Benzodiazepine use disorder

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INTRODUCTION

Benzodiazepines have anxiolytic, hypnotic, anticonvulsive, and muscle-relaxing properties, which have made them a widely prescribed treatment, primarily for anxiety and insomnia. They also are associated with physical dependence and addiction. Benzodiazepine use disorder can involve misuse of prescribed benzodiazepines and use of diverted benzodiazepines.

Benzodiazepine use disorder can be a chronic, relapsing disorder and benzodiazepine use has been associated with increased morbidity and mortality in some studies. Misuse of benzodiazepines can be difficult to distinguish from undertreated anxiety or insomnia.

The epidemiology, pathogenesis, clinical manifestations, course, diagnosis, and treatment of benzodiazepine use disorder are reviewed here. Clinical assessment of substance use disorders is also reviewed separately. Identification and management of prescription drug misuse, including misuse of benzodiazepines, are also reviewed separately. (See "Substance use disorders: Clinical assessment" and "Prescription drug misuse: Epidemiology, prevention, identification, and management".)

TERMINOLOGY

- **Controlled substances** – Because of their potential for misuse, addiction, and illicit diversion and sale, opioid analgesics, stimulants, and benzodiazepines and other sedatives/hypnotics are regulated, restricting whether and how they can be prescribed. In

the United States, these medications are referred to as "controlled substances" and subject to federal regulations (table 1).

- **Prescription drug (eg, benzodiazepine) misuse** – Any use of a prescription medication that is outside of the manner and intent for which it was prescribed; this includes overuse, use to get high, diversion (sharing or selling to others), and having multiple prescribers or nonprescribed sources of the medication, or nonprescribed controlled medications. Misuse is a necessary but not sufficient criterion for a substance use disorder. (See "Prescription drug misuse: Epidemiology, prevention, identification, and management".)

- **Nonmedical use** – A narrower definition of prescription drug misuse, defined as use of a medication that was not prescribed to the individual or use “only for the feeling or experience it caused” [1].

- **Prescription drug (eg, benzodiazepine) use disorder** – Misuse of a prescription drug meeting the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) criteria as a substance use disorder [2].

EPIDEMIOLOGY

Prevalence — Precise data are not available, but estimates suggest a lifetime prevalence of benzodiazepine use disorder of somewhat less than 1 percent. In epidemiologic surveys, benzodiazepines are often categorized with other drugs to create therapeutic drug classes such as sedatives, tranquilizers, and hypnotics; thus, the prevalence of benzodiazepine use disorder specifically in the United States can be difficult to tease out. Nevertheless, the existing data sources roughly describe the scope of the disorder from the late 1990s through the late 2010s:

- The lifetime prevalence of tranquilizer and sedative use disorders (including benzodiazepines, barbiturates, and other older sedative medications) in the United States was estimated to be 1.0 and 1.1 percent respectively [3].

- Past-year prevalence of tranquilizer or sedative use disorder in the United States was estimated to be 0.2 percent [4].

- In persons age 12 years or older in the United States, nearly 2 percent reported past-year illicit use of benzodiazepines. This represents nearly 9 percent of total illicit drug use in this age range [4].

- Substance use disorder treatment admissions for benzodiazepines as the primary substance used have consistently risen and have doubled from 0.5 percent to 1 percent

over a 10-year interval (2007 to 2017) [5].

- Nationally representative surveys were largely limited to the United States, but as an international point of comparison, in Australia, among Australian individuals 14 years or older, 1.6 percent had past-year nonmedical tranquilizer use [6].

Risk factors — Several risk factors for benzodiazepine use disorder have been identified [7]:

- Longer duration of benzodiazepine use
- Higher benzodiazepine doses
- Lower level of education

Misuse of prescribed benzodiazepines, which can contribute to or result from benzodiazepine use disorder, is associated with a [8]:

- Greater insomnia severity
- Current antidepressant use

High rates of misuse of benzodiazepines have also been found among people who use injection drugs [9] and those receiving methadone maintenance treatment [10,11].

