# Aetiology and management of opioid dependence syndrome

# Outline

- Introduction
- Historical background
- Epidemiology
- Aetiology
- Comorbidity
- Investigation
- Management

# Introduction

**Opioid**: class of psychoactive compounds related to opiates found in the ***opium poppy plant***, ***Papaver somniferum***

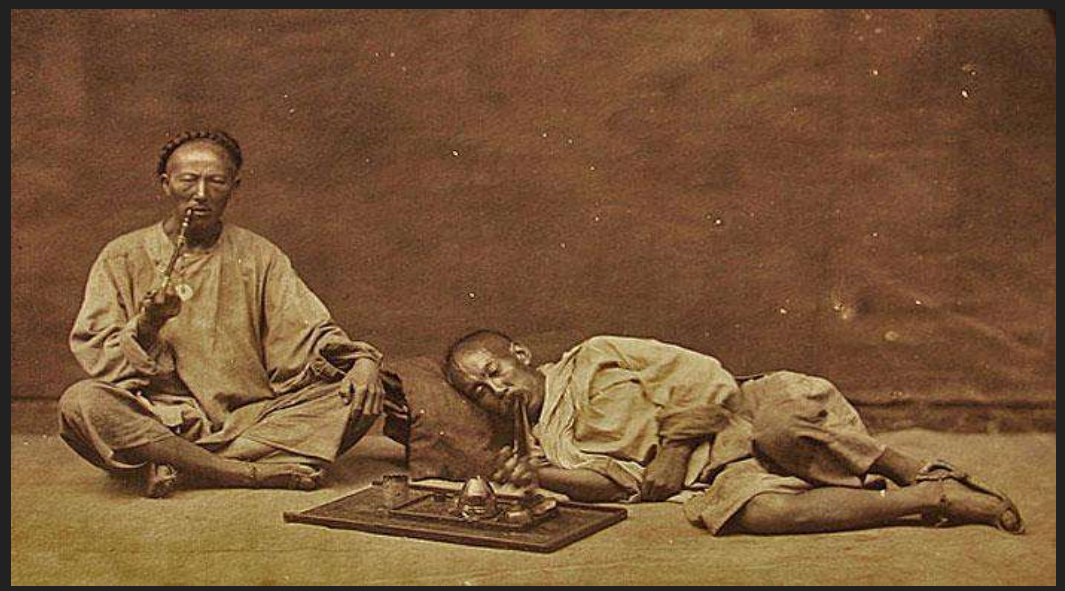
# Historical background

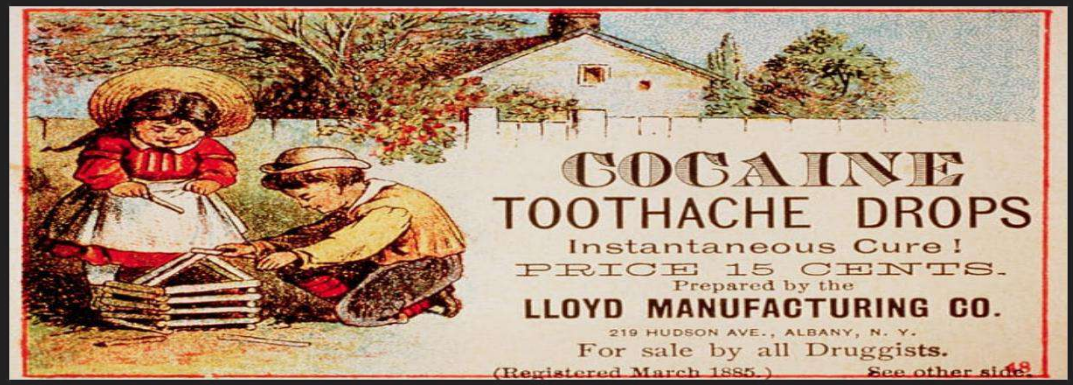
## A brief history of Opioids

"Presently she cast a drug into the wine of which they drank to lull all pain and anger and to bring forgetfulness of every sorrow."

-*The Odyssey*, Homer, 9th Century BC

- Sumerians cultivated poppies ~ 300 BC
- Arab traders brought opium to India and China ~700 AD
- Manuscripts document addiction in Europe and Middle East ~ 1500 AD
- Morphine isolated in 1806
- Heroin produced in 1898 and thought to have no addictive properties.





