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AHC Media

Legal Drugs of Abuse

This issue might be subtitled "What will they think of next?" Getting high does not always require the purchase of illegal drugs, and all substances that alter sensorium, such as nutmeg, cannot be regulated. However, the emergency physician must remain aware of the latest fads of drug abuse, and should be able to recognize the symptoms they cause. Currently, those drugs are K2, Spice, "bath salts," and "plant food," along with some recycled favorites from the past — nutmeg and canned air. Luckily, most of these cause time-limited changes in sensorium without major physiologic effects. Sedation and time generally are all that is needed for emergency treatment.

— Sandra M. Schneider, MD, FACEP, Editor

Introduction

Drugs of abuse are all too commonly seen in the emergency department (ED), no matter where your practice is located. Most emergency physicians are comfortable dealing with alcohol intoxication, methamphetamine, cocaine, heroin, and other common "street drugs." This paper will discuss other common drugs that are perhaps less well known and considered "legal." We will present five different drugs, including synthetic tetrahydrocannabinol (THC), "bath salts," salvia, nutmeg, and canned air cleaners. Management of the intoxicants is discussed at the end.

Case 1

A 20-year-old college student is brought into the ED by his friend because the patient started to not feel well after smoking something at a party. The patient's friends state that they do not know what it was but it was legal. The patient's vital signs are: heart rate of 114 beats per minute; respiratory rate of 16 breaths per minute; blood pressure of 148/89 mmHg; oxygen saturation of 98% on room air; and an oral temperature of 37.2°C. He appears somewhat anxious and is mildly tremulous. He does not appear to be in any acute distress, but he is somewhat confused. He states he is slightly nauseated and feels his heart beating. He denies any visual disturbances, hallucinations, or pain. His physical examination is unremarkable.

The patient is placed on a cardiac monitor. One liter of IV 0.9% normal saline and 4 mg of IV ondansetron are administered. Laboratory tests are remarkable for a mild leukocytosis without an increase in bands, and a mildly elevated BUN/creatinine ratio. The chemistry panel, urine drug screen, ethanol, acetaminophen, and salicylate tests are negative. An ECG shows sinus tachycardia without any ST or T-wave abnormalities. QRS complexes are narrow, and QTc is within normal limits.

Two hours after presentation, the patient states that he wants to go home. He is alert, oriented, and no longer tremulous or anxious. His discharge vital signs have returned to normal. One of his friends is in the ED and is willing to take him home. The friend states that they were smoking "Spice."

Pathophysiology and Pharmacology

Tetrahydrocannabinol, or THC, is the principle active ingredient in

Executive Summary

- K2 and Spice are the names of commonly available synthetic cannabinoids. Patient may present with hypertension, tachycardia, agitation, anxiety, and, rarely, seizures and arrhythmias.
- "Bath salts" and "plant food" are designer drugs that often contain MDPV or mephedrone. They can cause elevations in blood pressure, pulse, and temperature, as well as seizures and paranoia.
- Salvia is a plant derivative that targets the same receptor as LSD and causes mood changes and lightheadedness.
- All of these "legal" drugs of abuse cause time-limited symptoms. Supportive care and, when needed, benzodiazepines, are generally all the care that is needed in the ED.

marijuana. It is well known for its classic effects of relaxation, euphoria, and analgesia. It is also frequently used for its anti-emetic properties, which is the basis for its legal use in multiple U.S. states. However, in individuals who are naïve to THC, the opposite effects of anxiety, tachycardia, and nausea are often seen. There is a substantial amount of literature suggesting that heavy and chronic marijuana usage is associated with psychosis and schizophrenia.[1,2]

JWH-018 is probably the most studied synthetic cannabinoid. It has been found in multiple preparations and has been shown to be a potent cannabinoid receptor (CB) agonist.[3] CB1 is the principal receptor thought to be most highly responsible for the euphoria and psychoactive effects of THC. The CB2 receptor resides mostly in the immune system but has some effect on pain control and mood regulation.[1]

Most individuals who smoke a synthetic cannabinoid typically do not present to the ED and report symptoms consistent with classic THC effects.[2] However, there is an increased rate of adverse reactions associated with synthetic cannabinoids, as evidenced by the new phenomenon of patients presenting to the emergency department with synthetic cannabinoid intoxication. While reliable pharmacokinetic data do not exist on all the specific synthetic cannabinoids, clinical data in case reports suggest that adverse effects typically occur within 30 minutes, wane within 3-4 hours, and completely disappear by 6 hours.[2,4-6]

Clinical Features

Symptoms described with synthetic marijuana use are elevated heart rate, elevated blood pressure, palpitations, diaphoresis, tremulousness, anxiety, and agitation.[4,5,7,8] Other physical findings may include mydriasis, although this finding is not consistent with intoxication. Psychosis with auditory and visual hallucinations is mentioned in rare circumstances, most commonly with individuals who have underlying psychiatric disorders.[9,10] Seldom have seizures and arrhythmias been reported.[1,2]

Diagnostic Studies

Because the toxidrome of synthetic cannabinoid intoxication may be similar to that of sympathomimetic substances, a full toxicologic workup may be warranted, especially if the patient presents with severe alterations of vital signs, changes in mental status, or cannot give a history of synthetic cannabinoid use. Hypokalemia has been reported by some case reports[4], but it is not a consistent finding across the literature in patients presenting with synthetic cannabinoid intoxication.[4,5]

Although there are structural similarities between synthetic marijuana and THC, commonly used urine drug screens are unable to detect the presence of synthetic cannabinoids in the urine. It is important to note that urine drug screens may be positive for THC weeks after use, and a positive test does not exclude the use of synthetic cannabinoids.[11] Currently, there is no emergency department test that can confirm intoxication with synthetic cannabinoids and further testing is not useful in the acute management.

Differential Diagnosis

In patients who present with severe synthetic cannabinoid intoxication, sympathomimetic intoxication should be considered, especially in those patients with abnormal vital signs. Sympathomimetic substance intoxication with methamphetamines, "bath salts," cocaine, ecstasy, etc., should be considered. In individuals presenting with psychosis, phencyclidine (PCP) intoxication should also be entertained.

Adulterated marijuana or synthetic THC should be considered in the differential diagnosis. PCP can be dissolved into a solvent and then allowed to permeate a marijuana cigarette (known as "Sherm"). Patients with PCP-laced marijuana will frequently present with symptoms of psychosis, agitation, and violent behavior. Typically, patients who are intoxicated with PCP alone do not necessarily have elevated heart rate or blood pressure; however, the psychomotor agitation associated with PCP intoxication can secondarily promote both tachycardia and hypertension. Cocaine-adulterated marijuana use, called "dusting" or "snow-capping," may present with similar symptoms. Both PCP and cocaine may be detected in some urine drug screens.

Background and Epidemiology

Synthetic cannabinoids, more popularly known as "K2" or "Spice,"

have become a new phenomenon in the United States within the last 18 months. Synthetic marijuana analogues first became available in the United States in 2006, but did not start becoming a widespread "legal" drug of abuse until early 2010.

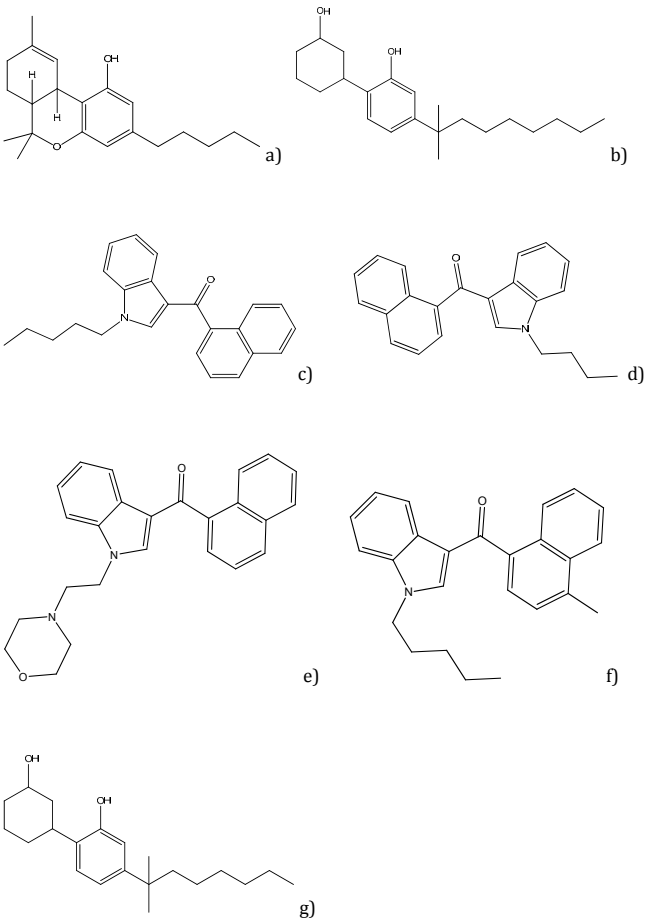
According to the American Association of Poison Control Centers (AAPCC), there were 13 calls to poison centers in 2009 regarding exposure to synthetic cannabinoids, but in 2010 there were 2,915 documented calls.[12] As of May 31, 2011, there were already 2,476 calls to poison centers regarding synthetic cannabinoid exposure.[7]

The widespread availability of the drug is one of the most concerning aspects in this new drug of abuse. Because synthetic cannabinoids are marketed as incense or potpourri, they have been sold virtually everywhere. The statement, "not intended for human consumption," is printed on these products so the products avoid Food and Drug Administration (FDA) regulation. Ubiquitous in head shops and tobacco shops, synthetic marijuana has been sold in gas stations, convenience stores, and even grocery stores.

Synthetic cannabinoids obtained the mainstream media's attention in June 2010 after an Iowa teenager with no past medical history of depression or other psychiatric illness committed suicide while intoxicated with K2. According to the police investigation, the teenager began to "freak out," according to his friends. Next, he got his parents' rifle and shot himself in the head, ending his life.[13] Later, investigations suggested the patient might have had an underlying depression. Iowa, as well as several other states, went on to pass bans of synthetic cannabinoids.

