Sedative-, Hypnotic-, or Anxiolytic-Related Disorders

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Introduction

Sedative, hypnotic, and anxiolytic substances include benzodiazepines, barbiturates, and non-benzodiazepine hypnotics. Phenobarbital was introduced in 1912, but due to its potential for toxicity and abuse, was largely supplanted by the benzodiazepines, when chlordiazepoxide came into existence in the early 1960s [5, 13]. The non-benzodiazepines, the so-called Z-drugs, are a newer class, initially thought to occupy a lower level of abuse liability than benzodiazepines, though it has since been demonstrated that they too pose a significant risk of dependence.

The clearest indications for benzodiazepines are in panic disorder, generalized and social anxiety disorders, simple phobias, and for short-term use in acute anxiety and acute insomnia. They are also utilized as the core treatment of alcohol withdrawal in the inpatient setting. It has been estimated that up to 50% of regular benzodiazepine users will experience clinically significant signs of withdrawal with sudden discontinuation [21]. Dose-dependent side effects of benzodiazepines include drowsiness, lethargy, fatigue, sedation, disturbances in concentration and attention, development of dependence, and rebound of insomnia or anxiety after lowering doses [2]. The Z-drugs come with their own set of adverse experiences such as anterograde amnesia, somnambulism, difficulty acquiring new learning, agitation, and hallucinations [4]. Currently, benzodiazepines are considered relatively safe for short-term use in most populations, but their safety has not been established beyond two to four weeks of treatment.

The number of benzodiazepine prescriptions in the United States has increased substantially since the mid-1990s [1, 19]. Dependence develops in approximately half of patients who use benzodiazepines for longer than 1 month [6, 13]. High-risk groups for developing dependence include those with chronic pain syndromes,

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alcohol or opioid use disorders, chronic sleep disorders, or personality disorders [19]. Additionally, females have an elevated risk of dependence [4]. Among those prescribed benzodiazepines for psychiatric disorders, individuals with anxiety disorders are not as likely to develop use disorders compared to those with affective disorders [4]. Sedative-hypnotic use disorders can also be associated with other substance use disorders, as substance users will often turn to sedatives to mitigate undesirable side effects of other substances or to use synergistically with their primary substance of abuse for mood enhancement. For example, studies have shown that approximately 15–20% of alcoholic patients presenting for treatment may be abusing benzodiazepines [4].

Understanding the mechanism of action of benzodiazepines is critical to grasping their clinical effects, side effects, and pathways to development of a use disorder. The agents in the sedative-hypnotics class have similar mechanisms of action in that they bind to allosteric sites on the gamma-aminobutyric acid subtype A ($GABA_A$) receptor, increasing the frequency of the chloride channel opening. This results in enhancing the inhibitory effect of GABA, translating to the clinical effects of decreased anxiety, increased sedation, muscle relaxation, amnesia, hypnosis, and anticonvulsion [19]. Long-term benzodiazepine use leads to tolerance through downregulation of GABA receptors and upregulation of the excitatory glutamate system [11]. More recent findings show that benzodiazepines may increase the activity of dopaminergic neurons in the ventral tegmental area (VTA), indicating that benzodiazepines may have a mechanism in common with opioids in terms of dopamine release [19]. The benzodiazepines that have the greatest abuse potential have a quick onset of action due to their lipophilicity, enabling them to produce hedonic effects rapidly [6].

Within both the patient and clinician populations, there are barriers to recognizing patterns of misuse and thus diagnosing sedative-hypnotic use disorders. In contrast to opioid intoxication and alcohol withdrawal, benzodiazepines, when ingested alone or being withdrawn from, are rarely fatal. As a result, misuse of these benzodiazepines, in contrast to opioids or alcohol, does not often draw as intensive interventions and treatments. Additionally, sedative, hypnotic, and anxiolytic use disorders are often iatrogenic, arising in the setting of benzodiazepines being taken in doses within the therapeutic range, causing both the prescriber and patient to not view use patterns as problematic. Additionally, some clinicians believe that benzodiazepines are more effective than first-line pharmacologic and nonpharmacologic approaches for insomnia and anxiety, and certain individuals, in particular older people, are less willing to try alternative, more labor-intensive treatments such as cognitive behavioral therapy (CBT). This unwillingness to consider reducing or discontinuing benzodiazepines for an alternative treatment method, along with there being limited resources for alternative treatments such as CBT, leads to benzodiazepine use disorders going unaddressed [8, 15].

