Drug of abuse and opioid analgesics

Introduction

Drug abuse is a serious public health problem that affects almost every community and family in some way. Each year drug abuse causes millions of serious illnesses or injuries in populations. The most commonly abused substances are:

1- Stimulants (Amphetamines, Cocaine and Methylenedioxymethamphetamine (MDMA)).
2- Hallucinogens (such as marijuana)
3- other drugs (ethanol and prescription drugs (particularly opioid)).

SYMPATHOMIMETICS (SPMCs) or STIMULANTS

- SPMCs are stimulants that mimic the sympathetic nervous system, producing "fight-or flight" responses. SPMCs usually produce a relative increase of adrenergic neurotransmitters at their sites of action, thereby causing **tachycardia, hypertension, hyperthermia, and tachypnea.**

- Aside from their stimulant effect, many of these have a remarkable ability to produce pleasure. Consequently, their addictive potential and monetary value on the illicit market offer a huge profit motive.

A- Cocaine (IMPORTANT)

- It causes CNS stimulation by inhibiting the reuptake of norepinephrine into the adrenergic neuron, thus increasing the amount of catecholamines available at the synapse.
- The profound ability of cocaine to stimulate the pleasure center of the human brain is thought to result from inhibition of reuptake of dopamine and serotonin.
- Cocaine has minimal bioavailability when taken by the oral route. Instead, the cocaine hydrochloride powder is snorted, or solubilized and injected.
- The cocaine powder cannot be effectively smoked, as it is destroyed upon heating. However, crack cocaine, an alkaloidal form, can be smoked. Smoking is an extremely effective route of administration, as the lungs are richly perfused with blood and carry the drug within seconds to its site of action, the brain.
- This causes an intense euphoria or "rush" that is followed rapidly by an intense dysphoria or "crash." It is this immediate positive reinforcement, followed rapidly by the negative reinforcement, that makes the drug, particularly in this form, so addictive.

- The clinical manifestations of cocaine toxicity are a function of its stimulant effects. Common reasons for cocaine users to present to the emergency department include psychiatric complaints (depression precipitated by cocaine dysphoria or agitation), convulsions, hyperthermia, and chest pain.
- The **hyperthermia** is caused by cocaine-induced CNS stimulation that generates increased heat production, coupled with vasoconstrictive effects of cocaine that minimize the ability to dissipate the heat.
- **Cocaine-related chest pain** can be chest muscle pain or cardiac in nature, as cocaine causes vasoconstriction of the coronary arteries and accelerates the atherosclerotic process.
- Commonly, cocaine is consumed with alcohol, which creates a secondary metabolite called **cocaethylene**. This metabolite is cardiotoxic and further contributes to the cardiac issues related to cocaine consumption. Cocaine chest pain can also be due to pulmonary damage caused by inhaling this hot impure substance.
- Cocaine convulsions are a natural extension of the CNS stimulant effect.
- Cocaine toxicity is treated by calming and cooling the patient.
- Benzodiazepines, such as lorazepam, help to calm the agitated patient and can both treat and prevent convulsions. In addition, the calming effect helps cool the patient and manage the hyperthermia. This is an important effect, as hyperthermia is one of the major causes of cocaine fatalities. The remainder of cocaine toxicity is treated with short-acting antihypertensives, anticonvulsants, and symptomatic supportive care.

B- Amphetamines (ATNs)

ATNs such as methamphetamine are sympathomimetics with clinical effects very similar to those of cocaine. In many cases, these effects may last longer and be associated with more stimulation and less euphoria when compared to cocaine. Treatment of amphetamine toxicity is similar to that of cocaine toxicity. The main therapeutic uses of ATNs can be summarised in the treatment of the following:

1- Attention deficit hyperactivity disorder (ADHD)
2- Narcolepsy
3- Appetite suppression

On the other hand, ATNs may cause addiction, leading to dependence, tolerance, and drug seeking behavior.

Adverse effects

1- CNS effects: Adverse effects of ATN usage include insomnia, irritability, weakness, dizziness and tremor. ATN can also cause confusion, delirium, panic states, and suicidal tendencies, especially in mentally ill patients.

Chronic ATN use produces a state of "amphetamine psychosis" that resembles the psychotic episodes associated with schizophrenia. Whereas long-term ATN use is associated with dependence, tolerance to its effects may occur within few weeks.