In November 2010, the Drug Enforcement Agency (DEA) placed a 12-month ban on the sale of products containing five of the most prevalent synthetic THC analogues: JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol. The ban took effect on March 1, 2011. The DEA news release bans the substances, "for at least one year while the DEA and the United States Department of Health and Human Services (DHHS) further study whether these chemicals and products should be permanently controlled."[8]

Figure 1: Chemical Structure of THC and Synthetic Analogues



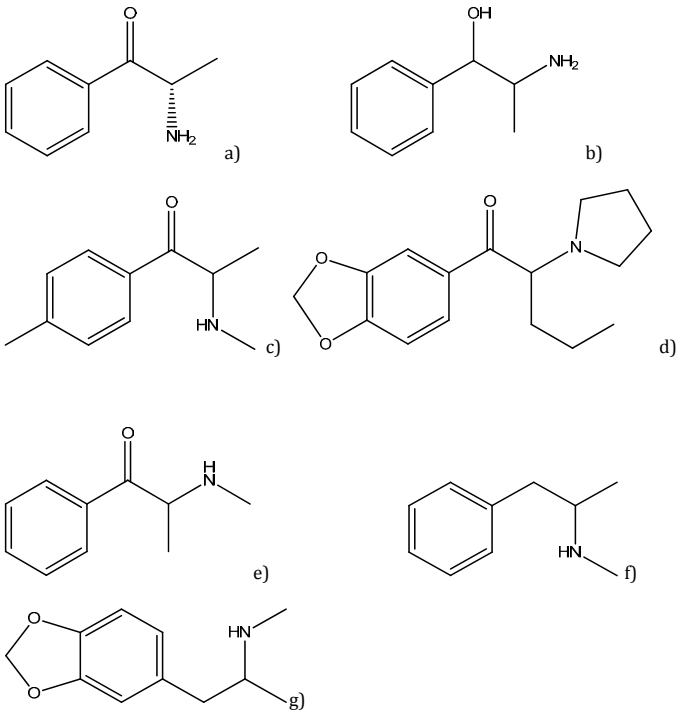
a) THC b) Cannabicyclohexanol c) JWH-018 d) JWH-073 e) JWH-200 f) JWH-122 g) CP-47,497

During the one-year ban, these compounds will be restricted as schedule I substances, which are highly abused and serve no medical benefit. The DEA also has the option to extend their emergency ban up to an additional six months while studying whether or not to permanently ban the substances.

Despite the aggressive DEA ban, new synthetic cannabinoids have already been popping up on the Internet. Because the DEA only bans five distinct substances, new cannabinoid analogs circumvent the ban by altering the original molecular make-up of JWH-018. The exact structure of these new compounds has not been detailed.[14]

In Germany, a new synthetic cannabinoid, JWH-122, has been isolated. Marketed as "Lava Red," side effects of elevated heart rate, blood pressure, agitation, and psychosis have been noted.[15] Even more concerning, seizures, cardiac arrhythmias, and loss of consciousness requiring intubation have been reported with this drug, though rarely.[16] JWH-122 has been shown to be a very potent cannabinoid (CB) receptor agonist and is similar in structure to its parent compound, JWH-018.[15] This suggests that even minor alterations in the chemical structure can have profound changes in clinical effect. While chemists attempt to avoid the restrictions of

Figure 2: Chemical Structures



Chemical structures of a) cathinone b) cathine c) mephedrone d) MDPV e) methcathinone f) methamphetamine g) MDMA.

governmental agencies, they are creating potentially hazardous, and even lethal, new compounds.

Most of the brands of synthetic cannabinoids have a variety of scents or flavors available. There is also considerable concern that the additives to the synthetic cannabinoids may be, at least in some part, responsible for the variability in side effects seen with these products. These additives are not listed on the packages because they are labeled as "not for human consumption."

Case 2

Staff and hospital security are wrestling with a man who is yelling, swearing, agitated, and combative. He appears to be delusional. He has a heart rate of 125 beats per minute, a blood pressure of 160/100 mmHg, a respiratory rate of 22, oxygen saturation of 96% on room air, and temperature of 38.2°C. IV access is established, and the patient is placed on a cardiac monitor including continuous pulse oximetry. He is sedated with benzodiazepines and is given IV fluids. Both rapid blood glucose and ECG are normal. The basic blood work, serum alcohol level, acetaminophen level, aspirin level, urinalysis, and urine drug screen are unremarkable. After several hours, he is calm. You can carry out a reasonable conversation, and he admits to snorting and injecting "bath salts" with his friends.

Pathophysiology and Pharmacology

These products known as "bath salts" or "plant food" contain stimulant compounds such as 3,4-methylenedioxypyrovalerone (MDPV) or 4-methylmethcathinone (mephedrone). The products are being ingested, snorted, and injected.

Bath salts are structurally similar to cathinones. (*See Figure 2.*) There are multiple synthetic derivatives of cathinones. One of the longest known and most studied compounds in this class comes from the Khat (quat or gat) (*Catha edulis*) shrub that grows in eastern and central Africa. This plant has long been used by native people for its stimulant properties. The fresh leaves or stems are chewed or brewed into tea. The plant releases cathinones and the less toxic cathines, which are used to boost energy and suppress appetite. It is believed that cathinones act by inhibiting monamine transporters for dopamine, serotonin, and norepinephrine within the central nervous system (CNS).[17-20] Cathinone and its derivative compound cathine are controlled substances in the United States (Schedule I and IV, respectively).[20] Cathinones are similar to amphetamine in chemical appearance and clinical effects.

Although human studies with mephedrone are limited, rat studies showed a relationship between 3,4-methylenedioxymethamphetamine (MDMA or ecstasy), mephedrone, and amphetamines. This study looked at the effects of mephedrone on the nucleus accumbens of rats. It was found that mephedrone had similar neurochemical and functional properties to MDMA. Both chemicals caused a rapid increase in serotonin levels. There was a similar effect in dopamine release and elimination from mephedrone that resembled that of amphetamines. Mephedrone appears to have properties of both MDMA and amphetamine on the brain's reward system, which may account for its use as a designer drug of abuse.[21]

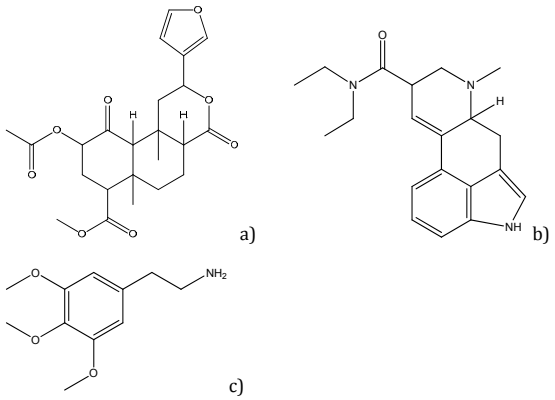
Clinical Features

The clinical presentation of this ingestion is similar to other stimulant/sympathomimetic compounds. The patient's clinical presentation is most consistent with methamphetamine or cocaine intoxication: Hypertension, tachycardia, hyperthermia, agitation, tremor, seizure, delusions, hallucinations, paranoia, and mydriasis may occur. There is no readily available test that detects bath salt intoxications. Standard ED urine drug screens do not detect its use.

Differential Diagnosis

Patients presenting with bath salt ingestion will appear to have a sympathomimetic intoxication. The differential diagnosis should include

Figure 3: Chemical Structures of Salvinorin A, LSD, Mescaline



Chemical structure of a) salvinorin A b) LSD c) mescaline

methamphetamines, cocaine, ecstasy, PCP, and others. Co-ingestion or multidrug abuse should also be considered.

Background and Epidemiology

Bath salts conjure up an image of a luxurious bathtub overflowing with bubbles, aromatherapy, perhaps a glass of wine, and relaxation. The term "bath salts" now has a much more sinister connotation. These "bath salts" are not sold in expensive packaging from bath and beauty supply stores as inorganic salts used for bathing. Bath salts containing mephedrone and other related compounds now connote a new sort of designer drug of abuse. Sold as "bath salts" or "plant food" and labeled "not for human consumption," this new type of designer drug can be bought at grow shops, head shops, convenience stores, gas stations, and online for recreational drug use. They are sold under such names as "Vanilla Sky," "Ivory Wave," and many others.[22,23]

Bath salts first made their appearance as a designer drug of abuse in the end of the first decade of the 21st century in Western Europe. The first case of confirmed toxicity associated with mephedrone use comes from the United Kingdom in 2010.[24] A 22-year-old man ingested and injected 4 g of mephedrone powder and then presented to a U.K. emergency department with palpitations, blurred vision, chest pressure, diaphoresis, anxiety, and delusions of mercury poisoning. He was tachycardic and hypertensive on presentation. His physical examination and labs, including mercury level, were otherwise normal. He was treated with benzodiazepines and discharged. Liquid chromatography and mass spectrometric detection were used on a serum sample and revealed mephedrone. Gas chromatography/mass spectroscopy (GC/MS) toxicology screen did not reveal any other drugs of abuse.[24]

Bath salts also have been reported to cause a number of fatalities. Four deaths related to mephedrone were reported in April 2011 in the United Kingdom.[25] In this case series, four fatalities were linked to mephedrone by femoral venous blood analysis using high-performance liquid chromatography (HPLC). Each of the four patients was found to have levels of mephedrone on autopsy. One case involved a 49-year-old woman who inhaled some of the drug and was found dead, with coronary artery disease and myocardial fibrosis being a contributing cause of death. A second case involved a 19-year-old man who suffered cardiopulmonary arrest after using mephedrone. A third case involved a 55-year-old woman who was found dead after a night of drug use. A fourth case involved a 17-year-old boy who was involved in a fatal motor vehicle collision after being high on mephedrone.[25]

MDPV has also been used as a designer drug of abuse. It has also been found in patients who have ingested bath salts.[26] It is not licensed for medical use in the United States.[27] In Finland, it has been a drug of abuse and concern since 2008. Since the autumn of 2009, blood screens of intoxicated drivers have included an assay for MDPV, which has been found to be positive in 5.7% of intoxicated drivers (not alcohol only) both alone and in combination of other substances of abuse.[28]

Methcathinone is another synthetic derivative of cathinone. It was first seen in Russia and the former Soviet Union in the late 1980s and 1990s. Several cases of methcathinone (otherwise known as "Cat") toxicity were reported in the rural Midwest in the early 1990s. These patients presented in a similar fashion, with a sympathomimetic toxidrome of agitation and hallucinations.[29]

Bath salts were first described in a published article as a drug of abuse in the United States in May 2011. A Michigan ED reported a case series of 35 patients from November 13, 2010 to March 31, 2011. During this period, many cases were reported and presented to the local emergency department with symptoms consistent with bath salt intoxication. One death was reported.[26]

The American Association of Poison Centers released its first clinical statement on these toxins in December 2010.[30] Recent preliminary Poison Center data show 303 calls in 2010 and already 3,740 calls as of July 7, 2011, in regard to bath salts.[31]

Several states are taking a stand and passing legislature to make bath salts illegal. Governor Bobby Jindal of Louisiana was one of the first to make the sale of these drugs illegal.[32] Many other states, including Illinois and Florida, are taking similar steps to regulate these substances. The DEA has listed bath salts as a drug of concern. It is currently under investigation.[33]

Case 3

A 21-year-old man presents to the ED for hallucinations. His girlfriend states that the patient smoked "Seer's sage" approximately 15 minutes prior to arrival. She says he smoked it in the past, but his hallucinations are worse today. He is having a "bad trip" and "demons are trying to get him."

