

BENZODIAZEPINES

ABSTRACT

Benzodiazepines are used as anticonvulsants, anxiolytics, hypnotics, and muscle relaxers. Because these drugs are highly effective, they are widely prescribed and used. Benzodiazepine medication are considered a controlled substance with significant risk of developing a substance use and addiction disorder. Additionally, there are significant drug-drug interactions with the combined use of benzodiazepines and medications used to treat mental illness, such as antipsychotic drugs, that clinicians should be aware of during crisis interventions. The basic pharmacology of benzodiazepines, benzodiazepine use disorder, withdrawal, and overdose, as well as treatment are discussed.

Introduction

The first benzodiazepine, chlordiazepoxide, was commercially introduced in 1960, and benzodiazepines continue to be widely used for a variety of medical conditions and procedures. Common name brands include lorazepam, diazepam and midazolam, which are typically provided during procedural sedation. Benzodiazepines are obtainable in different formulations ranging from intranasal, oral and parenterally by muscle or venous injection. When benzodiazepines are prescribed to manage severe anxiety or panic disorders there is a significant risk of a substance use disorder and addiction. Patients should be educated on this risk and screened to prevent addiction from developing.

Basic Pharmacology Of Benzodiazepines

The primary mechanism of action of the benzodiazepines is binding to γ -aminobutyric acid (GABA) type A receptors.^{1,2} GABA is the major inhibitory neurotransmitter, and there are GABAergic neurons distributed throughout the central nervous system. GABA is released from pre-synaptic neurons and then binds to one of two types of GABA receptors on post-synaptic cell membranes, GABA-A or GABA-B.

Binding of GABA to a GABA-A receptor increases the movement of chloride ions into the cell; binding of GABA to a GABA-B receptor increases the movement of potassium ions into the cell. In either case the post-synaptic cell is hyperpolarized and is less able to respond to an action potential or initiate an action potential, hence the neuroinhibitory actions of GABA.³ The benzodiazepines bind to GABA-A receptors and this increases the receptors' affinity for GABA and produces their pharmacological effects.^{1,2}

The benzodiazepines are prescribed as anxiolytics, hypnotics, and sedatives, and are used as muscle relaxants, for emergency treatment of generalized seizures, and as adjuncts to anesthesia. There are currently thirteen benzodiazepines that are available in the United States, and they are listed in Table 1 (the generic name is followed by the brand name). The benzodiazepines are controlled substances and are classified as Schedule IV medications. Controlled substances are drugs that have the potential for a substance use and addiction disorder, illegal diversion and sale.

Table 1: Benzodiazepines

Alprazolam (Xanax)
Chlordiazepoxide (Librium)
Clobazam (Onfi)
Clonazepam (Klonopin)
Clorazepate (Tranxene)
Diazepam (Valium)
Estazolam (ProSom)
Flurazepam (Dalmane)
Lorazepam (Ativan)
Midazolam (Versed)
Oxazepam (Serax)
Temazepam (Restoril)
Triazolam (Halcion)

The benzodiazepines are available as oral solution and tablets, solution for injection, intramuscular (IM) or intravenous (IV), and rectal gels. They are often categorized into three groups, based on the duration of the half-life, as short-acting (*i.e.*, triazolam), intermediate-acting (*i.e.*, alprazolam), and long-acting (*i.e.*, diazepam).¹ Common adverse effects of the benzodiazepines include (but are not limited to) drowsiness, fatigue, and sedation.¹ Elderly patients may develop a paradoxical reaction from a benzodiazepine and become agitated and have psychomotor restlessness, but this adverse effect rarely occurs.⁴

Benzodiazepines should not be used if the patient has angle-closure glaucoma, ataxia, chronic respiratory insufficiency, myasthenia gravis, sleep apnea, spinal and cerebellar ataxia, or intoxication with a central nervous system (CNS) depressant medication.¹

Benzodiazepine Use And Addiction Disorder

Benzodiazepine use and addiction disorder involves a pattern of drug use that is problematic in that the patient's use of the drug is recurrent, causes significant clinical and functional impairment, has the potential to cause serious health problems, and has the potential to and often does result in the inability to fulfill occupational, personal, and social responsibilities.⁵ A sedative, hypnotic, anxiolytic use and addiction disorder can be said to be present if the following Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria are met. Substance use disorders are categorized in the DSM-5 as mild, moderate, or severe. The diagnosis requires that at least two of the criteria are met.⁶

DSM-5 Criteria

The DSM-5 definition of a benzodiazepine use and addiction disorder is: 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.

