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.

A- Cocaine

- 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.
- **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.

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.
- 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).

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.

- 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 encephalopathy and macrocytic anemia. Extremely high levels can be dialyzed, although that is rarely necessary.

- 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. 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

Opioid receptors are G protein-coupled receptors (GPCRs) on nerve cells that respond to both natural body chemicals (endorphins) and external drugs (opioids) to regulate pain, reward, and addiction; the main types are **mu (μ), delta (δ), and kappa (κ),** which mediate pain relief (analgesia) but also cause euphoria, respiratory depression (mu), or dysphoria (kappa). They are crucial for pain management but also drive addictive behaviors, acting as key targets for medications like morphine and heroin, as well as newer addiction therapies

OPIOID AGONISTS

Opioid agonists are drugs that activate opioid receptors in the brain and body, mimicking the effects of natural opioids like endorphins to block pain signals, providing analgesia for severe pain and treating opioid dependence by reducing cravings and withdrawal.

How They Work

Receptor Binding: They bind to opioid receptors (especially mu-receptors) in the central and peripheral nervous systems.

Pain Relief: This binding inhibits pain signals from reaching the brain, creating strong analgesia.

Reward System: They also trigger dopamine release in reward centers, contributing to their euphoric effects and potential for addiction.

Types of Opioid Agonists

Full Agonists: Fully activate receptors (Morphine, Oxycodone, Fentanyl, Methadone).

Partial Agonists: Partially activate receptors, producing weaker effects (Buprenorphine).

Naturally Occurring: Morphine, Codeine, Heroin (semisynthetic).

Synthetic: Fentanyl, Methadone, Meperidine (Pethidine).

Examples of Common Agonists

Morphine: A classic full agonist.

Fentanyl: A powerful synthetic agonist, much stronger than morphine.

Oxycodone: Used for pain relief, found in medications like Percocet.

Buprenorphine: A partial agonist, crucial for addiction treatment (Suboxon).

Methadone: A long-acting full agonist used for pain and addiction.

Side Effects

Common: Sedation, nausea, constipation, respiratory depression .

Long-term: Physical dependence, tolerance, and addiction.

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.

Side effects

Nausea, constipation, dry mouth, drowsiness, dizziness, vomiting.

4- ANTAGONISTS

Opioid antagonists are medications that block opioid receptors in the brain and body, reversing or preventing opioid effects like overdose, respiratory depression, and addiction, with common examples being **naloxone** (for emergency overdose reversal) and **naltrexone**

(for treating addiction and alcohol use disorder). They work by binding tightly to opioid receptors without activating them, effectively kicking opioids off the receptors.

How They Work

-They compete with opioids (like morphine, heroin, fentanyl) for opioid receptor sites.

-With higher affinity, they displace the opioid, preventing it from causing euphoria or slowing breathing.

-Some, like naloxone, act centrally (brain/spine), while others, like methylnaltrexone, are peripheral (gut).

Examples & Uses

Naloxone (Narcan): Rapidly reverses overdose, available as nasal spray, injection (IV, IM).

Naltrexone (Vivitrol): Blocks opioid effects, used long-term for opioid and alcohol addiction.

Methylnaltrexone (Relistor), Alvimopan (Entereg): Peripheral antagonists for opioid-induced constipation.

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.

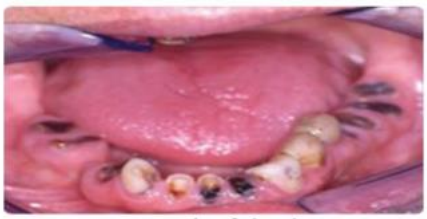

Figure 3: Devastating oral effect of methamphetamine abuse

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

References:

1- Katzung, B.G., 2018. Basic and clinical pharmacology. Mc Graw Hill.
2- Whalen, K., 2019. Lippincott illustrated reviews: pharmacology. Lippincott Williams & Wilkins.
3- https://dimensionsofdentalhygiene.com/article/the-complexity-of-addiction/