2- Cardiovascular effects: In addition to its CNS effects, ATN causes palpitations, cardiac arrhythmias, hypertension, and anginal pain.

3- GI system effects: ATN acts on the GI system, causing anorexia, nausea, vomiting, abdominal cramps, and diarrhea.

C- Methylenedioxymethamphetamine (MDMA) (IMPORTANT)

- MDMA, commonly known as ecstasy or Molly, is a hallucinogenic amphetamine with profound serotonin- releasing effects.

- Because of its unique serotonin properties, it is sometimes referred to as an "empathogen," and tactile stimulation is particularly pleasurable to users. Many users describe a sense of well-being and social interactivity.

- The Internet is replete with warnings to drink plenty of water while using ecstasy, and, indeed, some of the early deaths associated with MDMA toxicity involved dehydration and renal failure.

- Like many amphetamines, MDMA can cause bruxism (teeth grinding) and trismus (jaw clenching), which explain the baby pacifiers and lollipops that have been popularized among "ravers."

HALLUCINOGENS

Lysergic acid diethylamide (LSD), marijuana, and synthetic **cannabinoids** are substances that fall into this category.

Marijuana

- Nowadays, marijuana is the most frequently used illicit drug, and the illicit drug that new users are most likely to try.

- The main psychoactive alkaloid contained in marijuana is Δ9-tetrahydrocannabinol (THC).

- Specific receptors in the brain, cannabinoid or CB1 receptors, were found to be reactive to THC. When CB1 receptors are activated by marijuana, the effects produced include physical relaxation, hyperphagia (increased appetite), increased heart rate, decreased muscle coordination, and conjunctivitis. Moreover, THC can produce euphoria, followed by drowsiness and relaxation.

- The effects of marijuana on γ-aminobutyric acid (GABA) in the hippocampus diminish the capacity for short-term memory in users, and this affect seems to be more pronounced in adolescents. In addition to adversely affecting short-term memory and mental activity, THC decreases muscle strength and impairs highly skilled motor activity such as that required to drive a car.

- The effects of THC appear immediately after the drug is smoked, but maximum effects take about 20 minutes. By 3 hours, the effects largely disappear. Long-term effects of use may include chronic bronchitis, chronic obstructive pulmonary disease, and exacerbation of mental illness.

- Marijuana may be found in the body up to 3 months after last usage in heavy chronic users. For this reason, withdrawal occurs much later in individuals who previously used marijuana heavily. Withdrawal may include depression, pain, and irritability.

- Although not well studied for medicinal use, marijuana has been used to help in the treatment of chemotherapy-induced nausea and vomiting.

OTHER SUBSTANCES

- Ethanol (EtOH) is a clear colorless hydroxylated hydrocarbon that is the product of fermentation of fruits, grains, or vegetables. It is a major cause of fatal automobile accidents, drownings, and fatal falls and is a related factor in many hospital admissions. Alcohol is the most commonly abused substance in modern society.

- It is thought that EtOH exerts its desired and toxic effects through several mechanisms, including enhancing the effects of the inhibitory neurotransmitter GABA, inducing the release of endogenous opioids, and altering levels of serotonin and dopamine.

- EtOH is a selective CNS depressant at low doses while at high doses, it is a general CNS depressant, which can result in coma and respiratory depression.

- Drinking EtOH traditionally has been the most common route of administration, although recently the inhalation of aerosolized ethanol has gained popularity.

- Peak of levels are generally achieved in 20 minutes to 1 hour of ingestion.

- Medical management of acute EtOH toxicity includes symptomatic supportive care and the administration of thiamine and folic acid to prevent/treat Wernicke encephalopathy and macrocytic anemia. Extremely high levels can be dialyzed, although that is rarely necessary, and could precipitate withdrawal in an alcoholic.

- Chronic EtOH abuse can cause profound hepatic, cardiovascular, pulmonary, hematologic, endocrine, metabolic, and CNS damage.

- Sudden cessation of EtOH ingestion in a heavy drinker can precipitate withdrawal manifested by tachycardia, sweating, tremor, anxiety, agitation, hallucinations, and convulsions.

- Alcohol withdrawal is a life-threatening situation that should be medically managed with symptomatic/supportive care, benzodiazepines, and long-term addiction treatment.

