Opioid and Benzodiazepine Overdose

Objectives:

At the end of this lesson, the student should be able to:

1. Discuss the epidemiology of opioid and/or benzodiazepine medication overdose.
2. Discuss the pathophysiology of addiction.
3. Discuss the pharmacodynamics of the most common benzodiazepines and opioids.
4. Discuss the pharmacodynamics of the opioid and benzodiazepine antagonists.
5. Describe the management and special considerations for patients with opioid and/or benzodiazepine overdose.

Case Study

It is 2300 on a late autumn night when your unit is dispatched to a call for an unconscious and “blue looking” 57-year-old woman at a nearby residence. Dispatch reports the caller saying that the patient is barely breathing. Upon arrival at the scene you are met by law enforcement that was called to the scene by neighbors who heard glass breaking and a loud crash from the house.

You enter the house and proceed to the main bathroom where you find the patient lying in a left lateral recumbent position. The first arriving law enforcement officers performed their CABs (circulation-airway-breathing), detected a pulse and breathing, and placed the patient in this position. Law enforcement reports there are no other people in the house.

Your general impression is that the patient is pale, cyanotic, and making a pathetic respiratory effort. There is a blood smear on the sink and a 3 cm laceration on the patient's left forehead which is no longer bleeding (you estimate no more than 100 mL of blood loss from this wound). There is broken glass everywhere from a smashed mirror and a drinking glass. There are some blue, elliptical-oval pills as well as some white, round pills scattered all over the sink and counter.

Given that safety is always the main priority, you instruct your partner and the officers to help move the patient out of the bathroom away from the blood and glass. After giving clear instructions on how to move the patient with minimal cervical spine movement, and how to avoid being cut by the glass, the patient is moved to the bedroom where there is more space to work. The patient is limp and mostly unresponsive.

The patient localizes to pain, does not open her eyes, makes incomprehensible sounds, is breathing shallowly at a regular rate of six breaths per minute (BPM), there are no palpable radial pulses, the pulse is slow and weak, and the pupils are pinpoint. The patient is also cold to the touch. As you progress with your assessment, one of the officers fetches a blanket to cover the patient.

Given the unknown mechanism of the head injury, your partner opens the airway with a modified jaw thrust, inserts an oropharyngeal airway with no issue and assists the patient's respiratory effort with a bag valve mask attached to oxygen while you carry on with the assessment. Given the patient's current status, you decide to intubate and instruct your partner to carry on oxygenating the patient. A fire crew arrives on scene and the members kindly assist you by attaching a pulse oximeter, capnography, electrocardiogram (ECG), and blood pressure monitor. The SPO2 level is 90%, the ETCO2 is 52 mm/Hg with poor waveform, the ECG shows a sinus bradycardia of 50 beats per minute and the blood pressure is 90/70. The blood glucose level is 80 mg/dL.

One of the officers presents you with two empty medicine bottles with one containing Halcion (triazolam) 0.25 mg and the other, Demerol 50 mg. Each bottle contained 20 tablets, of which only 10 Halcion (the white capsule shape) and 12 Demerol (the white round shape) remain. Given that the prescription fill date on each of the bottles is over a week old it is uncertain how many tablets were taken. The officers also report several open containers of alcohol (ETOH) in the dining room.

Despite being well-oxygenated the patient’s respiratory effort is poor and the gag reflex remains absent. While you prepare to intubate the patient an IV line with normal saline is quickly established in the left antecubital vein and set to keep open (TKO). Although the SPO2 level is now at 98% and the ETCO2 has improved, attempts to see if the patient will breathe on her own result in the saturation levels quickly dropping.

On standing orders you draw up 2 mg of naloxone (an opioid antagonist) into a syringe and slowly administer it to the patient looking for a response. After 1 mg there is no improvement in respirations; after 2 mg, respirations have increased to 10 BPM and there is only a marginal improvement in the vital signs.

You contact medical control as you have reached your maximum dose of naloxone, and your standing orders to
administer flumazenil (a benzodiazepine (BDZ) antagonist) do not apply in this situation due to the possibility of a mixed overdose and mechanism of injury for a head injury. It is also not completely apparent what may be causing the decreased level of consciousness (LOC). Medical control tells you that naloxone was your best chance to revive the patient and given that it made no significant improvement, instructs you to complete the intubation and transport to the emergency department (ED) for definitive care.

Introduction

The cause of altered mental status (AMS), especially when related to drug overdose, can be complex and range from single to multiple mechanisms such as drugs causing respiratory depression, and the respiratory depression causing AMS. The paramedic should consider all causes and treat those in order of highest priority which can usually only be decided on scene. There are a huge variety of medications available that can cause AMS and patients are not always aware of the serious adverse effects with even the smallest of overdoses.

When it comes to pharmacology, including that of illicit and non-prescribed drugs, there are several terms that need to be understood, the first of which is therapeutic index. Therapeutic index is the relationship between the average effective dose and the average lethal dose (which is when given a particular dose 50% of the people will die). The higher the therapeutic index, the safer and less toxic drugs are. For example, if someone took two or three times the normal dose for aspirin by mistake, and assuming no underlying medical conditions, he or she will most likely experience no ill effects. Always consider the therapeutic index of medications that have been taken by a patient. A single extra tablet of one drug or an entire handful of tablets of another drug may have similar harmful effects. It is not the quantity of the drug that is harmful, but how far outside the therapeutic index a person is.

