Management of acute benzodiazepine intoxication and withdrawal in the Emergency department setting

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MANAGEMENT OF ACUTE BENZODIAZEPINE INTOXICATION AND WITHDRAWAL IN THE EMERGENCY DEPARTMENT SETTING

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Abbreviations

BZD – benzodiazepine

GABA – gamma-amino butyric acid

CT – computerized tomography

CK – creatine kinase

ALT – alanine transaminase

AST – aspartate aminotransferase

ALS – advanced life support

GCS – Glasgow coma scale

CBC – complete blood count

ABC – airway, breathing, circulation

ECG – electrocardiogram

NICE – National Institute for Health and Care Excellence

DSM-5 – Diagnostic and Statistical Manual of Mental Disorders: Fifth Edition

Contents

Summary

Karlo Matic

Title: MANAGEMENT OF ACUTE BENZODIAZEPINE INTOXICATION AND WITDRAWAL IN THE EMERGENCY DEPARTMENT SETTING

The last few decades have seen a rise in the prescribing and abuse of benzodiazepines (BZDs). Due to this, there has been an increase in emergency department visits involving drug intoxication with BZDs and withdrawal. Groups at risk are the elderly, pregnant women, children, and individuals with mental health disorders. Although neither of these presentations is typically fatal in BZD use alone, there have been reported fatal cases, along with a large number of fatal cases involving mixed drug intoxication with BZDs. The presentation of isolated BZD intoxication varies from patient to patient, but involves a suppression of the central nervous system, leading to symptoms such as slurred speech, double vision, nystagmus, ataxia, anterograde amnesia, balance/coordination issues, respiratory depression, and sedation. Comatose patients are at high risk for aspiration pneumonia and developing complications such as rhabdomyolysis. Management of BZD intoxication is typically done through supportive care and flumazenil (BZD antagonist) when specific criteria are met. Recent data in the medical community has shown that the use of flumazenil is limited and may cause more harm than benefit, due to increased seizure risk and withdrawal symptom presentation. BZD withdrawal manifests after a cessation or reduction in BZD use after prolonged or high dose exposure. Patients present with autonomic hyperactivity, tactile/visual hallucinations, anxiety, insomnia, nausea/vomiting, hand tremor, and possible grand-mal seizures. Management of BZD withdrawal is typically done through the use of BZDs and implementing a tapering regime involving BZDs to effectively manage symptoms over time. Previous studies have suggested that flumazenil may be of benefit to BZD withdrawal management since patients who have added flumazenil to a tapering regime demonstrated higher success rates in treatment compared to placebo-treated groups. As flumazenil use is typically reserved for patients with severe

respiratory depression, sedation, those with isolated BZD intoxication, and individuals who are not taking pro-convulsant drugs, the use of this BZD antagonist is very limited in use. Due to these factors, the management of BZD intoxication and withdrawal proves to be difficult as history and physical examinations may not give enough data to meet criteria for flumazenil use. Goals for reducing the presentation of BZD intoxication and withdrawal should be aimed at primary prevention. Even though benzodiazepine use should be limited at 2-4 weeks, many primary care physicians continue to prescribe BZDs to their patients for chronic use. Ultimately, this leads to an increased population of BZD abusers who are at risk for intoxication and withdrawal.

Keywords: benzodiazepine, emergency department, drug intoxication, withdrawal, flumazenil

Sažetak

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Naslov: OBRADA I LIJEČENJE AKUTNOG OTROVANJA BENZODIJAZEPINIMA I NJIHOVOG SUSTEZANJA U ODJELU HITNE MEDICINE

U zadnjih nekoliko desetljeća vidi se porast u propisivanju i zloupotrebi benzodiazepina (BZDs). Zbog ovoga, vidi se porast posjeta hitne službe uslijed trovanjem droge s benzodiazepinima i odvikavanjem droge. Rizične skupine su starije osobe, trudnice, djeca i osobe s poremećajima mentalnog zdravlja. Iako nijedna od ovih slučajeva nije tipično smrtonosna u samom korištenju BZD-a, zabilježeni su smtni slučajevi, zajedno s velikim brojem smtrnih slučajeva koji uključuju kombiniranu intoksikaciju lijekovima s BZD-om. Prikaz izoliranih intoksikacija s BZD-ima varira od pacijenta do pacijenta, ali uključuje suzbijanje središnjeg živčanog sustava, koji dovodi do simptoma kao što su nerazgovjetni govor, dvostruki vid, nistagmus, ataksija, anterogradna amnezija, problem s ravnotežom/koordinacijom, respiratorna depresija i sedacija. Komatozni pacijenti su kod visokog rizika od aspiracijske pneumonije, i razvoju komplikacija kao rabdomiloze. Liječene intoksikacije BZD-om obično se provodi putem potporne skrbi i flumazenilom (antagonist BZD-a) kada se zadovolje određene kriterije. Nedavni podaci u medicinskoj zajednici su pokazali da je uporaba flumazenila ograničena i može uzrokovati više štete nego koristi, zbog rizika od epileptičkog napada i simptoma odvikavanja. Odvikavanje BZD-a iskazuje se nakon prestanka ili smanjenja uporabe BZD-a nakon produžene ili visoke doze izloženosti. Pacijenti predstavljaju s autonomnom hiperaktivnošću, taktilnim/visualnim halucinacijama, anksioznošću, nesanicom, mučninom/povraćanjem, tremorom ruke i mogućim grand-mal epileptičkim napadajima. Liječenje odvikavanja BZD-a obično se postiže korištenjem BZD-a i primjenom uprave sužavanja lijeka (BZD-a) kako bi učinkovito smanjili simptome tijekom vremena. Prethodna istraživanja su predložili da se flumazenil može koristiti za liječenje odvikavanja BZD-a jer su pacijenti koji su dodali flumazenil u upravu sužavanja lijeka pokazali veću uspješnost u usporedbi sa skupinom pacijenta koje su primale placebo. Kako je upotreba