Psychiatric comorbidity — Benzodiazepine use disorder has been associated with a broad range of comorbid psychiatric disorders. In a survey of the United States general population, sedative and tranquilizer use disorders were strongly associated with [3]:

- Other substance use disorders
- Other prescription drug misuse
- Panic disorder with agoraphobia
- Bipolar I disorder
- Antisocial personality disorder

PHARMACOLOGY

Mechanism of action — Benzodiazepines bind to gamma-aminobutyric acid type A ($GABA_A$) receptors, which are responsible for most of the inhibitory neurotransmission in the central nervous system and a major target of alcohol, barbiturates, muscle relaxants, and other medications with sedative effects. $GABA_A$ receptors are ligand-gated chloride ion channels. When gamma-aminobutyric acid (GABA) binds to these receptors, it increases the amount of chloride current generated by the receptor. Benzodiazepines augment GABA's inhibitory effect

by increasing the frequency of channel openings [12]. This inhibitory effect leads to the anxiolytic, hypnotic, anticonvulsive, and muscle-relaxing properties of benzodiazepines.

Pharmacokinetics — Benzodiazepines can be categorized into short (15 to 30 minutes), intermediate (30 to 60 minutes), and long-acting agents (one hour or longer). There are at least three determinants of the speed of action of benzodiazepines: half-life, rate of absorption, and lipophilicity. Half-life is determined by how the drug is metabolized and whether it has any active metabolites. A table (table 2) provides data on the dosing and pharmacology of individual benzodiazepines, including their comparative potency, time to onset, metabolism type, and elimination half-life.

As an example, diazepam has a long half-life because it is oxidized by the liver (a relatively slower process) and is metabolized into oxazepam, which is an active anxiolytic.

Most benzodiazepines are absorbed completely but have differing rates of absorption. Clorazepate and diazepam are both rapidly absorbed, which leads to more rapid increases in plasma levels of these drugs. The greater the lipophilicity of a benzodiazepine, the quicker it enters the brain and therefore a more rapid anxiolytic effect. Lipophilicity varies by >50-fold among benzodiazepines [13]. Diazepam is an example of a highly lipophilic benzodiazepine and lorazepam of a less lipophilic drug.

Physical dependence — Chronic benzodiazepine use can cause physical dependence, as evidenced by the benzodiazepine withdrawal syndrome observed in many people who use benzodiazepines long-term upon cessation of the drug. The exact molecular mechanism for physical dependence from benzodiazepine use is not clear [14].

Chronic exposure to benzodiazepines causes reduced $GABA_A$ receptor response, and there are changes to $GABA_A$ receptor subtype expression with chronic benzodiazepine exposure, which leads to a reduced inhibitory response. There is an increased expression of excitatory glutamatergic receptors upon benzodiazepine withdrawal after chronic exposure, which could underlie the symptoms observed in the benzodiazepine withdrawal syndrome.

Addiction liability — In a review of animal and human studies that incorporated both human laboratory self-administration and epidemiological data, the liability to misuse benzodiazepines varied by type [15,16]. Speed of onset appears to play a major role in the addiction liability of different benzodiazepine types. Diazepam and flunitrazepam (widely available in Europe, Mexico, and Colombia, but not in the United States), two benzodiazepines with rapid onset, and lorazepam appear to have the greatest likelihood for misuse, although several commonly prescribed benzodiazepines, such as alprazolam and clonazepam, were not included in these studies.

In a study that used doctor shopping as a proxy for benzodiazepine misuse, flunitrazepam had the highest potential for misuse, followed by diazepam, alprazolam, and clonazepam [17]. Flunitrazepam and diazepam are highly lipophilic and are rapidly absorbed. This causes a more rapid onset of action and may lead to a higher liability for misuse.

PATHOGENESIS

The pathogenesis of addiction is not fully understood; however, use of all addictive drugs, including benzodiazepines, involves increases in dopamine levels in the mesolimbic dopamine system, the reward system of the brain. The ventral tegmental area, located at the origin of the mesolimbic dopamine system, consists of gamma-aminobutyric acid (GABA) interneurons, and dopamine and glutamate neurons. When benzodiazepines bind gamma-aminobutyric acid type A ($GABA_A$) receptors on GABA interneurons, they decrease the release of GABA onto dopamine neurons. This lowers the inhibitory effect of GABA interneurons on dopamine neurons, leading to increased dopamine transmission, a process called disinhibition. Benzodiazepines bind a pocket between the alpha and gamma subunits on $GABA_A$ receptors, and the alpha-1 subunit isoform is believed to be responsible for addictive behavior [18]. $GABA_A$ receptors with the alpha-1 subunit are abundant in GABA interneurons in the ventral tegmental area of mice [19].