The patient's vital signs are a heart rate of 105 beats per minute, respiratory rate of 16 breaths per minute, blood pressure of 127/79 mmHg, oxygen saturation of 98% on room air, and an oral temperature of 37.2°C.

By the time you see the patient, he is calm, lying in bed, and requesting to go home. He is alert and oriented, and he denies visual or auditory hallucinations. He has not had a "trip" like that before, and he denies any other co-intoxicants. After a period of observation, the patient is discharged home.

Pharmacology and Pharmacokinetics

The principle psychoactive ingredient in *Salvia divinorum* is salvinorin A, a molecule that was first isolated in the early 1980s. Its exact mechanism of action was not well understood until 2002, well after it became commercially available. Salvia acts as a K-opioid receptor agonist, as opposed to the serotonin or 5-HT receptor, which is the main receptor targeted by classic hallucinogens such as lysergic acid diethylamide (LSD) and mescaline. The K-opioid receptor is widely distributed throughout the brain, spinal cord, and peripheral nerves. K-opioid agonists typically cause dissociation and delirium. It also appears that salvinorin A has significant dopamine (D2) receptor action, similar to LSD and mescaline.[34]

The most interesting aspect of salvinorin A pharmacology is its short duration of action. When smoking salvia, the onset of action is virtually immediate, with the duration of action typically cited between 20-30 minutes. There is mild variation depending on whether it is smoked or if the vaporized salvia was extract, leaf, or pure salvinorin A. Hallucinogens, such as LSD, can cause "trips" that last 6-12 hours depending on quantity consumed and the patient's tolerance. Mescaline's effect can last 12 hours or more.[35-37]

The preferred route of salvia administration is inhalation or vaporization. It is rarely chewed and swallowed because of the gastrointestinal deactivation of salvinorin A.[38]

Clinical Effects

Salvia is principally abused for its hallucinogenic and psychogenic effects. In one survey, the most frequent effects were "increased insight," "improved mood," "calmness," "increased connection with the universe or nature," "weird thoughts," and "things seeming unreal." Approximately 93% of those who responded to the survey reported smoking or vaporizing as forms of abuse, with a minority masticating the leaves. The majority used concentrated leaf extract as opposed to dried leaves. A very small percentage use pure salvinorin A (1.3%).[36]

The most commonly cited adverse reactions include "increased swelling," "lightheadedness," "drowsiness," "dizziness," and "lack of coordination," with almost all being noted about 20% of the time.[36]

Background and Epidemiology

Salvia divinorum, more frequently referred to as salvia, the plant's genus name, is known for its psychoactive and dissociative effects. It also carries the street names "Seer's Sage," "Diviner' Sage," "hierba Maria," and "SD." Salvia was originally used by the Mazatec Indians in the Sierra Mazatec Oaxaca, Mexico. Predominantly used by the Mazatec shamans to help produce visions during religious ceremonies, the plant has become an increasingly popular legal drug of abuse during the past decade.[39]

Salvia became commercially available in the late 1990s, mostly available through Internet sales. Since that time, the substance has been banned by about a dozen U.S. states, but has managed to escape federal regulation by the DEA. *Salvia divinorum* is a controlled substance in multiple European countries, and recently became regulated in Canada in early 2011.[40]

Results from the 2006 National Survey on Drug Use and Health, a survey sponsored by the Substance Abuse and Mental Health Services Administration, suggest that 1.2 million Americans have tried salvia during their lifetime, with approximately 750,000 individuals having used it that year.[41] The 2009 survey did not specifically address salvia use, but based on increased media attention and governmental legislation, some have estimated the number of individuals using salvia well into the millions per year.[42]

Case 4

A 19-year-old woman is brought from the local college campus by EMS with altered mental status. They state that she is nauseated and acting "bizarre." On arrival, her vital signs are: heart rate of 128 beats per minute, blood pressure of 108/68, respiratory rate of 20 breaths per minute, oxygen saturation of 98% on room air, and a temperature of 36°C. She feels like she is "soaring" but is very anxious. She has paresthesias and feels like she needs to urinate but is unable to do so. On physical examination, she is altered, her face is mildly flushed, her mouth is dry, and she is gagging. Her pupils are 4 mm and sluggishly reactive. She has mild ataxia. An IV is established with a normal saline infusion. The basic laboratory results include CBC, basic metabolic panel, beta-hCG, urinalysis, urine drug screen, ethanol, aspirin and acetaminophen levels are all normal. An ECG is unremarkable. She receives an antiemetic and a benzodiazepine for anxiolysis. She admits to ingesting three whole nutmeg ground into a milkshake to obtain a "fresh, safe, natural high."

Pharmacology and Pharmacokinetics

Nutmeg oil may be extracted from the nut of the evergreen tree *Myristica fragrans.* Clinical

Figure 4: Whole Nutmeg and Ground Nutmeg

intoxication is usually seen after ingestion of 1-3 whole nuts (5-15 g) or 1-2 tablespoons (7-14 g) of ground nutmeg.[43] (*See Figure 4.*) A single jar contains approximately 75 g of nutmeg.[44] The spice is commonly mixed in other liquids, such as beer or juice, and ingested as a drink. There are reports of people injecting or inhaling nutmeg. Nutmeg contains approximately 5-15% volatile oils. These oils are considered to be the primary component leading to toxic effects. It is widely believed that myristicin and elemicin, alkylbenzene derivatives, are the toxicologically active compounds.[45,46] Myristicin has been shown to inhibit monoamine oxidase and is thought to be converted to the amphetamine derivative 3-methoxy-4,5-methylene dioxyamphetamine, leading to its clinical effects. Elemicin is thought to have anticholinergic and psychotropic properties. The combination of these effects leads to hallucinations, an anticholinergic-type toxicity, and other variable symptoms.[43-48] There is a case report of one patient who developed non-specific T-wave changes on his ECG, which resolved once intoxication resolved.[49]

Clinical Effects

Nutmeg intoxication may appear clinically as feelings of euphoria, hallucinations, paranoia, fatigue, tachycardia, nausea, vomiting, nonspecific neurologic complaints, or other alterations. Many patients will complain of dry mouth. There are a large number of patients who report a feeling of "soaring" or other types of movement hallucinations.

Background and Epidemiology

Nutmeg is typically used for flavoring in fresh-baked breads, pies, or cookies. Nutmeg is not something that immediately comes to mind when thinking about drug abuse. However, using the spice as a drug is not a novel use for this compound. Nutmeg has been used to treat stomach and skin ailments, to induce hallucinations, and as an abortifactant since the Middle Ages.[43] Many case reports of nutmeg intoxication are in the literature scattered throughout the past 200 years. There are intervals of time when it is more abundant, such as during the 1960s and 1970s. Certain demographic groups are more predisposed to present with nutmeg intoxication, including adolescents, college students, and prisoners. Reasons for this include the low cost and availability of nutmeg.

Nutmeg intoxication, while not new, is certainly not common. An 11-year retrospective review of the California Poison Center revealed only 119 single-substance exposures to nutmeg.[50] A review of calls placed to the Poison Information Center of Erfurt revealed that seven cases of nutmeg intoxication were reported from 1996-1998, with no cases reported from 1994-1995.[45] One reason for the low number of reports may include ingestion of a large amount of fairly non-palatable substance in order to have the psychotropic and hallucinogenic effects. The "high" is variable, with significant negative side effects.

There have been two fatalities from nutmeg reported in the literature. The first case is from 1887 and involved an 8-year-old boy who is reported to have ingested two nutmegs and was found altered. He died approximately 24 hours later. Whether the death was from nutmeg ingestion or other causes (such as the treatment with injection of ammonia, brandy, and other compounds) is unclear.[46,51] A more recent fatality was reported in Germany in 2000. In this case, myristicin (4 µg/mL) was detected in serum during a postmortem examination of a 55-year-old woman. A nutmeg-like smell was noted on the autopsy examination of the stomach contents, so a myristicin level was ordered. The concentration was twice as high as previously reported. It was concluded that nutmeg ingestion, along with flunitrazepam, contributed to her death.[45]

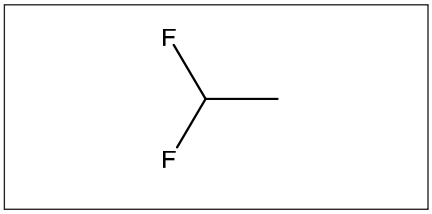
Case 5

A concerned parent brings his 13-year-old son to the ED. He has been acting "funny" since his father got home about one hour ago. The patient is complaining of an abnormal sensation in his chest, as well as palpitations. Since arriving 10 minutes ago, the boy has returned to his baseline mental status. Vital signs are as follows: heart rate 106 beats per minute, blood pressure 114/68 mmHg, respiratory rate of 16, temperature 36.8°C, and oxygen saturation of 97% on room air. He is placed on a monitor, an IV is established with a liter bolus of normal saline, and laboratory testing is obtained. An ECG shows a prolonged QTc of 495 milliseconds. The laboratory work is normal. The urine drug screen is negative. The patient's mother arrives, bringing a can of generic "compressed dust remover" for computer keyboards. She found the can underneath the patient's bed.