flumazenila obično rezervirana za pacijente s teškom respiratornom depresijom, sedacijom, izoliranom BZD-skom intoksikacijom i pacijentima koji ne uzimaju prokonvulzivne lijekove, uporaba ovog antagonista BZD-a je vrlo ograničena. Zbog toga se pokazalo da je liječenje intoksikacije i odvikavanje BZD-a teško, buduči da nema dovoljno značajnih podataka za ispunjavanje kriterija za uporabu flumazenila. Cilj smanjenja intoksikacije i simptoma odvikavanja BZD-a trebali bi biti usmjereni osnovnoj prevenciji. Iako bi uporaba benzodiazepina trebala biti ograničena na 2-4 tjedna, mnogi liječnici primarne zdrastvene zaštite i dalje propisuju BZD-e pacijentima za kroničnu upotrebu. Konačno, to dovodi do povećanja broja pacijenata koji zloupotrebljavaju BZD-e i stoga su izloženi riziku intoksikacije i simptoma odvikavanja BZD-a.

Ključne riječi: benzodiazepina, hitna služba, trovanje drogom, odvikavanje, flumazenil

Introduction/Epidemiology

Benzodiazepines (BZDs) represent one of the most prescribed and consumed drugs in the outpatient and inpatient setting. BZD use is seen highest in Canada, United States, Brazil, Japan, and many westernized countries in Europe. A Canadian study had demonstrated that BZDs are the 7th most prescribed pharmaceuticals, making up 4.1% of all prescriptions (1). The last few decades have seen a substantial increase in the prescription of benzodiazepines, with an even faster rate of emergency department visits involving intoxication with benzodiazepines (2). With mental health affecting roughly 1 in 6 individuals, the use of benzodiazepines has been a staple in providing relief for a large group of disorders. Anxiety disorders are the largest target disorders for the use of BZDs, with prevalence rates in Canada ranging from 5-12%. From treating anxiety disorders to sleep disorders, BZDs have a wide range of indications with minimal severe symptoms, compared to other drugs with similar indications, like phenobarbital (1). Although BZD intoxications only represent a very small proportion of emergency department visits, 31% of all fatal poisonings reported in the United States involved BZDs (2). These numbers are higher in other parts of the globe such as Pakistan where up to 80% of self poisoning cases involved the ingestion of BZDs (3). From 1995 – 2015, there has been a 141% increase in visits to the emergency department due to the abuse of BZDs (4). Data from Canada shows that BZDs are the second most abused drug, behind cannabis (excluding alcohol from the data) (1). Similar trends have been seen in Costa Rica. From 2007-2014, there were 5243 cases of benzodiazepine intoxication, in which only 53 of these cases were shown to be fatal (5). Women have a higher rate of use of BZDs and this is seen in the higher amount of females seen in BZD poisoning in comparison to males (5). Contrarily, a study in Mexico had demonstrated that men have greater dependence of BZDs. Age groups with the highest incidence of poisonings were seen from 30-44 years and fatal poisonings were seen highest in the age range from 45-59 years in Costa Rica (5). As chronic BZD use continues to be an on-going issue in our population, benzodiazepine withdrawal management becomes an important topic in health care. It has been reported that 15-44% of chronic BZD users have moderate to severe symptoms after discontinuation (6). Although benzodiazepine withdrawal is not typically managed in an emergency department setting, initial symptoms after cessation/reduction may result in an emergency department visit.