The clinical case in this chapter will illustrate many of the key points about benzodiazepine use disorder, highlighting the signs and symptoms of dependence and withdrawal. The case will also give cause for further discussion about how to

prescribe and taper benzodiazepines while being mindful of the challenges of achieving abstinence.

Clinical Case

Dr. Smith is a psychiatry resident in her second year of training, rotating through the Consultation-Liaison Psychiatry service at a hospital in a large urban area. On Dr. Smith's list of consults for the day is a 43-year-old woman, Maya, admitted to a general medicine floor for management of altered mental status. She has a history of generalized anxiety disorder, depression, and anorexia nervosa, in remission, but no significant past medical history. She has been treated by outpatient psychiatrists for a decade. When Maya started seeing her current outpatient psychiatrist two years ago, she was on a regimen consisting of multiple benzodiazepines, including alprazolam, clonazepam, and lorazepam (exact amounts unknown). Since being under the care of her current psychiatrist, Maya's medication regimen has been consolidated to alprazolam 1 mg daily and clonazepam 6.5 mg daily.

Maya was brought by ambulance to the hospital's emergency after her outpatient psychiatrist noticed that earlier that day, during their weekly virtual check-in appointment, Maya presented as disorganized, inattentive, and not oriented to time or place. Upon this evaluation, Maya slurred her speech, exhibited paranoid delusions (e.g., she accused her psychiatrist of posting about her on social media), and reported having not slept in three days. Per collateral from Maya's parents, who live in Florida, Maya started behaving bizarrely four days ago, when she sent several aggressively worded text messages to her father, which was uncharacteristic of her.

After Maya was admitted to the medicine floor, the primary team of doctors initiated an altered mental status workup, including a metabolic panel, ammonia level, carboxyhemoglobin level, and head imaging, none of which had pathological findings. Additionally, Maya's urine toxicology screen and blood alcohol level were insignificant. The primary team gave her fluids and placed orders for a Clinical Institute Withdrawal Assessment (CIWA) to be completed every four hours to monitor for benzodiazepine withdrawal.

When Dr. Smith first came to see Maya the day following her admission, Maya presented as a thin woman lying calmly in bed who appeared stated age, but was disheveled and displayed limited eye contact. Maya reported a "scared" mood and had an anxious affect. Her thought process was linear but vague. No paranoia, delusions, or perceptual disturbances were elicited in her thought content. She denied auditory and visual hallucinations. Maya explained that she had not taken her alprazolam or clonazepam in over a week because she had abruptly run out of pills and could not manage to get them refilled for unclear reasons. Maya did not recall sending text messages to her father or speaking with her psychiatrist the day she was brought to the emergency department.

Dr. Smith recommended starting Maya on clonazepam 1.5 mg every 8 h in the hospital, to be held for sedation, and keeping Maya on CIWA for benzodiazepine withdrawal precautions. After two days in the hospital, Maya became clearer and

cognitively intact. She denied using any illicit substances, though admitted that in the last few months she was drinking alone more often, consuming at least one or two glasses of wine most nights, and sometimes up to a bottle of wine on a weekend. She explained that the social isolation she was experiencing was making her anxious, so she took it upon herself to self-medicate with tablets of alprazolam and clonazepam every day. She recalled that approximately one day after she ran out of her benzodiazepine prescriptions, she began to experience heightened anxiety, irritability, and confusion. She described feeling as though she were in a fog and having an "out of body experience." During this time, she stopped running her usual daily six miles. Maya discussed multiple life stressors including her father's recent diagnosis with lymphoma, her dog's illness, migraines, and social isolation in the setting of the pandemic, compounded by the loss of her job in the setting of layoffs early in the pandemic. Her mother, who had arrived in the city by time of discharge, was planning on staying with her for at least the next couple of weeks. The discharge plan was for Maya to follow up with her outpatient psychiatrist the next day.