Pathophysiology and Pharmacology

It is believed that inhalation of volatile hydrocarbons, such as the common component of canned air, 1,1-difluoroethane, exert their clinical effects via stimulation of gamma-aminobutyric acid (GABA) receptor complexes. The enhanced GABA receptor increases chloride permeability, which leads to hyperpolarization of the cell membrane and then inhibits excitability. This is similar to the way ethanol inhibits GABA. This

Figure 5:
1,1-difluoroethane



effect explains why patients who are high on inhalants may also appear to be drunk. It is thought that inhaled hydrocarbons inhibit N-methyl-D-aspartate (NMDA) receptors and interfere with glutamate-mediated excitatory neurotransmission.[52,53]

One of the most feared complications of inhalant abuse is called "sudden sniffing death."[54] This is an acute, fatal cardiotoxicity associated with hydrocarbon inhalation. Sudden death occurs immediately after use of the compound and the onset of physical activity or stress. Witnessed examples of this phenomenon include running away after abuse with the shock of being caught by parents or police. Hydrocarbon inhalation sensitizes the myocardium by blocking potassium current and prolonging repolarization. Sudden activity or a catecholamine surge produces a fatal dysrhythmia.[55]

Clinical Effects

Patients may present to the ED with signs and symptoms of alcohol intoxication with primarily CNS effects such as euphoria, giddiness, agitation, ataxia, and dizziness. Hypoxic injury and respiratory arrest may occur when the patient abuses inhalants in a closed space where oxygen is displaced with CO_2 and the volatile substance. Occasionally, evidence of what was ingested may be seen around the mouth and on mucus membranes, such as in the case of inhaled spray paint. There may be signs of mucosal irritation such as sneezing, tearing, etc. Frostbite may occur on the fingertips and lips from the container, which chills as it empties.

Cardiac complaints such as palpations may present with dysrhythmias from premature beats, atrial fibrillation, and supraventricular tachycardia. Cardiac arrest can occur in those with sudden sniffing death.

Long-term inhalant abusers may develop long-term sequelae, including liver and kidney disease. Chronic solvent abusers have been found to have significantly more brain abnormalities on MRI than abusers of other drugs such as cocaine.[54]

Continuous cardiac monitoring is of utmost importance in these patients. Obtaining a chest X-ray is worthwhile because an ARDS-like lung injury or aspiration pneumonitis may develop. Avoid a noisy environment and sympathetic stimulation to reduce the risk for sudden sniffing death. Patients should be monitored for a few hours in the ED with oxygen therapy until their symptoms resolve.

Background and Epidemiology

Inhalant abuse is recreational exposure to inhaled vapors to obtain a sensation of being high.[56] Many compounds can be inhaled to obtain a high, such as spray paint and gasoline. One item commonly abused is computer keyboard cleaner that contains a halogenated hydrocarbon, difluoroethane. (*See Figure 5.*) Many reports in the mainstream media have discussed the dangers of inhaling these types of compounds. Inhalation abuse can take several forms: "sniffing" or "snorting" fumes from their containers; spraying the aerosol directly into one's nose or mouth; "bagging," which is inhaling fumes of a substance that is sprayed into a plastic or paper bag; and "huffing," which is placing a soaked rag or cloth with the substance around the nose and mouth.[57]

There are multiple case reports of deaths due to inhalation abuse. Data obtained from national and state surveys suggest that inhalant abuse is most common among 7th through 9th graders. Another national survey from 2003-2004 found that 2.5% of 4th graders had used inhalants at least once in the year prior to being surveyed.[57]

Although any volatile compound can be used, cleaning sprays such as the air compounds used to clean computer keyboards are some of the most common. Many companies have come under scrutiny for their products; Phil Lapin, president and CEO of Falcon Safety Products (manufacturer of common cleaning product Dust-Off), has made significant efforts to raise public awareness about safety and the potential for misuse of the products.[58]

Inhalation of volatile hydrocarbons has been reported in many deaths. A report from Japan in 2011 describes three cases of 1-1-difluoroethane inhalation-related deaths. In each case, a significant level of this chemical was found in the patient's system.[59] Inhalational volatile hydrocarbons have also been associated with sudden cardiac death from dysrhythmia.[60] Sudden cardiac death has also been associated with these compounds.

Management

Management for all of these intoxications is primarily supportive. Patients should be placed on a cardiac monitor with continuous pulse oximetry, and intravenous fluids may be given, especially for those who appear fluid depleted or are tachycardic. In those patients with alterations in mental status, point of care blood glucose measurement should be performed as soon as possible.

For patients in whom a history is unreliable or cannot be obtained, laboratory studies may include chemistries, total creatinine-kinase, acetaminophen, salicylate and ethanol levels, and a urine drug screen. An electrocardiogram should also be considered, with specific attention looking for ischemic changes, dysrhythmias, and QRS widening or QT prolongation. For patients who are febrile and altered, consider lumbar puncture and cerebral spinal fluid studies. Imaging of the brain, such as with a CT scan, may also be considered. It is important to remember that salvia, LSD, bath salts, nutmeg, inhaled hydrocarbons, and mescaline will not be detected on a standard urine drug screen.

In patients who have severe anxiety and/or psychomotor agitation, benzodiazepines should be the mainstay of therapy for all of these ingestions. Protecting staff from a potentially combative, agitated patient through the use of medications such as benzodiazepines is of utmost importance. Patients who exhibit sympathomimetic toxicities should be physically restrained with caution due to the risk of rhabdomyolysis and self injury. In the case of synthetic cannabinoid intoxication, the agitation and anxiety seem to be fairly short-lived,[9-11] and shorter-duration benzodiazepines, such as midazolam, may be an appropriate choice. Antipsychotics may be considered in those individuals who present with severe psychosis or agitation with a normal QT. Patients may require sedation and mechanical ventilation if agitation is severe and prolonged.

Avoid the use of beta-antagonist medications in patients with severe tachycardia and hypertension because of concern for concomitant intoxication with sympathomimetic agents such as cocaine.

It is important to keep in mind that these drugs are often synthesized in clandestine, unregulated laboratories, raising concern for contaminants, other additives, and incorrectly synthesized products. Polysubstance abuse is a common problem and should always be considered on the differential diagnosis.

Consultation with a poison control center or a toxicologist may assist in patient management in cases of an uncertain diagnosis or moderate to severe clinical symptoms. Any patient who remains altered, from whom a reliable history cannot be obtained, or with metabolic or other abnormalities should be considered for admission and further management.

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Physician CME Questions

1. Which of the following toxidromes is most consistent with classic synthetic cannabinoid intoxication?
   A. tachycardia, elevated blood pressure, agitation, and anxiety
   B. respiratory depression, pupillary constriction, and coma
   C. tachycardia, slurred speech, ataxia, and lateral nystagmus
   D. bradycardia, hypotension, and altered mental status

2. Which of the following most accurately describes legality of synthetic cannabinoids in the United States?
   A. Since marijuana is illegal, so are all synthetic cannabinoids.
   B. The DEA recently placed a ban on all synthetic cannabinoids.
   C. The DEA recently placed a ban on a few specific synthetic cannabinoids, but new substances are frequently being discovered and marketed legally.
   D. All synthetic cannabinoids are currently legal in the United States, since they are marketed as incense or potpourri.

3. Which of the following is true regarding patients with synthetic cannabinoid intoxication in the emergency department?
   A. All patients with synthetic cannabinoid intoxication can be discharged home.
   B. Most patients should have symptoms resolve within six hours since onset of symptoms.
   C. All patients with synthetic cannabinoid intoxication should be admitted to the hospital for delayed effects.
   D. Patients can be discharged once the drug screen is positive for synthetic cannabinoid.

4. Which toxidrome is likely to be exhibited by a patient who has ingested bath salts?
   A. anticholinergic
   B. opiate
   C. sympathomimetic
   D. cholinergic

5. How should a patient who is intoxicated with bath salts be managed?
   A. Admit all patients with clinical intoxication.
   B. Observe the patient for 12-18 hours in the emergency department.
   C. Administer benzodiazepines and supportive care.
   D. Patients should be transferred to a psychiatric facility.

6. A patient who presents to the ED took "Ivory Wave" purchased at a local

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Emergency Medicine Reports

CME Objectives

Upon completion of this educational activity, participants should be able to:

- recognize specific conditions in patients presenting to the emergency department;
- apply state-of-the-art diagnostic and therapeutic techniques to patients with the particular medical problems discussed in the publication;
- discuss the differential diagnosis of the particular medical problems discussed in the publication;
- explain both the likely and rare complications that may be associated with the particular medical problems discussed in the publication.

convenience store. What drug of abuse is this presentation most consistent with?

A. marijuana
B. heroin
C. ethanol
D. methamphetamine

7. Nutmeg intoxication may appear clinically with:

A. urinary retention and altered mental status
B. somnolence and a decreased respiratory rate
C. apnea
D. cough and fever

8. Sudden sniffing death is caused by:

A. adult respiratory distress syndrome
B. platelet dysfunction
C. cardiac dysrhythmias after being surprised or physical active immediately after use
D. spinal cord air embolism

9. The demographic most likely to be intoxicated from inhalational ingestion would be:

A. a 35-year-old woman with a history of IV heroin abuse
B. a 14-year-old boy in 9th grade
C. a 25-year-old man with a history of alcohol abuse
D. a 16-year-old girl with a history of nutmeg ingestion

10. Which of the following is true regarding the testing of the intoxicants mentioned in the article?

A. Synthetic cannabinoid intoxication should only be diagnosed if the urine drug screen is positive for THC.
B. "Bath salts" and "plant food" are readily detected by most ED drug screens.
C. Nutmeg may be detected by through standard chest X-rays.
D. Intoxication with these substances is generally diagnosed through history and clinical signs and symptoms and is not detected on routine urine drug screens.