This article focuses on two main types of drugs, namely benzodiazepines and opioids, as well as their respective antagonist drugs flumazenil and naloxone. Benzodiazepines are in the category of sedative-hypnotics and used in a wide variety of circumstances discussed in later objectives. Opioids are a subcategory of narcotics which are used to induce sleep and analgesia. An important distinction to make is that between opioids and opiates, both of which are narcotics. Opiates are drugs derived from natural opium such as heroin which often have little or no medicinal value (and are often illicit), and opioids are non-opium based synthetic substances with widely accepted therapeutic use. For the purposes of this text, the term opioid is used to describe either opiates or opioids used for therapeutic reasons.

Opioids and BDZs are studied under both pharmacology and toxicology. When studied under pharmacology one is learning how to use them to a therapeutic end point. When studied under toxicology, it generally means that the drugs have not been used correctly, are causing harm to the body and need to be neutralized, removed, or their effects controlled. One aspect of toxicology that will assist in dealing with overdoses and potentially identifying a toxic agent (which in this article are opioids or BDZs) is that of toxicodromes. A toxicdrome is the syndrome-like symptoms of a particular class of drug or toxic substance. The narcotic toxidrome, in the context of an unintentional overdose, includes the following signs and symptoms: pinpoint (very constricted) pupils, severe respiratory depression, drowsiness, stupor, and coma. The toxidrome related to BDZs is the sedative/hypnotics toxidrome and the signs and symptoms include: uninhibited behavior, drowsiness, ataxia, dysarthria, AMS, respiratory depression, central nervous system (CNS) depression, apnea, seizures, and coma. Understanding these and other toxicodromes will assist in potentially identifying which substance has been overdosed on.

Epidemiology of Unintentional Prescription Drug Overdose

Drug overdose in the US is epidemic. There has been a five-time increase in overdose related deaths since 1980, and in 2009 there were more overdose deaths than motor vehicle collision deaths.opioid deaths accounted for almost 60% of overdose deaths in 2010 which now exceeds overdose deaths from heroin and cocaine combined. Visits to the emergency department (ED), and the subsequent costs related thereto, have also increased in recent times.

Prescription drug overdose is a deep and complex problem that has no single identifiable cause. The problem is driven by administrative, socioeconomic, physician, insurance, and other factors that all build up to a situation that make prescription drugs readily available and easily affordable. There is no single example to describe all the factors that can build up to an unintentional prescription drug overdose. The solution to combating prescription drug overdose is a sustained effort by all parties involved to implement procedures and policies, as well as to educate patients and the public as to the dangers of prescription drugs. The biggest offender in prescription overdose is opioid (narcotic) drugs. These drugs are primarily used for pain management and if mixed with alcohol, can quickly cause an overdose. In 2010, opioids were involved in 16,651 deaths, benzodiazepines (BDZ) were involved in 6,497 deaths, and antidepressants were involved in 3,889 deaths. These deaths were often caused in combination with each other or other drugs (referred to as a “mixed bag” overdose).

In addition to causing an increasing mortality rate, prescription overdoses (either from misuse or from abuse) are also responsible for an increased morbidity rate as indicated by a 114% increase in visits to the ED from 2004 to 2011.
2011 there were 1.4 million pharmaceutical-related ED visits, with 30% of those related to opioid analgesics and 30.4% related to BDZs. Eighteen percent of these cases involved alcohol abuse. The number of admissions to substance abuse treatment centers (aka rehab) increased six times from 1999 to 2010. Other morbidities that relate to the increase in prescription drug use include infections such as hepatitis C and human immunodeficiency virus (HIV), especially if patients switch from oral to injected medications. Trauma due to altered mental status and poor judgement can cause falls and accidents. Neonatal opioid withdrawal syndrome can occur as a result of pregnant mothers abusing opioids.

There is also a high incidence of people using prescription drugs for non-medical reasons. In 2011, over 14 million people reported using prescription drugs for nonmedical purposes, and 11 million people reported specifically using opioids for nonmedical purposes. Chronic nonmedical use of opioid drugs is defined when a person uses opioids for nonmedical purposes for 200 or more days per year, and in 2009 to 2010 it is estimated that almost one million people made chronic nonmedical use of opioids.

Opioid drug abuse costs $72 billion in annual medical, substance abuse treatment, downtime at work, and legal costs, all of which are comparable to the costs of diseases such as asthma and HIV. In many cases the costs of prescription drug abuse are carried by taxpayers.

The population group most susceptible to nonmedical opioid abuse is men (almost twice that of women), and the group most susceptible to prescription opioid abuse is women. The rate of visits to the ED for opioid overdose is roughly equal between men and women (53.9% of men and 46.1% of women). Men have a higher mortality rate than women with prescription drug overdoses. Those in the 18 to 25-year-old range have the highest rate of chronic nonmedical use.

ED visits as a result of overdose of opioids or BDZs were highest among 21 to 29-year-olds. The overdose death rates for opioids are highest among people aged 45- to 54-years-old. In terms of race: whites, Native Americans, and Alaskan natives have the highest incidence of opioid nonmedical use and opioid deaths. Whites have the highest admission rate to the ED and substance abuse treatment centers for issues related to opioid analgesics.