Groups at Risk

The largest vulnerable group to benzodiazepine dependence, overdose, and withdrawal is the elderly population. As individuals age, insomnia can be become an increasing problem that can significantly decrease the quality of life in any individual. Consequently, the satisfaction of older patients in inducing and managing sleep with BZDs is very high. The chronic use of these drugs in the elderly population results in severe withdrawal symptoms. As many of these patients may experience terrible withdrawal symptoms such as rebound insomnia, chronic users tend to develop a hypnotic-dependent insomnia, where they rely on the use of BZDs to be able to sleep. More importantly, the use of benzodiazepines in the elderly results in an increase in falls and decrease in cognitive functioning. As the elderly are frail and cannot assist themselves in falls, they are susceptible to fractures and the complications that these injuries can carry out. For these reasons, it is important for the overlooking physician to evaluate the benefits/cons to the use of these drugs in the elderly. It is normally recommended to discontinue use in the elderly to prevent these issues and allow for a return to psychomotor and cognitive baseline (1,7).

Other risk groups for benzodiazepine poisoning/withdrawal include pregnant woman (and their fetus), children, individuals with abuse disorders, and those with psychiatric disorders. The fetus of a pregnant woman is very vulnerable to the effects of BZD as neonates metabolize the drug slowly, allowing for the BZD levels to be elevated even 2 weeks after birth. The fetus is at risk for fetal intrauterine growth restriction and developing floppy baby syndrome later in life. Children in the pediatric intensive care unit settings are at risk with benzodiazepine use as the typical withdrawal symptoms shown can be masked by clinical signs of anxiousness, fear, and lack of sedation. Individuals, who have abuse disorders such as those with alcohol, are at risk for long term BZD use as it helps to control the symptoms of chronic depression and anxiety that are induced with long term alcohol use. Lastly, psychiatric patients are at risk for BZD overuse as they are at higher risk for drug dependent disorders (1,7).

Benzodiazepine pharmacology

Benzodiazepines were accidentally discovered by an Austrian man named Leo Sternbach in 1955. The first drug of its kind was chlordiazepoxide (Librium by its name on the market at the time) (6). Several years later, in 1963, the infamous diazepam (market name Valium) was discovered and released on the market (8). Benzodiazepines are a group of pharmaceutical drugs that possess sedative and anxiolytic effects. On a molecular level, BZDs act on y-aminobutyric acid (GABA)-a receptors, which act as one of the main inhibitory receptors in the central nervous system. These receptors normally respond to the presence of GABA, which is the most common inhibitory neurotransmitter in the central nervous system and is predominantly concentrated in the cortex and limbic systems. GABA is able to reduce excitation of neurons and produce an overall calming effect on the CNS. GABA-a receptors are ligand gated chloride channels that are comprised of two alpha subunits, 2 beta subunits, and one gamma subunit. These receptors have two different GABA binding sites and an additional binding site that is reserved for the binding of BZDs. The binding site for BZDs is situated specifically between the alpha and gamma subunits. Once the BZD binding site has been occupied, it induces a change in the conformational structure of the receptor, allowing for GABA to bind. The conformational change will also induce a change in the receptors chloride channel, leading to hyperpolarization of the cell and producing an overall inhibitory effect. Several drugs are able to produce effects at these GABA receptors through different mechanisms of action. BZDs increase the inhibitory effect by binding to the modulatory site between the alpha 1,2,3 or 5, and gamma subunits, leading to an increased frequency in opening of the ligand-gated chlorine channels (only in the presence of GABA). The alpha subunit subtypes are responsible for the noticeable physiological effects of BZDs. More specifically, the alpha 1 subunit is associated with the BZ1 receptor site, which is responsible for the sedation and amnesia effect that comes from BZDs. As these alpha-1subunits are present in 60% of GABA-a receptors, it is noticeable that some of the most common effects seen in BZD use are sedation and anterograde amnesia. The alpha-2 subunit is associated with the BZ2 receptor site and produces the anxiolytic and myorelaxant effects that BZDs produce. These BZ2 receptor sites on GABA-a receptors are concentrated in the limbic system, which most likely produces the anxiolytic effect. BZ2 receptor sites are also concentrated in the spinal cord and motor neurons, which likely reduces excitation of muscle fibers. Lastly, it has been shown that the alpha-5 subunit is responsible for the decreased in

cognitive function seen in those who take BZDs. It is important to note that each type of BZD interacts with these binding sites differently and in different locations of the CNS, ultimately producing different clinical effects (9).

There are several routes of BZD administration including oral, sublingual, intravenous, intranasal, intramuscular, or topically applied through a gel form. When ingested orally, BZDs are absorbed well through the gastrointestinal tract with little variation in distribution. Intravenous administration of BZDs results in a rapid distribution in the central nervous system. Diazepam in the intramuscular route has been shown to vary in absorption, but most often absorbs slowly and in a sporadic fashion. Contrarily, lorazepam in the intramuscular form is absorbed rapidly and completely (9). The process of elimination of BZDs starts with oxidative metabolism by cytochrome p450 enzymes and then finishing through conjugation with glucoronide. Ultimately, the drug is mainly excreted via urine. It is crucial to note that patients with liver disease may have toxicity from the use of long-acting BZDs such as diazepam as its metabolites are able to increase the duration and effects of BZD intake (8).