The following are drugs, which can be used in the treatment of alcohol dependence:

1- Disulfiram

Disulfiram interrupts the metabolism process of alcohol, resulting in the accumulation of acetaldehyde in the blood (a primary metabolite of alcohol) leading to flushing, tachycardia, hyperventilation, and nausea. A conditioned avoidance response is induced so that the patient abstains from alcohol to prevent the unpleasant effects of disulfiram induced acetaldehyde accumulation.

2- Naltrexone

Naltrexone is a competitive and relatively long-acting opioid antagonist that helps decrease cravings for alcohol. It should be used in conjunction with supportive psychotherapy. Naltrexone is better tolerated than disulfiram and does not produce the aversive reaction that disulfiram does.

PRESCRIPTION DRUG ABUSE:

Some commonly abused prescription drugs include opioids, benzodiazepines, and barbiturates, with opioids outpacing the other prescription drugs by a large margin. To understand the abuse of opioids, firstly, we need to know some information about them. All opioids are chemically related and interact with opioid receptors on nerve cells in the body and brain. Opioid pain relievers are generally safe when taken for a short time and as prescribed by a doctor, but because they produce euphoria in addition to pain relief, they can be abused (taken in a different way or in a larger quantity than prescribed or taken without a doctor's prescription). Regular use even as prescribed by a doctor can lead to dependence and, when abused, opioid pain relievers can lead to addiction, overdose incidents, and deaths.

OPIOID RECEPTORS

The major effects of the opioids are mediated by three receptor families, which are commonly designated as **μ (mu), κ (kappa), and δ (delta).** Each receptor family exhibits a different specificity for the drug(s) it binds. **For example**, the analgesic properties of the opioids are primarily mediated by the μ receptors that modulate responses to thermal, mechanical, and chemical nociception.

OPIOID AGONISTS

Morphine is the major analgesic drug contained in crude opium and is the prototype strong μ receptor agonist. Codeine is present in crude opium in lower concentrations and is inherently less potent, making codeine the prototype of the weak opioid agonists. The currently available opioids have differences in receptor affinity, pharmacokinetic profiles, available routes of administration, and adverse effect profiles. Comparing other available opioids to morphine is helpful in identifying the unique differences to guide the selection of a safe and effective pain management regimen.

1- Morphine

Mechanism of action: Morphine and other opioids exert their major effects by interacting with opioid receptors on the membranes of certain cells in the CNS and other anatomic structures, such as the gastrointestinal (GI) tract and the urinary bladder. Morphine also acts at κ receptors of the spinal cord. It decreases the release of substance P, which modulates pain perception in the spinal cord. It also appears to inhibit the release of many excitatory transmitters from nerve terminals carrying nociceptive (painful) stimuli.

Actions and therapeutic uses: Some selected morphine actions are summarised in Figure 1-A while some therapeutic uses of morphine and other opioids are listed in **Figure 1-B.**

A

Action	Explanation
Euphoria	It produces a powerful sense of well-being.
Respiration	It causes respiratory depression by reduction of the sensitivity of respiratory center neurons to CO_2. This can occur with ordinary doses of morphine in patients who are opioid-naïve and can be accentuated as the dose is increased until ultimately respiration ceases. Respiratory depression is the most common cause of death in acute opioid overdoses.
Depression of cough reflex	The receptors involved in the antitussive action appear to be different from those involved in analgesia.
Miosis	The pinpoint pupil characteristic of morphine use results from stimulation of μ and κ receptors. There is little tolerance to the effect, and all morphine abusers demonstrate pinpoint pupils. This is important diagnostically, because many other causes of coma and respiratory depression produce dilation of the pupil.
Cardiovascular	With large doses, hypotension and bradycardia may occur.
Histamine release	It releases histamine from mast cells causing urticaria, sweating, and vasodilation. Because it can cause bronchoconstriction, morphine should be used with caution in patients with asthma.
Hormonal actions	It increases growth hormone release and enhances prolactin secretion. It increases antidiuretic hormone and leads to urinary retention.

B

Therapeutic Use	Comments
Analgesia	*Morphine* is the prototype opioid agonist. Opioids are used for pain in trauma, cancer, and other types of severe pain.
Treatment of diarrhea	Opioids decrease the motility and increase the tone of intestinal circular smooth muscle. [Note: Agents commonly used include *diphenoxylate* and *loperamide*
Relief of cough	*Morphine* does suppress the cough reflex, but *codeine* and *dextromethorphan* are more commonly used.
Treatment of acute pulmonary edema	Intravenous *morphine* dramatically relieves dyspnea caused by pulmonary edema associated with left ventricular failure, possibly via the vasodilatory effect. This, in effect, decreases cardiac preload and afterload, as well as anxiety experienced by the patient.
Anesthesia	Opioids are used as preanesthetic medications, for systemic and spinal anesthesia, and for postoperative analgesia.