# History: India

- *'Dhanvanatari Nighantu'* an ancient Indian medical treatise of the 10th century lists opium as a remedy for a variety of ailments.
- In the early part of 16th century, opium was cultivated in India during the Moghul period.
- After the decline of Moghuls, the Britishers controlled opium production from year 1773.
- After independence the Indian Government checks and monitors its production and usage.

# Cultivation in India

- Legal cultivation of opium for medicinal purposes is carried out in India, only in selected areas. Legal cultivation for medical use is permissible within the ambit of **United Nations, Single Convention on Narcotic Drugs 1961.**
- India is the only country authorised by the United Nations Single Convention on Narcotic Drugs (1961) to produce ***gum opium.***
- Eleven (11) other countries, i.e, Australia, Austria, France, China, Hungary, the Netherlands, Poland, Slovenia, Spain Turkey and Czech Republic cultivate opium poppy, but they do not extract gum
- The NDPS Act empowers the Central Government to permit and regulate cultivation of opium poppy for medical and scientific purposes.
- Opium cultivation is permitted in the notified tracts in the states of Madhya Pradesh, Rajasthan and Uttar Pradesh.

# Epidemology

- NSDUH: 2006 in US, lifetime prevalence of heroin use among persons aged 12 years or older to be approximately 3.8 million or 1.5 percent of community dwellers.
- Persons who used heroin past year – 0.2% and past month 0.1% and were low
- But not significantly different from 2002
- Increase in prescribed opioid misuse in 2006, lifetime: 13.6, past yr: 5, past month: 2% (18-25yr olds mainly)
- 296,000 heroin &1.1 million opioid dependent.

# Opioids

- NATURAL – Morphine , codeine
- SEMI SYNTHETIC – Heroin , oxycodone, hydrocodone
- SYNTHETIC – Pethidine , fentanyl, methadone , tramadol, dextropropoxyphene
- ENDOGENOUS OPIOIDS –Endorphins, enkepalins,dynorphin, endomorphins

- 1mg of methadone - 1 to 2mg heroin
  3 to 4 mg morphine
  20mg pethidine
  30mg codiene

# Aetiology

# AETIOLOGY

Multiple factors

Neurobiology

Psychosocial

# OPIOID RECEPTORS

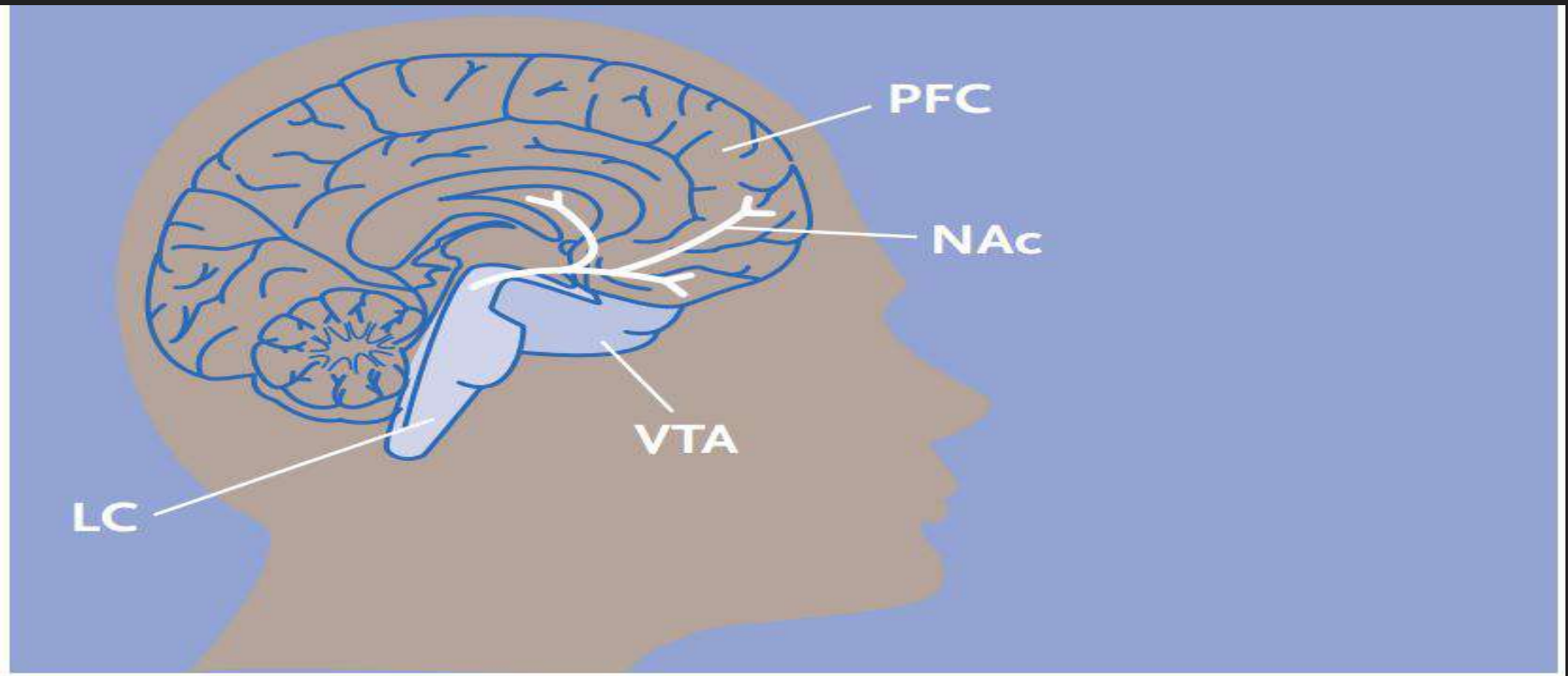
- Opioid receptors: group of GPCRs with opioids as ligands and respond to endogenous opioids(Endorphins)
- Widely distributed : brain, spinal cord, digestive tracts
- Currently four types of receptors are known
- Delta (d), Kappa(k), mu, & nonciceptin receptor(NOP)