- Sedatives, hypnotics, or anxiolytics are often taken in larger amounts or over a longer period than was intended.
- A persistent desire or unsuccessful efforts to cut down or control sedative, hypnotic, or anxiolytic use.
- A great deal of time is spent in activities necessary to obtain the sedative, hypnotic, or anxiolytic; and to use the sedative, hypnotic, or anxiolytic, or recover from its effects.
- Craving, or a strong desire or urge to use the sedative, hypnotic, or anxiolytic.
- Recurrent sedative, hypnotic, or anxiolytic use resulting in a failure to fulfill major role obligations at work, school, or home.

- 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.
- Important social, occupational, or recreational activities are given up or reduced because of sedative, hypnotic, or anxiolytic use.
- Recurrent sedative, hypnotic, or anxiolytic use in situations in which it is physically hazardous.
- 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.
- Tolerance.
- Withdrawal.

Tolerance and withdrawal are not necessary criteria if the patient is taking the sedative, hypnotic, or anxiolytic under medical supervision. A *mild* disorder has the presence of two to three of the criteria, a *moderate* disorder has the presence of four to five, and a *severe* disorder has the presence of six or more criteria.

Incidence

Accurate data about benzodiazepine use disorder is not available, but Woo (2017) stated that "... estimates suggest a lifetime prevalence of benzodiazepine use disorder of somewhat less than 1 percent."⁷ In addition, there is evidence suggesting that conditions leading to benzodiazepine use disorder have become more common. Admissions for substance use in which benzodiazepines were the primary drug increased by 109% from 2003 to 2013, and⁸ from 2004 to 2011 the number of visits to emergency rooms for non-medical use of benzodiazepines increased 149%.⁹

Etiology

As with other substance use disorders, the pathophysiology of benzodiazepine use disorder is not completely understood, but the benzodiazepines act in the same way (an increase in dopamine transmission) and in the same areas of the brains as do other addictive drugs.^{1,7} During screening of a substance use disorder, clinicians need to evaluate patients specifically for their history of benzodiazepine use, prior treatments, and use of addictive substances by the patient and/or close family members. Also, a history of patient uncooperativeness to be compliant with prescribing orders and requests for frequent refills should be a red flag to clinicians.

Addicted patients will require increasing amounts of benzodiazepines regardless of how they consume the drug. While online databases help clinicians that are prescribing benzodiazepines and pharmacists dispensing them, benzodiazepine use and addiction disorder is a growing national health problem and clinicians need to be constantly observant and intervene appropriately when a benzodiazepine addiction is suspected or confirmed. There is considerably more clarity about patient and situational risk factors that predispose people to developing benzodiazepine use disorder. These risk factors are listed in Table 2.^{1,7,11,12}

Table 2: Risk Factors for Benzodiazepine Use Disorder

**Current use of an anti-depressant
High doses of benzodiazepines
Long duration of benzodiazepine use
Lower education level
Psychiatric comorbidities
Significant problem with insomnia**

A long duration of benzodiazepine use has been positively associated with benzodiazepine use and addiction disorder.^{1,7} There is no accepted definition of what constitutes long-term use of these drugs;¹ 6-12 months has been advanced as a definition of long-term use,¹⁰ but it should be noted that benzodiazepine use for 3 to 6 weeks may lead to physical cravings.^{1,13} Little is known about benzodiazepine tolerance, but it does appear that tolerance to the anticonvulsant and sedative effects can happen quickly, but tolerance to the amnesic effects and anxiolytic effects do not happen.¹⁴

Clinical Course

The DSM-5 criteria for benzodiazepine use disorder presents a clear outline of its clinical effects, but there is very little information - and no recent information - on the natural history of this substance use disorder. The consequences of long-term use (but not necessarily benzodiazepine use disorder) have been investigated. Long-term benzodiazepine use may cause an increase in mortality and a decrease in cognitive function but the data on these issues is conflicting.¹⁵⁻¹⁷

Benzodiazepine Withdrawal

Benzodiazepine withdrawal can begin within 2-3 three days after cessation of use and sometimes a bit longer, within 5-10 days.¹ The signs and symptoms of benzodiazepine withdrawal can be organized into two

categories, and these signs and symptoms can include (but are not limited to) neuropsychiatric and physical symptoms.^{1,13}

- *Neuropsychiatric*

Anxiety, confusion, delirium, delusions, depression, dysphoria, hallucinations, hyperacusis, irritability, memory impairment, nervousness, panic attacks, and sleep disturbances.