Synaptic plasticity, or changes in synaptic strength determined by prior synaptic activity, is thought to underlie learning and memory processes. Addictive drugs can cause long-lasting changes to the reward system. Early in this process, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors move from the interior to the surface of dopamine neurons, which leads to greater susceptibility to be stimulated by the excitatory neurotransmitter glutamate [20]. Because of the AMPA receptor migration, future use of addictive drugs can lead to even greater dopamine transmission. Similar to other addictive drugs, benzodiazepine use in mice also leads to the same AMPA receptor migration and the synaptic plasticity found in other addictive drugs [19,21].

The majority of genetic risk factors for benzodiazepine misuse or use disorder is believed to be nonsubstance specific and thus shared among different substances. In two twin studies, genetic influences were shared across multiple substances including sedatives, cannabis, and stimulants and not specific to substance [22,23]. Twin studies also suggest that the majority of environmental risk factors for substance use disorders shared between twin pairs, such as family environment, is not specific to substance [23,24].

CLINICAL MANIFESTATIONS

Benzodiazepine use disorder — Patients with a benzodiazepine use disorder may present with a range of severity. Milder cases may have no signs of benzodiazepine use or aberrant medication-taking behaviors only, while patients with greater severity may present with acute intoxication or benzodiazepine withdrawal.

Patients with a benzodiazepine use disorder may have symptoms or behaviors related to benzodiazepine use, including:

- Benzodiazepines taken in larger amounts or over a longer period than intended
- Persistent desire or unsuccessful efforts to control benzodiazepine use
- Great deal of time spent obtaining or using benzodiazepines
- Craving to use benzodiazepines
- Recurrent benzodiazepine use resulting in failure to fulfill major role obligations
- Continued benzodiazepine use despite persistent interpersonal problems
- Important activities given up or reduced because of benzodiazepine use
- Recurrent benzodiazepine use in hazardous situations
- Continued benzodiazepine use despite persistent resulting problems
- Evidence of tolerance or withdrawal from benzodiazepine use

Withdrawal

Timing and course — Abrupt or overly rapid discontinuation of benzodiazepines after regular use at a recommended dose most commonly leads to a short period (two to three days) of rebound anxiety and insomnia that can occur as soon as one day after discontinuation, depending on the half-life of the benzodiazepine. Some individuals will experience a broader range of symptoms (listed above) that can last up to two weeks.

Clinical manifestations — Typical signs and symptoms of benzodiazepine withdrawal include [25]:

- Mild (2 to 3 days)
  - Anxiety
  - Insomnia
- Moderate (2 to 14 days)
  - Sleep disturbance
  - Irritability
  - Anxiety, panic attacks
  - Tremor

- Diaphoresis
- Poor concentration
- Nausea, vomiting
- Weight loss
- Palpitations
- Headache
- Muscle pain and stiffness

- Severe (2 to 14 days)

  - Seizure
  - Psychosis

Risk factors — Withdrawal seizures may be more likely in patients with a history of [26]:

- Brain damage
- Alcohol addiction
- Electroencephalogram abnormalities

Factors associated with increased severity of benzodiazepine withdrawal include [27]:

- Abrupt discontinuation after regular use
- Longer duration of use prior to discontinuation
- Higher doses
- Shorter half-life

Benzodiazepine withdrawal is reviewed further separately. (See "Benzodiazepine poisoning and withdrawal".)

Intoxication — Signs of benzodiazepine intoxication include slurred speech, incoordination, unsteady gait, and cognitive impairment (in particular, anterograde amnesia or the inability to create new memories). Benzodiazepine intoxication is reviewed separately. (See "Benzodiazepine poisoning and withdrawal".)

Overdose — Signs of benzodiazepine overdose include nystagmus, stupor or coma, and respiratory depression. Signs of benzodiazepine withdrawal include anxiety, autonomic hyperactivity, tremor, insomnia, and nausea or vomiting [2]. More severe benzodiazepine withdrawal may lead to transient hallucinations, generalized tonic-clonic seizures, and delirium. Benzodiazepine overdose is reviewed separately. (See "Benzodiazepine poisoning and withdrawal".)

COURSE

Little is known about the natural history of benzodiazepine use disorder; the more severe form is believed to be a chronic, relapsing disorder similar to other substance use disorders.

