Drugs of Abuse

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. Abused drugs are summarised in figure 1.

STIMULANTS
Amphetamines
Cocaine
Methylenedioxymethamphetamine (MDMA)
Cocaine
Synthetic cathinones ("bath salts")
HALLUCINOGENS
Lysergic acid diethylamide (LSD)
Marijuana
Synthetic cannabinoids
OTHER DRUGS OF ABUSE
Ethanol
Prescription drugs (particularly opioids)

Figure1: Summary of commonly abused substances.

1- SYMPATHOMIMETICS

- Sympathomimetics are stimulants that mimic the sympathetic nervous system, producing "fight-or-flight" responses. Sympathomimetics 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

- It causes central nervous system (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 not just a function of its inherent toxicity, but also of its adulterants. An example of a common adulterant that has been found in street samples of cocaine is levamisole, an anthelmintic used to deworm cattle and pigs. Levamisole has the ability to cause agranulocytosis, a profound decrease in neutrophils, leaving a weakened immune system prone to opportunistic infections, which have been described among cocaine users.
- A few of the more common reasons for cocaine users to come to the emergency department include psychiatric complaints (depression precipitated by cocaine dysphoria, 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

Amphetamines 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. Therapeutic uses of amphetamines can be summarised in the treatment of the following:

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

On the other hand, amphetamines may cause addiction, leading to dependence, tolerance, and drug-seeking behavior. In addition, they have the following undesirable effects:

a. CNS effects: Adverse effects of amphetamine usage include insomnia, irritability, weakness, dizziness, tremor, and hyperactive reflexes. Amphetamine can also cause confusion, delirium, panic states, and suicidal tendencies, especially in mentally ill patients.

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

b. Cardiovascular effects: In addition to its CNS effects, amphetamine causes palpitations, cardiac arrhythmias, hypertension, and anginal pain.

c. GI system effects: Amphetamine acts on the GI system, causing anorexia, nausea, vomiting, abdominal cramps, and diarrhea.

C. Methylenedioxymethamphetamine (MDMA)

- 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."**

2- 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.
- Tolerance develops rapidly in users, and withdrawal has been observed.
- 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.

3- ETHANOL

- 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 ethanol 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.
- Ethanol 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 ethanol 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. There is a greater subjective feeling of intoxication while levels are ascending (absorption), as compared to when levels are descending.
- Medical management of acute ethanol 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 ethanol abuse can cause profound hepatic, cardiovascular, pulmonary, hematologic, endocrine, metabolic, and CNS damage
- Sudden cessation of ethanol 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.

Naltrexone

Naltrexoneis a long-acting opioid antagonist that should be used in conjunction with supportive psychotherapy. Naltrexone is better tolerated than disulfiram and does not produce the aversive reaction that disulfiram does.

4- 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 various 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.

Morphine

1. Mechanism of action: Morphine and other opioids exert their major effects by interacting stereospecifically 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.

Morphine also appears to inhibit the release of many excitatory transmitters from nerve terminals carrying nociceptive (painful) stimuli.

Actions:

a. **Analgesia:** Morphine and other opioids cause analgesia (relief of pain without the loss of consciousness) and relieve pain both by raising the pain threshold at the spinal cord level and, more importantly, by altering the brain's perception of pain. Patients treated with opioids are still aware of the presence of pain, but the sensation is not unpleasant.

b. **Euphoria:** Morphine produces a powerful sense of contentment and well-being. Euphoria may be caused by disinhibition of the dopamine-containing neurons of the ventral tegmental area.

c. **Respiration:** Morphine causes respiratory depression by reduction of the sensitivity of respiratory center neurons to carbon dioxide. 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.

d. **Depression of cough reflex:** Both morphine and codeine have antitussive properties. In general, cough suppression does not correlate closely with the analgesic and respiratory depressant properties of opioid drugs. The receptors involved in the antitussive action appear to be different from those involved in analgesia.

e. **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. [Note: This is important diagnostically, because many other causes of coma and respiratory depression produce dilation of the pupil.]

f. **Emesis:** Morphine directly stimulates the chemoreceptor trigger zone in the area postrema that causes vomiting.