- *Physical*

Diaphoresis, elevated blood pressure and heart rate, dyspnea, headache, fasciculations, muscle spasms, nausea, seizures, tremor, and vomiting

When an addiction and withdrawal are suspected, clinicians should consider and rule out the existence of other substance use withdrawal, such as to alcohol and other sedative-hypnotics, such as, barbiturates. Importantly, when assessing a patient for a benzodiazepine use disorder, the clinical picture can be complicated by patients with undertreated anxiety or insomnia and distinguishing an appropriate request for treatment from those with aberrant medication use and symptoms related to withdrawal, as noted below in Table 3 that lists DSM-5 criteria for benzodiazepine withdrawal.⁶

Table 3: DSM-5 Criteria for Benzodiazepine Withdrawal

- A. Prolonged cessation of, or reduction of use of benzodiazepines.**
- B. Two or more of the following signs and symptoms that begin within several hours to several days after the cessation of, or reduction of benzodiazepine use.**
- **Anxiety**
 - **Autonomic hyperactivity, *i.e.*, diaphoresis, tachycardia**
 - **Grand mal seizures**
 - **Hand tremor**
 - **Insomnia**
 - **Nausea or vomiting**
 - **Psychomotor agitation**
 - **Transient auditory, tactile, or visual hallucinations or illusions**
- C. The signs/symptoms in criterion B cause clinically significant distress or impairment in occupational and social functioning.**
- D. These signs and symptoms of criterion B are caused by intoxication, a medical condition, another mental disorder, or withdrawal from another drug.**

Signs and Symptoms

The signs and symptoms and the general presentation of benzodiazepine withdrawal are nonspecific and unless it is confirmed that a patient has been taking a benzodiazepine, clinicians should consider other possible diagnoses,¹⁸ which are listed in Table 4.

As already mentioned, when patients are suspected to have, or are being evaluated for, a benzodiazepine use disorder they will often present with symptoms of anxiety and depression, irritability and possibly a labile mood, that can occur with other comorbid psychiatric and even medical conditions, and a comorbid condition should be ruled out. This comorbid condition could

include an underlying medical condition or multiple psychiatric DSM-5 diagnoses, such as comorbid thought and mood disorder or substance use and addiction. These conditions can complicate the diagnosis of an individual who may be going through acute withdrawal, as the symptoms can mimic a mood and thought disorder.

Table 4: Differential Diagnosis for Benzodiazepine Withdrawal

Acute hypoglycemia
Alcohol withdrawal
Anxiety
Depression
Epilepsy
Hepatic encephalopathy
Infection
Opioid withdrawal
Panic attack

The clinical picture of benzodiazepine withdrawal may be mild to severe, and severe benzodiazepine withdrawal has been associated with a high dose of benzodiazepines, oral use more so than injectable, a longer duration of use, a benzodiazepine with a short half-life, using multiple benzodiazepines, and patient issues such as anxiety, depression, other substance use disorders, and other mental disorders.¹⁸⁻²² Withdrawal from benzodiazepines can be acute and of relatively short duration and it can also be prolonged with a duration of 12 months or longer.^{13,18}

Treatment

There is comparatively little that has been written about the treatment of benzodiazepine withdrawal, and there is no standard method for treating

benzodiazepine use and addiction that is universally advocated or used.¹⁸ The current approaches to the treatment of benzodiazepine withdrawal can be divided into two basic approaches: 1) controlled tapering of the drug, and 2) pharmacologic intervention. With either approach psychotherapy can be used, as well. There appears to be more evidence and a preference for controlled tapering.

Controlled tapering can be done with the patient remaining at home or admitted to a hospital.^{1,13} If the circumstances are such that the patient is at risk for a severe withdrawal then the controlled tapering should be done in a hospital.¹ In either case the benzodiazepine dose should be gradually decreased over a period of 4 to 6 weeks;¹ a faster rate of tapering increases the risk for severe withdrawal symptoms.¹ Dose reductions of 10%-25% every two weeks and 50% per week have been recommended, but the rate at which the medication is withdrawn should be guided by the patient's response and ability to tolerate withdrawal symptoms.¹ Most patients will be able to complete the program in 4 to 8 weeks.¹ However, complete withdrawal may take months to years and these prolonged periods can reduce the chances that the patient will remain abstinent.¹³ A long-acting benzodiazepine can be used as part of the tapering program.²

Pharmacologic intervention for managing benzodiazepine withdrawal has been in use for many years. There are no medications that are approved for the treatment of benzodiazepine withdrawal and there is little in the way of evidence-based therapies.¹ Anticonvulsants, antidepressants, antihistamines, antipsychotics, barbiturates, beta-blockers, flumazenil, selective serotonin re-uptake inhibitors and other medications have been used to treat benzodiazepine withdrawal.^{1,13,18} Some of these medications are intended to provide symptomatic relief and others are used as a direct treatment for the

drug-induced disorder. None of these medications have been able to produce sustained success.²