Figure 1: A- Selected Actions of morphine. B-Selected clinical uses of opioids.

Adverse effects:

Many adverse effects are common across the entire opioid class. With most μ agonists, severe respiratory depression can occur and may result in death from acute opioid overdose. Elevation of intracranial pressure, particularly in head injury, can be serious. Morphine should be used with caution in patients with asthma, liver disease, or renal dysfunction. Because of respiratory depression and carbon dioxide retention, cerebral vessels dilate and increase cerebrospinal fluid pressure. Morphine is usually contraindicated in individuals with head trauma or severe brain injury.

Tolerance:

Repeated use produces tolerance to the respiratory depressant, analgesic, euphoric, and sedative effects of morphine. However, tolerance usually does not develop to the pupil-constricting and constipating effects of the drug.

2- Methadone (MTD)

MTD is a synthetic, orally effective opioid that has variable equianalgesic potency compared to that of morphine, and the conversion between the two products is not linear. MTD induces less euphoria and has a longer duration of action. The actions of MTD are mediated by μ receptors. In addition, MTD is an antagonist of the N-methyl-d-aspartate (NMDA) receptor and a norepinephrine and serotonin reuptake inhibitor.

MTD is also used in the controlled withdrawal of dependent abusers from opioids and heroin. Oral MTD is administered as a substitute for the opioid of abuse, and the patient is then slowly weaned from MTD. MTD is also constipating, but less so than morphine. An understanding of the pharmacokinetics of MTD is important for proper use of this medication. MTD is very lipophilic, leading to accumulation in the fat tissues. The half-life of methadone ranges from 12 to 40 hours.

Consequently, the time frame it takes for an individual patient to reach steady state can vary dramatically, from 35 hours to 2 weeks. Upon repeated dosing, MTD can accumulate due to the long terminal half-life, thereby leading to toxicity.

MTD can produce physical dependence like that of morphine but has less neurotoxicity than morphine due to the lack of active metabolites. MTD can prolong the QT interval and cause torsades de pointes, possibly by interacting with cardiac potassium channels.

3- OTHER ANALGESICS

Tramadol

Tramadol is a centrally acting analgesic that binds to the μ opioid receptor. The drug undergoes extensive metabolism via CYP450 2D6, leading to an active metabolite

with a much higher affinity for the μ receptor than the parent compound. In addition, it weakly inhibits reuptake of norepinephrine and serotonin. It is used to manage moderate to moderately severe pain.

Its respiratory depressant activity is less than that of morphine. Overdose or drug–drug interactions with medications, such as SSRIs (Selective serotonin reuptake inhibitors), MAOIs (Monoamine oxidase inhibitors), and tricyclic antidepressants, can lead to toxicity manifested by CNS excitation and seizures. As with other agents that bind the μ opioid receptor, tramadol has been associated with abuse.

4- ANTAGONISTS

The opioid antagonists bind with high affinity to opioid receptors but fail to activate the receptor-mediated response. Administration of opioid antagonists produces no profound effects in normal individuals. However, in patients' dependent on opioids, antagonists rapidly reverse the effect of agonists, such as morphine or any full μ agonist, and precipitate the symptoms of opioid withdrawal. Figure 2 summarizes some of the signs and symptoms of opioid withdrawal.