In regards to the BZDs that are used in clinical practice, they are often categorized by their half life and potency. These drugs may be short acting lasting from 1-12 hours, while those with long-half lives can last up to 250 hours. Some examples of short-acting BZDs are alprazolam, midazolam, and lorazepam. Diazepam and clonezepam are examples of long-acting BZDs. The potencies of BZDs are also important as the highly potent BZDs are able to produce greater therapeutic effects at a faster onset of action. Some examples of highly potent BZDs include alprazolam and clonazepam. Assessing the potency of a BZD is highly important when managing a patient with these drugs as BZDs with higher potency are associated with an increased chance of adverse effects. Patients may not tolerate the side effects of these high potent drugs and may request to switch to one of lower potency (8).

Flumazenil Pharmacology

Flumazenil is considered to be the antidote of BZD poisoning. It was first developed in 1980 by the company Hoffman-Laroche (10). This drug is a derivative of imidazobenzodiazepine, with its function being a neutral modulator antagonist at the binding site of GABA-a/BZD receptors (11).

Flumazenil is delivered to the system very well orally, but 25% of the drug is eliminated during the first pass phase in the liver (12). In the typical emergency department setting where a BZD overdose is seen, intravenous access is the preferred route of administration of flumazenil. Once an intravenous bolus of flumazenil is administered, its action lasts only from 30-60 minutes as this drug is metabolized quickly by hepatic metabolism. The onset of action is typically within the first two minutes, with 80% of the response coming within the first three minutes after administration. Peak of action is seen from 6 – 10 minutes. (13)

Benzodiazepine Intoxication

Presentation

Benzodiazepines have several different effects on the body with all of them mainly involving depression of the central nervous system. By enhancing the effect of GABA at GABA-a receptors, BZDs are able to produce sedation, reduce anxiety, act as a hypnotic, abort/decrease seizures, and also have a calming effect on muscle fibers producing relaxation (8). At even higher doses, BZDs can produce dissociation and anterograde amnesia. The presentation of BZD overdose can be evaluated through several measurements that can be calculated at sight of the patient. IV benzodiazepine poisoning has been shown to cause respiratory depression in certain cases. As this may be severe, calculation of a GCS score is crucial in understanding the concurrent steps in management. Physicians often follow the code of "intubate at eight", which acts as a useful and quick guideline for further management. GCS scores are done through assessment of a 15 point scoring system, with a minimum score of 3 (representing the worst outcome) and a maximum of 15 (representing the best outcome). Three categories are present for evaluation function based off of eye response, verbal response, and motor response (14).

In the case of isolated BZD poisoning, the presentation of the patient is usually not one that is fatal. A typical patient with BZD poisoning may arrive to the emergency department with slurred speech, double vision, nystagmus, ataxia, anterograde amnesia, and balance/coordination issues. All of these symptoms may vary in severity. One of the key features to isolated BZD poisoning is that normal vital signs are typical, despite the significant observable findings (8). In the case that there is mixed drug intoxication, there is a higher likelihood that cardiac abnormalities and

respiratory depression can be seen in these presentations which need to be evaluated for. These two adverse events are two of the most important clinic manifestations that can occur with BZD or BZD/mixed drug intoxication. Previous cases of severe BZD overdose showed patients who were comatose, hypotensive, bradycardic, and developed aspiration pneumonia. Some patients who are under heavy sedation from the overdose may develop rhabdomyolysis during this state, due to the direct contact pressure leading to ischemic muscle compression or by drug-induced rhabdomyolysis (14). Presentation of BZD overdose in children typically presents differently than in adults, with ataxia being the most prominent symptom. Studies have shown that ataxia is present in 90% of pediatric cases, while respiratory depression was a small concern in comparison with only 10% of cases having this presentation (8).

Diagnosis

History

Diagnosis of BZD intoxication can be done in various ways, but can often be confirmed through witnesses, family, friends, or a good clinical examination. Luckily, most isolated BZD intoxication cases do not result in a fully unconscious patient, allowing for a history that can sometimes be acquired by the patient themselves. If the patient or witness is able to confirm the drug that has been taken, management can be streamlined immediately for the offending agents. In certain cases, a family member or friend is not able to recall which medications the patient is taking. It can be crucial to obtain medical health record information from a family doctor as this can narrow down the suspected agents.

Physical

A retrospective study done in Serbia from 2010-2012 demonstrated that out of 387 patients with suspected BZD overdose, 293 had a GCS score from 13-15, which can be described as being somnolent. Out of the 387 patients, 46 had a GCS score from 9-12, which described these cases as stupor. The remaining 48 patients had a GCS score below 8, which labeled them as comatose. Based off of these findings, it can be suspected that most patients will present as somnolent. As mentioned previously, vital signs are typically stable, although it is necessary to take them as severe cases do report hypotension as a symptom. The same study in Serbia demonstrated that

8.26% percent of their patients in the study were hypotensive, making this finding less common, but still significant in the physical examination component of suspected BZD overdose. In combination with a proper history and the classic presentation findings in the physical exam, a conclusion of drug intoxication with BZD involvement can be diagnosed (14).