Flumazenil is a competitive benzodiazepine receptor antagonist. It is categorized as an antidote and it has two labeled uses: 1) complete or partial reversal of sedation caused by a benzodiazepine in the setting of a patient receiving conscious sedation or general anesthesia; and, 2) treatment of benzodiazepine overdose. Flumazenil competitively inhibits the actions of benzodiazepines at the GABA/benzodiazepine receptor complex and, by doing so, will reverse the central nervous system depression caused by these drugs. Flumazenil is given intravenously and it has a very brief duration of action, 30-60 minutes.¹³

Using flumazenil to treat benzodiazepine withdrawal is not a new approach; the earliest article on the topic that could be found for the purposes of this discussion was published in 1992²³ and the latest article was published in 2017,²⁴ but a literature search found only 12 articles published on the topic. The most recent data from 2016 and 2017 is promising. Tamburin *et al.*, used low-dose subcutaneous delivery of flumazenil to treat 450 patients who were going through benzodiazepine withdrawal. Four patients had a seizure (0.9%) but 22 of the same patients (4.9%) had a seizure during previous attempts at withdrawal.²⁴ The subcutaneous and intravenous route and continuous subcutaneous infusion of flumazenil by use of a depot have been used to treat benzodiazepine withdrawal, but there are no studies that have directly compared one to another in terms of their effectiveness.

Benzodiazepine Overdose

Benzodiazepine overdose is very common. Benzodiazepines are one of the most common causes of death from drug overdose in the United States.^{25,26}

Benzodiazepines have also been associated with an increased risk for suicide attempts and completions.²⁷

Clinical Presentation

Fortunately, although benzodiazepine overdose is quite common serious effects and death from an overdose with a benzodiazepine alone is rare.^{2,28} In most cases, a patient who has taken an overdose of a benzodiazepine will have central nervous system depression, occasionally profound, but usually mild to moderate.² High doses can cause respiratory depression and occasionally the patient will be hypotensive.

Because the benzodiazepines rarely cause serious morbidity and because patients who overdose with these drugs frequently ingest another central nervous system depressant, it is prudent to rule out the presence of co-ingestants. The blood pressure, pulse, and temperature should be within normal limits and aside from central nervous system depressant effects, and there should be no abnormal findings in the physical examination.^{29,30}

Treatment

Treatment should include assessment and stabilization of the patient's airway, breathing, and circulation (ABCs). If the patient is unable to maintain his or her airway, and has significant respiratory depression, endotracheal intubation is appropriate.

Decontamination with activated charcoal (AC) would seldom be an appropriate intervention for a patient who has taken a benzodiazepine overdose. These drugs bind to AC but the benzodiazepines cause a relatively rapid onset of central nervous system depression, usually within 30 minutes to 2 hours after ingestion.²⁹

Nausea and vomiting is a common adverse effect of AC and a patient who is CNS-depressed is more likely to aspirate, so AC is unlikely to be needed. Gastric lavage is only used when a patient has taken a dangerous amount of a medication that is likely to cause serious morbidity or death, and whole bowel irrigation is only administered in a few specific poisoning situations.

Activated charcoal should be considered to be equivalent to any therapeutic intervention. There should be an indication for its use, its effectiveness should be assessed, it must be given within the proper time frame in relation to the ingestion, there should be no contraindications, the clinician should know or become familiar with its benefits and risks, the correct dose must be used, and, after giving activated charcoal, the patient must be observed for adverse effects. Activated charcoal should never be given to a patient simply because the patient has taken an overdose.

A history of the circumstances of the ingestion should be obtained, and a physical examination performed. Acetaminophen and salicylate levels should be measured in all patients who have taken a medication with the intent to cause self-harm. A urine drug screen (UDS) can be obtained, but it will only serve to confirm an ingestion; it will not provide information about how much was taken or when it was taken. In addition, many of the commonly used urine drug screens are sensitive to a metabolite that is produced by some of the benzodiazepines but not by many of the commonly prescribed and used benzodiazepines, such as alprazolam, clonazepam, and lorazepam,² so a false-negative UDS for benzodiazepines can occur after an overdose with those drugs.

Other laboratory tests or diagnostic tests like a 12-lead ECG can be done as needed; if the patient has an altered sensorium then at the least a blood

glucose level, a blood ethanol level, and oxygen saturation level should be measured. Blood tests can measure benzodiazepine levels, but the results would not be quickly returned and, regardless, they are not clinically useful. Symptomatic and supportive care is the mainstay of treatment of a benzodiazepine overdose. If a patient has taken a benzodiazepine alone, the patient may be discharged and sent home if after 4-6 hours of observation his or her clinical status and vital signs are normal, an appropriate psychiatric referral has been made, and the patient is going to a safe environment.²

Flumazenil

Flumazenil is an analogue of the benzodiazepines. It binds to the GABA receptors, displacing benzodiazepines from their receptor sites and preventing benzodiazepines from binding to the GABA receptors. Flumazenil reverses the sedation caused by benzodiazepines, and it has a labeled use for the treatment of benzodiazepine overdose. Flumazenil does not reverse the effects of other drugs that bind to GABA receptors, for example, barbiturates and ethanol.