In Future Issues

Dangerous Drug Interactions

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Emergency Medicine Reports
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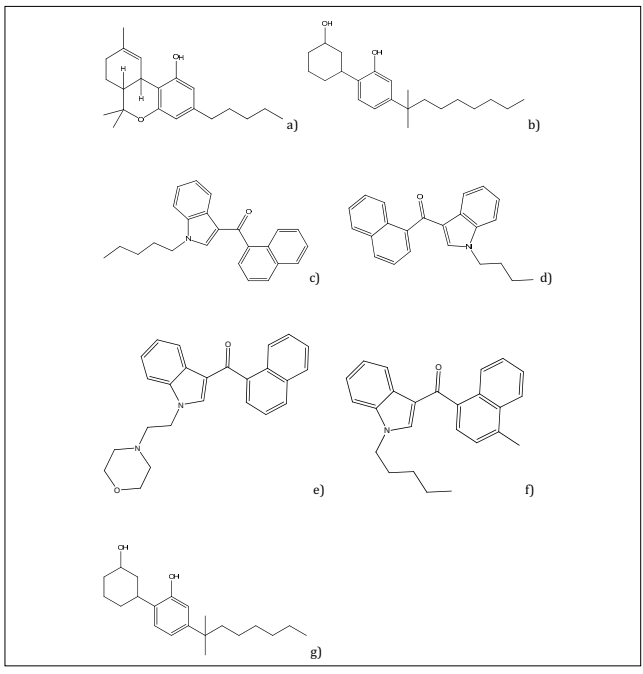
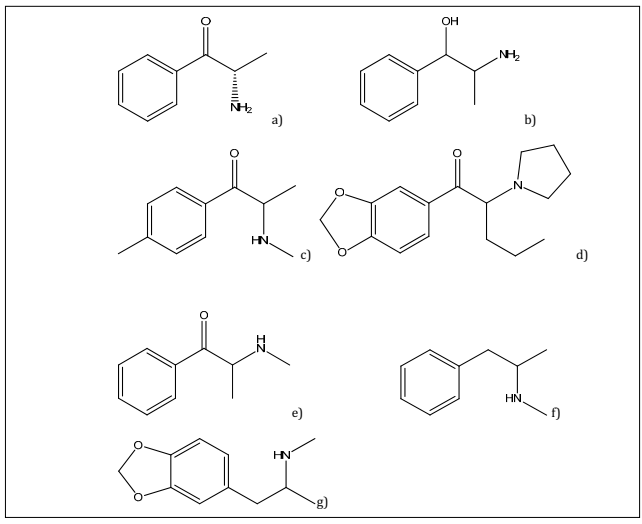
Legal Drugs of Abuse

Chemical Structure of THC and Synthetic Analogues



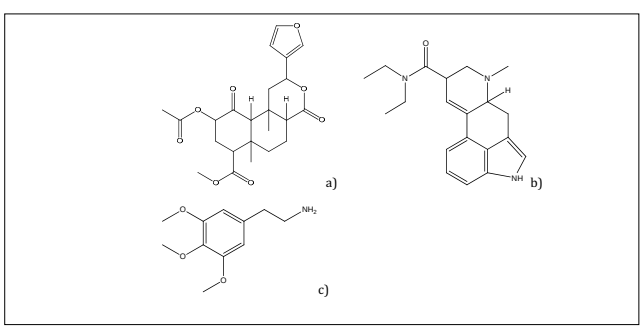
a) THC b) Cannabicyclohexanol c) JWH-018 d) JWH-073 e) JWH-200 f) JWH-122 g) CP-47,497

Chemical Structures



Chemical structures of a) cathinone b) cathine c) mephedrone d) MDPV e) methcathinone f) methamphetamine g) MDMA.

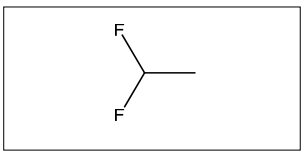
Chemical Structures of Salvinorin A, LSD, Mescaline



Chemical structure of a) salvinorin A b) LSD c) mescaline

Whole Nutmeg and Ground Nutmeg

1,1-difluoroethane



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Trauma Reports

EVIDENCE-BASED MEDICINE FOR THE ED

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AHC Media

Pain Control in Trauma Patients

Regardless of hospital trauma level designation, every emergency department (ED) manages patients with traumatic injury and needs to address the pain and discomfort that accompanies it. Pain control recently became a priority for the Joint Commission, with an emphasis on measures to overcome barriers with hospitals to facilitate appropriate pain management strategies. In addition, pain control allows earlier patient mobilization, decreases incidence of DVT/PE, and decreases pulmonary complications.

Adequate pain control is a necessity in the trauma population. Although pain control is straightforward in minor to moderate trauma, ED staff have been found to significantly under-treat pain in all patients.[2] In the moderate to severe trauma population, pain control becomes more complicated, as it must be balanced against potential hemodynamic instability and the frequent need for neurological reassessment in those patients with head injuries. An increasing proportion of trauma involves the geriatric population, in whom complex co-morbidities abound, and approaches to pain control should be altered in these situations.

This article reviews the current pain control recommendations in the moderate to severely injured trauma population. Many of the medication classes addressed are well-known to practitioners, but will be revisited with special emphasis on their use and potential contraindications in the trauma population. Newer applications and adjuncts that may help control pain with less risk and better outcomes will also be discussed. This article will present a cohesive approach to what used to be an often-overlooked but important aspect of trauma critical care.

—The Editor

Introduction

Trauma is a frequent ED presentation, accounting for 37 million visits annually. Although most trauma patients are discharged home with what would be considered mild to moderate injuries, 2.6 million patients are admitted as inpatients annually. In 2000, traumatic injury resulted in a loss of $406 billion from not only health care costs, but also lost productivity.[3] Although much of this cost and lost productivity is unavoidable, there is growing evidence and consensus that adequate analgesia in both the immediate and long-term post-injury period may positively impact these outcomes, based on data from military research examining the long-term outcomes of injured personnel.[4]

Accounting for all ED encounters, pain represents more than half of the presenting complaints for ED visits.[5] Pain, described as an unpleasant sensory and emotional experience associated with actual or perceived tissue damage, often starts with traumatic cellular damage, although inflammatory mediators can be released by the immune system without injury. The subsequent swelling and inflammation that follows injury further causes increased pain receptor stimulation until nerve fibers in the area reach a certain threshold and fire.

Myelinated A delta nerve fibers carry localized and sharp thermal and mechanical impulses to the spinothalamic tract. Unmyelinated C fibers carry achy or throbbing, dull sensations to the spinal cord, brainstem, and thalamus that are poorly localized. The A beta fibers modulate the number and intensity

Executive Summary

- Poor pain control has been correlated with a catabolic stress response as well as increased incidences of venous thromboembolic events, pulmonary complications, and immunosuppression.
- A recent meta-analysis of 8 trials (922 patients) found that administration of opioid analgesics as part of the diagnostic process for patients with acute abdominal pain prior to a diagnosis did not increase the risk of treatment errors. It did, however, significantly improve patient pain control when compared to placebo.
- In the young, healthy population, NSAIDs can be appropriate first-line agents for mild to moderate pain. In the geriatric population, if NSAIDs must be used, the lowest effective dose for the shortest amount of time is suggested.
- In cases of multiple rib fractures in which contraindications to epidural catheters exist (vertebral fractures, profound hypotension), intercostal nerve blocks can be useful.

of impulses sent up the spinal tracts through inhibition of the A delta and C fibers. Intermittent or short-term firing can occur without sequelae, but chronic stimulation leads to changes in firing potential and creates feedback loops via A beta fibers that may ultimately cause chronic pain.

The two major types of "pain" are the localized soft-tissue or bony pain that often accompanies penetrating or blunt trauma, and the ill-defined neuropathic pain that can occur from proximal nerve or spinal cord root injury (i.e., stingers). Neuropathic pain often is not exacerbated by movement of a body part unless traction is put on the injured nerve. As discussed later, traditional pain medications are not fully effective for neuropathic pain.

Alert and verbal patients will either state they have pain or will volunteer such information when asked (and should be asked frequently),[6] depending on ethnic background or the state of the patient-nurse relationship. Initial pain assessment and frequent reassessment (every 15 to 30 minutes, depending on the degree of injury) is required for adequate analgesia. In patients who are intubated or have altered mental status, the only clinical indicators of pain may be tachycardia, tachypnea, or hypertension. Improvement in any of these findings after pain medication may be the only guide for analgesia in this subset of patients.

Intractable pain or pain out of proportion with the physical exam after either blunt or penetrating trauma is worthy of special mention, particularly in extremities that are susceptible to compartment syndrome. Pain is often the earliest and sometimes only indication of an evolving compartment syndrome, as pallor and decreased pulses are late and ominous findings. Further evaluation of suspected compartment syndrome consists of frequent re-evaluation and, ultimately, is excluded by a compartment pressure that is less than 10 mm Hg in adults and children.[7] Similarly, severe abdominal pain not fully explained by physical exam should prompt concern for ischemic bowel, either from a mesenteric hematoma or arterial dissection.

In the past few decades, not only has the array of intravenous analgesia expanded, but other pain control adjuncts, such as peripheral nerve blockade, have become more readily available. The focus of this article is to review well-known analgesics, introduce more recent modalities, and to suggest a multifaceted approach to pain control in the trauma population. Although mild to moderate pain control will be briefly addressed, this article will center on control of moderate to severe pain stemming from acute trauma.