People with Medicaid have a higher incidence of opioid prescriptions (especially for long term care) compared to those without. Those with Medicaid also have the highest rate of overdose deaths. Those people residing in the Southeast and Northwest have the highest rates of opioid related death, sales, and nonmedical use. Additionally, rural areas have a higher incidence of opioid-related deaths than urban areas. The majority (50 to 80%) of people who have died from prescription opioid overdose had a history of chronic pain. The higher the dose prescribed, the more likely the chance of an overdose. People with mental health and addiction problems have a higher risk of death from an opioid overdose. People seeing multiple healthcare providers and having multiple prescriptions filled at pharmacies had an increased risk of opioid overdose, but could also be more easily predicted to misuse or abuse opioids.

Opioids were obtained either from legitimate sources such as with a prescription from a pharmacy, or from friends or family who had their own prescriptions. Opioids can also be obtained from illegal sources such as drug dealers; however, this is beyond the scope of this article. Since 1991, prescriptions, the duration of supply on the prescriptions, and the dose prescribed have all gradually increased. Healthcare providers without sufficient training in pain management and addiction can also contribute to the problem with inappropriate opioid prescriptions. New and more potent formulations of opioids have also been flagged as contributing to the opioid abuse problem.

In summary, what one can see is that there are many facets to this problem. Measures are continually being implemented, such as some ED departments not prescribing narcotics, and research is continually being updated. The one main issue that should be kept in mind, while being faced with a huge addiction problem, is not to lose focus of the needs of a patient who genuinely requires high quality pain management.

Addiction

Addiction is a complex and misunderstood chronic brain condition that causes compulsive action to seek out the addicted substance, often with harmful consequences to the person who is addicted and those around them. Society often considers addicts as people with low willpower and having made poor choices in life, whereas the truth of the matter is that addiction is mostly attributed to problems with brain function. Anyone of any age is susceptible to becoming addicted and sometimes not even through his or her own actions, such as the case with babies who are exposed to drugs and become addicted while in the womb.

Humans are instinctual creatures and have a built-in reward system that strongly influences how we behave. For the most part the reward system is designed to ensure we have adequate nutrition, seek stable environments, procreate, and receive all the basics of human life. As with any system in the human body things can malfunction. A malfunctioning reward pathway can cause a person to overindulge in any number of reward activities such as food, alcohol, sex, and drugs. Although the mechanism of addiction is not entirely understood, people can be genetically
predisposed to addiction.

The reward pathway is part of the CNS and includes three main parts of the brain: the ventral tegmental area (VTA), the nucleus accumbens, and the prefrontal cortex. When a reward is received neurotransmission travels from the VTA to the nucleus accumbens and then to the prefrontal cortex. The prefrontal cortex is of particular interest because it is responsible for evaluating situations, good decision-making, and keeping emotions and desires in check. Neurotransmitters are the communication medium between nerve cells. Dopamine is an important hormone with many significant roles in the body, one of those being a neurotransmitter in the brain. When the body indulges in a reward activity, there is a surge of dopamine (amongst other chemicals) in the brain which fulfills the instinct to seek out a particular reward. For example, someone goes to a bar because he or she feels like having an ice cold beer. He or she drinks a beer, burps, feels satisfied, gets up and walks out of the bar because his or her reward center is now satisfied. An alcoholic on the other hand would probably drink uncontrollably.

Basically, a reward pathway that is not working correctly will not tell the person that he or she is satisfied, and that person will continue to attempt to seek the reward looking for a fix. In the case of drug use, the drugs stimulate the reward system greatly, which in turn influences the areas of the brain that are responsible for governing reason and good judgement. The drugs trick the body into thinking a reward has been received, and then cause the body to seek out more of the drug. Unfortunately, in some people who are predisposed to addiction, this cycle cannot be broken without professional help.

Some narcotics and benzodiazepine drugs (BDZ) cause a decrease in gamma-amino butyric acid (GABA), which is an amino acid that is found in the CNS and is the main inhibitory neurotransmitter that controls the release of dopamine. An inhibitory neurotransmitter stops the CNS from being stimulated and causes sedation, relaxes striated muscles, reduces anxiety (anxiolysis) and has anticonvulsant properties. When GABA is decreased, dopamine is increased which once again causes the person to think he or she has received the reward.

Of course, different drugs affect this reward pathway in different ways -- cocaine for example -- causes dopamine to stick around longer to stimulate the dopamine receptors, and alcohol stimulates a particular area in the brain to increase dopamine levels and stimulate the reward pathway.

No single factor determines addiction but there are environmental, biological, and other factors that increase the chance of becoming addicted. The home and family environment during childhood is particularly important because if family members abuse drugs, the chance of the child abusing drugs is increased. The school environment as well as friends and acquaintances can often persuade someone to try drugs, even if that person has no other predisposing factors. Children with poor social skills or who are struggling with schoolwork are also at risk for becoming addicted. In terms of biological factors, it is estimated that between 40 and 60% of addiction is attributable to genetic factors and takes into account the influences of environmental factors. The stage of a person’s development and medical and mental disorders increases risk of addiction.

Additional risk factors include early use and route of administration of the drug. The earlier in life a person is exposed to a drug the more likely he or she will become addicted to it at some point in his or her life. It is however, important to note that people can become addicted to a substance at any point. In addition to the risk of addiction, the earlier in life the drug is used, the greater the chance the person has of developing medical problems other than addiction. In adolescence and earlier life, the prefrontal cortex is still being developed and younger people do not yet have the same good decision-making capabilities as adults.

