YU - MEDICINE
PASSION ACADEMIC TEAM

Central Nervous System

Sheet# 6 - Pharmacology

Lec. Title : Drugs of Abuse - CNS Stimulants

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Drugs of Abuse

Overview and Treatment

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Notes #1

- Difference between misuse and abuse:
- Misuse is the improper medical use. So, the patient In this case does not follow instructions properly for the prescribed drug.
- While drug abuse is the improper nonmedical use or the illegal use. In this case, the patient was not prescribed the drug to begin with.
- Drug abuse could be encouraged either by negative reinforcement or positive reinforcement. So, the drug could relieve negative unpleasant conditions such as insomnia, anxiety or…etc. , or it can induce positive and pleasant feelings such as euphoria.
- To tell the difference between dynamic and kinetic drug tolerance the amount of drug in the blood is measured. If the amount of drug in the blood is low, then this is kinetic tolerance. This is one easy way to know the kind of tolerance.

Objectives

1. Describe the clinical uses of the opioid receptor antagonists.
2. Describe methods of treatment of opioids dependency.
3. Describe the pharmacological types of drug dependence.
4. Describe the major pharmacological actions of drugs that are commonly abused.
5. Describe the major signs and symptoms of withdrawal of drugs that are commonly abused.
6. Identify the most likely causes of fatalities from commonly abused agents.
7. Describe methods of treatment of drugs abuse

Drugs of abuse and neurotransmitters

The four major neurons addressed in addictions/abuse are:

1. **DOPAMINE** (euphoria, stimulation) (Cocaine, amphetamines) (inhibitory neurotransmitter)
   In the ventral tegmental area dopamine inhibits the inhibition of abnormal behavior, and this induces euphoria.
2. **SEROTONIN** (manage mood; sleep, appetite, perceptions etc.) (Hallucinogens) (inhibitory neorotransmitter and stimulatory neurotransmitter or excitatory)
3. **GABA** (sedative; anti-anxiety) (Benzodiazepines) (inhibitory neurotransmitter)
4. **ENDORPHINS** (manage pain) (Opioids)
   opioids may have both positive and negative reinforcement; it induces euphoria with dopamine but can also act as a pain reliever with endorphins.

How Drugs Enter the Body

Orally (drinking, swallowing , etc.**)**

It usually takes approx. 20-30 minutes for full reaction time.

Snorting (sniffing)

When drugs are taken this way they are absorbed by the tiny blood vessels in the mucous membranes lining the nasal passages. It takes approx. 3-5 minutes for full reaction

Inhaling (smoking, huffing)

Smokes or inhales " heroin/crack", the vaporized drug enters the lungs and is "rapidly" absorbed thru tiny blood vessels lining the air sacs of the bronchi. acting more quickly than any other methods of use. (7-10 seconds for full reaction time).

Injection (IV or IM or under the skin)

Injecting with needles, either into the bloodstream, or under the skin.

IV takes approx. 15-30 seconds, where IM takes approx. 3-5 minutes for full reaction time.

Substances of abuse

- Stimulants: Cocaine & Amphetamines
- Opioids; Heroin or morphine
- Alcohol (CNS depressant)
- Benzodiazepines & Barbiturates
- Hallucinogens; LSD, Mescaline, Marijuana
- Solvents; Acetone …etc.
- Nicotine

ICD-10 Criteria

Addiction is characterized by:

- A strong desire/compulsion to take the substance
- Difficulties in controlling substance-taking
- A physiological withdrawal state
- Evidence of tolerance
- Persisting with substance use despite clear evidence of OVERTLY harmful consequences

Factors influencing drug abuse and dependence

- Pharmacological & physiochemical properties of drugs
- Personality & Psychiatric disorder - increased risk associated with schizophrenia and depression
- Genetic factors (that influence metabolism and the effects of drugs)

Notes #2

- It is important to know that short acting drugs such as Triazolam and Temazepam have a more intense, rapid and abrupt withdrawal effects.
- While long-acting drugs have way less intense withdrawal effects.