Discussion

Maya's initial presentation was consistent with delirium secondary to benzodiazepine withdrawal, in the setting of benzodiazepine use disorder. Within days of suddenly stopping her benzodiazepines, Maya experienced a concurrent acute change in mental status, marked by escalating confusion, disorientation, and memory impairment. This evolved into disorganization and frank psychosis, as evidenced by her paranoia that her psychiatrist was posting about her on social media. The differential diagnosis included benzodiazepine or alcohol acute intoxication, alcohol withdrawal, and unspecified psychosis.

Maya's delirious presentation was characteristic of the moderate-to-severe withdrawal that is usually experienced by individuals who abruptly stop taking medium-to-high doses of benzodiazepines after regularly taking them for at least two to six months. Maya's outpatient regimen of alprazolam 1 mg and clonazepam 6.5 mg daily, doses approximately equivalent to lorazepam 15 mg daily, was a high amount of benzodiazepines, relative to the average prescriptions of benzodiazepines. The severity and duration of withdrawal is multifactorial, depending upon the potency and half-life of the benzodiazepine, the amount taken, and the duration of use prior to discontinuation. Some sources suggest it may take as little as four weeks of regular use to develop withdrawal symptoms; others report that rebound insomnia can be seen after two weeks of daily use [7, 9]. With shorter half-life agents like alprazolam, symptoms can develop as early as 24 hours after discontinuation, and the severity of withdrawal peaks on average between one and three days. In contrast, for longer half-life agents like clonazepam, symptoms of withdrawal can begin later and peak as late as four to seven days after drug discontinuation [5]. For Maya, who was taking a combination of alprazolam and clonazepam, the onset of withdrawal symptoms is more difficult to predict, but based on her presentation, her withdrawal symptoms likely occurred within one or two days after sudden discontinuation. The

withdrawal from short-acting benzodiazepines tends to be experienced as more intense than that associated with long-acting benzodiazepines, but indeed, there is variability in the sensitivity of individuals to discontinuation. Variation among individuals is dependent upon several factors, including any that influence the metabolism of drugs, such as age and medical health. Furthermore, underlying psychopathology, for example, Maya's depression and anxiety, can elevate the severity of the withdrawal symptoms. Conversely, when benzodiazepines are administered for short periods and at therapeutic doses, the withdrawal syndrome is usually mild, consisting of anxiety, headache, insomnia, dysphoria, and tremor or muscle twitching. In individuals experiencing acute withdrawal like Maya, pharmacologic management is often recommended because of the risk of serious consequences, including seizures and delirium tremens. Thus, Maya was placed on standing benzodiazepines (clonazepam 1.5 mg every eight hours) as well as CIWA precautions, which would have also protected her had she been experiencing alcohol withdrawal, a syndrome that can mimic the appearance of benzodiazepine withdrawal. It is worth noting that the abrupt discontinuation of barbiturates, in contrast to that of benzodiazepines or alcohol, has the greatest propensity to result in severe symptoms, including grand mal seizures [7]. As such, barbiturates are considered less safe and tolerable than benzodiazepines, and thus the prescription of benzodiazepines has largely replaced that of barbiturates for inducing sleep and anxiolysis.

Maya's history of depression, anxiety, and an eating disorder made her vulnerable to developing benzodiazepine dependence. The risk of dependence on benzodiazepines is associated with a history of mental illness and with higher doses of drugs taken [10]. The greatest risk factors for benzodiazepine dependence include a longer duration of treatment with these agents, treatment at higher doses, and concurrent substance misuse [3, 12].