Using flumazenil for a CNS-depressed patient who has taken an overdose of a benzodiazepine would seem intuitive, especially if reversing the sedation will make endotracheal intubation unnecessary. However, flumazenil is rarely indicated for treating benzodiazepine overdose and its use can be harmful rather than helpful.^{2,28} The reasons for this depend on the flumazenil itself and on the circumstances that are often typical of an overdose.

Flumazenil has a short half-life, approximately 50 minutes, shorter than the half-life of most benzodiazepines and shorter than the duration of CNS

depression that is typical of a benzodiazepine overdose.²⁸ Repeat administration of flumazenil might be needed,^{2,28,31} and this would expose the patient to some of the risks outlined below.

Many people will take an overdose of a medication that is prescribed for them, and this includes patients who are addicted to benzodiazepine. Administering flumazenil to a benzodiazepine addicted patient can initiate acute withdrawal^{28,31} and this can cause serious effects like ventricular arrhythmias and seizures.²⁸

Flumazenil does not reverse respiratory depression caused by benzodiazepine overdose.² Central nervous system depression is more visible and more dramatic than respiratory depression, but the latter is more dangerous. Mixed overdoses are common, and the patient with a benzodiazepine overdose may have taken another drug that is seizure-genic.

Benzodiazepines are almost always the first choice for treating drug-induced seizures but if flumazenil has been administered they would not be effective. The risk of seizures when flumazenil is given empirically to patients who have taken or were suspected to have taken a benzodiazepine overdose has been investigated. Small studies (23 patients) reported that none of the patients given flumazenil had a seizure,³² but several literature reviews, for example, Penninga *et al.*, in 2016, found that empirical use of flumazenil was associated with a significant incidence of serious adverse effects, the most common being seizures and supraventricular arrhythmias.^{31,33}

Not all benzodiazepine overdose patients who receive flumazenil have a seizure or a serious adverse effect, and those events may only happen if the patient is at risk for serious adverse effects from flumazenil, for example,

patients who have taken a mixed overdose or are addicted to benzodiazepines. If that were true, then flumazenil could be safe for who had taken a benzodiazepine overdose, but the obvious difficulty would be accurately and consistently identifying patients who are not high-risk.

Case Study: Benzodiazepine Drug-Drug Interaction

A young 27-year old male with schizophrenia disorder, paranoid, bipolar type, had been residing in a hospital psychiatric unit while receiving long-term involuntary treatment. He carried other diagnoses of attention deficit hyperactivity disorder (ADHD), combined type, age 5 years, autism spectrum age disorder, age 8, depression, age 8, general anxiety disorder, age 8, and had developed medical conditions over the past several years of gastrointestinal esophageal reflux disease (GERD) and constipation, medication induced; by age 18 he was diagnosed with schizophrenia disorder, severe, paranoid and bipolar type. He was identified as being partially remitted with history of multiple failed trials of psychotropic medication, and his primary psychiatric symptoms included anxiety, panic, irritability, depression, delusional thought, hallucinations, hostility, aggression, and suicidal ideation.

The patient had received multiple combined treatment approaches to bring his symptoms under control, including intensive psychotherapy involving individual sessions and family sessions. After several failed trials of mood stabilizer and antipsychotic medications, he was started on a trial of clozapine for psychosis and lithium for mood dysregulation. Prior medications trialed included topiramate, divalproex, prolixin (oral and then decanoate), haloperidol, olanzapine, aripiprazole, ziprasidone, risperidone, methylphenidate, and atomoxetine. For severe impulsive aggressive behaviors that co-occurred with anxiety and panic he had also been treated

with catapres and propranolol that showed some benefit to control impulsivity as well as periodic hand tremors. While taking these varied medications, he continued to experience episodes of severe anxiety and panic associated with cycling mood and thought disorder including delusional and hallucinatory behavior.

The patient's decompensated condition would often lead to uncooperative and inappropriate responses to caregivers, severe aggression and at times assaultive actions or property destruction that required haloperidol with lorazepam as needed to help calm him, and to allow him the ability to endorse for safe behavior with a credible plan for safety. He was first offered haloperidol and lorazepam, combined, orally with an involuntary medication order approved by a medical review board to administer medication intramuscularly for escalated and dangerous conduct if he refused oral medication to control severe symptoms.

