdrawal phase may last between 5 and 28 days and may include anxiety, depression, hypersensitivity to sensory stimuli, insomnia, restlessness, agitation, palpitations, shortness of breath, and sweating.<sup>2</sup> Less common symptoms in this phase are seizures and delirium.<sup>1,2</sup> The prolonged withdrawal phase may persist for months and can include anxiety, depression, sensory and motor symptoms, and cognitive impairment.<sup>1,2</sup> Recurrence of pre-existing psychiatric conditions might also occur with the discontinuation of benzodiazepines.<sup>1,2</sup> To decrease the likelihood of acute withdrawal symptoms, a taper should be considered for patients who have been on benzodiazepines for longer than one month.<sup>6,8</sup>

**Table 1: Characteristics of the Benzodiazepines on the Medi-Cal Fee-for-Service List of Contract Drugs**<sup>1,2,6,10-14</sup>

Drug*	Approximate Oral Dosage Equivalents (mg)**	Elimination Half-life (hours)	Duration of Action
Chlordiazepoxide	10-25	5-30 35-200 for active metabolite	Long
Clonazepam	0.5-1	18-50	Long
Diazepam	5-10	20-100 36-200 for active metabolite	Long
Flurazepam	15-30	40-250 for active metabolite	Long
Lorazepam	1-2	10-20	Intermediate
Temazepam	15-20	8-22	Intermediate

\* Some medications may have restrictions to use. For current information on covered benzodiazepines, visit the online Medi-Cal Formulary search tool available on the [Search Medi-Cal Formulary](#) page of the Department of Health Care Services (DHCS) website.

\*\* Approximate equivalencies vary depending upon the resources referenced.

### Tapering Benzodiazepines

There are several organizational guidelines that outline methods to taper benzodiazepines.<sup>1,2,6-14</sup> There is not a clear-cut, single approach to the optimal rate of tapering and no evidence that one particular tapering strategy may be more successful than another; patient-specific considerations should be taken into account.<sup>6</sup>

Some factors to consider when determining the tapering schedule include the current dose of the benzodiazepine, the half-life of the benzodiazepine (**Table 1**), other substances or medications that the patient is using, as well as the patient age, physical and psychological comorbidities and duration of benzodiazepine use. In general, various tapering schedules are often categorized into rapid and slow tapers. In patients who receive benzodiazepines and opioids concurrently and need tapering for both of these medications, it is recommended to taper opioids first to avoid provoking anxiety.<sup>4</sup>

Rapid tapers may be considered for patients who have taken benzodiazepines for less than four weeks.<sup>7-9</sup> In this method, benzodiazepine discontinuation takes place by a relatively larger drop in dose and more frequent dose reduction than in a slow taper. A rapid taper might involve an initial 25-30% dose reduction weekly until 50% of the dose is reached, followed by 5-10% dose reductions weekly.<sup>7,8</sup>

For patients who have been on benzodiazepines for longer than four weeks or who have been on high doses, a slow taper might be better tolerated.<sup>2,6,8</sup> Patients over age 65 may also benefit from this approach as they may be more sensitive to rapid dose changes. There are various recommendations for this type of taper. A common approach is an initial dose reduction of 5-25%,<sup>2,8,9</sup> followed by further reductions of 10-25% every two weeks.<sup>2,4,8</sup> In general, taper schedules start with more rapid dose reductions followed by a slower taper at the end of the taper.<sup>2,5,12</sup> An example of a slow taper is shown in **Table 2** in which the rate of the taper is reduced once the dose is below 50% of the initial dose or less than 20 mg of diazepam equivalent.<sup>5</sup> It is important to note that the tapering schedule should be individualized for each patient and that the dose should be adjusted based on the patient's response.<sup>8</sup> Slow tapers are usually achieved over 8-12 weeks.<sup>7,14</sup> Referral to substance use specialists may be required for some patients.<sup>8,9</sup> There is some evidence that prolonged tapers of over six months may be associated with worse outcomes.<sup>8,14</sup> Nevertheless, longer tapers might be required in some patients for success.<sup>1</sup> Should withdrawal symptoms occur during a taper, return to the dose prior to the most recent reduction and to slow the rate of the taper.