# OPIOID RECEPTORS

- The μ-opioid receptors are involved in the regulation and mediation of analgesia, respiratory depression, constipation and drug dependence
- κ-opioid receptors: analgesia, diuresis, and sedation
- Δ-opioid receptors: analgesia.

# MECHANISM OF ACTION

- G protein coupled receptor
- inhibits adenylyl cyclase
- presynaptic inhibition of calcium entry
- post synaptic hyperpolarization
- Inhibits neuronal activity
- prevents pain transmission




When drugs stimulate mu opioid receptors in the brain, cells in the ventral tegmental area (VTA) produce dopamine and release it into the nucleus accumbens (NAc), giving rise to feelings of pleasure. Feedback from the prefrontal cortex (PFC) to the VTA helps us overcome drives to obtain pleasure through actions that may be unsafe or unwise, but this feedback appears to be compromised in individuals who become addicted to drugs. The locus ceruleus (LC) is an area of the brain that plays an important role in drug dependence.

- Heroin, the most commonly abused opioid, is more lipid soluble than morphine. This allows it to cross the blood–brain barrier faster and have a more rapid and pleasurable onset than morphine.

- Codeine is absorbed easily through the gastrointestinal tract and is subsequently transformed into morphine in the body.

- Results of a study using positron emission tomography (PET) have suggested that one effectof all opioids is decreased cerebral blood flow in selected brain regions in persons with opioid dependence

# Tolerance and dependence

- The **long-term use** of opioids results in **changes in the number and sensitivity of opioid receptors**
- the effect of opioids on the **noradrenergic neurons** is probably primary mediator of the symptoms of opioid withdrawal.
- associated with **increased sensitivity of dopaminergic, cholinergic, and serotonergic neurons**
- long-term use activates a **compensatory homeostatic mechanism** within the neurons; and opioid withdrawal results in rebound hyperactivity.
- **Short-term use** of opioids decreases activity of the noradrenergic neurons in the locus ceruleus

# Molecular genetics and genomics

- Twin studies: 50-60% liability for heroin addiction is genetic
- Linkage study for opioid dependence: clustered linkage on chromosome 17, region of chromosome 14 overlying neurexin 3 gene
- Male specific linkage peak on chromosome 10q
- Genome wide association study 2013: 5,697 subjects
- Involved  genes in potassium and calcium signalling pathway

# Psychosocial factors

- Social attitude
- Peer pressure
- Individual temperament
- Drug availability

# Psychosocial factors

- United states: high crime rates, unemployment, poor schooling system
- Epidemiological studies: less value to academic achievement
- Heroin use: novelty seeking, risk taking, impulsive traits, delinquency
- Antisocial personality disorder
- Dysfunctional family environment

# ROUTES

- ORAL
- SNORTTING
- PARENTRAL
- SUBCUTAENEOUS

# EFFECTS OF OPIOD USE

- Euphoric high
- Feeling of warmth, heaviness of extremities
- Dry mouth, facial flushing
- Nausea & vomiting
- Physical effects : respiratory depression, pupillary constriction, smooth muscle contraction , constipation
- Changes in vitals