Diagnostic Studies

Laboratory studies can prove to be crucial in the diagnosis of BZD intoxication and assessing the current status of the patient. When the presenting patient is a female, it is wise to perform a pregnancy test, as this may change treatment options. In any acute emergency involving decreased consciousness, it is vital to perform a quick finger stick to check for blood glucose levels as hypoglycemic episodes can present this way and be easily treatable. When there is suspected fall injury associated with an acute poisoning presentation, a head CT may be beneficial to rule out any causes that may be contributing to a state of altered mental status. A CBC can determine hemoglobin levels, which may be decreased in an internal bleed that may have resulted from a fall injury associated with the BZD poisoning. As heavy sedation and drug poisoning may cause rhabdomyolysis, obtaining CK, AST, and ALT levels proves to be important to pursue further management, and prevent the potential consequences of this pathology. Arterial blood gas monitoring can provide lab values to a clinical picture of respiratory depression. A urine analysis may prove to be beneficial to evaluate for all possible suspects in the overdose presenting, but it does come with its limitations. In an acute setting, using a urine drug screen typically only tests positives for BZDs that are metabolized to oxazepam glucoronide. Due to this, BZD overdose cases with alprazolam, lorazepam, clonazepam, and midazolam, will not show up on the urine drug screen as this is not one of their metabolites. Even though the drug screen may not pinpoint the exact causative agent, it may assist in the overall diagnosis. Blood tests for BZD levels are not very significant in an acute presentation, but may assist in a final diagnosis. Often acute presentations of poisoning involve more than BZD ingestion and therefore, alcohol, aspirin, acetaminophen, and other common poisoning agents should be tested during the initial evaluation in the emergency setting. In rare cases, severe respiratory depression and contraindications to using mechanical ventilation may be present, leading to the need for flumazenil. This BZD antagonist is sometimes able to provide a diagnosis of BZD overdose in the case that suspected agent is not known by family members,

friends, etc… In order to use flumazenil in these patients, it is crucial to obtain a normal ECG from the patient as this drug can be known to precipitate cardiac arrhythmias. Furthermore, using flumazenil as a diagnostic tool can be problematic when the intoxication is due to a mixture of BZDs and pro-convulsant drugs, as its use can precipitate seizures in the individual and prove to be fatal in certain cases. For these reasons, it is contraindicated to use flumazenil as a diagnostic tool (15).

Management of Benzodiazepine Intoxication

Any individual who is presenting to the emergency department with a suspected drug poisoning is to be treated in a supportive fashion first and foremost. Overdose with drugs such as BZDs, opioids, and alcohol can present with full loss of consciousness with very low GCS scores. In these situations, it is important to evaluate the patient for stability. Advanced life support methods are to be assessed and evaluated as soon as the patient presents. Airways are to be patent and intubation be performed properly and quickly. Next, breathing is of significant importance as many of these drug intoxications result in respiratory depression. As the patient may not be able to breathe on their own, mechanical ventilation should be started in order to meet the patient's oxygen demands. Continuing with ALS, circulation needs to be assessed. In the case where circulation is compromised, it is necessary to establish intravenous lines early in the presentation where it may be easier to access veins. Once intravenous lines are established, a choice must be made of which fluid might be most beneficial, along with the amount of fluids that are to be given. Excessive fluids given to the patient may precipitate their condition and cause complications such as pulmonary edema. In some cases of shock, the patient may require increased circulation support with the use of vasopressors, such as vasopressin or norepinephrine. Many studies show that the use of activated charcoal may be beneficial in patients coming to the emergency department with unknown drug intoxication. Ensuring that the patient is stable with the basics of ALS is of upmost importance to keeping the patient alive while proper histories may be taken, further physical examinations, lab orders, and other diagnostic tests are processed. Many drugs that are involved in intoxication have an antidote that may be able to reverse all of the effects of poisoning. Examples include the use of naloxone in suspected opioid overdose or acetylcysteine in the case of acetaminophen overdose (16). As a

BZD antagonist, the use of flumazenil has long been suspected as an appropriate antidote in BZD overdose. Throughout the last several decades, the use of flumazenil has been questioned due to the efficacy and safety (17).