A study of 221 Swedish individuals (average age of 43 years old when first hospitalized) interviewed approximately 40 years after hospitalization for primary sedative-hypnotic dependence found that approximately [28]:

- Half were misusing sedative-hypnotics at follow-up
- One-fourth died of an unnatural death
- Eighteen percent died of suicide

Longitudinal studies of patients who successfully discontinued benzodiazepine use after long-term use and/or developing physically dependence (not assessed for benzodiazepine use disorder) found:

- After 3 years, 73 percent continued to be abstinent from benzodiazepines [29]
- After 10 years, 59 percent continued to be abstinent [30]

Few studies have examined the medical consequences of benzodiazepine use disorder. A study of 384 persons with benzodiazepine use disorder found that their mortality was increased compared with the general population but not compared with those without benzodiazepine use disorder who had similar psychiatric illnesses [31]. Numerous studies of benzodiazepine use have found an increased risk of:

- Falls in older adults [32]
- Fractures in older adults [33]
- Cognitive dysfunction [34]
- Overdose death when combined with opioids [35,36]

Benzodiazepine use has also been associated with an increased risk of all-cause mortality [37,38], but a 2017 study of a large, population-based cohort did not find an increased risk of all-cause mortality with benzodiazepine initiation [39].

ASSESSMENT

- **Substance use history** – When assessing a patient for benzodiazepine use disorder, it is important to take a complete substance use history including details of benzodiazepine

use, past treatment, and use of other addictive substances.

Patients may obtain benzodiazepines by prescription or by illicit means. Those that are receiving benzodiazepines by prescription may be nonadherent to the prescriber's instructions. It is important to ask patients, regardless of the source of medication, about the amount of benzodiazepines being consumed. Shorter half-life benzodiazepines have been associated with greater benzodiazepine withdrawal severity [25], and longer duration of benzodiazepine use and higher benzodiazepine dose have been associated with greater benzodiazepine use disorder severity and benzodiazepine withdrawal severity [7].

Online prescription monitoring programs in the United States and other countries allow clinicians to identify all prescriptions for a patient of a controlled substance, including benzodiazepines, by all prescribers in a given state or region. When possible, prescribers should (and, in some cases, are required to) query these online databases before further prescription to verify a patient's reported medication history and to detect undisclosed prescriptions from other clinicians. Prescription monitoring programs are reviewed further separately. (See "Prescription drug misuse: Epidemiology, prevention, identification, and management".)

Patients should be asked specifically about:

- Benzodiazepine type
- Dose
- Average number of tablets consumed daily
- Duration of use
- Date of last use

Date of last use and half-life provide information on when withdrawal symptoms may begin.

- **Other substance use** – Patients should be assessed for use and disorders associated with alcohol and other drugs, in particular opioids and alcohol [40,41]. Combined use of benzodiazepines with other sedating drugs may increase risk of over-sedation and overdose death. Addiction to benzodiazepines may predispose patients to other substance use disorders. (See 'Risk factors' above.)

- **Current or past substance use disorder treatment** – Treatment for benzodiazepine use disorder and other substances includes medically supervised withdrawal (detoxification), residential rehabilitation treatment, mutual help groups, or outpatient substance use

disorder services (eg, counseling or medication for addiction). (See "Substance use disorders: Determining appropriate level of care for treatment", section on 'Levels of care'.)

- **Comorbidities** – Patients should be assessed for psychiatric comorbidities including depression, anxiety disorders, and insomnia. Antidepressant use and greater insomnia severity have been found to be risk factors for benzodiazepine use disorder among outpatients using benzodiazepines [7]. Treating depression can reduce anxiety and insomnia [42], which may reduce reliance on benzodiazepines [43]. (See 'Risk factors' above.)

  Because benzodiazepine use has been associated with an increased risk of cognitive dysfunction and Alzheimer disease, it is important to assess for cognitive functioning [35,44].

  Assessing for medical comorbidities, particularly chronic obstructive pulmonary disease (COPD) and chronic noncancer pain, is important in determining the risks of further benzodiazepine use. Benzodiazepine use in patients with COPD has been associated with an increased risk of mortality in a dose-response fashion [45]. Benzodiazepine use is common among patients who take opioids for chronic pain [46]. Benzodiazepines have a dose-response relationship with an increased risk of overdose death in patients receiving opioid analgesics [34]. While assessing for COPD and chronic pain, patients with these conditions who use benzodiazepines can be educated about the mortality risks.