# Physical signs/ pathology

- Snorting heroin – nasal necrosis and fungal infections
- Drug injectors – needle tracks over veins on the arms, legs, and, in some cases, the feet, backs of the hands, and the femoral and jugular veins.
- Infections, venous scleroses, and lymph obstruction may lead to severe edema of the hands and feet.
- skin abscesses or scars on accessible skin surfaces
- rock-like hardening of subcutaneous and muscle tissue as a result of repeated intramuscular (IM) injections of meperidine

# COMPLICATIONS

- **NEUROLOGIC**
  - Toxic amblyopia (optic nerve pathology)
  - Polyneuropathy
  - Meningitis
  - Brain abscess
- **DERMATOLOGIC**
  - Abscess
  - Lymphangitis

# COMPLICATIONS

- **PULMONARY**
  - Aspiration
  - Pneumonia
  - Lung abscess
  - Pulmonary emboli (clots going to the lung)
  - Pulmonary fibrosis (scarring of the lung)
  - Noncardiogenic pulmonary edema (lung fills with fluid not as a result of heart dysfunction)
- **HEPATIC**
  - Hepatitis B,C,D,G
- **INFECTIONS**
  - Endocarditis
  - Tetanus
  - HIV

# COMORBID PSYCHIATRIC DISORDERS

- Mood disorders
- Anxiety disorders
- Other substance use
- Personality disorders –antisocial , borderline,

# OPIOD WITHDRAWAL

- Depressed mood , anxiety, dysphoria
- craving
- piloerection, lacrimation , rhinorrheoa
- hyperalgesia
- Pupillary dilatation , photophobia
- insomnia, yawning
- autonomic hyperactivity
- Diarrheoa, nausea , vomitting, cramps

# OPIOD INTOXICATION

- Miosis
- Hypotension
- Facial flushing , feeling of warmth
- Depressed  respiration
- Bradycardia (slow heart rhythm)
- Impaired judgement
- Constipation
- Analgesia, apneoa , coma

# INVESTIGATIONS

**URINE TOXICOLOGY CAN SHOW:**

- Free morphine
- Morphine Glucuronide
- Free codeine
- 6 – Monoacetylmorphine (6 – MAM)
  - This metabolite, or breakdown product, is only seem with heroin use and no other opiate. It has a very short half – life and is difficult to detect after heroin use.

# INVESTIGATIONS

- High levels of total morphine in urine(>5000 ng/ml) are indicative of abuse of opiate product (heroin, morphine, codeine).
- High levels of codeine (>300 ng/ml) with a morphine-to-codeine ratio <2 is indicative of codeine use
- Presence of 6 – Monoacetylmorphine in urine is a positive indication of heroin use.

# Assessment of opioid use

Clinical assessment:

1. Current consumption
2. Typical day
3. Drug use history
4. Biopsychosocial complications
5. Past treatments and abstinent periods
6. Motivation for change

- Confirmation of dependance: objective opiate withdrawal scale

# Treatment

- There are currently a number of effective pharmacological and behavioral therapies for the treatment of opioid dependence with these two approaches often combined to optimize outcome

- The treatment plan should be made jointly between the clinician and patient

# Treatment goals

- Harm reduction
- Abstinence
- Rehabilitation

# Steps

- Detoxification
- Maintenance
- Relapse prevention – Long term treatment
  Harm reduction
  Abstinence

# DETOXIFICATION

- goal of detoxification is the achievement of a drug free state while minimizing withdrawal
- generally ineffective in achieving sustained remission unless combined with long term pharmacologic , psychosocial or behavioral therapies

- Detoxification may involve use of:

1. Opioid agonist: methadone
2. Partial agonists: buprenorphine
3. Antagonists :naloxone ,naltrexone
4. Non opioid alternatives: clonidine, benzodiazepines or non steroidal anti-inflammatory agents
5. Dose depends on the amount of drug and half life

# Pharmacological managemant

# FDA APPROVED DRUGS

- METHADONE ( 1972)
- NALTREXONE( 1984)
- LAAM (1993)
- BUPRENORPHINE (2002)

- Long term - typically 180 days
- Intermediate - upto 70 days
- Short term - upto 30 days
- Rapid - 3-10 days
- Ultra rapid - 1-2 days

# DETOXIFICATION

- GOAL - sufficient dose to supress withdrawal symptoms
- Objective opiod withdrawal scale rates withdrawal as absent, mild - moderate & severe
- Dose depends on the amount of drug and half life
- METHADONE - 10 - 20mg