As with any drug, the route of administration will determine the speed of onset. Drugs that are swallowed will take longer to work than drugs that are injected, and they are subject to the first-pass effect of the liver. Drugs that are injected or inhaled can reach the brain within a few seconds and create an incredible “high” for just a few minutes before returning the drug user to a normal state. It is believed that the greater the contrast between the high and the low, the more compulsive the behavior is to seek the high again.

**Pharmacodynamics of Common Benzodiazepines and Opioids**

Benzodiazepines are in the class of sedative-hypnotics and are commonly prescribed to treat anxiety, seizures, and to provide sedation. Colloquially, BDZs are referred to as tranquilizers. They primarily affect the CNS, and as a result of this, an overdose will present with CNS deficits such as decreased respirations, slow pulse, decreased LOC and lowered blood pressure. Benzodiazepines are typically the “pam” drugs with names such as diazepam, lorazepam, alprenolam, temazepam, triazolam, clonazepam, and so on. BDZs are listed as Schedule IV drugs (potential for abuse).

The mechanism of action of BDZs is that the drugs bind to the GABAA receptor sites on CNS cells and actually potentiate the neurotransmission inhibitory properties of GABA. Additionally, BDZs can cross the blood-brain barrier which is why the onset of these drugs is quick (within a few minutes). The different brands of benzodiazepines have
different onsets of action based on whether they are fat or water soluble (or a mix of the two). Given the same route of administration, the drugs that are more fat soluble, such as diazepam, have a quicker onset, but the drugs that are more water soluble, such as lorazepam, will have a longer duration of action. BDZs are often sub-classified according to how long they last: ultrashort-acting, short-acting, medium-acting, and long-acting.

Long-acting means the drug has a half-life of more than 24 hours, medium-acting has a half-life of 12 to 24 hours, and short-acting has a half-life of less than 12 hours. Drugs with a very short half-life (6 or fewer hours) can also be classed as ultra-short-acting.34

It is important to understand the onset and duration of any overdose as you will be able to get an idea of long you have before a condition will deteriorate as well as how long you will need to perform emergency treatment. Of the estimated 2,000 different types of BDZs in production, only 15 of these are Food and Drug Administration (FDA) approved.

BDZs are prescribed for sleep aids, premedication for anesthesia, retrograde amnesia (to stop a patient from remembering a painful procedure), to lessen anxiety and panic disorders, to prevent and treat seizures, to ease alcohol withdrawal, and as a muscle relaxant.

When used as a short-term sleep aid, BDZs allow the patient to fall asleep quicker and stay asleep longer. Typically, BDZs with shorter duration of action are used to treat sleep disorders to reduce the level of grogginess when the patient wakes up. There are newer, non-BDZ drugs available for the treatment of sleep disorders.35

Premedication for anesthesia and inducing retrograde amnesia are conditions that are not usually treated by patients themselves and are discussed only for the sake of completeness. BDZs can be used for conscious sedation where the patient remains awake but pain free for certain procedures such as dentistry where general anesthesia is not required or even desirable. The type of BDZ is selected for its duration of action compared to the length of the procedure. BDZs may be combined with narcotics for enhanced effect. However, should a patient return home while still under the influence of these drugs, he or she may conceivably overdose if an additional dose of BDZs or narcotics is taken.36

Anxiety is a normal response in most cases, but should anxiety last for more than six months without an easily identifiable cause (such as money troubles), a diagnosis of Generalized Anxiety Disorder (GAD) can be made. GAD affects 5% of the adult, primary-care population. Medication for GAD can include long term antidepressants and short term BDZs to reduce anxiety while the antidepressants take effect. It is generally accepted that long term BDZ use is undesirable. Panic disorders are a type of anxiety disorder. A person with a panic disorder will experience uncontrollable fear and often the inability to have a normal response in a difficult situation. The treatment is similar to that of anxiety.37

Management of seizures with the use of BDZs is also usually limited to emergencies and administration by medical professionals. Although BDZs have been used long term to prevent seizures, this is not usually the first choice as the majority of patients quickly develop a tolerance to BDZs.38

The simultaneous use of BDZs and alcohol is dangerous and discussed further down in this objective. BDZs are used to ease the wide array of symptoms experienced when a patient is withdrawing from long term and excessive alcohol use. The symptoms include "the shakes," insomnia, anxiety, hallucinations, seizures, and a condition called delirium tremens. BDZs are the first-line and often life-saving treatment option for a patient experiencing any of these symptoms.39

Skeletal muscle relaxants are the first-line treatment of conditions requiring muscle relaxation. BDZs are used short term to induce hypotonia (reduced muscle tone) to relieve severe skeletal muscle spasms.40

With a basic understanding of how BDZs work and what they are prescribed for, one can begin to see the potential for intentional or unintentional abuse. An overdose that involves only BDZs usually has low morbidity and mortality.41 Simultaneous intake of BDZs with alcohol, narcotics, other BDZs, and other drugs can cause their effect to be potentiated with a significant reduction in respiratory effort to the point where apnea (and subsequently, death) will occur.42