**Table 2: Example of a Slow Benzodiazepine Taper<sup>8</sup>**

Week	Milestone Suggestions	Example: Lorazepam 4 mg bid converts to 40 mg daily diazepam equivalents
1		35 mg/day
2	Decrease dose by 25%	30 mg/day (25%)
3		25 mg/day
4	Decrease dose by 25%	20 mg/day (50%)
5-8	Hold dose 1-2 months	Continue at 20 mg/day for 1 month
9-10		15 mg/day
11-12	Decrease dose by 25% at week 11	10 mg/day
13-14	Decrease dose by 25% at week 13	5 mg/day
15		Discontinue

Patients may be continued on their current benzodiazepine during taper, or short-acting agents may be switched to longer-acting agents such as diazepam, chlordiazepoxide or clonazepam.<sup>1,7-9,12</sup> Switching from a short-acting to a long-acting agent may be beneficial in patients who are at risk of severe withdrawal symptoms by decreasing the fluctuations of the plasma levels of the medication over time.<sup>1,6</sup> Short-acting benzodiazepines have been associated with higher dropout rates in benzodiazepine discontinuation studies, and more severe withdrawal symptoms.<sup>14</sup> Clinicians might also consider switching agents if the available formulations for a specific short-acting or intermediate-acting benzodiazepine do not allow for small dose reductions.<sup>1</sup> It might be prudent to substitute the new agent for the current benzodiazepine one dose at a time in intervals of a few days to a week, starting with the evening dose.<sup>1</sup>

Use of diazepam is not recommended in patients 65 years and older due to the risk of delirium.<sup>1,9</sup> The safest benzodiazepines for older adults are lorazepam, oxazepam, and temazepam.<sup>1,2,9,14</sup> These medications are mainly metabolized through conjugation and do not have any active metabolites.<sup>2</sup> Therefore, they will not accumulate in patients who have decreased liver function.<sup>2</sup> Among these medications, lorazepam is most commonly used in benzodiazepine tapering for patients with normal hepatic function.<sup>1,2,9</sup>

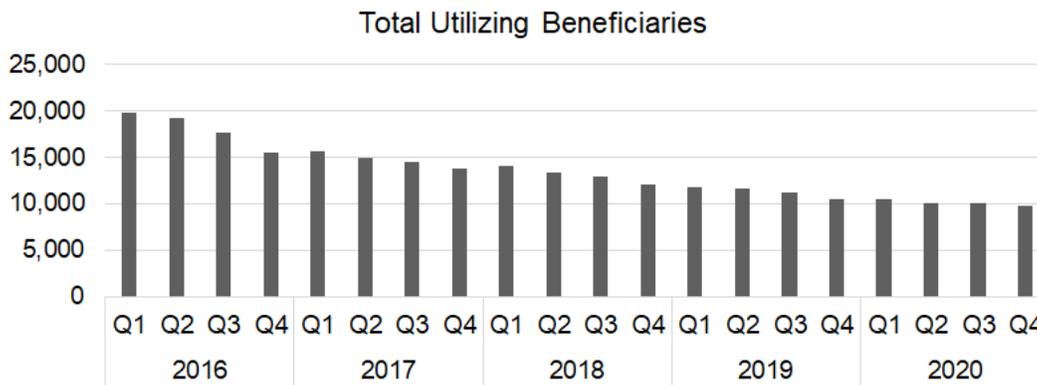
Use of other treatment modalities or adjunctive medications may be beneficial in some patients. Most guidelines recommend use of supportive psychological and behavioral therapies, such as concomitant Cognitive Behavioral Therapy (CBT), both for a better management of withdrawal symptoms and to assist with the underlying psychological disorders for which benzodiazepines were originally prescribed.<sup>1,2,5,8</sup> Supplemental or alternative pharmacological options might also be considered for the same reasons.<sup>1,2,5,6,8</sup>

Finally, it is important to involve the patient in the decision making regarding the taper schedule, provide frequent monitoring and follow-up with the patient, and allow flexibility with the schedule based on the patient's response to the reductions in dose.<sup>8</sup> Minimal educational interventions that may be helpful before the taper include providing written materials to patients in support of tapering, reviewing the benefits of discontinuation with patients, providing information about self-help treatment for topics such as sleep hygiene, providing clear written instructions on how to conduct the taper, and educating patients on signs and symptoms of withdrawal.<sup>14</sup> If the patient is struggling with withdrawal or rebound symptoms, consider stabilizing the patient on the reduced dose before further reductions.<sup>8</sup> Re-addressing the underlying condition before starting or continuing the discontinuation might also be helpful for some patients.<sup>1</sup>

### **Benzodiazepine Use in the Medi-Cal Population**

A retrospective cohort study was conducted to evaluate use of benzodiazepines in the Medi-Cal population. All paid pharmacy claims for benzodiazepines with dates of service from January 1, 2016, through December 31, 2020, were reviewed. As shown in **Figure 1**, overall use of benzodiazepines in the Medi-Cal population has decreased steadily over the last five years, with a 50% reduction in utilizing beneficiaries with at least one paid claim for a benzodiazepine from the 1<sup>st</sup> quarter of 2016 to the 4<sup>th</sup> quarter of 2020.