Pharmacologic and physiochemical properties

- Liposolubility increases the passage through the blood-brain barrier
- Water solubility facilitates injection
- Volatility favours inhalation in vapour form e.g aerosols / solvents
- Rapid onset and intensity of effect increase the potential for abuse
- A short half-life produces abrupt & intense syndromes of withdrawal

CNS STIMULANTS

- CNS Stimulants: are a group of drugs which produce an increase in mental and motor activity when administered.
  - The CNS stimulants have few clinical uses, but they are familiar (or important) as drug of abuse

- There are two groups of drugs that act primarily to stimulate the CNS.

1. The first groups the **psychomotor stimulants** (Amphetamine)
   - cause excitement & euphoria (power of bearing easily)
   - decrease feeling of fatigue & increase motor activity. Abuse.

2. The second groups, **psychomimetic drugs** or **hallucinogens**,
   - produce profound changes in **thought patterns & mood**

Signs and symptoms

General Signs & Symptoms of CNS Stimulation

1- Elevate Mood.

2- Increase in motor activity.

3- Increase Alertness.

4- Decrease sleeping./ decrease appetite

5- In case of overdose, convulsion and death.

6. ↑ Heart rate

7. ↑ Respiratory rate

8. Instability, Tremors,

MOA of CNS Stimulants

- Block neurotransmitters reuptake: ex. Cocaine.
- Promote neurotransmitters release: ex. Amphetamine.
- Block Metabolism (MAO inhibitors): ex. Phenelzine.

HALLUCINOGENS

Primarily <u>Psychologically</u> Addicting

- **LSD** (lysergic acid Diethylamide)
- **MESCALINE (mesc, buttons)**
- **MARIJUANA (grass, pot, weed, chronic, herb,)**

Marijuana

LSD (Lysergic acid Diethylamide)

- LSD is classified as a Hallucinogen,
- it induces abnormal **sensory** perceptions.
- Its effects are unpredictable depending on the amount and purity, as well as the user's personality, mood
- Effects begin approx. 30-90 minutes.
- Physical effects include **dilated pupils** (Mydriasis), higher body temp., increased heart and blood rates, sweating, loss of appetite, sleeplessness, dry mouth and nausea.

STIMULANTS

Both Physically & Psychologically Addicting

Caffeine

Amphetamine (release norepinephrine)

Cocaine (inhibits reuptake of norepinephrine)

Cocaine

- cocaine is an inexpensive, widely available & highly addictive drug.
- **Mechanism of action:-** The primary mechanism of is blockade by NE, serotonin & dopamine reuptake into the presynaptic terminals from which these neurotransmitter are released.
- Cocaine is self administrated by chewing, intranasal snorting, smoking I/V injection
- peak effect occur at 15 to 20 minutes after intranasal intake of cocaine powder, & the high disappears 1 to 1 1/2 hours.
- the potential for overdosage & dependence is greatest with I/V injection & CRACK smoking.
- cocaine can induce seizure as well as fatal cardiac arrythmias

Amphetamines

- A toxic, addictive stimulant that affects many areas of the central nervous system.
- Smoked, snorted, injected or orally ingested.
- Easily dissolves in beverages.
- Serious health consequences, (**memory loss, aggression, violence, psychotic behaviors, and potential cardiac and neurological damage**.
- Side effects: Signs of agitation, excited speech, decreased appetite, and increased physical activity levels.

Primarily amphetamine gives pleasant effects and help the person concentrate but continuity and increasing of dosage will cause severe damage
Excitotoxicity: is damage of neurons due to the overactivation of receptors of excitatory neurotransmitters. The overstimulation of the CNS due to elevated doses of amphetamine will cause serious damage.