The signs and symptoms of a BDZ overdose are commonly CNS depression, dizziness, decreased mentation, drowsiness, slurred speech, blurred vision, loss of consciousness, hypotonia, weakness, amnesia, hypotension, anxiety, and agitation.43,44 Interestingly, the last two signs, anxiety and agitation are paradoxical effects of sedative medications in the very old or very young.45 Should the patient present with hypotension or respiratory depression, it is most likely a "mixed dose" overdose where alcohol or narcotics have been taken simultaneously with the BDZ.46

Opioid analgesics are a class of narcotics used mostly in the management of pain. Opioids bind to the opioid receptor sites in the CNS, peripheral nervous system (PNS), and the immune system. There are four different opioid receptor sites with the mu and kappa receptor types being the most common sites to which opioids bind.47 These receptor sites
are responsible for several different bodily functions including pain, stress, thermoregulation, respiration, endocrine and gastrointestinal (GI) functions, mood, and motivation. As a result, when opioids bind to these receptors they inhibit neurotransmission and cause pain relief, euphoria, respiratory depression, decreased GI movement, cough suppression, suppression of some hormones released during stress, and pinpoint pupils (a classic narcotic overdose sign) as well as nausea and vomiting. Most prescription opioids are classified as Schedule II drugs with a high potential for abuse.

Examples of opioids include hydrocodone (Vicodin), oxycodone (Oxycontin, Percocet), morphine (Kadian, Avinza), codeine, meperidine (Demerol), and other drugs. The “-one” drugs such as hydrocodone, oxycodone, oxymorphone, and methadone are the most commonly prescribed pain medications that are involved in prescription overdose deaths. Morphine is typically used in the prehospital or hospital setting to manage severe pain. Codeine is more often prescribed for relief of mild pain and is also used as a cough suppressant.

It is a common misconception that opioids stop pain. They simply reduce the perception of pain, dull sensitivity to external stimulation, and provide euphoria. Opioids can be taken orally which is the usual route for prescribed medication and undergo first-pass metabolism in the liver which lessens the effects of the drugs. Some opioids such as fentanyl can be taken transdermally in the form of fentanyl patches for longer-term and more controlled doses. When taken orally the peak effects occur after about 90 minutes. The transdermal patches will take about two to four hours to reach peak effect. Opioids are metabolized by the liver, and patients with liver disease can be expected to have a prolonged duration of action and to be more prone to accidental overdose if the drugs are not excreted quickly enough.

The main issue with an opioid overdose is that it can lead to severe respiratory and CNS depression as well as severe hypotension and bradycardia. The main cause of morbidity and mortality is respiratory compromise. Throughout the wide range of opioid medications available, the potency and effects vary greatly from drug to drug. Doses between some of the drugs such as 2 mg of hydromorphone will have the same effect as 100 mg of meperidine.

The signs and symptoms of opioid overdose, similar to BDZ overdose, are related to the CNS and PNS depression. The classic triad for opioid overdose is CNS depression (altered mental status, drowsiness, and euphoria), respiratory depression and miosis (pinpoint pupils). It is important to note that miosis is not always present (especially with meperidine). Mydriasis (dilated pupils) may be present if the opioids have caused an anoxic brain injury. Of these signs, respiratory depression is the best indicator of opioid overdose. Opioids reduce both the rate and the depth of respirations, and respiration rates as low as four breaths per minute are not uncommon with severe overdose. Even though the respiratory drive is suppressed, the body’s hypoxic drive stimulates breathing unless the CNS depression is severe enough to suppress this. Hypotension is a possibility but it is usually not severe unless there are other drugs that have been ingested.

Pharmacodynamics of Benzodiazepine and Opioid Antagonists

Benzodiazepine Antagonists

The primary BDZ antidote is flumazenil (Romazicon) which competes with BDZs at the GABAA receptor complex. The use of flumazenil is controversial and may cause more problems than it solves. One of the main issues with a BDZ overdose is respiratory depression, a condition which is not consistently reversed with flumazenil. If a patient is using BDZs to treat a specific condition, the administration of flumazenil may cause the condition to suddenly worsen. As mentioned previously, BDZs are addictive and using flumazenil in these situations, as well as in patients who have been using BDZs long term, may precipitate serious withdrawal symptoms including seizures.

Flumazenil should only be used when there has been a BDZ overdose caused by a medical provider in a patient who is BDZ-naïve (basically a patient who is not addicted or using BDZs long term). The contraindications include hypersensitivity to flumazenil or benzodiazepines, tricyclic antidepressant (TCA) overdose, chronic BDZ use, and a coma of unknown origin.

BDZ withdrawal can present with a variety of symptoms in patients who have been using BDZs for even short periods. The withdrawal symptoms can begin from 24 hours to several days depending on whether the BDZs used are shorter or longer-acting, respectively. In general, patients withdrawing from BDZs should do so slowly over a period of four weeks to six months – if you administer flumazenil, you are, in effect, taking them off BDZs in a matter of minutes. Part of the withdrawal process might include putting the patient onto other longer-acting BDZs. BDZ withdrawal must be monitored by a physician.