The patient would often refuse oral medication when escalated and became very disruptive, and he was unable to redirect from severe aggressive conduct, and would require emergency medication intramuscularly with a brief restraint/seclusion intervention to ensure the safety of all involved in his psychiatric and medical care. At times the patient was so dysregulated, he would require 4-point body restraints to control psychotic rage.

During an evening shift, the patient began to escalate, yelling loudly, banging on the walls, threatening to kill staff, and throwing objects in the direction of staff standing nearby. He was yelling that he could see a man standing outside his room window facing the hospital parking lot, and thought he was trying to enter his room. At the same time, he could hear his mother's voice although his mother resided in a distant location to the

hospital. He manifested somatic ideation of feeling odd sensations and thought he was “dead”. His speech was rambling although understandable and coherent and pressured. After multiple attempts to engage with the patient and to redirect him to avoid a crisis medication intervention, staff eventually called a facility code for security staff and other staff trained to respond from designated hospital locations to arrive on the unit, and to emergently contain the patient, because it was believed the patient would physically harm either himself or attending staff.

Just prior to this event, the patient had received a routine evening dose of clozapine 300 mg, which was in addition to his earlier morning dose of clozapine 300 mg for a total daily dose of 600 mg. A recent clozapine serum level was 350 ng/ml after the initial month of starting and titrating the patient’s clozapine dose. He received a baseline electrocardiogram and complete blood count (CBC) with differential prior to initiating clozapine and the CBC with differential was performed weekly during the initiation of clozapine. The patient’s EKG showed a normal sinus rhythm and CBC was unremarkable; the platelet count and absolute neutrophil count (ANC) remained within normal limits. The patient had reported expected side effects of constipation and of feeling tired but was otherwise evaluated as tolerating clozapine without serious adverse effects.

The emergency medication in the patient’s routine order set to treat psychosis and to help him calm and return to safe behaviors included haloperidol 10 mg and lorazepam 2 mg combined, administered intramuscularly. Shortly, after the haloperidol/lorazepam injection, the patient became diaphoretic, syncopal and hypotensive. He was given an emergency intravenous infusion and then was immediately transferred to the hospital emergency department for evaluation by an internal medicine

physician where he received flumazenil intravenously and was maintained on intravenous fluids.

While in the emergency department laboratory testing of a complete blood count and comprehensive metabolic panel were done that showed normal results. A 12-lead electrocardiogram test showed the patient had a normal sinus rhythm. The patient's mental status by the emergency physician was evaluated as oriented to person, place and situation, hypomanic and voicing some delusional thought, reporting to the emergency room staff "I died", however he was reported to show no overt hallucinatory behavior, and was calmer than he had previously appeared to the psychiatry team.

The patient recovered without further complications following administration of combination haloperidol and lorazepam to control aggressive behavior, and after being observed for six hours in the emergency department. He remained calm and cooperative, and returned to the psychiatric unit in physical stable condition.

The hospital department's clinical pharmacy director completed a review of the adverse event, and raised the following concerns to the treatment team:

- Haldol and clozapine both have a moderate risk electrocardiogram changes involving QTc prolongation
- Haldol and ativan both carry a significant risk of central nervous system (CNS) depression.

The Lexicomp drug-drug interaction also reported that:³⁹

- Lorazepam "*binds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the central nervous system, including the limbic system, reticular formation. Enhancement of*

the inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization."

- Clozapine is an antipsychotic medication also with significant CNS and cardiac side effects. Given with benzodiazepines, clozapine *"may enhance the adverse/toxic effect"* of clozapine, and clinicians should *"consider decreasing the dose of (or possibly discontinuing) benzodiazepines prior to initiating clozapine"* and consider therapy modification. Additionally, clozapine was associated with *"QT prolongation and ventricular arrhythmias"* and the pharmacy department recommended cautious use for patients with *"conditions that may increase the risk of QT prolongation."*

The pharmacy also recommended that clinicians managing the patient's medication consider obtaining a repeat electrocardiogram and a repeat serum chemistry panel because of the combination antipsychotic medication being prescribed.

With regard to the combined use of clozapine and lorazepam, the pharmacy quality review included a recommendation to reduce or discontinue benzodiazepine use alongside clozapine administration in this specific patient. Significant physiological considerations included respiratory depression and hypotension with combined benzodiazepine and clozapine use, especially during the initial month of starting clozapine. The addition of haloperidol further complicated the patient's outcome because it also enhanced CNS depression combined with lorazepam.