- **Physical examination** – The physical examination of patients with benzodiazepine use disorder may reveal signs of benzodiazepine intoxication or withdrawal. Signs of benzodiazepine intoxication include slurred speech, incoordination, unsteady gait, and cognitive impairment. Signs of benzodiazepine withdrawal include anxiety, autonomic hyperactivity, tremor, insomnia, and nausea or vomiting. (See 'Intoxication' above and 'Withdrawal' above.)

- **Laboratory evaluation** – Patients assessed for a possible benzodiazepine use disorder can usefully be tested for benzodiazepines using a standard urine drug screen, typically performed by immunoassay. Certain benzodiazepines can be more difficult to detect, due to differences in their metabolic pathways. Screening assays are typically able to detect diazepam, chlordiazepoxide, temazepam, oxazepam, and nordazepam (a metabolite). Newer benzodiazepines such as alprazolam, clonazepam, and lorazepam are often more difficult to detect, producing false negative results [47,48].

A standard urine drug screen that tests for other substances, including opioids, cocaine, barbiturates, and amphetamine is also suggested, along with testing for alcohol use with a breathalyzer (alcohol detectable up to six hours after use) and/or a biomarker such as ethyl glucuronide (alcohol detectable up to 80 hours after use).

DIAGNOSIS

Benzodiazepine use disorder — Benzodiazepine abuse and dependence were replaced by benzodiazepine use disorder. Although the crosswalk between these disorders is imprecise, benzodiazepine dependence is approximately comparable to benzodiazepine use disorder, moderate to severe subtype, while benzodiazepine abuse is similar to the mild subtype [49].

DSM-5-TR diagnostic criteria for benzodiazepine use disorder are [2]:

"A problematic pattern of sedative, hypnotic, or anxiolytic use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

- 1. Sedatives, hypnotics, or anxiolytics are often taken in larger amounts or over a longer period than was intended.
- 2. A persistent desire or unsuccessful efforts to cut down or control sedative, hypnotic, or anxiolytic use.
- 3. A great deal of time is spent in activities necessary to obtain the sedative, hypnotic, or anxiolytic; use the sedative, hypnotic, or anxiolytic; or recover from its effects.
- 4. Craving, or a strong desire or urge to use the sedative, hypnotic, or anxiolytic.
- 5. Recurrent sedative, hypnotic, or anxiolytic use resulting in a failure to fulfill major role obligations at work, school, or home.
- 6. Continued sedative, hypnotic, or anxiolytic use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of sedatives, hypnotics, or anxiolytics.
- 7. Important social, occupational, or recreational activities are given up or reduced because of sedative, hypnotic, or anxiolytic use.
- 8. Recurrent sedative, hypnotic, or anxiolytic use in situations in which it is physically hazardous.

- 9. Continued sedative, hypnotic, or anxiolytic use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the sedative, hypnotic, or anxiolytic.
- 10. Tolerance.*
- 11. Withdrawal.*

*These criteria are not considered to be met for individuals taking sedatives, hypnotics, or anxiolytics under medical supervision.

Specifiers for the diagnosis include:

- In early remission – After full criteria for sedative, hypnotic, or anxiolytic use disorder were previously met, none of the criteria for sedative, hypnotic, or anxiolytic use disorder have been met for at least three months but for less than 12 months.
- In sustained remission – After full criteria for sedative, hypnotic, or anxiolytic use disorder were previously met, none of the criteria for sedative, hypnotic, or anxiolytic use disorder have been met at any time during a period of 12 months or longer.
- In a controlled environment – If the individual is in an environment where access to sedatives, hypnotics, or anxiolytics is restricted.

Specifiers for disorder severity are based on the number of criteria met:

- Mild – Presence of two to three criteria.
- Moderate – Presence of four to five criteria.
- Severe – Presence of six or more criteria."

Benzodiazepine withdrawal — Patients with benzodiazepine use disorder may present in benzodiazepine withdrawal. Because symptoms of benzodiazepine withdrawal are similar to those of alcohol withdrawal or withdrawal from other sedative-hypnotics such as barbiturates, it is important to rule out other substance use disorders.