Flumazenil will reverse conscious sedation, but won’t necessarily reverse amnesia. Flumazenil may in itself cause CNS depression and should not be used as a differential diagnosis to confirm BDZ-induced sedation. Patients may experience seizures after flumazenil administration and a BDZ overdose may outlast the effects of the flumazenil,
causing the patient to become sedated once again. It is important to note that flumazenil does not reverse opioids.62

The main adverse effects of flumazenil include nausea and vomiting, dizziness, disturbed vision, agitation (especially in patients being treated for anxiety with BDZs), dyspnea, hyperventilation, pain at the injection site (make sure the IV is free running), chest pain, seizures, dysrhythmias (such as junctional tachycardia) and hypertension.63,64

The onset of action of flumazenil is one to two minutes and the duration and peak effect is related to the concentration of the BDZs in plasma. Essentially, flumazenil will only exert its BDZ antagonist effects if there are actually BDZs in the plasma to antagonize. Flumazenil is designated as Pregnancy Category C (may adversely affect the fetus but potential benefits may outweigh the potential risks).65,66 Flumazenil is not recommended for pediatric patients.67

Flumazenil is contraindicated in patients who are hypersensitive, taking TCAs, are prone to seizures, have head injuries or raised intracranial pressure, or who are in a coma of unknown causes.68 As was discussed in the previous objective, patients starting on TCAs, may take a course of BDZs to control symptoms until the TCAs take effect. It is a real possibility that a patient who has overdosed on prescription BDZs may be taking TCAs.

Opioid Antagonists

The primary opioid antagonist is naloxone (Narcan, Evzio). Naloxone causes partial or complete reversal of opioids by binding to the opioid receptor sites and can reverse respiratory depression caused by opioids. Interestingly, naloxone completely prevents the effects of morphine.69

Naloxone is so effective that the FDA has approved a Naloxone auto-injector for use by lay people such as family and caregivers. The injector works in a similar fashion to an EpiPen and is administered intramuscularly or subcutaneously into the thigh.70 There is also a naloxone nasal spray intended for use by first responders and caregivers that is currently awaiting approval by the FDA.71

The only contraindication to naloxone is hypersensitivity. There are, however, several precautions that need to be considered. When using naloxone in large doses in narcotic-dependent patients it is possible that you can cause intense withdrawal symptoms that can endanger both the patient and the paramedic such as violent outbursts and vomiting. Similarly, caution should be used when administering naloxone to infants of narcotic-dependent mothers as convulsions, intense crying, and hyperactive reflexes can occur. It should be noted that naloxone might not reverse hypotension. Naloxone is pregnancy safety Category C.72,73

Given the topic of this article as “unintentional prescription drug overdose,” one must also consider the plight of a patient who is not a drug abuser, but does require long term analgesics. Not all opioids are habit- or dependence-forming, but can nonetheless cause withdrawal like symptoms if the long term administration of an opioid is suddenly stopped. If naloxone is administered to these patients it can cause acute abstinence syndrome which presents with aches, diarrhea, tachycardia, fever, abdominal cramps, restlessness, insomnia, piloerection (goosebumps), nausea and vomiting, generalized weakness, diaphoresis, hypertension, and other signs and symptoms.74,75

The onset of action of naloxone is less than two minutes and duration of action of 30 to 60 minutes. The peak effect is variable and depends on the amount of opioids in the body.76 Side effects include the already discussed (and sometimes acute) withdrawal symptoms, cardiovascular, respiratory, CNS, GI, and genitourinary side effects. Often side effects are only seen at very high doses of naloxone.

The cardiovascular side effects, which are often as a result of an underlying cardiac condition, can include hypo- and hypertension, tachycardia, ventricular fibrillation, left ventricular failure and cardiac arrest. Respiratory side effects include pulmonary edema (with an onset of less than one minute) and dyspnea. CNS side effects include seizures, paresthesias, agitation, tremors, and headaches. Naloxone is also known to worsen obsessive compulsive behaviors. The most notable GI side effects are nausea and vomiting. Naloxone has been noted to have mild diuretic effects and the only genitourinary side effect is that of polyuria.77

One last important consideration for naloxone is that its half-life is often less than that of opioids and it may be necessary to repeat dosing.78

Management of Patients with Opioid and/or Benzodiazepine Overdose

There is an almost endless permutation of prescription, over-the-counter and illicit drugs that can be mixed and overdosed on. Additionally, if alcohol or inhalants (such as glue sniffing) are added to the mix, the situation can become exponentially worse. With that said, add on top of that any pre-existing medical or traumatic conditions and the patient will become extremely difficult to treat. To keep things simple this objective will focus on three situations: pure BDZ overdose, pure opioid overdose, and mixed BDZ, opioid, and ETOH overdose. The three situations will also
assume that the patient does not require cardiopulmonary resuscitation (CPR), and the use of naloxone during cardiac arrest is not recommended. In reality it will be almost impossible to make a diagnosis of either a pure BDZ or opioid overdose in the field as there are many possible causes of altered mental status, all of which need to be considered.

In the management of a patient with a pure BDZ or opioid overdose, the treatment includes body substance isolation (BSI), scene size-up, primary survey, history and secondary assessment, and continual reassessment. At the minimum BSI would include gloves.

The following is a discussion of the treatment of any patient with CNS and respiratory depression caused by BDZ or opioid overdose. In real life, treatment is seldom as linear as described below, and local protocol should always be adhered to.

Scene size-up includes scene safety, determining the nature of illness (NOI), the number of patients, if additional resources are needed, and whether spinal immobilization is needed. Scene safety goes without saying and any incident involving the use of possibly illicit drugs should warrant extra attention or law enforcement assistance. The NOI could be determined through caller information or from open medication bottles or prescription information (rifling through pockets, purses, wallets and bathroom cupboards can reveal a ton of information). There is also the possibility of more than one patient on a call, especially in the case where people may share medication or where children could get hold of medication. If the overdose is unintentional, it is possible that the patient tried to move to get help and passed out while standing up which gives a high index of suspicion for cervical spinal injury. Given the available methods for c-spine clearance, virtually all of them negate clearing the c-spine if the patient is not alert.