No abnormality had been detected on the patient's electrocardiogram report from the emergency department, however, the pharmacy review of the incident included a recommendation of cautious use of haloperidol with clozapine, and the haloperidol dosing for psychosis and severe aggression was replaced with a second generation antipsychotic, Olanzapine, to be given with diphenhydramine, orally or intramuscularly, as needed for symptoms of psychosis and anxiety. Until the patient could be better stabilized on Clozapine, the clinical decision was made for all benzodiazepine drug use to be avoided. It was hypothesized that the patient was unable to tolerate the combination of benzodiazepine drugs with clozapine, so a warning was placed on the patient's record to avoid a similar incident.

Other possible side effects of combined clozapine and benzodiazepine use include hypersalivation, severe respiratory depression/arrest, hypotension, and unconsciousness. Some of these physical effects were reportedly observed during research studies involving some individuals within a few hours of clozapine drug initiation, and these were individuals otherwise stable on benzodiazepine drug treatment.³⁶⁻³⁸

There have been other studies reviewing the use of clozapine and a benzodiazepine, which reported no morbidity or fatality associated with this drug combination. Some researchers have reported the drug combination to be safe. Although such studies are based on limited data.

Discussion

In psychiatric practice, augmentation of antipsychotics with other medications is a controversial yet not uncommon method of treating chronic and severe mental illness. When an individual is showing a partial response to treatment, a combination of various drug categories may be trialed.

Anxiety and panic is a common symptom of individuals diagnosed along the schizophrenia spectrum.³⁵⁻³⁷ Such individuals will experience periods of feeling a loss of control, positive signs of schizophrenia such as hallucinations, and behavioral dysregulation that can include self-harming and suicidal thoughts. Aggressive conduct is not unexpected in individuals who hallucinate, which can lead to heightened anxiety, panic and unsafe interactions with others.

Haloperidol and lorazepam is a common emergency medication combination administered to psychiatric patients who show behavioral dysregulation and aggression.³⁶ When a patient begins to act unsafely in an inpatient setting, or when brought by crisis mental health personnel or law enforcement escorting the patient to a hospital emergency department, for evaluation and treatment, this is an actual true *emergency* that requires prompt attention. During a crisis intervention involving a psychiatrically unstable individual, rapid medication interventions may be done by attending clinicians, especially if the patient's history of medication treatment for schizophrenia indicates partial response to treatment, as in the patient discussed in this case.

Adjustments to a routine antipsychotic dose involving clozapine and/or adjunctive non-clozapine antipsychotic drugs may not always be possible during a crisis situation. A psychiatric emergency situation is similar to any other life threatening situation where serious harm can occur to the patient and to others without an immediate and rapid intervention to control a dangerous situation. For example, a patient with a stable physical response to a psychotropic medication regime may suddenly not physically tolerate their routine medications being administered, such as with a new titration of clozapine that increases the risk of cardiovascular and CNS adverse

responses when combined with other routine medication for episodic mood cycling and behavioral dysregulation. The treatment team needs to be aware of the potential for a serious adverse event and prepared to respond quickly.

Anxiety in patients diagnosed with schizophrenia is often a primary symptom in individuals with chronic and fixed thought and mood disorders. In this case example, the patient is experiencing anxiety induced by a delusional thought process. Also, studies have shown that anxiety in individuals with schizophrenia is more common in younger individuals than in those at a later age of schizophrenia onset. Anxiety has been identified as a common feature in the prodrome leading to a diagnosis of schizophrenia.³⁶ It is a very prevalent condition in individuals diagnosed with schizophrenia.

There have been both observational and open trials of panic disorders in individuals with schizophrenia. Treatment included alprazolam and diazepam with a reported reduction in the patient's anxiety level. While anxiety occurring due to an acute psychotic episode is expected to improve with proper treatment through use of an antipsychotic medication, if a patient becomes manic and aggressive then it would be appropriate to administer a benzodiazepine in combination with other emergency medication given.

Lorazepam 2 to 4 mg is typically given to patients in three to four divided doses. The drug may be titrated up to a target dose ranging from 3 to 8 mg per day, depending upon efficacy and tolerability, although doses as high as 24 mg per day have been reported.³⁶ Side effects include sedation and respiratory depression, and disinhibition has also been reported with benzodiazepine use.

Proper treatment before commencing benzodiazepine use in a patient with a

chronic mental illness would include obtaining a medical history, physical exam, review of the patient's medications and adherence, and laboratory testing to identify organic factors contributing to anxiety in patients. Laboratory testing should include a complete blood count, complete metabolic panel, and thyroid function tests.