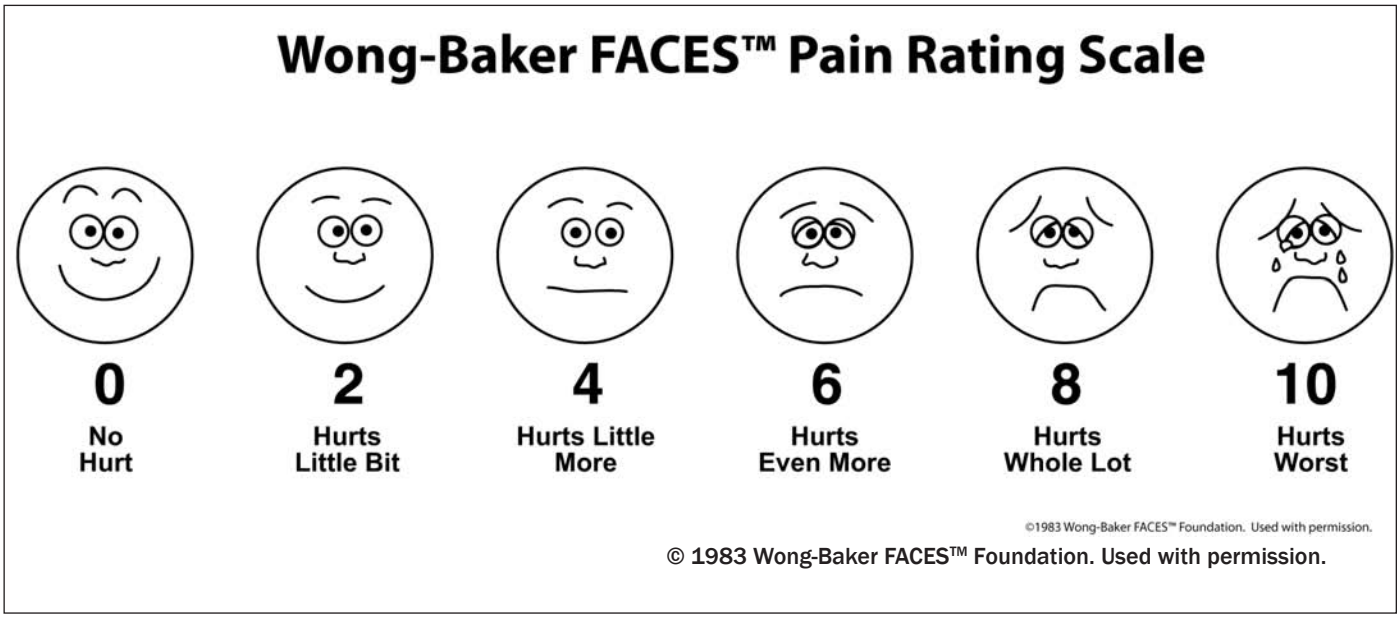
Table 1. Pain Control

Positive Effects
• Earlier patient mobilization
• Decreased neuroendocrine side effects of injury
• Slightly decreased cardiac complications
• Decreased incidence of DVT/PE
• Decreased pulmonary complications
Poor Pain Control Associated With:
• Increased incidence of chronic pain syndromes
• Post-traumatic stress disorder
• Increased morbidity and mortality

Why Analgesia in the Trauma Population Is Important

Inadequate pain control has received much attention in the ED and critically ill trauma patient populations. Poor pain control has been correlated with a catabolic stress response as well as increased incidences of venous thromboembolic events, pulmonary complications, and immunosuppression.[4,8] (*See Table 1.*)

Figure 1. Wong-Baker FACES™ Pain Rating Scale, One Commonly Used Pain Rating Scale



Adequate pain control in the ED setting has been associated with higher patient satisfaction and patient compliance,[9] although there are data suggesting the quality of analgesia provided in an ED cannot be inferred from patient satisfaction surveys.[10] (*See Table 1.*) The release of the new pain assessment and management compliance standards from the Joint Commission[1] have facilitated improvement in pain assessment and pain control delivery.[11]

Despite findings that suggest aggressive analgesia is imperative, pain control in the pre-hospital setting through hospital discharge has been described as inadequate.[12] Recent studies suggest the pre-hospital setting is one area in which adequate analgesia is particularly lacking in both the adult[13,14] and pediatric populations.[15] Inadequate analgesia continues once that patient arrives in the ED setting,[16] attributed to, among other causes, a lack of quality management programs that evaluate pain management, clinician attitudes toward opioid analgesics (i.e., drug-seeking behavior and addiction), concerns about opioid safety, and cultural or gender differences in pain assessment and reporting.[17] In discharged patients, inadequate analgesia continues, as 20% of patients, even those with a documented bone fracture, did not receive an analgesic prescription.[18] Factors associated with inadequate analgesia are older age,[11,19] minority race[20] and ethnicity,[21,22] and trauma.

One of the most contentious subjects concerning pain control in any setting is the ability to quantify the severity of the pain and track the patient's response to treatment. This is most often done through a pain score (*see Figure 1*), comprised of several illustrations of faces that represent varying degrees of discomfort. The use of imaging rather than text allows children and non-English-speaking patients to rate their pain severity. A 0–10 visually enlarged laminated numerical rating system has been found to be superior to written scales in the critically ill patient subgroup.[23] Assessing pain and trending its response to treatment gets more complicated in the elderly population or those who have cognitive impairment.[24] Frequent reassessment by physicians and nurses has been found to be a key determinant in adequately treating pain.

Opiates

Although most drugs in the opiate class are no longer derived from the opium poppy (*Papaver somniferum*), the mu pain receptor is the site of action for both organic and synthetic agents. These receptors are present in both the brain and in the dorsal horn of the spinal cord, as well as the intestines (the cause of constipation that accompanies narcotic usage). Narcotics are the mainstay for control of moderate to severe pain because of their potent efficacy. They are classified as Schedule II drugs under the Controlled Substances Act. Use of a protocol-driven approach that incorporates reassessment is particularly efficacious.[28,29]

The quintessential opiate is morphine sulfate, which serves as the gold standard for analgesia. Intravenous dosing at 0.1 mg/kg for analgesia is the classic teaching, but the clinical effectiveness of this dose has been called into question,[25] with dosing around 0.15 mg/kg appearing to be more effective.[26] An approximate equivalent to morphine[27] is intravenous hydromorphone at 0.015 mg/kg that has been found to be effective for moderate to severe pain, preferably by the intravenous route rather than by mouth.

Table 2. Equianalgesic Dosing of Commonly Used Opiates

Opioid	Acute Equianalgesic Dose (mg) Oral	Parenteral
Morphine	30 (acute)	10
Codeine	120	60
Hydrocodone	15	–
Fentanyl	–	0.1
Hydromorphone	7.5	1.5
Levorphanol	4	2
Oxycodone	20	–
Oxymorphone	–	1
Meperidine	Not recommended	Not recommended

Adapted from: Ashburn MA. Principles of analgesic use. Treatment of Acute Pain and Cancer Pain, American Pain Society 2003 and AHCPR.

The intravenous route does not ensure adequate analgesia, as poor analgesic outcomes were common in one cohort of ED patients prescribed IV opioids, particularly those patients already taking long-acting opioids (higher drug tolerance), those thought by their health care provider to be drug-seeking, older patients, and patients with significant pain at presentation.[19]

Fentanyl is the best known synthetic agent and is widely used in pain control. It is 50 to 100 times more potent than morphine and has the added benefit of not causing histamine release and peripheral vasodilation, as found with morphine administration. Based on this physiology, fentanyl should not impact blood pressure as much as other narcotics and, therefore, is preferential in the critically ill trauma population who may have tenuous cardiovascular status from hypovolemic shock. Its method of delivery is diverse, ranging from intravenous to transdermal routes. More recently, the intranasal route has proven to be useful, particularly in the pediatric population.[30] It is excreted in breast milk and, therefore, breastfeeding should be held for 24 hours after its use.[31] Ultra-short-acting synthetic opioids, such as sufentanyl, have been found to be no more efficacious than protocol-driven morphine administration.[32]

One method of opiate delivery worthy of particular mention is patient-controlled analgesia (PCA), although it may not be available in the ED setting. As the name suggests, patients are able to control the amount of analgesia they receive, usually in the form of pressing a button that delivers a bolus. Inadvertent overdosing can be avoided by a built-in lockout period or maximal amount of drug that is programmed into the PCA unit. For those with significant pain, boluses can occur on top of a set basal infusion rate. One meta-analysis examining 55 studies (2,023 patients receiving PCA and 1,838 patients receiving intravenous pain medication) found better pain control and patient satisfaction than conventional parenteral "as-needed" analgesia, although there was no difference in the length of hospital stay.[33]

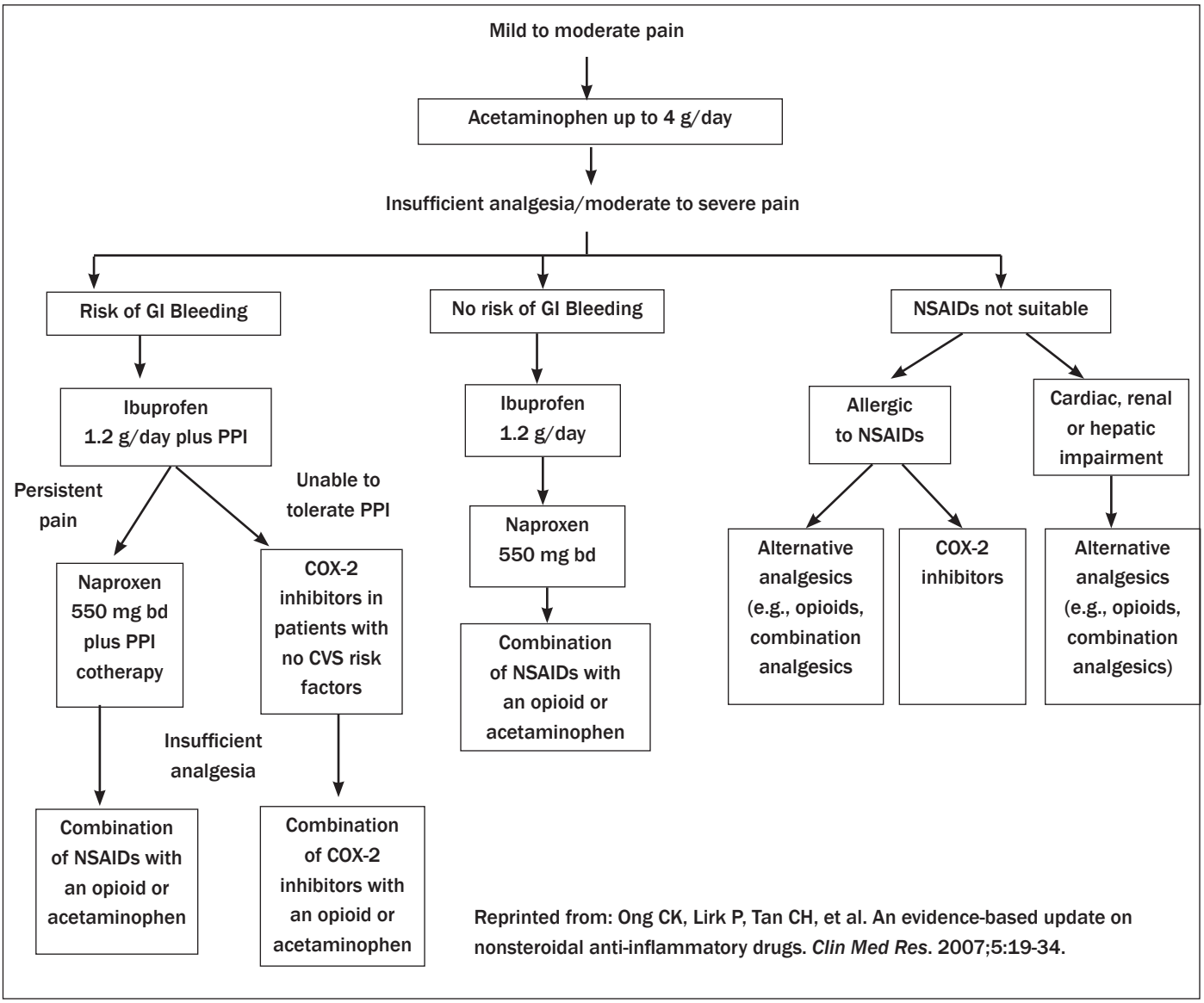
One of the most worrisome side effects of opiate use is respiratory depression, which is usually dependent on the rate and dose that is administered. More common side effects include drowsiness (75%), constipation (55%), and nausea (44%).[34] There also has been some concern in the past that opiate use may impact physical exam findings. This concept has been more thoroughly explored in the setting of acute abdominal pain. A recent meta-analysis of 8 trials (922 patients) found that administration of opioid analgesics as part of the diagnostic process for patients with acute abdominal pain prior to a diagnosis did not increase the risk of treatment errors. It did, however, significantly improve patient pain control when compared to placebo.[35,36] However, pain in the trauma setting has not been exclusively examined.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