Among individuals who abuse substances, it is uncommon for benzodiazepines to be the primary drug of use [7]. Individuals with current or remote alcohol and/or opioid use disorders comprise two groups with high rates of benzodiazepine abuse-related problems. Concurrent use of other substances, such as opioids or stimulants, can conflate or exacerbate the benzodiazepine withdrawal and intoxication presentation, as their intoxication syndromes can present similarly with impaired motor performance and sedation. If a clinician suspects opioid use in a patient who has altered mental status, naloxone can be administered without any negative repercussions. Although Maya's blood alcohol level was negligible on her admission labs, her increased alcohol intake in recent months should be addressed in subsequent treatment to prevent a potentially fatal overdose if she were to combine alcohol with benzodiazepines. Such poor outcomes underscore the importance that clinicians screen for benzodiazepine use in patients with co-occurring substance use disorders [7].

Lower on the differential for Maya's clinical presentation was intoxication with benzodiazepines or alcohol, as well as other metabolic disturbances, given that her metabolic panel, blood alcohol level, and urine toxicology screen were unremarkable. Severe toxicity with benzodiazepines can manifest, in the most severe cases, as stupor, coma, respiratory arrest, or cardiovascular collapse [7]. Management in

severely intoxicated patients is largely supportive, with the goal of maintaining the airway. Flumazenil is indicated only in those with confirmed benzodiazepine toxicity who are losing consciousness; however, it has limited use due to its risk of precipitating seizures [5]. Mild-to-moderate acute toxicity of benzodiazepines—which can occur even within a therapeutic context of benzodiazepine use—is characterized by sedation, slurred speech, psychomotor impairment, ataxia, altered visuospatial skills, and memory problems [4]. Maya exhibited lapses in memory, but this was more likely secondary to her delirious state, not necessarily a result of benzodiazepine use. The cognitive side effects of benzodiazepines, such as difficulty with attention, concentration, and acquiring new learning, tend to be insidious, rather than acute [20]. Benzodiazepines, as well as Z-drugs, have the potential to produce acute anterograde amnesia; in fact, impairment of learning new information is a drawback of this class of medications. There is a multitude of documented cases of zolpidem and zaleplon, especially at high doses, being associated with bizarre behaviors like somnambulism and nocturnal eating, shopping, and driving. Tolerance can develop to some of these cognitive effects, but not in all patients, and not always to the same degree. Although benzodiazepines can contribute to cognitive impairment, the association between benzodiazepine use and late-life cognitive disorders such as dementia remains controversial [17].

Treatment

Benzodiazepine discontinuation plans are heterogeneous; the approach taken is largely determined by the severity of benzodiazepine dependence. Benzodiazepine discontinuation can be managed in either the inpatient setting, where rapid dose reduction may occur, or in the outpatient setting, with close monitoring and a slower taper over weeks to months. Individuals with medical comorbidities, comorbid use of other substances, high-dose sedative-hypnotic use, or extensive mental health issues are best managed in inpatient facilities for detoxification [19]. The outpatient setting is best suited for those with long-term use and physical dependence at therapeutic doses, as well as for individuals who do not have significant comorbid substance use disorders and can reliably present for outpatient appointments.

Prior to determining the discontinuation protocol in an individual, a thorough sedative-hypnotic history is recommended, encompassing the doses taken, the duration of use, and the overall clinical response to these agents throughout the course of use [7]. To complete this history, it is necessary to find out all of the sources from which the individual is obtaining benzodiazepines from, as some individuals may be using a combination of prescribed and non-prescribed benzodiazepines, the latter of which may be related to a form of diversion, such as taken from family members or friends or purchased off the street. It is key for the provider to be cognizant that the prescription monitoring database is not necessarily comprehensive and probe about other avenues of obtaining benzodiazepines. It is also imperative to know which other psychoactive substances are currently being taken, as other substances can conflate the withdrawal picture. This can be further ascertained with regular

drug screens at appointments. Prior to discontinuing, it is important to provide psychoeducation, including the reasons for discontinuation, the signs and symptoms likely to be experienced, and the pros and cons of the various withdrawal strategies.