OPIATES

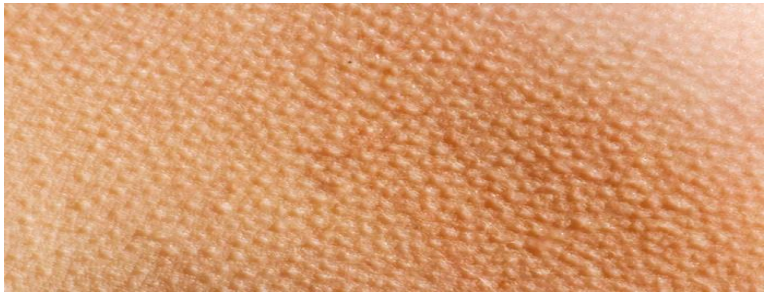
- Strong narcotic analgesics
- Derived from the ripe seed capsule of the poppy
- Crude opium contains morphine, codeine, other alkaloids
- Diamorphine (heroin) made by acetylation
- Eaten, sniffed, smoked, injected
- Short term effects – Euphoria, analgesia, sedation & a feeling of tranquillity
- Long term effects / Repeated use – Rapid tolerance & physical dependence
- Overdose – Lethal respiratory depression

Opiates &The dopamine pathway

- Stimulate the release of dopamine from neurones of the presynaptic **ventral tegmental area (VTA)** causing euphoria & reinforcement of the behaviour
- Opioids release dopamine mainly by an indirect mechanism
- Physical dependence are mediated by the activation of μ receptors
- Short term administration of opiates activates the μ-opioid coupled receptor, this leads to a decrease in the number of opioid receptors and to the development of tolerance
- Stimulation of κ receptors decreases dopamine levels in the VTA and produces aversive responses

IMPORTANT SLIDE

Opiate withdrawal



Goose flesh

- Grade 0 – drug craving, anxiety, drug seeking
- Grade 1 – yawning, sweating, runny nose, restless sleep
- Grade 2 – dilated pupils, hot and cold flushes, goose flesh (“cold turkey”), aches and pains
- Grade 3 – insomnia, restlessness and agitation, abdominal cramps, N+V, diarrhoea, increased pulse , BP and RR (autonomic withdrawal manifestation appear in this stage)

Treatment of opiates withdrawal Methadone

- Synthetic opiate
- Administered orally
- once daily dosage
- Steady state 4-5 days
- Dosage 30-60mg
- Stabilises lifestyle
- safe" substitution drug (buprenorphine)
- Effective in engaging and retaining people in treatment
- Reduces risk, reduced levels of injection
- A factor in improving physical/Mental health and quality of life of patients and their families
- Aim for a dose of 60mg

Notes #3

- Treatment of morphine withdrawal:
  - Morphine doses are reduced gradually and then morphine is substituted with methadone or preferably buprenorphine.
  - The patient is administered the safe substitute for almost 10 days.
  - Then the buprenorphine doses are gradually lowered. Methadone withdrawal will give some withdrawal manifestations but way less severe than that of morphine.
- While withdrawing morphine if the patient suffered from tachycardia or hypertension then the patient will be given Lofexidine or Clonidine to reduce autonomic manifestations.
- **Naloxone** is an emergency drug used to treat morphine poisoning or morphine overdose but not morphine addict. (if naloxone is administered to a morphine addict to treat addiction more intense withdrawal manifestations will occur). It can be administered to addicts as a final step after withdrawal of morphine to prevent relapse or recurrence.