The actual indications of flumazenil are quite limited. In the United Kingdom, the label on flumazenil states that it can be used to reverse sedative effects in BZD intoxication, typically in anesthesia or in the intensive care setting. One of the contraindications stated on the vial of flumazenil is mixed BZD poisoning with tri-cyclic antidepressants, due to antidepressant toxicity being masked by BZD effects (10). The use of flumazenil in the emergency setting in the case of BZD intoxication is problematic as it can prove to be beneficial in some situations, but also problematic in many others. According to the current NICE guidelines of self harm, flumazenil is a good choice in the presence of an individual who presents with BZD intoxication and fit the criteria for use. More specifically, those individuals who present with reduced consciousness in the suspicion of drug intoxication. Some other indications for the use of flumzenil include paradoxical-responses to midazolam during the loading phase of pre-operative anesthesia. As disinhibition occurs by midazolam, these rare responses may occur, causing agitation and erratic behaviour. Furthermore, during general anesthesia with propofol and/or sevofluorane, flumazenil is able to cause awakening in patients. An important indication for flumazenil may lie in the intensive care unit where patients require long midazolam infusions for mechanical ventilation. After long infusions of midazolam, diaphgram function and respiratory support decreases. IV infusions of flumazenil have shown to be able to reverse respiratory depression episodes in these cases (10).

Contraindications to the use of this BZD antagonist include individuals who are dependent on the use of BZDs. For example, a normal healthy individual who attempts to poison himself with his mother's alprazolam, and fits other indications, would be a candidate for the use of flumazenil in the emergency department setting. Furthermore, the use of flumazenil is contraindicated in individuals who have intoxicated themselves with other drugs at the same time. This proves to be a crucial fact as most of the self poisonings that present to the emergency department involve BZDs, but with the co-ingestion of other drugs. Some of these drugs include pro-convulsants, like tri-cyclic anti-depressants. Due to all of these factors, actually choosing flumazenil as an

agent in the management of BZD intoxication proves to be difficult with all of the contraindications and factors that would usually come in to play with a patient in the emergency department (18).

The most important argument against the use of flumazenil is the adverse effects that are associated with its use. Studies have shown that there is a higher incidence of adverse effects in groups treated with flumazenil against the placebo-treated group. The most common adverse effects in flumazenil use include gastrointestinal symptoms, agitation, and anxiety. Serious adverse effects from flumazenil include cardiac arrhythmias and seizures. As BZDs are known to increase seizure threshold, any antagonist to BZDs can reverse this effect and precipitate seizures in individuals who are vulnerable. In this study, serious adverse effects were reported to be supraventricular arrhythmias, unspecificed tachycardias, convulsions, multiple ventricular beats, and hypotensive events (17). Prior to using flumazenil in these cases, most countries require that you first contact a poison information service to evaluate the situation of flumazenil use. Furthermore, as many of these patients may end up in the intensive care unit for a period of time, it is important to assess the benefit-risk ratio of using flumazenil as there is a trade-off between increased seizures with flumazenil and a possibility of ventilator-associated injuries with increased respiratory depression (19).

Benzodiazepine Withdrawal

Presentation

BZD withdrawal is never typically considered to be an emergency case as it is something that can be timed and treated in an outpatient setting. In certain cases following intravenous sedation for prolonged periods of time in an in-patient setting, the patient may be brought to an intensive care unit setting where management can be performed. Although rare, when flumazenil is used in an emergency setting to antagonize a BZD overdose, BZD withdrawal symptoms can appear which may be initially managed in an emergency setting. Furthermore, emergency department visits may occur in individuals who have been using BZDs for more than 6 months, leading these people to have a high risk of seizures after abrupt discontinuation (20). Withdrawal symptoms are present in any individual who has a decline in tissue/blood concentration of a dependent

substance. The use of BZDs over a period longer than 3 weeks can lead to physical dependence of the drug, producing withdrawal symptoms after cessation (6). The symptoms of BZD withdrawal vary from patient to patient, and also depend heavily on the half-life of the BZD that has been taken. Factors related to the severity include high dosages of BZDs used prior, multiple BZDs, oral intake, long durations of use, BZDs with short half lives, and discontinuing BZDs without tapering management. Typically, the symptoms of withdrawal are split up into two different categories with the first category including anxiety and anxiety-related symptoms. The first group of symptoms in this category belong to those that present with psychological manifestations. Some of these symptoms include sleep disturbance, cognitive impairment, sensor hypersensitivity, anxiety, phobias, panics, mood disturbances, and other psychotic symptoms. The second group of symptoms in this category belong to those that present with physical symptoms. These symptoms include pain, muscle twitches, hyperventilation, spasms, bodily sensations, malaise, gastrointestinal manifestations, blurred vision, dry mouth, tremor, and headache. The second category of symptoms includes changes in perception. Individuals may present with hypersensitivity to stimuli including touch, pain, and sound. On the contrary, hyposensitivity to stimuli, such as taste and smell, has been reported. Dizziness, depersonalization, and abnormal body tingling also belong to this category. Lastly, a third category of withdrawal symptoms from BZDs may result in more serious events such as grand mal seizures, catatonic states, delirium, and other states related to psychosis (21).