The method of withdrawal considered to be most effective and safe features a fixed taper, usually occurring over a period ranging from 4 to 12 weeks [22]. The taper is extended weeks to months in order to prevent severe withdrawal symptoms such as seizures and delirium. If an individual is using multiple benzodiazepines, as was the case for Maya, the clinician can consolidate to a single agent. More specifically, the clinician may substitute short-acting benzodiazepines (e.g., alprazolam or lorazepam) for longer-acting benzodiazepines (e.g., chlordiazepoxide or clonazepam) at equivalent doses, since longer-acting benzodiazepines minimize the interdose withdrawal symptoms [19]. The dose can then be decreased on a weekly or every-other-week basis over the course of 4–12 weeks [5, 7]. Recommendations range from reducing the initial benzodiazepine dose by 50% approximately every week to reducing by between 10% and 25% every two weeks [19]. Prolonged reductions over many months should be avoided to prevent the withdrawal treatment from becoming the individual's "morbid focus" [14]. Lastly, the rate of withdrawal is often determined by the individuals' ability to tolerate symptoms, but generally, the first 50% of the taper is experienced as smoother and mildly symptomatic, in contrast to the last 50% of the taper [16, 18, 19]. If intolerable symptoms of withdrawal do occur, the dose can be increased slightly until the symptoms resolve. Following the development of intolerable withdrawal symptoms, subsequent dose reductions should be more conservative in terms of amount and speed of reduction [5].

Clinicians conducting benzodiazepine discontinuation should be prepared to manage the emergence of psychiatric disorders—such as insomnia or anxiety—during the withdrawal period. Concomitant psychopharmacotherapy for withdrawal lacks robust evidence, but is generally symptom-based. Medications to mitigate withdrawal symptoms include sleep-inducing agents such as mirtazapine and trazodone, as well as anxiolytic agents such as pregabalin, gabapentin, hydroxyzine, or diphenhydramine [19]. Individuals can also experience a state known as "pseudo-withdrawal," defined as "overinterpretation of symptoms secondary to the expectations of withdrawal" [11]. Additionally, individuals undergoing tapering may experience rebound symptoms, in which their pre-benzodiazepine symptoms of anxiety or insomnia return but are experienced more intensely than their original symptoms were [5]. It is key that clinicians counsel individuals about the variety of potential adverse responses during the withdrawal period and provide reassurance that rebound symptoms usually dissipate or return to original levels within weeks. Additionally, employing psychotherapeutic treatments, such as cognitive behavioral therapy, helps the individual manage psychosocial stress factors and likewise addresses situations that are high risk for relapse [19].

Although benzodiazepines are rarely the first-line treatment for anxiety and sleep disorders, when the first-line approaches fail to control symptoms, benzodiazepines should not be withheld. After trialing first-line treatment modalities, such as

cognitive behavioral therapy, group therapy, relaxation therapy, stress management, antidepressants, and buspirone, benzodiazepines may be considered as adjunctive treatments for individuals experiencing refractory anxiety, panic, or phobias, at least for the short term. Particularly important for the aging and elderly in these cases, the goal when administering benzodiazepines is to use the lowest possible dose for the shortest period of time [7]. However, for individuals with current or history of substance use disorder, benzodiazepines should be avoided at all costs due to the higher risk of fatal overdose. If there is uncertainty about how effective a benzodiazepine is for the refractory symptoms once the individual begins taking it, a brief taper can be tried to determine whether continued administration of the benzodiazepine is indeed indicated [16]. When selecting a benzodiazepine agent, one can consider both the potency and pharmacokinetics (e.g., speed of onset and duration of action of the agent). Clinicians should aim to prescribe the lowest potency and longest-acting agents (e.g., clonazepam instead of alprazolam) at the lowest effective doses, because these qualities decrease the abuse potential. See Table 8.1 for a list of commonly used benzodiazepines, their half-lives, and dose equivalencies. In the outpatient setting, clinicians typically prescribe to achieve a steady state, so the critical variable to consider when selecting a benzodiazepine is elimination half-life. In contrast, in the emergency setting, the critical variable is the distribution half-life, with the goal being fastest onset of action.