Lofexidine / Or clonidine

- **Alpha-2 adrenergic agonist inhibiting noradrenaline release**
- Useful in short term users
- Detoxify over 2-3 weeks using up to 2mg daily to treat any autonomic manifestation during morphine withdrawal
- Daily BP monitoring is essential
- Mainly used in in-patient units

Naltrexone

- Narcotic antagonist
- Half-life 96 hours (long duration of action)
- Dose 50mg daily
- Used with or **after detoxification preferred**
- Best when supervised by family
- Breaks the cycle of craving

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Alcohol

- Hydrophilic, with rapid absorption through the gut
- Peak plasma levels reached 30-60 mins post ingestion
- Metabolized by hepatic oxidation
- **Neurobiology of alcohol**
  - Stimulant at low doses, sedative at higher concentrations
  - Anxiolytic effects mediated by potentiating of inhibitory effects GABA at GABA-A receptors
  - Disturbs glutamate transmission by inhibiting NMDA receptors,- related to withdrawal seizures, delerium etc

Alcohol related physical problems

- GIT – gastritis, reflux, pancreatitis, portal HT,
- Liver – hepatitis, fatty liver, cirrhosis, hepatic Ca, hepatic encephalopathy
- Cardiovascular – arrythmias, cardiomyopathy, coronary/cerebrovascular disease, hypertension
- Endocrine e.g. pseudocushings, hypogonadism, infertility, low libido/impotence
- Musculoskeletal e.g. gout, fractures, osteoporosis
- Haematological e.g. anaemia, thrombocytopaenia
- Dermatological e.g. erythema, eczema, worsening psoriasis

Alcohol – intoxication

- Neurological problems
  - Amnesic (Korsakoff's) syndrome " an abnormal mental state in which memory and learning are affected more than other aspects of cognition in clear consciousness" due to decrease in thiamine levels and so to treat it u have to give the patient thiamine.
  - neuritis; may be associated with peripheral neuropathy
  - Dementia, amnesia
  - Fatal alcohol syndrome

- Psychological related disorders
  - Alcoholic Hallucinosis- 10-20% > after six months
    -5-20%... Cause schizophrenia
  - Suicide – approx 25% attempt; male, divorced, personality disorder, older, unemployed, medical issues,
  - Anxiety states- panic, OCD, phobias

Alcohol withdrawal

- Occurs from 6-24 hours after cessation, peaking at day 2-3, highest risk in first 24-48hrs
- Range of features
  - sweating, tremor, nausea, anorexia, vomiting,
  - anxiety, insomnia, restlessness,
  - hallucinations, seizures, nightmare, confusion,
  - Delirium Tremens treated by benzodiazepine because it does not react with alcohol.

Delirium tremens

- Toxic confusional state with somatic disturbance, occurring in < 5%
- Mortality rate of approx 10%(-20%)
- Symptoms peak at 3-4 days of withdrawal
- sensory distortion and tremor
- Agitation, fear and insomnia, worse at night

Features of DT's

- Confusion and disorientation.
- Delusions and hallucinations.
- Psychomotor agitation.
- Perceptual disturbance and fear.
- Insomnia and truncal ataxia.
- Electrolyte disturbance and dehydration .
- Leukocytosis