Benzodiazepines for Mania and Aggression:

Benzodiazepine use for patients with mild to moderate manic or mixed mood episodes is considered a reasonable drug alternative, especially in treatment resistant individuals where multiple psychotropic drug trials have been used. Benzodiazepines are typically given as an adjunctive therapy for an anxiety disorder in patients with severe mood dysregulation. Although there have been mixed research reports, there have been study conclusions of moderate to marked improvement in patients diagnosed with mania who had received lorazepam.

When treating an anxiety disorder where there is a co-occurring mental illness such as schizophrenia, clinicians should proceed with treatment of the anxiety disorder with caution and they need to be aware of potential drug-drug interactions. Most treatment recommendations in the psychiatric literature suggest that combined benzodiazepine and antipsychotic drug administration is appropriate for individuals with a comorbid anxiety and panic disorder in the general population of individuals with a severe mental illness such as schizophrenia.³⁶⁻³⁸

Clearly, as in the case presented of the young male with schizophrenia who received an emergency combination dose of lorazepam and haloperidol close to the time of scheduled clozapine administration in the first month of an initial titration, close observation and monitoring is indicated. Moreover, a

quality review of the incident recommended avoiding benzodiazepine use with haloperidol where clozapine had recently been started.

Future Trends Of Benzodiazepine Use

The use of benzodiazepines in developed countries, such as the U.S., Canada, and Europe, show a higher rate of use among women compared with men, and in older individuals rather than in younger adults. Primary care clinicians and not psychiatrists prescribe the majority of benzodiazepines for patients. Interestingly, benzodiazepine-prescribing patterns in the United States are not as well-known as those occurring in Canada and European countries.³⁷

Less than 1 in 10 individuals in all age and gender groups reportedly used long-acting benzodiazepines that was prescribed by a psychiatrist. This was especially true of older adults using benzodiazepines, aged 65 to 80 years, who reportedly visited a psychiatrist less than other age groups. Yet, the percentage of individuals with long-term use increased with age from 33.5% of younger adults to 53.5% of older adults.³⁷

In the current research, clinical reasons why benzodiazepines are prescribed to older adults tend to suggest that insomnia and anxiety are the most common indications. The prevalence of insomnia increases with age.³⁷ Benzodiazepine use was approximately 3 times more prevalent in older than younger adults. This poses an increased risk of fall and bone fractures. The risk of benzodiazepine addiction in older adults also includes a concern of cognitive decline, especially since older adults tend to use benzodiazepines for the long-term.

Benzodiazepines are used to treat anxiety and insomnia, which increases

with age and poor health, depressed mood, and can be associated with respiratory symptoms. In practice, benzodiazepines are also commonly prescribed in combination with antidepressants for sleep disturbances or anxiety related to depression.³⁶⁻³⁸ Benzodiazepines continue to represent one of the most widely prescribed psychotropic medications for all medical and psychiatry fields. As newer psychoactive drugs come into wider and growing discussion, the use of combination benzodiazepine with other drugs has been reported to lose some of the attention of medical clinicians, although it continues to be widely prescribed as a whole.

Summary

Benzodiazepines are prescribed as anxiolytics, hypnotics, and sedatives, used as muscle relaxants, for emergency treatment of generalized seizures, and as adjuncts to anesthesia. Thirteen benzodiazepines are available in the United States and are classified as Schedule IV medications, controlled substances. The primary mechanism of action of the benzodiazepines is binding to γ -aminobutyric acid (GABA) type A receptors.

Benzodiazepines are widely prescribed. Some of the common adverse effects of the benzodiazepines include drowsiness, fatigue, and sedation. Individuals with a benzodiazepine use and addiction disorder has become a common problem in the United States, and they carry the risk of serious health and social problems. Risk factors for a benzodiazepine use disorder are current use of an antidepressant, high doses of benzodiazepines, a long duration of benzodiazepine use, lower education level, psychiatric comorbidities, and severe insomnia.

Withdrawal from benzodiazepine occurs approximately within 2-3 three days after drug cessation, or longer. Controlled tapering of a benzodiazepine is

the general recommendation when a person has developed an addiction. The taper can be done while the patient is at home or in the hospital, and the dose should be gradually lowered over 4 to 6 weeks to avoid severe withdrawal symptoms.

Benzodiazepine overdose is very common, however the incidence of death from an overdose when the drug is used by itself is rare. Treatment of a benzodiazepine overdose involves an initial assessment and stabilization of the patient's airway, breathing, and circulation (ABCs). The pharmacological management of benzodiazepine withdrawal includes flumazenil, which has an antagonist effect and competes at the GABA receptor sites. Symptomatic and supportive care during withdrawal is the mainstay of treatment.

Benzodiazepines are generally prescribed to manage severe anxiety or panic disorders and carry a significant risk of a substance use disorder and addiction. Patients should be educated on this risk and screened by their health clinicians to prevent the development of addiction.

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