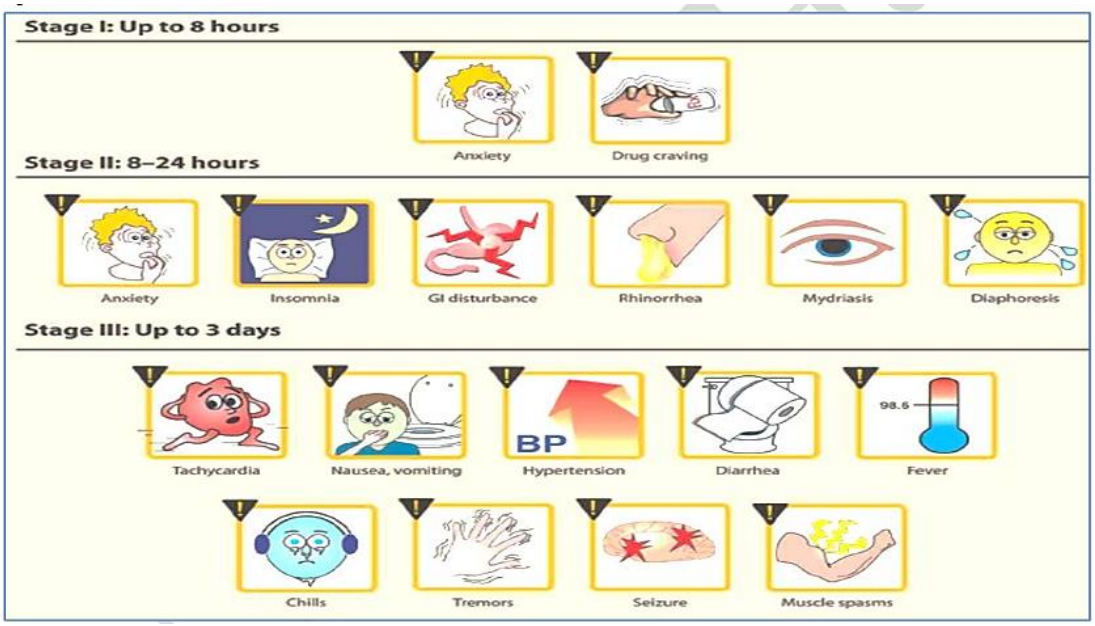

Figure 2: Opiate withdrawal syndrome. GI = gastrointestinal.

Naloxone

Naloxone is used to reverse the coma and respiratory depression of opioid overdose. It rapidly displaces all receptor-bound opioid molecules and, therefore, is able to reverse the effect of a morphine overdose. Within 30 seconds of IV injection of naloxone, the respiratory depression and coma characteristic of high doses of morphine are reversed, causing the patient to be revived and alert.

Naloxone has a half-life of 30 to 81 minutes; therefore, a patient who has been treated and recovered may lapse back into respiratory depression. Naloxone is a competitive antagonist at μ, κ, and δ receptors, with a 10-fold higher affinity for μ than for κ receptors. This may explain why naloxone readily reverses respiratory depression with only minimal reversal of the analgesia that results from agonist stimulation of κ receptors in the spinal cord.

Oral manifestations for drug abusers

Drug abusers often present with telltale signs of their addiction. Some symptoms will not be determinable during a dental appointment, such as loss of appetite and sleeplessness, but others may be quite noticeable even during routine examinations.

Oral problems of drug abuse are complex and include not only the direct effects of the drug but also the results of poor dietary and oral hygiene habits. **Table 1** lists some common oral manifestations of drug abuse. Drug abuse may cause suppression of the immune system, making patients more susceptible to other health problems. Diminished self-esteem, depression, and lack of motivation are also signs of drug abuse and may negatively affect patients' ability to adequately perform oral hygiene and regularly visit their dental provider.

Xerostomia is often a side effect of opiates, amphetamines, barbiturates, hallucinogens, marijuana, and alcohol. The resulting decreased salivary flow makes users much more susceptible to dental caries and periodontal diseases. Furthermore, chemically dependent patients often crave sugar, which leads to the consumption of large quantities of sweetened carbonated beverages, thereby increasing enamel erosion by decreasing salivary pH (**Figure 3**). Drug addicts may also be at a higher risk of bruxism, dentin hypersensitivity, and necrotizing ulcerative gingivitis.

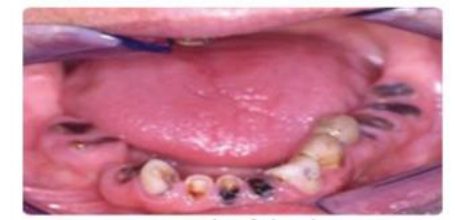

Figure 3: Devastating oral effect of methamphetamine abuse

Drug and alcohol/tobacco users have a higher incidence of oral lesions, oral candidiasis, oral ulcerations, and gingival laceration. Aangular cheilitis, and stomatitis are more common among users. The use and abuse of alcohol and tobacco also greatly increases the risk of oral

TABLE 1. ORAL MANIFESTATIONS OF SUBSTANCE ABUSE.

- Angular cheilitis
- Bruxism
- Missing teeth
- Oral candidiasis
- Oral lesions
- Oral ulcerations
- Periodontal diseases
- Rampant dental caries

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