The process of withdrawal from BZDs has been shown to be present in an acute and chronic phase. The initial acute phase can begin as early as 4 days after last intake and last up to a month long. The chronic phase is variable lasting longer than a month and sometimes can last longer than one year. The symptoms presenting with the withdrawal can vary in presentation, timing, and duration and can increase in severity with time, decrease in severity, or in some cases remain persistent for longer than a year (21).

Diagnosis

Diagnosis of BZD withdrawal is based off of criteria set out in the DSM-5. As the presentation between alcohol and BZD withdrawal share most features, they are grouped together in the DSM-5 and therefore, follow the same diagnostic criteria (Table 1) (21).

Table 1 – DSM-5 Criteria for Benzodiazepine and Alcohol Withdrawal	
Criteria A	A cessation or reduction of BZD/alcohol use
Criteria B – 2 or more present after cessation/reduction	- Autonomic hyperactivity (elevated HR, diaphoretic appearance, etc…) - Hand Tremor - Sleep Disturbance/Insomnia - Nausea/Vomiting - Hallucinations (tactile, auditory, visual) - Agitation - Anxiety - Grand Mal Seizures for BZDs, generalized tonic/clonic seizures for alcohol
Criteria C	If 2 or any more of the features in Criteria B are causing difficulties in overall function including work, social life, and other aspects to daily life
Criteria D	None of the presenting features are attributed to another pathology or withdrawal from another class of drugs

Modified from the Diagnostic and Statistical Manual of Mental Disorders: Fifth Edition

Management of Benzodiazepine Withdrawal

The management of BZD withdrawal begins with assessment of airways, breathing, circulation and performing ALS techniques in patients who need it. Once the criterion for diagnosis is met, management can be started with the use of benzodiazepines. Initially, diazepam at 5mg IV is to be repeated until severe symptoms from withdrawal are under control. Special care is to be taken with doses and duration of diazepam in order to prevent severe respiratory depression and/or sedation. If the withdrawal is due to cessation of orally ingested BZDs then it should be evaluated if the patient is a chronic BZD user or not. If the patient is using BZDs in chronic treatment management, then the BZD used should be initiated again and decreased in dose by 25% every 7 days. Patients, who are not chronically using BZDs, are recommended to use an intermediate-acting BZD such as oxazepam. The tapering protocol for the use of oxazepam recommends that if >100 mg is being taken, 50mg should be decreased every 2 days. If more than 50mg is being used, 25 mg is to be decreased every 2 days. If less than 50 mg is being used, then decrease 10 mg every 2 days. Lastly if less than 20 mg of oxazepam is initially being used, then the dose should be reduced by 5 mg every 2 days. Although the oral route of BZD withdrawal is more common, intravenous BZD use withdrawal is also still present. In these cases, it is important to start a BZD infusion through IV and slowly titrate the infusion until there

is a cessation of symptoms. Once symptom cessation is achieved, a dose reduction of 10% is to be done every 2 days. When possible, it is suggested that the patient be switched to an oral BZD for the rest of the tapering protocol. In the ICU setting where many patients are being administered IV benzodiazepenes, there is no current weaning protocol, but as long as the dosage of the BZD is reduced over a period of several days and not stopped immediately. In the intensive care unit setting, it may be beneficial to use a drug such as dexmedetomidine. This drug is ideal in these settings as it allows for a reduction in withdrawal symptoms from BZDs, without producing significant respiratory depression or heavy sedation. Several other drugs including several antidepressants, flumazenil, anti-convulsants, and B-blockers have been used in helping with the management of withdrawal, but with varying results amongst studies (21).

Use of flumazenil in Benzodiazepine Withdrawal Management

Traditionally, it has been shown that flumazenil is an effective drug for reversing sedation and respiratory depression in BZD intoxication, but recent studies have suggested that flumazenil may also be used for the management of withdrawal symptoms from BZD use. Flumazenil has been shown to be effective in conjuction with an oxazepam taper in managing withdrawal symptoms. The exact mechanism behind flumazenils benefit in these situations is currently unclear. It has been demonstrated that flumazenil has the ability to act as a positive allosteric modulator on GABA-a receptors that contain the alpha-6 subunit. The change in confirmation of the receptor along with its subunits may be the key for reversing the withdrawal state. The studies that have been conducted in regards to flumazenil use in BZD withdrawal, all demonstrated that the clinical effectiveness of the drug varied with different doses and routes of delivery (6).