DSM-5-TR diagnostic criteria for benzodiazepine withdrawal are [2]:

- A. Cessation of (or reduction in) benzodiazepine use that has been prolonged.
- B. Two (or more) of the following, developing within several hours to a few days after the cessation of (or reduction in) benzodiazepine use described in criterion A:

- 1. Autonomic hyperactivity (eg, sweating or pulse rate >100)
- 2. Hand tremor
- 3. Insomnia
- 4. Nausea or vomiting
- 5. Transient visual, tactile, or auditory hallucinations or illusions
- 6. Psychomotor agitation
- 7. Anxiety
- 8. Grand mal seizures

- C. The signs or symptoms in criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

- D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

  Specify if:

- **With perceptual disturbances** – This specifier may be noted when hallucinations with intact reality testing or auditory, visual, or tactile illusions occur in the absence of a delirium.

Differential diagnosis — Assessing a patient for benzodiazepine use disorder can differ depending on whether a patient is receiving a prescribed benzodiazepine or through illicit means. In patients prescribed benzodiazepines, it is often difficult to distinguish between treatment-seeking behavior in patients with undertreated anxiety or insomnia and behaviors to obtain benzodiazepines for nonmedical use. Assessing for aberrant medication taking behaviors can help with assessing for medication misuse. These behaviors include requests for dose increases, running out of medications early, resisting a change in therapy despite adverse effects of the medication, nonadherence with monitoring (eg, pill counts), and “lost” or “stolen” prescriptions [50]. (See "Prescription drug misuse: Epidemiology, prevention, identification, and management".)

Patients with benzodiazepine use disorder may present with symptoms of anxiety and depression; anxiety and mood disorders should be ruled out as possible comorbid diagnoses.

TREATMENT

Treatment of benzodiazepine use disorder consists of safely tapering patients off of benzodiazepines and preventing return to use once the medications are fully discontinued [51].

Medically supervised taper

Inpatient versus outpatient treatment — Most patients, even those on relatively high doses of benzodiazepines (eg, 100 mg diazepam equivalent), can undergo successful benzodiazepine taper in the outpatient setting [30]. Inpatient treatment may occasionally be warranted if the patient has been unable to successfully taper in the outpatient setting despite several attempts or has complicated medical comorbidities, such as a history of seizures, that should be monitored during the taper.

Taper rate — In the outpatient setting, we recommend gradual reduction of the benzodiazepine by 25 to 50 percent every 1 to 2 weeks over a period of 6 to 10 weeks. Within this range, individualization of the taper rate depends on patient capacity to tolerate withdrawal symptoms, as well as the dose and duration of benzodiazepine use. Some patients may require longer tapers but prescribers should set clear and realistic goals for decreases in dose.

Longer durations of use are associated with a higher likelihood of symptoms during the taper. Subjective benzodiazepine withdrawal symptoms during taper can worsen as the reduced dose reaches 25 percent of the initial dose prior to improving as the dose reaches zero [52,53].

There are limited data on the rate of inpatient benzodiazepine taper. In one small prospective study, 16 out of 23 patients on a mean dose of 150 mg of diazepam equivalent were successfully tapered off benzodiazepines in the inpatient setting [52]. A loading dose of diazepam equal to approximately 40 percent of their reported daily dose was followed by a taper of 10 percent per day. While this is a reasonable rate to taper, it should be noted that these patients were not followed up after discharge. For inpatient taper, we suggest that the taper be completed prior to discharge to prevent return to use related to withdrawal symptoms. (See 'Benzodiazepine withdrawal' above and 'Monitoring and symptom management' below.)

Clinicians should clearly convey the plan and schedule for tapering to the patient. (See "Benzodiazepine poisoning and withdrawal".)

Choice of benzodiazepine for taper — Options include directly tapering the benzodiazepine that the patient is already taking or switching the patient to a long-acting agent to complete the taper. Our approach is to switch patients who are using a single short-acting benzodiazepine to a long-acting benzodiazepine, typically diazepam or chlordiazepoxide, at an equivalent dose. For those who are on several benzodiazepines, we add up the total daily dose and switch to a

single long-acting agent at that equivalent dose. Dosing equivalencies are listed in the table (table 2).

There is no direct evidence that long-acting benzodiazepines perform better than short-acting benzodiazepines in a taper. However, short-acting benzodiazepines are associated with higher dropout rates from benzodiazepine discontinuation studies, worse "rebound" anxiety (eg, return of underlying anxiety symptoms after benzodiazepine discontinuation), and more severe withdrawal symptoms compared with long-acting benzodiazepines [27].

Other medication options — Several other agents have been evaluated to taper patients off benzodiazepines, but we do not routinely use them.