**Figure 1. Benzodiazepine Use in the Medi-Cal Population (2016 – 2020)**



From January 1, 2020, through December 31, 2020, there were a total of 23,152 Medi-Cal beneficiaries with at least one paid claim for a benzodiazepine and a total of 103,737 paid claims for benzodiazepines during this time period. A summary of these paid claims is shown in **Table 3**. Of the 23,152 beneficiaries, almost half (n = 10,721; 46%) had only one paid claim for a benzodiazepine medication in 2020. Of note, there were 2,289 (10%) utilizing beneficiaries with paid claims for more than one benzodiazepine medication during the year. These beneficiaries were included in **Table 3** for each benzodiazepine in which they had a paid claim during 2020.

**Table 3. Benzodiazepine Use in the Medi-Cal Population during 2020, by Drug**

<b>Drug</b>	<b>Total Utilizing Beneficiaries (n = 23,152)</b>	<b>Total Paid Claims (n = 103,737)</b>
Lorazepam*	13,701 (59%)	31,154 (30%)
Clonazepam*	6,481 (28%)	27,522 (27%)
Diazepam*	5,499 (24%)	13,585 (13%)
Clobazam	2,572 (11%)	23,879 (23%)
Temazepam*	1,120 (5%)	3,656 (4%)
Alprazolam	425 (2%)	1,331 (1%)
All others	931 (4%)	2,610 (3%)

\* As of the publication of this bulletin, these drugs are on the Medi-Cal fee-for-service List of Contract Drugs, although there may be additional restrictions to use.

In addition, a total of 3,110 (3%) of paid claims for benzodiazepines during this time period were for 850 adults 65 years of age or older. Of the 13,585 paid claims for diazepam, 138 (1%) were for adults 65 years of age or older even though diazepam is contraindicated in this population due to increased risk of delirium.

## **Conclusion/Discussion**

While there are benefits associated with the short-term utilization of benzodiazepines, these medications are also associated with higher risks for both short and long-term adverse events, including death. When benzodiazepine therapy is no longer indicated or when the risk associated with the use of benzodiazepines outweighs the benefit, a benzodiazepine taper may be indicated. Strategies that can help patients with tapering include gradual dose reduction and discontinuation, use of educational interventions, and psychotherapy.

## **Clinical Recommendations:**

- New prescriptions for benzodiazepines should be limited to the lowest dose and shortest duration possible.
- The dose and half-life of the benzodiazepine, concomitant substances or medications, patient age, and physical and psychological comorbidities should be considered when designing a taper.
- A rapid taper is usually recommended for individuals who have been on benzodiazepines for 4 weeks or less. A slow taper should be considered for patients who have been on benzodiazepines for greater than 4 weeks.
- In patients who receive benzodiazepines and opioids concurrently and need tapering for both of these medications, it is recommended to taper opioids first to avoid provoking anxiety.
- To decrease fluctuations of plasma levels of the medication, short-acting benzodiazepines can be switched to longer-acting agents, such as diazepam before starting the taper.
- Educate patients before starting the taper by reviewing the benefits of discontinuation, offering information about self-help treatment for topics such as sleep hygiene, and providing clear written instructions on how to conduct the taper.
- Involve the patient in decision making regarding the taper schedule and frequently monitor and follow-up with the patient.
- Tailor the rate of the taper based on the patient's level of tolerance and consider incorporation of other treatment modalities, such as adjunctive medications if the patient has psychological comorbidities or is at risk of severe withdrawal symptoms. Staying at a dose for longer than expected is acceptable, but do not increase the dose once a taper has started and avoid "as needed" use of benzodiazepines during the taper.
- If the patient is struggling with withdrawal or rebound symptoms, consider stabilizing the patient on the reduced dose before further reductions. Re-addressing the underlying condition before starting or continuing the discontinuation might also be helpful for some patients. Non-pharmacological strategies should also be considered for the management of withdrawal symptoms, such as deep breathing, psychotherapy, and exercise.
- If complete discontinuation of benzodiazepines is not possible, taper the benzodiazepine to the lowest dose possible dose and encourage only as needed or intermittent use. Caution patients to avoid mixing benzodiazepines with other depressant drugs or alcohol, advise patients to never take other people's prescribed medications, and advise patients to avoid driving or other dangerous activities after taking benzodiazepines.

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