In order to prevent iatrogenic benzodiazepine dependence when prescribing benzodiazepines, clinicians can check the state's prescription drug monitoring program, available in the vast majority of states in the United States, as this helps to avoid situations in which multiple providers are prescribing controlled substances. Further, clinicians can educate individuals about the regulation of benzodiazepines, specifically about the policies of no early refills and no prescriptions for benzodiazepines from multiple physicians. See Table 8.2 for a list of signs and symptoms of benzodiazepine use disorder. Furthermore, providers should explain that benzodiazepines are viewed as short-term therapies, the need for which will be re-evaluated at frequent intervals and be discontinued as soon as clinical symptoms improve or if the indication changes [7]. In situations that allow for it, family members can be educated about the risks of combining benzodiazepines with opioids or alcohol, since family members are often the first to recognize misuse.

Table 8.1 Benzodiazepine doses and equivalencies

Benzodiazepine	Onset after oral dose	Distribution half-life	Elimination half-life (h)	Dose equivalency
Diazepam (Valium)	Fastest	Fast	Slow (30–100 h)	5 mg
Lorazepam (Ativan)	Fast (IV), intermediate (PO)	Intermediate	Fast (10–20 h)	1 mg
Alprazolam (Xanax)	Intermediate-fast	Intermediate	Fast (6–20 h)	0.5 mg
Clonazepam (Klonopin)	Intermediate	Intermediate	Intermediate (18–50 h)	0.25 mg

Table 8.2 Signs and symptoms of sedative-, hypnotic-, and anxiolytic-related use disorders

History of sedative overdose
History of or current prescription misuse
History of taking benzodiazepines for years, especially with history of increasing dose instead of tapering
History of "doctor shopping" as evidenced by multiple providers listed in prescription monitoring database
History of emergency room visits for prescriptions
Concurrent substance misuse
Patient initially reporting improvement in anxiety symptoms and at a later date seeking to increase dose for anxiety
Patient reporting lost or stolen prescriptions >1 time
Patient refusal to accept alternative non-benzodiazepine treatments (e.g., buspirone, pregabalin, antidepressant, hydroxyzine, CBT) for anxiety

Conclusion

Sedative-, hypnotic, and anxiolytic-related disorders can develop in a variety of individuals, including those taking them at therapeutic doses for anxiety or phobia disorders, as well as those seeking them for different motives, such as mood enhancement or to mitigate unwanted side effects from other substance misuse. The withdrawal symptoms are often experienced as unpleasant if not intolerable, and a monitored discontinuation protocol is the optimal management for long-term success in overcoming a use disorder. Individuals taking these agents must be educated about the signs of dependence and symptoms of withdrawal prior to initiating their use. If the medications are prescribed at reasonable doses for limited periods of time, sedative hypnotics can be used safely and effectively to treat severe anxiety, panic, and phobia disorders.

Key Points

- For individuals prescribed with benzodiazepines, the continued need for these medications should be reassessed on a regular basis.
- Benzodiazepine withdrawal can be inadvertently initiated by a physician due to concerns of misuse, dependence, or co-occurring substance use disorders.
- For discontinuation of benzodiazepines, the consensus is a slow taper over a period of 4–12 weeks, largely dependent upon the individual's ability to tolerate dose reduction.
- Clinicians should discuss the risks in prescribing sedative hypnotics, such as dependence and withdrawal, and counsel individuals about benzodiazepines' potentially lethal interactions with other substances such as opioids and alcohol.

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