# DETOXIFICATION

- BUPRENORPHINE - 2 TO 8 mg
- CLONIDINE - 0.1 to 0.3mg TDS / QID
- Duration - 2 to 3 weeks

RAPID & ULTRA RAPID DETOXIFICATION:

mainly to decrease hospital stay

naltrexone and clonidine use

SYMPTOMMATIC TREATMENT

# METHADONE

- Oral absorption
- Bioavailability
- Non specific binding to tissues
- Large reservoir & slow peaking of plasma levels
- Minimises withdrawal
- Supresses the opioid drug craving
- Cross tolerence blockade of effects of illicit opiod - serum level of 400ng/ml adequate

# METHADONE

- DOSE – long term therapy 60 – 120mg
- T ½ - 24 hrs
- longer the detoxification period better the outcome
- SIDE EFFECTS - Constipation , decrease libido, insomnia , alteration in liver functions and QTc prolongation
- Dose reduction in liver / renal failure

# METHADONE

- long acting opioid agonist
  - most effective treatment for opioid dependence
  - controlled studies have shown significant
    - decreases in illicit opioid use
    - decreases in other drug use
    - decreases in criminal activity
    - decreases in needle sharing
    - improvements in prosocial activities
    - improvements in mental health

# BUPRENORPHINE

- **Partial opioid agonist**
  - Desirable properties
    - Low abuse potential
    - Lower level of physical dependence
    - Safety if ingested in overdose quantities
    - Weak opioid effect as compared to methadone
  - Poor oral bioavailability - sublingual
  - Slow dissociation rate : Prolonged therapeutic effect - so can be given every other or every third day

# BUPRENORPHINE

- DOSE - 4 to 8 mg
- T ½ -27 hrs
- Peak concentration in 2 hrs
- 25 to 30 times more potent than morphine
- Ratio of 4: 1

# BUPRENORPHINE

- High receptor affinity - opioid blockade
- Ceiling effect
- Efficacy - same as methadone
- SIDE EFFECTS - fatal respiratory depression when used with alcohol / BZD , LFT are altered, jaundice, constipation, nausea, headache

# NALTREXONE

- For opiate-dependent patients
  - Must wait 5 - 7 days after last use of a short acting opiate (heroin) or 7 - 10 days after a long-acting opiate to prevent withdrawal.
  - Can perform a narcan challenge test* to see if withdrawal can be induced, thus not safe to start naltrexone yet

# NALTREXONE

Should always have a negative urine drug screen for opiates before starting

Start with 25 mg first day, then 50 mg per day thereafter.

Can dose for 3 times a week (100mg - 100mg - 150 mg on Monday, Wednesday and Friday)

# NALTREXONE

- Narcan Challenge Test

  - Do not do test if patient is showing symptoms of opiate withdrawal
  - Do not do test is patient is suspected of recent opiate use
  - Do not do test if urine drug screen is still positive for opiates
  - PRECIPITATE WITHDRAWAL

# NALTREXONE

- Side effects
  - Nausea in 10% of the patients
  - Other side effects include
    - Anxiety
    - Headache
    - Sleeping trouble
    - Weakness
    - Skin rash

# NALTREXONE

- Poor compliance appears to be a major limiting factor

- Use of this medication is not addictive; by itself, it will not cause opiate withdrawal

# NON PHARMACOLOGICAL

# PSYCOSOCIAL TREATMENT

- Counselling - IP , OP , day care & prison setting
- Started early & integral part of program
- Medical / psychiatric / employment / family counselling
- Coping stratergies
- Decrease in illicit opioid use
- Increase in prosocial behavior

- CBT :

  More effective in patients with psychiatric symptoms

  Decrease in HIV risk behaviour

- PSYCHODYNAMIC & INTERPERSONNEL THERAPY
- NARCOTIC ANONYMOUS
- METHADONE ANONYMOUS

# FAMILY & NETWORK THERAPY

- Involves family & friends in counselling sessions
- Knowledge about treatment plan
- Monitor patients compliance
- Improves compliance with medication
- Decreases illicit drug use
- Not cost effective

- BEHAVIOURAL THERAPY

Voucher incentives

Therapeutic work place

Take home methadone

# THERAPEUTIC COMMUNITIES

- GOALS :

  Abstinence

  social skills & development of honesty

  elimination of antisocial / criminal behaviour

- Social environment
- Time period - 12 to 18 months
- Drop out rates 30% - 50%

# THANK U