The primary survey will begin with the general impression of the patient, which in the case of a BDZ/opioid overdose would quite likely present with a patient who has respiratory depression and appears cyanotic or ashen. As BDZs and opioids are CNS depressants, determining the LOC will give you a clue as to how severe the overdose is. The less responsive the patient is, the higher the dose or potency of the BDZ/opioid or the more progressed the respiratory or CNS depression is.

After LOC any immediate life-threats should be determined. The airway and breathing should be given careful consideration and the appropriate method to open the airway must be used (head-tilt, chin-lift, or jaw thrust). Insert airway adjuncts (such as an oropharyngeal airway) and suction as needed. If the patient has inadequate respirations these should be assisted with a bag-valve mask (BVM) attached to oxygen at a rate of 15 L/min. Pulse oximetry should be maintained at least at 94% using supplemental oxygen as needed. NB: Have a suction unit at the ready, and if the patient is conscious have a vomit bag or a plastic dish easily accessible.

The management of circulation should include controlling any major bleeding, assessing the skin for color, temperature and condition as well central and/or radial pulses. Assessing a radial pulse can give an indication of blood pressure, although the lack of peripheral pulses does not necessarily indicate lack of perfusion. Capillary refill will also give an indication of perfusion.

Inserting an advanced airway such as an endotracheal tube should be considered in any patient who is unable to maintain his or her own airway – this is particularly true in BDZ and opioid overdoses. Part of the sequence of endotracheal intubation is to pre-oxygenate the patient with a BVM attached to 100% oxygen flowing at 15 L/min. While you are oxygenating keep a close eye on the patient’s end tidal carbon dioxide (ETCO2) levels. If these ETCO2 levels are elevated this indicates respiratory acidosis and ventilating the patient will reverse this. This reversal may in actual fact improve the patient’s condition to such an extent that endotracheal intubation is not needed, as may the administration of naloxone. Once the primary survey is complete and any life-threats have been dealt with, a decision to load-and-go or stay-and-play should be made.

With a transport decision made, which would probably be to load-and-go (but dependent on many factors and local protocols), the history taking and secondary assessment will follow. SAMPLE (signs and symptoms, allergies, medications, last in and out, events leading up) history can be obtained from the patient (including medical bracelets), physical clues such as prescription bottles, and family or friends. The secondary assessment would focus on the body systems affected and would most likely indicate major deficits in the neurological and pulmonary systems. A set of vital signs should be taken with close attention being paid to respiratory status and level of consciousness.

Throughout the assessment consideration must be given to the other potential causes of altered mental status. One method of remembering these causes is the mnemonic AEIOUTIPS which stands for A – allergies, anaphylaxis, altitude (hypoxia), alcohol, acidosis; E – environment (hyper- and hypothermia), epilepsy (seizures); I - insulin (diabetes); O - overdose (such as BDZs and opioids); U - uremia (failed kidneys) or underdose (such as cardiac medications); T - trauma or toxins; I - infection (such as sepsis or meningitis), P - psychological factors, S – stroke.

An intravenous (IV) line should be established and an electrocardiogram (ECG) monitor should be applied. Capnography is also an essential tool to monitor the correct placement of airways, efficiency of breathing, effectiveness of ventilations, and the state of metabolism (low metabolism will yield low CO2 output). In respiratory
depression one can expect the partial pressure of CO2 in the blood (PaCO2) readings to be greater than 45 mm/Hg (normal is 35 to 45 mm/Hg). Getting a blood glucose reading should be among your priorities and a low blood glucose level, in the absence of any contraindications, should be corrected.82

In terms of specific interventions for pure BDZ overdose, treatment is typically supportive with close attention to the airway and breathing. If approved and not contraindicated, flumazenil can be administered at a dose of 0.2 mg slow IV push over 15 seconds, if no response, a second dose of 0.3 mg over 30 seconds can be administered, if there is still no response, a dose of 0.5 mg over 30 seconds, and if there is still no response, 0.5 mg over 30 seconds every minute to a maximum of 3 mg. Reassess for the possibility of re-sedation as the BDZ's half-life outlasts the half-life of the flumazenil.83 As mentioned previously, flumazenil is not recommended for pediatric patients.84

In terms of specific interventions for a pure opioid overdose, the treatment is similar to the management of BDZ overdose in terms of priorities with particular attention given to airway and breathing. The most notable difference between the management of opioids and BDZs is that you can give naloxone to a patient in a coma of unknown etiology, whereas with flumazenil you can't.85 Naloxone is administered for opioid reversal at a dose of between 0.4 to 4 mg via IV, IM (intramuscular) or SC (subcutaneous). Naloxone can be administered via an endotracheal tube or intranasally. Typically, you will titrate to effect and give only enough naloxone to improve respiratory effort and airway management, or any other life-threatening condition resulting from the narcotic overdose. If you completely reverse the opioid effect you may precipitate dangerous withdrawal symptoms and compromise both paramedic and patient safety.86 The pediatric dose for naloxone is 0.1 mg/kg dose via IO (intraosseous), IV, IM, SC, and repeated every two minutes. The maximum total dose is 10 mg. If there is no response after 10 minutes then an additional dose may be administered at the same dosage.87