- Flumazenil, a benzodiazepine receptor antagonist/partial agonist, has shown early promise in limiting acute withdrawal symptoms and long-term sequelae of benzodiazepine withdrawal in benzodiazepine use disorder; however, further studies on dose, duration of infusion, and safety are needed [54-56]. As an intravenous medication, its use is also limited to the inpatient setting.

- Phenobarbital taper has historically been used for medically supervised benzodiazepine taper. While it appears to be effective, we do not recommend its use due to safety concerns, such as a narrow therapeutic index, and limited supporting data [57].

Adjunctive therapies (eg, antidepressants and mood stabilizers) have also been evaluated in combination with benzodiazepines during the taper but have a limited role in the absence of specific comorbidities. Meta-analyses are inconclusive regarding the effect of such adjunctive pharmacologic interventions on the success of medically supervised taper or on the frequency of withdrawal symptoms; overall, the quality of evidence for these interventions is low [58,59]. Populations studied in trials were heterogenous, and very few included only patients with benzodiazepine use disorder diagnosis.

Monitoring and symptom management — We recommend weekly sessions to monitor patients who are being tapered off of benzodiazepines in the outpatient setting. If patients cannot meet that frequently, we still limit prescriptions for the taper to a week supply to minimize potential overuse.

If physical symptoms such as anxiety, concentration difficulties, appetite changes, palpitations, restlessness, headache, tremor, or sweat on palms are noted (see 'Withdrawal' above), we favor returning to the dose prior to the most recent reduction and slowing down the rate of taper. As an example, if reducing diazepam from 20 mg daily to 10 mg daily precipitates tachycardia and

diaphoresis, we suggest increasing back to 20 mg daily and lowering to 15 mg instead of 10 mg the next week.

In inpatient settings, monitoring symptoms using a standardized scale such as the Clinical Institute Withdrawal Assessment-Benzodiazepines is recommended. In this case, a tapering dose can be adjusted or augmented according to a scheduled assessments of score.

Managing comorbidities — There is limited evidence that treating comorbidities can improve outcomes of benzodiazepine taper. Use of antidepressants and mood stabilizers has been described for commonly occurring symptoms such as mood instability, anxiety, and insomnia, though further studies are needed [60-62]. Further, evaluation and treatment of symptoms that the patient may have been self-treating with benzodiazepines is prudent to help prevent return to benzodiazepine use.

Depression or anxiety — For patients with pre-existing depression or anxiety, we recommend ongoing treatment and close monitoring of comorbid symptoms during medically supervised taper of benzodiazepines. Worsening depression or anxiety may affect the patient's ability to tolerate symptoms of withdrawal and may lead to early termination of planned taper and escalation of use of benzodiazepines. Management of depression and anxiety are discussed elsewhere. (See "Unipolar major depression in adults: Choosing initial treatment" and "Unipolar depression in adults: Treatment with antidepressant combinations" and "Generalized anxiety disorder in adults: Management" and "Comorbid anxiety and depression in adults: Epidemiology, clinical manifestations, and diagnosis".)

Insomnia — We suggest melatonin for treatment of subjective insomnia during benzodiazepine withdrawal. Melatonin has been shown in one small study to facilitate discontinuation of benzodiazepines while maintaining sleep quality during taper of benzodiazepines [63]. Limited evidence has supported the use of pregabalin on subjective sleep disturbance during withdrawal from long-term benzodiazepine use; however, this must be weighed against misuse potential [59,61,63-66]. (See "Overview of the treatment of insomnia in adults".)

Opioid use disorder — Benzodiazepine use is widely reported in individuals with opioid use disorder, including those on opioid agonist therapy. In patients with benzodiazepine use disorder who are receiving opioid agonist therapy, we suggest maintaining a stable dose of opioids throughout the benzodiazepine reduction period in order to prevent opioid withdrawal. The partial opioid agonist buprenorphine may carry a lower risk of respiratory suppression in combination with benzodiazepine than the full agonist methadone [67]. (See "Opioid use disorder: Pharmacologic management".)

Psychosocial augmentation — We suggest cognitive-behavioral therapy (CBT) for patients undergoing medically supervised taper of benzodiazepines. In a meta-analysis that included nine trials, adding CBT to a benzodiazepine taper resulted in higher rates of benzodiazepine discontinuation compared with taper alone at three-month follow-up (relative rate of effect 1.51, 95% CI 1.15-1.98) [68]. However, the effects were less certain at six months and longer.

