Part VI: Benzodiazepines

Introduction

Benzodiazepines are effective anxiolytics, but they are associated with serious harms. Health care providers find it difficult to mitigate against these harms because they tend to be unpredictable, vague and hard to detect, and multifactorial (e.g., falls, fatigue, depression). Therefore, as with opioids, safe benzodiazepine prescribing requires careful patient selection, close monitoring, and tapering when indicated. This section provides guidelines on safely prescribing benzodiazepines and managing adverse effects, including benzodiazepine use disorder.

Benzodiazepine therapy

Indications

- Severe acute anxiety
- Generalized anxiety disorder that is unresponsive to other treatments (e.g., SSRIs, SNRIs)
- Panic disorder that is unresponsive to other treatments (SSRIs are first-line agents)
- Depression, bipolar disorder, or schizophrenia (adjunct therapy)
- Insomnia
- Alcohol withdrawal
- Seizures, spasms
- Pre-procedure sedation

Adverse effects

Effect	Factors that increase risk
Depression Suicidal ideation	• High doses • Concurrent use of alcohol/opioids • Underlying mood disorder
Falls Hip fractures	• Older adults • Neurological/cognitive impairment • Long-acting agents (e.g., diazepam)
Confusion Worsening dementia	• Older adults • Dementing condition
Motor vehicle accidents	• Early in therapy before tolerance develops • Concurrent use of other sedating agents
Decreased respiratory drive	• Early in therapy • Respiratory illness/dysfunction • Concurrent use of other sedating agents
Sleep apnea	• Underlying risk (e.g., obesity) • Concurrent use of other sedating agents
Blackouts Parasomnias	• Triazolam or alprazolam • Higher doses

Prescribing benzodiazepines

- Consider alternative therapies before prescribing benzodiazepines.
  - For anxiety: SSRIs, SNRIs, mood stabilizers, psychotherapy
  - For insomnia: trazadone, tryptophan, low-dose TCA, sedating SSRIs, zopiclone
- Initial prescriptions should be for a maximum of **3 weeks**.
- Prescribing for anxiety:
  - Titrate patient to lowest effective dose.
  - Long-term therapy should be prescribed only to patients with severe anxiety interfering with daily function who have failed an adequate trial of psychotherapy and of other anxiolytics (e.g., SSRIs, mood stabilizers).
  - Taper dose when indicated (see below).
- Prescribing for insomnia:
  - Patients should avoid daily use for prolonged periods, as tolerance for sedation develops quickly, and abruptly stopping after several weeks of daily use will result in rebound insomnia.
  - Patients should be advised on sleep hygiene:

Go to bed and get up at a reasonable time; don't sleep late, even if you're tired.
Eat only small amounts before bed.
Avoid caffeine and alcohol at night.
Only use the bed for sleeping and sex; don't read, watch TV, use your phone, etc.
If you can't sleep, get up and do something else for 15 minutes (but don't turn on a screen).
Exercise most days of the week.
If you get up frequently to urinate, avoid drinking too much at night.

Benzodiazepine equivalent table (107)

Benzodiazepine	Equivalent to 5 mg diazepam*
Alprazolam**	0.5 mg
Bromazepam	3–6 mg
Chlordiazepoxide	10–25 mg
Clonazepam	0.5–1 mg
Clorazepate	7.5 mg
Flurazepam	15 mg
Lorazepam	0.5–1 mg
Nitrazepam	5–10 mg
Oxazepam	15 mg
Temazepam	10–15 mg
Triazolam**	0.25 mg

* Equivalences are approximate. Careful monitoring is required to avoid over-sedation, particularly in older adults and those with impaired hepatic metabolism.

** Equivalency uncertain.

Benzodiazepine withdrawal

Clinical features	Abrupt discontinuation of benzodiazepines after daily use for 2+ months Can occur even at therapeutic doses, though more severe with high doses, long duration of use, or underlying anxiety disorder
Time course	Onset 2–4 days after abrupt cessation May take weeks or months to resolve
Symptoms and signs	Anxiety-related symptoms (panic, irritability, poor concentration) Neurological symptoms (dysperceptions, tinnitus, déjà vu) Sweating, tremor usually not seen except with sudden cessation of high doses
Complications	Abrupt cessation of high doses (50 mg of diazepam/day or equivalent) can cause acute hypertension, seizures, delirium Can trigger suicidal ideation in patients with mixed anxiety and mood disorder
Effect on sleep	Rebound insomnia (vivid dreams, fitful sleep) Takes several weeks to resolve

Benzodiazepine tapering

Rationale

- Recommended over abrupt cessation unless patient has only been taking the medication intermittently or for a few weeks.
- Periodic tapering attempts are warranted even for patients taking therapeutic doses with no apparent adverse effects:
  - Patients sometimes feel more alert and energetic at lower doses, and are better able to engage in psychotherapy.
- Controlled trials have shown that many adults are able to successfully reduce their benzodiazepine dose with appropriate support (108, 109) and that tapering can be performed in primary care (110).