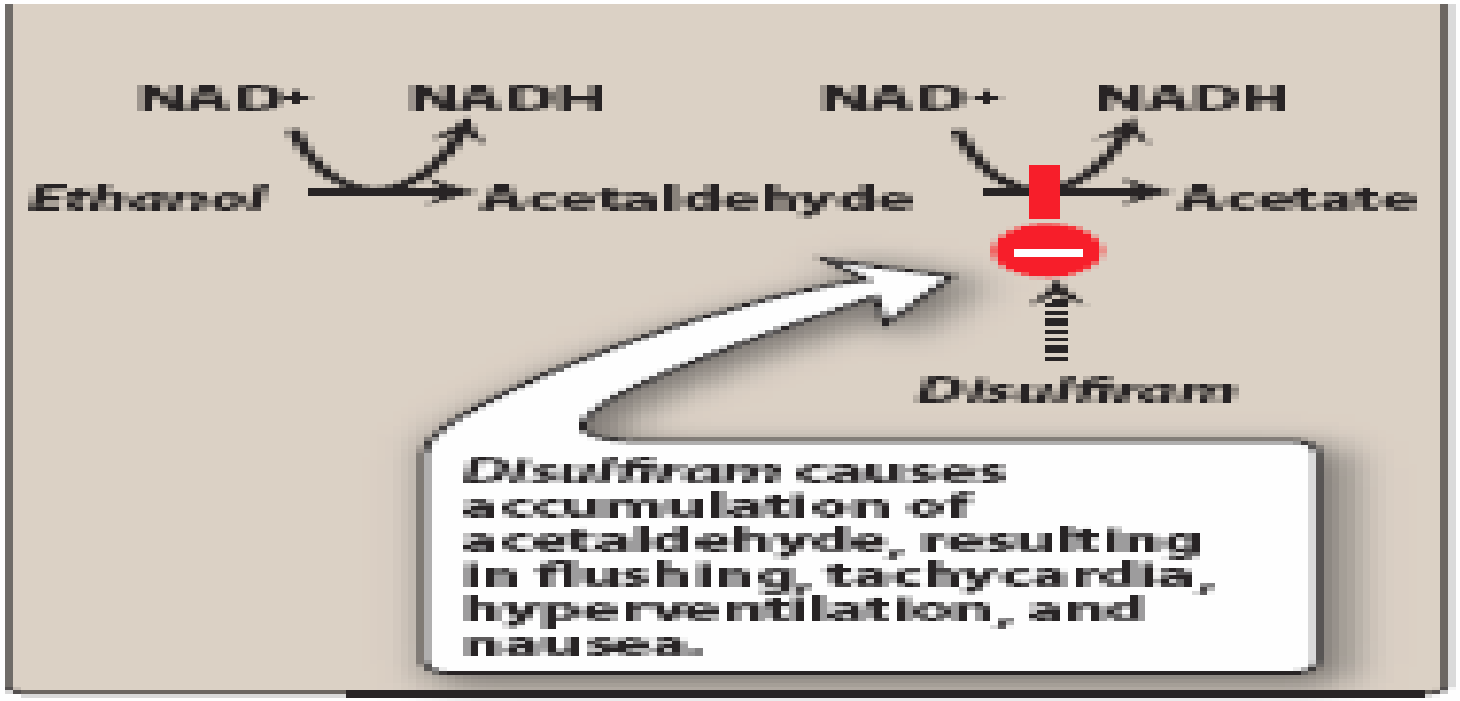
Treatment

- Acute withdrawal – Short acting benzodiazepines; **chlordiazepoxide,** – minimise the risk of seizures
- 40 mg chlordiazepoxide, 6 hourly, (Max 300mg in 24hrs)
- Reducing doses over 5-10 days
- Consider anticonvulsants (carbamezepine)
- **Multivitamin preparations- Thiamine / B vitamin**

  - Korsakoff psychosis
- Treat infection, dehydration, suicidal ideation etc

Post-detoxification

- **Disulfuram** (Antabuse) – Inhibitor of aldehyde dehydrogenase. Blocks ethanol metabolism at the acetaldehyde level. 'Flushing reaction' (given during alcohol abuse for the acetaldehyde to accumulate)
  - Loading dose 600-800mg per day for 3-4 days
  - Maintenance 200mg daily
  - Hypotension and MI with heavy alcohol consumption, potentially fatal
  - Useful in highly motivated groups and where assisted by family or friends
- **Naltrexone-** Opiate receptor antagonist, thought to negate the euphoria associated with alcohol


NAD+
NADH
Ethanol
Acetaldehyde
NAD+
NADH
Acetate
Disulfiram
Disulfiram causes accumulation of acetaldehyde, resulting in flushing, tachycardia, hyperventilation, and nausea.

Post Detoxification

- Psychological interventions; Relapse prevention, social skills, relaxation techniques, CBT, Family therapy etc
- Rehabilitation programmes- social skills, relaxation, structured relapse prevention