The NSAID class non-selectively inhibits cyclo-oxygenase (COX), an enzyme that catalyzes the formation of prostaglandins and thromboxane from arachidonic acid. Through this mechanism, NSAIDs interrupt or mitigate inflammation. The most commonly available and used NSAIDs are from the propionic acid (ibuprofen, naproxen) and acetic acid (indomethacin, ketorolac, diclofenac) derivative classes. Ketorolac is the only available NSAID in intravenous form. Selective COX-2 inhibitors (celecoxib) have been found to have adverse cardiac events and have no role in the acute management of pain. A topical NSAID form is a relatively new method of delivery that does not have the systemic side effects and has been found to have good analgesia.[37] There are no data on how large an area can be covered, and the injury needs to be relatively superficial. In general, for mild to moderate pain, NSAIDs have been found to be better pain-control agents than acetaminophen alone, but have a higher risk of adverse effects such as gastrointestinal bleeding.[38] Additionally, there are more concerning drug-to-drug interactions, with the most important one being that co-administration with aspirin decreases aspirin's anti-platelet effect.[39]

In the pediatric population, ibuprofen at 10 mg/kg was found to be equivalent[40] or superior to

Figure 2. Mild to Moderate Pain Management



Reprinted from: Ong CK, Lirk P, Tan CH, et al. An evidence-based update on nonsteroidal anti-inflammatory drugs. *Clin Med Res*. 2007;5:19-34.

codeine and acetaminophen in minor musculoskeletal injuries[41] and in the outpatient management of extremity fracture was equivalent to acetaminophen/codeine.[42]

There has been some hesitation in the past to use NSAIDs, which were thought to impede healing and growth through inhibition of the COX-2 mechanism, and increase bleeding. Neither the selective COX-2 inhibitor celecoxib nor naproxen affected secondary hemostasis in healthy male volunteers.[43] But bench research has shown retardation of bone growth in animal models, particularly in the early phase of healing, although these findings do not correlate with the limited clinical studies addressing nonunion and delayed fracture healing.[44] Because there are insufficient data examining bone healing and NSAIDs, other analgesic agents are preferred.[45] Soft-tissue healing has a similar paucity of data, but because bone formation is not involved, short courses of NSAIDs may be of therapeutic value in protecting the microcirculation and preserving skeletal muscle from secondary inflammatory tissue damage following closed soft-tissue injury and may play a role in the postoperative management following ligament reconstructions and repairs by reducing pain and swelling and allowing an earlier return of motion.[44]

Other risks occur with NSAID use, with some particularly germane to the trauma population. Perhaps the most well-known risk factor of NSAID use is gastrointestinal hemorrhage, and the trauma population is at high risk for this complication, particularly among those who:

- are greater than 65 years in age (risk increases by five times);
- are taking oral steroids (risk increases by five times);
- have a history of peptic ulcer

disease or upper GI bleeding (risk increases by five times); or

• are taking anticoagulants (risk increases by 10–15 times).[46]

These high-risk patients should receive anther pain medication or at least receive gastro-protective agents, such as sucralfate, H_2 receptor blockers, or a proton pump inhibitor. Recent evidence has suggested NSAID use, particularly ketorolac use, increases the incidence of hemorrhagic and ischemic stroke. Oral agents increase the odds of a stroke from 1.2 to 1.9 (depending on the agent used), but the odds ratio increased to the 4-to-6 range with intravenous ketorolac.[47]

Other Drugs

Other medications have been evaluated for use in the acute pain setting, with mixed results. Although gabapentin has significant value in chronic neuropathic pain, its use in the acute pain setting is not supported.[48,49] Rather, the combination of gabapentin and nortriptyline was found to be more efficacious than either drug given alone for neuropathic pain.[50,51] While carbamazepine appears to be effective in chronic neuropathic pain, there has been no meaningful comparison with other interventions, and its use in the acute pain setting has no evidence-based role.[48,52] Selective serotonin reuptake inhibitors (fluoxetine, paroxetine, citalopram) also have limited and inconsistent results, but have a superior tolerability profile compared with tricyclic antidepressants.[53]

Adjuncts: Spinal and Epidural Blocks

Epidural blocks have proven useful in thoracic and abdominal surgery as well as in cesarian sections and childbirth. This adjunct has been advocated for use in trauma, specifically for chest trauma and multiple rib fractures, an injury that is complex and has significant morbidity and mortality.[54] In 2005, epidural pain control was endorsed as a Level I recommendation for the treatment of blunt thoracic trauma by the Eastern Association of the Surgery of Trauma, specifically citing that, "Use of epidural analgesia (EA) for pain control after severe blunt injury and non-traumatic surgical thoracic pain significantly improves subjective pain perception and critical pulmonary function tests compared with intravenous narcotics. EA is associated with less respiratory depression, somnolence, and gastrointestinal symptoms."[55]

Since then, epidural anesthesia has become a modality to be considered only after patient-controlled analgesia and NSAID use have failed.[56] This is because more recent meta-analyses of previous studies specifically looking at multiple rib fractures cast a less certain light on the use of epidural pain control, finding no reduction in mortality or ICU and inpatient length of stay when compared to other pain-control modalities.[57] The placement and removal of epidurals is further limited by DVT prophylaxis, such as low molecular weight heparin, which can increase the risk of epidural hemorrhage. However, in older patients (> 65 years) with multiple rib fractures in whom high-dose narcotics or NSAIDs are contraindicated or who have serious risks (renal insufficiency, heart failure, tenuous cardiovascular reserve), an epidural catheter may be a good initial approach. The elderly, in particular, benefit from spinal opioids,[58] although they are at higher risk for complications.[59]

Epidural catheter delivery of opioids and topical anesthetics has been of great benefit in post-operative patients, particularly in orthopedic procedures that, physiologically speaking, are similar to the trauma mechanism.[60] Although the usual epidural infusion combinations are an opioid and a local anesthetic (i.e., bupivacaine), epinephrine is used as well.[61]

Adjuncts: Localized Injections and Nerve Blocks

In cases of multiple rib fractures in which contraindications to epidural catheters exist (vertebral fractures, profound hypotension), intercostal nerve blocks can be useful. Various systems have been brought to market in which a percutaneous catheter can be placed in the soft tissue adjacent to the vertebral column, through which a continuous infusion of local anesthetic can be administered to provide a thoracic paravertebral block.[62,63] The degree of pain control from this block is comparable to spinal epidurals with fewer side effects and complications.[63,64]

A host of other regional blocks are well known and used in elective, non-traumatic surgeries. They have a better safety profile than epidurals,[65] but are limited by the availability of physicians with this expertise. Ongoing studies looking at femoral blocks in post-operative and hip-fracture patients, based on prior work suggesting femoral blocks in hip fracture lead to faster pain relief and decreased opiate use, are currently underway and hold promise.[66] A recent literature review examining this issue found that studies evaluating regional blocks are hindered by small sample size and a wide variety of measurements and outcomes. Therefore, it is difficult to determine if nerve blocks confer any significant clinical benefit when compared with other analgesic methods as part of the treatment of a hip fracture. Despite these limitations, nerve blocks appear to reduce the degree of pain experienced by the patient from the hip fracture and subsequent surgery.[67]

Although joint and tendon-sheath injections with steroids or analgesics are not part of mainstream emergency medicine practice, they can be useful in traumatic pain management. Depending on the site, patient history, and level of provider comfort at performing these procedures, local injections can provide pain relief without resorting to systemic medications or may, at least, decrease the need for systemic medications. There are many small case series and prospective trials, but larger studies that allow for a definitive answer regarding effectiveness are lacking. One systematic review specifically

looking at non-traumatic tendinitis found that corticosteroid injections did provide short-term pain control. Generalized conclusions were limited because of the variation in effect between body sites.[68,69] Although traditional teaching has associated steroid injections with an increased risk of tendon rupture, there are few data to support this claim.[70,71]

Adjuncts: Ice and Heat

Despite decades of use, topical application of ice has minimal support for its use in traumatic injury.[72,73] From a physiological standpoint, vasoconstriction should decrease swelling and distention as well as release of pain mediators, but this has yet to be proven in a rigorous, prospective study. One small study evaluating ankle sprains found that applying ice for 10 minutes, then allowing re-warming, followed by another 10 minutes of ice had better ankle pain control with activity after one week when compared to the standard 20 minutes of ice every 2 hours in the acute injury phase.[74] Heat and cold application for minor musculoskeletal strains appears to be equivalent when used in conjunction with NSAIDs,[75] although heat has some potential to improve low back pain.[76]

Education

Nearly half of all ED patients in pain do not desire analgesics, despite having an average pain score in the moderate-to-severe range. Therefore, asking patients whether they have pain and whether they want analgesics should be the first step in determining the need for analgesia.[6] Educating nursing staff, physicians, and housestaff on this issue alone would greatly improve pain control.[2]

Often education of ED staff and patients can decrease oligoanalgesia through simple education,[77] namely remembering to consider pain control as part of the treatment plan. Prior work has demonstrated that nursing staff were more likely to assess pain and to respond to education centering on pain assessment, while physicians were less concerned about problems with analgesics than nurses.[78] In a busy ED or trauma center setting, the necessary reassessment can be difficult, but the institution of a standard protocol for physicians and nurses to follow (including pain medication regimens with milligram per kilogram dosing as well as frequent reassessment) improved patient pain ratings and satisfaction.[77] Treatment protocols administered by nurses have also been shown to be effective in improving the level of analgesia.[79]

Approaches to Pain Control in the Trauma Population

Early and aggressive pain control is the ideal approach for moderate to severe trauma, but other issues that pertain to the underlying traumatic injury must be considered.