Indications

- At higher risk for sedation, falls, and sleep apnea (e.g., elderly, heavy drinkers, on opioids or other sedating medications)
  - Benzodiazepines markedly increase opioid toxicity and the lethality of an opioid overdose (111).
- Daily responsibilities requiring alertness and clear thinking (e.g., students, drivers, looking after small children)
- Cognitive impairment, fatigue, depression
- At risk for unsafe medication use

Approach to tapering

- Explain benefits of tapering (improved energy, mood, and function; reduced risk of falls; etc.).
- Work with patient to determine rate of taper.
  - Slow, flexible tapers work better than rapid tapers.
- Halt or reverse taper if patient experiences clinically significant increase in anxiety.
- Follow patient regularly (every 1–4 weeks).
- At each visit, ask not just about withdrawal symptoms but benefits of tapering: more alert, less fatigued, improved mood.
- Involve family members if possible; they often notice improvement before patient does.
- Ideal time to introduce comprehensive management strategies for underlying anxiety disorder, including psychotherapeutic techniques (mindfulness, CBT), lifestyle modification (exercise, sleep, reduce coffee and alcohol) and pharmacotherapy (antidepressants).

Tapering protocol

Formulation	Safest to taper with patient's current benzodiazepine (but see below).
Dosing interval	Scheduled doses rather than PRN. Keep dosing interval the same for as long as possible (e.g., bid or tid). Advise patients not to skip or delay doses (in an attempt to speed up the taper), as this causes a sharp increase in anxiety.
Rate of taper	Taper slowly, no more than 5 mg diazepam equivalent/day at each office visit. Can taper as slowly as 1–2 mg diazepam equivalent/month. Can taper according to proportional dose remaining: taper by 10% of dose every visit until at 20% of original dose, then taper by 5% every visit. Let patient choose which dose is decreased (AM, PM, or HS). Adjust rate of taper according to patient response. Slow pace of taper once daily dose below 20 mg diazepam equivalent.
Dispensing interval	If patient runs out early, increase dispensing frequency to weekly, alternate days, or daily.
Endpoint of taper	Abstinence preferred. Reduced dose if patient experiences significant anxiety or insomnia with abstinence.

Tapering with clonazepam

- If patient is emotionally attached to their benzodiazepine and resistant to tapering or repeatedly runs out early, consider switching patient to another agent for tapering.
- Little clear evidence for best agent for tapering; however, **clonazepam** is recommended over diazepam.
  - Although diazepam has a longer duration of action and therefore may result in a smoother withdrawal, clonazepam is less likely to cause prolonged sedation in the elderly and has a lower risk of euphoria and misuse.
- Protocol:
  - Initial dose should be lower than that of current agent, as patient may not be tolerant to new agent; convert to one half equivalent dose of original agent.
  - Increase dose until patient is comfortable, but try not to go above fully equivalent dose.
  - Prescribe on bid or tid schedule.

Benzodiazepine use disorders

As with opioid use disorders, a patient with a benzodiazepine use disorder is not using the medication for therapeutic purposes but to achieve sedation and euphoria. While tolerance for the anxiolytic effects of benzodiazepines develops very slowly, allowing patients to stay on a moderate dose for months or years, tolerance to the sedating and euphoric effects of benzodiazepines develops quickly, forcing patients to escalate the dose. The features of benzodiazepine **intoxication** are similar to those of alcohol intoxication: sedation, emotional lability, and impulsive or dangerous behaviour.

Risk factors

- Male
- Younger
- Current or past history of problematic use of other substances
- Current active psychiatric disorder

Clinical features

- Patient is taking a dose well above the usual therapeutic range.
- Patient frequently runs out early or accesses benzodiazepines from other sources.
- Patient has a pattern of binge use with recurrent intoxication and withdrawal.

Management

Treatment setting	Outpatient taper recommended for patients on moderate doses who do not access benzodiazepines from non-medical sources. Residential treatment best for patients on very high doses (e.g., 100+ mg diazepam equivalent/day) or patients whose main source of benzodiazepines is the illicit market.
Outpatient tapering	Patients will have trouble tapering if they are given large amounts of benzodiazepines to take home. Dispense every 1–2 days with a strict agreement that prescriptions will not be refilled early. Patients experiencing significant sedation or intoxication should be tapered quickly (e.g., 5 mg diazepam equivalent every 3–7 days). Taper may be slowed when intoxication resolves.
Psychosocial treatment	Similar to treatment of other substance use disorders: formal treatment programs and self-help groups. Encourage patient to try different options to see what suits them best.
Treatment of concurrent conditions	Addiction to alcohol or opioids should be treated at the same time as the benzodiazepine addiction to reduce risk of dangerous drug interactions. Most patients with a benzodiazepine use disorder will also have a significant mental illness, which should be treated concurrently. Anticonvulsant medications (e.g., gabapentin, topiramate) may be helpful for both underlying mood disorder and alcohol/benzodiazepine withdrawal. Antidepressants and atypical antipsychotics may also be helpful. Shared care with psychiatrist is recommended.