One major side effect of a patient being sedated and lying on a hard surface for long periods (usually over four hours) is rhabdomyolysis. Rhabdomyolysis is literally translated as "dissolution of skeletal muscle" and is caused when skeletal muscle is injured and leaks large amounts of sometimes toxic intracellular contents into the plasma.88 In the case of sedation, or lying immobile on a hard floor, circulation to the areas bearing most of the body weight will experience reduced circulation – this is what causes the muscle injury. It is only once a patient is moved and reperfusion to these areas is restored that problems such as kidney failure and cardiac arrest can occur. If you suspect your patient may be at risk for rhabdomyolysis you should put interventions in place such as IV lines and ECGs before you move the patient. In these cases you should avoid using lactated ringers due to its potassium content which may exacerbate the condition.89

Mixing opioids and BDZs is a recipe for disaster as they can potentiate the respiratory depression effects of one another. Further mixing these drugs with ETOH will also increase morbidity and mortality. Given the high percentage (almost 25%90) of visits to the ED involving (any) drugs and alcohol, it is important to understand how to manage this particular combination – which is actually no different to the management of the pure opioid and BDZ overdoses described above, except that flumazenil may be contraindicated if the coma is caused by the ETOH, and naloxone administered for opioids may be ineffective if the amount of ETOH consumed is sufficient to cause a coma.91

When managing mixed overdose patients you need to ensure, as you should with any patient, that there are no comorbidities that accompany long term use of drugs. Such conditions may include subdural hematomas from falls, gastrointestinal bleeding, hypoglycemia, seizures, dysrhythmias, and other conditions.92 Hypothermia should also be treated early on. The immobility of patients and the possibility of them becoming unconscious in a cold environment can cause hypothermia which will bring its own set of challenges such as reduced LOC and cardiac problems (including ventricular fibrillation).

Case Study Conclusion

One can always speculate the course of events that led up to an incident. In the case study it seems that the loud crash that was heard was the patient losing consciousness, falling, and causing glass to break. If this was the case it is fortunate that the neighbors heard the commotion and notified law enforcement as quickly as they did. Sedated patients can easily lose control of their airways which invariably leads to cessation of breathing and death.

The fact that law enforcement arrived on scene, had to place the patient in recovery position, and that the patient was "blue," indicates that the patient suffered a hypoxic event, either from airway obstruction or from respiratory depression. Law enforcement on scene is always a good indicator of safety, but not all dangers are law enforcement related. In this case there was both blood and glass (which is a sharp) scattered around the patient which yielded the potential for the equivalent of a needle stick if the glass was covered in blood and pierced the skin.

On your general impression you noted the head injury, and although the mechanism of injury did not seem significant, you could not discount the possibility of comorbidities such as impaired clotting factors or malnutrition which could cause blood vessels to rupture or bones to break more easily. Also, the patient could have been hit on the head and
then fallen. When in doubt protect the cervical spine.

The patient clearly had AMS, and the obvious clue seemed to be an overdose. Tunnel vision is never a good thing in EMS, and you should always run through your AEIOUTIPS or other methods of determining possible causes of AMS. One of the great things about naloxone is that coma of unknown causes is an indication for its administration which would allow you to confirm or dismiss opioid overdose if there is only a suspicion of opioid overdose.

Although it may seem that a transport decision is an easy one to make, there are many instances where it is a difficult call. IV lines are often put up en route, except where the IV line is needed for life-threatening interventions such as large volume fluid administration or to administer drugs. Many services will allow only a single attempt to put up a line on scene, otherwise it must be done in the ambulance or using alternative access such as interosseous. There was a short delay in this case to stay on scene to see if the naloxone would improve the patient’s condition to such a point that she could maintain her own airway and improve respirations, but unfortunately this was not the case. As soon as you realized the problem couldn’t be improved on scene the decision to transport was made.

Delegation is also a powerful tool and EMS sometimes forgets that other first responders are medically trained and often eager to help, even with the most basic of tasks such as getting equipment from a vehicle (such as the blanket), carrying equipment and even making suggestions that are useful to the treatment (such as the officers telling you about the alcohol).

**Conclusion**

Addiction is a complex and devastating disease, and paramedics should understand it with the same level of knowledge as they would any other condition such as shock, cardiac dysrhythmias, and pulmonary conditions. Addiction can manifest in a wide variety of chronic and acute conditions which will challenge the skills of any healthcare provider. Addiction does not necessarily mean a person will overdose, and an overdose does not necessarily mean the person is addicted.

Overdoses, especially mixed-bag overdoses, can present with a confusing array of signs and symptoms and false clues. Just as a paramedic may have difficulty in diagnosing an illness or injury, it is often best to treat an overdose of unknown substance symptomatically, keep the patient from deteriorating, and transport to the hospital where more definitive treatment can be given.

As is the life of the paramedic, you need to continually learn about new drugs (both licit and illicit), new treatments and protocols, how priorities may need to be shuffled around a bit under certain circumstances (such as delaying intubation until naloxone is tried), and just generally stay sharp.

The management of unintentional prescription drug overdoses may seem like a daunting task, but is really not if you approach things in a calm, logical and structured way.

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