Is the Patient Stable? Although pain control should be one priority in the management of trauma patients, it may not be the most important initial priority. An isolated injury, such as an open femur fracture or a dislocated shoulder, may prompt the trauma team to treat pain early, but the primary and secondary ATLS surveys should be the priority and should be completed in a short period of time to identify most causes of hypovolemic shock and hemodynamic instability that would otherwise lead to an adverse outcome.

Is There a Potential That the Patient Might Need to Go to the Operating Room or Require Procedural Sedation? Once the patient has been deemed "stable," the route of pain control should be the next consideration. For moderate to severe pain, there is a high likelihood that these patients will need intravenous access and pain control, so the intravenous route should be established early and utilized. The route of delivery becomes more complex in those patients with isolated injuries that, in most cases, could be treated with oral pain control. One such example is a deformed, swollen ankle, which may be a severe strain, a fracture, or a dislocation. Since there is a high likelihood of operative interventions or procedural sedation (such as to reduce a severely distracted fracture), intravenous pain control while the patient undergoes imaging may be a more prudent route than oral pain medication, as the oral route may delay further intervention. (Although the risk of aspiration from 50 mL of water and two pills is low, many anesthesiologists will not intervene on patients who have not been nil per os for at least 8 hours.) More recently, acetaminophen has become available in an intravenous form and could be considered for mild to moderate pain (15 mg/kg every 6 hours) or fever in those who are unable to take medications orally (such as those awaiting a procedure).

How Will Medication Impact Management of Traumatic Injuries? Ideally, longer-acting pain-control agents should be used to avoid frequent episodic pain that requires repeated dosing that occurs with shorter half-life medications. However, in the trauma population, the potential side effects of pain medicines must be considered. A common example is the patient with a subdural hematoma or intraparenchymal hemorrhage who will need serial neurological reassessments. Any decrease in mental status can result in an emergent head CT, placement of an intracranial pressure monitor, or operative intervention, so every effort should be made to minimize medications that impair mental status. Another example is a patient with an aortic injury, in whom a drop in blood pressure could potentially be from aortic hemorrhage, so medications that may cause hypotension are best avoided. In both head and aortic injuries, fentanyl would represent an ideal choice given its short half life and side effect profile discussed earlier.

With these questions in mind, a reasonable approach comes from the American Geriatric Society 2002 recommendations:

- Introduce one agent at a time,

at a low dose, followed by slow dose titration;

• Allow a sufficient interval between drugs to allow assessment of the effect;

• Monitor the patient and adjust if required to limit adverse events.

Although these recommendations are for chronic pain, the stepwise approach holds true in the acute pain setting as well.[80]

For mild to moderate pain in patients with a low likelihood of surgery or procedural sedation, acetaminophen at 4 g/day is considered first line, provided there is no underlying hepatic dysfunction or ethanol abuse.[81] If heavy alcohol use is suspected or documented, acetaminophen should be limited to 2 g/day.[39] This total daily limit should be kept in mind when other acetaminophen-containing products (i.e., Percocet) are also prescribed or are already being taken.

In the young, healthy population, NSAIDs can be appropriate first-line agents for mild to moderate pain. In the geriatric population, if NSAIDs must be used, the lowest effective dose for the shortest amount of time is suggested. Ibuprofen has been shown to be the least potentially harmful agent.[38] If there is a risk for GI bleeding, either an H_2 blocker or proton pump inhibitor can be co-administered to avoid bleeding. (*See Figure 2*). Drugs to avoid in the geriatric population include propoxyphene, indomethacin, pentazocine, and ketorolac (which has a four-fold higher risk of gastrointestinal bleeding than ibuprofen).[82]

The next level of pain control (moderate to severe) is the opiate class, with morphine, fentanyl, or hydromorphone representing the typical agents. Orally administered opiates have equal efficacy to the intravenous preparations, but if surgery is a realistic possibility (i.e., an open ankle fracture), or if pain control is needed sooner rather than later, the intravenous route should be chosen over the oral route. Caveats for the cautious use of opiates include the presence or possibility of hypovolemic shock/hypotension and respiratory depression or tenuous respiratory function (i.e., rib fractures in a COPD patient). In patients with major trauma who have suspected significant injury, fentanyl (2 mcg/kg for low dose, 2-20 mcg/kg for moderate dose, 20-50 mcg/kg for high dose) is an ideal agent, given that its half life is shorter than morphine or hydromorphone (1-2 hours vs. 4-6 hours) and the lack of histamine release that can cause hypotension. It can be used in patients with mild to moderate renal and/or hepatic dysfunction.[83]

Regardless of the agent used, frequent reassessment, ideally through a protocol that can be initiated in the ED and continued in the inpatient unit, has led to improved pain control, outcomes, and decreased cost.[84] In most patients, medication usage is a stopgap measure until definitive care (i.e., epidural for multiple rib fractures, splinting of a fractured wrist) can be obtained. Although adjuncts such as epidurals and whole extremity nerve blocks rarely occur in the ED setting, obtaining personnel who can do the procedure is the rate limiting factor, and that can at least be initiated in the ED after discussion with the trauma team.

Conclusions

The moderate to severely injured trauma population represents complex patients in whom adequate analgesia must be considered against life- and limb-threatening injury and hemorrhagic shock. Once the potential for operative intervention and hemodynamic instability have been addressed, a stepwise approach of escalating pain management can be used, with frequent reassessment incorporated into the treatment plan.

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CME/CNE Questions

1. A 38-year-old male arrives at the ED after a fall from a tree stand while hunting. His chief complaint is right leg pain. Per EMS, the patient suffered a brief loss of consciousness, but was awake upon their arrival, although slightly confused. The patient has no allergies and no medical problems. Initial vitals are: heart rate = 115 beats per minute, blood pressure = 102/50 mm Hg, temperature = 98.7° F, respiratory rate = 30 breaths per minute. On your exam, there is an obvious deformity of the right thigh with intact distal perfusion and pulses. Appropriate initial pain control would be (patient weight is 70 kg):
   A. 7 mg morphine IV
   B. 2 tablets of 5 mg oxycodone/350 mg acetaminophen PO
   C. fentanyl 50 mcg IV
   D. ketorolac 60 mg IM
   E. acetaminophen 650 mg PO
2. An excellent first-line agent for mild to moderate pain in a geriatric patient with little chance of needing immediate operative intervention is:
   A. propoxyphene
   B. pentazocine
   C. ketorolac
   D. acetaminophen
   E. meperidine
3. Fentanyl is a better agent to use in the critically injured trauma patient because:
   A. Its longer half-life decreases frequent dosing.
   B. Its lack of histamine release decreases the likelihood of hypotension.
   C. It is more easily reversible with naloxone if untoward effects occur.
   D. It has less abuse potential than other opioids.
   E. It is less expensive than other narcotic agents.
4. Application of ice or cold compresses:
   A. has been clinically proven to decrease the inflammatory response.
   B. should be avoided because of the risk of cold injury.
   C. may improve mobilization and pain control in the short term.
   D. is always beneficial for long-term pain control.
   E. can cause tissue ischemia from vasoconstriction.
5. Epidural pain control is most useful in:
   A. patients with rib and vertebral fractures.
   B. patients with a high opioid tolerance.
   C. those with only a few isolated rib fractures.
   D. patients in whom systemic pain control carries a higher risk.
   E. intubated patients on positive pressure support.
6. Pain in the acutely injured is unique because:
   A. Pain in this population tends to be moderate to severe and requires frequent reassessment.
   B. Other competing factors such as hypotension must be considered.

CNE/CME Objectives

Upon completing this program, the participants will be able to:

a.) discuss conditions that should increase suspicion for traumatic injuries;
b.) describe the various modalities used to identify different traumatic conditions;
c.) cite methods of quickly stabilizing and managing patients; and
d.) identify possible complications that may occur with traumatic injuries.

C. There is a high potential for emergent surgery, making oral medications less desirable.
D. A substantial proportion of the trauma population is elderly, in whom first-line pain medications may be contraindicated.
E. All of the above.

7. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) in the elderly:
   A. is the first-line agent unless they are allergic to NSAIDs.
   B. must at all times be given with a proton pump inhibitor or H2 blocker.
   C. should be used with caution with the lowest dose and shortest duration that provides pain control.
   D. is contraindicated.
   E. should be used at half the usual dose because of impaired renal and kidney function.

8. Tendon-sheath or bursa local injections:
   A. have been well validated in multiple, large, prospective trials that support their use.
   B. can have systemic side effects despite their local use.
   C. can be a useful adjunct in practitioners familiar with their use.
   D. of steroids or local anesthetics have equal onset and efficacy.
   E. should be avoided at all times.

9. Use of gabapentin alone has significant value in acute and chronic neuropathic pain.
   A. true
   B. false

10. Populations who are well known to receive inadequate analgesia include:
    A. older patients.
    B. minorities.
    C. intubated patients.
    D. non-English-speaking patients.
    E. all of the above.

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To earn credit for this activity, please follow these instructions.

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