Dosage and Delivery of Flumazenil in Withdrawal Syndrome

The various delivery modes of flumazenil have been studied throughout the last three decades. Previous studies from the 1990s showed physicians delivering 1.0 – 2.0 mg of flumazenil as an IV bolus over 1-3 hours (6). This regime had shown to effectively reduce withdrawal symptoms in patients who had discontinued BZDs after 1 month to 2 years. Individuals who continued to have persistent withdrawal symptoms had benefits from prolonged intake of flumazenil. A study done in 2002 was conducted to evaluate the benefit of using flumazenil in conjuction with an oxazepam taper vs. using a placebo with an oxazepam taper. Withdrawal symptoms, relapse rates, and treatment negligence were all decreased in the flumazenil group in comparison to the placebo group. This evidence suggests that the use of flumazenil is effective in treating withdrawal syndrome from BZDs, but there is still high evidence of increased seizures in groups being treated with flumazenil (6).

Non-pharmacological measures for benzodiazepine withdrawal

Although pharmacological measures for BZD withdrawal represent the staple of management, non-pharmacological measures are often implemented to increase withdrawal success and compliance to management. Immediate pharmacological treatment is essential in providing symptomatic relief for BZD withdrawal patients, but managing symptoms that persist for months to years may need the help of non-pharmacological measures. Cognitive behavioural therapy, group therapy, and family support plans have been shown to be effective in combination with pharmacological measures (22).

Issues with current management/Setbacks

The presentation of a benzodiazepine overdose varies in each patient in the emergency department. With the plethora of symptoms that may be present with overdose, it is crucial as a health care professional to recognize the key signs present. Sedation and respiratory depression are amongst the most serious events and patients may present with varying intensities. Due to these discrepancies between presentations, it can become difficult to choose what management

pathway would be most beneficial. The use of flumazenil in clinical practice continues to be a topic of controversy. The benefits of flumazenil have been seen through several studies, but many studies still demonstrate increased risks of seizures with use (23). As with any overdose, it is always a primary goal to achieve the ABCs of emergency care (12). With these supportive techniques, physicians can choose to administer drugs that may assist in decreasing any life threatening events. With the lack of studies analyzing the management of BZD overdose, it becomes difficult to produce guidelines that can statistically provide higher rates of success in all patient presentations.

One of the minor limitations of flumazenil use in the clinical and outpatient setting is its route of delivery. Typically, this drug is administered intravenously, but there are several setbacks with the use of this route. The maintenance of using IV lines can be extensive and provide time consuming tasks for health care workers. Additionally, the use of a line restricts the patient from having a larger range of mobility and precipitates discomfort that can be felt in any setting. These setbacks can discourage patient recovery and decrease compliance to the appropriate treatment that is needed. One of the possible routes to administration that can fix most of these problems is the use of subcutaneous administration. The largest issue that arrives with current application of subcutaneous administration is that the drug available on the market is acidic and is therefore not appropriate for subcutaneous delivery. It is evident that trials need to be made in order to assess the effectiveness of our current methods in comparison to a subcutaneous administration route. Results favoring subcutaneous administration would decrease cost from health care works and allow a patient to feel more comfortable, despite the situation they may be in (6).

The actual potential benefits of flumazenil are still being investigated. There are several diagnoses that may have potential benefit from the use of this antagonist including serotonin depleted panic disorders. Patients in this state benefited from an IV bolus of flumazenil 2mg in a 10 minute duration. Although effective in this anxiety-state disorder, other disorders producing anxiety have not been shown to receive benefit from flumazenil as an anxiolytic drug (6). Flumazenil has also shown to not be anxiogenic in individuals who are prone to anxiety and those who are not. The mechanism behind flumazenils action is not well understood and it is clear that future investigations look into this.

Primary Prevention

As data suggests that most cases of BZD poisoning and withdrawal come from chronic users of BZDs, it is important to inquire the need for BZDs in the long term. Guidelines in the United Kingdom state that there are no reasons for prescribing a BZD longer than 2-4 weeks for any indication (1). Although this is true, chronic use of BZDs in the world is still an on-going problem with the elderly being the most vulnerable in this group. The United Kingdom may have these features in their guidelines, but some countries have different policies on the prescribing of BZDs and often give physicians the ability to perform an "act of faith" in prescribing BZDs for their patients. Monitoring physicians' prescriptions has become an important tool in being able to reduce the amount of long term BZD prescriptions. In the period from 2011-2013 in Ontario, BZD prescriptions were seen to decrease by 50% after implementation of monitoring programs (1). Asides from these programs, there needs to be further actions done in order to prevent overprescribing. Education is always the key of primary prevention as knowing the consequences of an action may reduce and/or eliminate the action. Although most physicians understand the consequences of long-term BZD use, it is important that physicians consistently receive up-to-date information and understand the statistics behind this problem. BZDs may be preferred by the patient for their condition, but physicians need to educate their patients about the safer alternatives. Educating your patient about BZD addiction and withdrawal in people may prove to be beneficial for future decisions made by your patient. These primary prevention acts will not only reduce the amount of poisoning and withdrawal cases in the emergency department, but will also reduce the amount of fall injuries, cognitive impairment cases, and other issues related with BZDs to the emergency department (24).

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