g. **GI tract:** Morphine relieves diarrhea by decreasing the motility and increasing the tone of the intestinal circular smooth muscle. Morphine also increases the tone of the anal sphincter. Overall, morphine and other opioids produce constipation.

h. **Cardiovascular:** Morphine has no major effects on the blood pressure or heart rate at lower dosages. With large doses, hypotension and bradycardia may occur. Because of respiratory depression and carbon dioxide retention, cerebral vessels dilate and increase cerebrospinal fluid pressure. Therefore, morphine is usually contraindicated in individuals with head trauma or severe brain injury.

i. **Histamine release:** Morphine 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.

j. **Hormonal actions:** Morphine increases growth hormone release and enhances prolactin secretion. It increases antidiuretic hormone and leads to urinary retention.

k. **Labor:** Morphine may prolong the second stage of labor by transiently decreasing the strength, duration, and frequency of uterine contractions.

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.

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.

Methadone

Methadone 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. Methadone induces less euphoria and has a longer duration of action. The actions of methadone are mediated by μ receptors. In addition, methadone is an antagonist of the N-methyl-d-aspartate (NMDA) receptor and a norepinephrine and serotonin reuptake inhibitor.

Methadone is also used in the controlled withdrawal of dependent abusers from opioids and heroin.

Oral methadone is administered as a substitute for the opioid of abuse, and the patient is then slowly weaned from methadone. Methadone is also constipating, but less so than morphine.

An understanding of the pharmacokinetics of methadone is important for proper use of this medication. Methadone 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, methadone can accumulate due to the long terminal half-life, thereby leading to toxicity.

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

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. Naloxone can only partially reverse the analgesia produced by tramadol or its active metabolite. Anaphylactoid reactions have been reported. 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.

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.

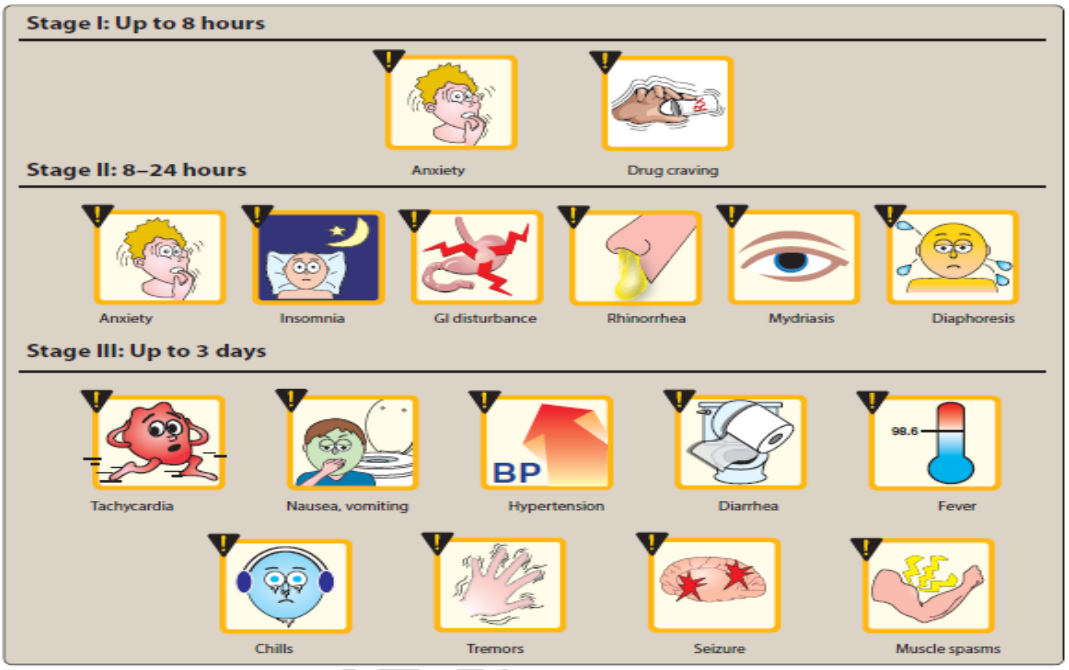

Figure 2: Opiate withdrawal syndrome. GI = gastrointestinal.

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.