CBT is the best studied psychosocial intervention in this context. Other options include relaxation training and education material, such as self-help books or tailored clinician letters, which have also been shown to improve benzodiazepine discontinuation rates compared with usual care [59,60,66,68-74]. These methods are discussed in detail elsewhere. (See "Substance use disorders: Psychosocial management".)

Prevention of recurrence — For patients who have successfully tapered off benzodiazepines, we continue counseling regarding the risks of benzodiazepine use disorder. We recommend avoiding therapeutic use of benzodiazepines in such patients. For those who do need benzodiazepine treatment for a different indication, we suggest careful evaluation of the indication for treatment, adherence to dosing suggestions, and timely discontinuation of treatment after four to six weeks [64]. Additionally, we favor referral to a mental health professional for those patients with psychiatric comorbidity. (See 'Risk factors' above.)

As above, prevention of recurrent benzodiazepine use disorder mainly consists of avoidance of benzodiazepines and psychosocial support. There are no randomized controlled trials that have specifically tested an intervention aimed at preventing return to use after successful benzodiazepine discontinuation.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Benzodiazepine use disorder and withdrawal".)

SUMMARY AND RECOMMENDATIONS

- **Prevalence** – The lifetime prevalence of benzodiazepine use disorder is less than 1 percent. Substance use disorder treatment admissions for benzodiazepines as the primary substance used have consistently risen over the past decade. Benzodiazepine-related treatment admissions, emergency department visits, and overdose deaths have also increased over that time. (See 'Epidemiology' above.)

- **Benzodiazepine use disorder** – Patients with a benzodiazepine use disorder may present with a range of severity. Milder cases may have no signs of benzodiazepine use or aberrant medication-taking behaviors only, while patients with greater severity may present with acute intoxication or benzodiazepine withdrawal. (See 'Clinical manifestations' above.)

  - **Symptoms** – Predominant signs or behaviors of benzodiazepine use disorder include taking larger amounts over a longer period than intended, unsuccessful efforts to control benzodiazepine use, use of benzodiazepines despite persistent resulting problems, and evidence of tolerance or withdrawal from benzodiazepine use. (See 'Benzodiazepine use disorder' above.)

  - **Intoxication** – Signs of benzodiazepine intoxication include slurred speech, incoordination, unsteady gait, and cognitive impairment (in particular, anterograde amnesia or the inability to create new memories). (See 'Intoxication' above.)

  - **Overdose** – Signs of benzodiazepine overdose include nystagmus, stupor or coma, and respiratory depression. (See 'Overdose' above.)

  - **Withdrawal** – Signs of benzodiazepine withdrawal include anxiety, autonomic hyperactivity, tremor, insomnia, and nausea or vomiting. More severe benzodiazepine withdrawal may lead to transient hallucinations, generalized tonic-clonic seizures, and delirium. (See 'Withdrawal' above.)

  - **Course** – Little is known about the natural history of benzodiazepine use disorder; the more severe form is believed to be a chronic, relapsing disorder similar to other substance use disorders. (See 'Course' above.)

- **Assessment** – When assessing a patient for benzodiazepine use disorder, we ask about a history of past substance use or treatment, benzodiazepine type being used, dose, average number of daily tablets consumed, duration of use, date of last use, and use of other substances with potential for misuse or dependence. (See 'Assessment' above.)

- **Treatment** – Treatment of benzodiazepine use disorder consists of safely tapering patients off of benzodiazepines and preventing return to use once the medications are fully discontinued. Tapering can occur in outpatient or inpatient settings. We suggest using a long-acting benzodiazepine rather than a short-acting benzodiazepine in the medically supervised taper of individuals with benzodiazepine use disorder (**Grade 2C**). (See 'Medically supervised taper' above.)

We suggest cognitive-behavioral therapy as adjunctive treatment for medically supervised taper of benzodiazepines in patients with benzodiazepine use disorder (**Grade 2B**). (See 'Psychosocial augmentation' above.)

We recommend weekly sessions to monitor patients who are being tapered off of benzodiazepines in the outpatient setting. If patients cannot meet that frequently, we still limit prescriptions for the taper to a week supply to minimize potential overuse. (See 'Monitoring and symptom management' above.)

Preventing return to use or recurrent disorder consists of avoidance of therapeutic use of benzodiazepines when possible, and psychosocial support. No pharmacotherapy has demonstrated efficacy. (See 'Prevention of recurrence' above.)

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