OPIOID ANALGESICS: By Prof Khalida Ajmal

Learning Outcome: Classify opioids & their receptors. Describe their mechanism and evaluate the role of opioids as analgesics, identify their adverse effects & contraindication. (BLO-1)

Learning objectives: After completion of the topic the students should be able to:

- Define pain. Outline how it can be relieved?
- Describe endogenous opioid peptides
- Classify opioids.
- Describe the opioid receptors in detail.
- Describe prototype opioid drug MORPHINE, regarding:
  - Chemistry, Pharmacokinetics
  - Mode of action & Pharmacologic Effects
  - Therapeutic uses
  - Adverse effects, D/I & Contraindications
  - Describe various groups of opioids briefly
  - Justify use of opioids in various clinical indications , with examples of drugs used.
  - Design a management plan for opioid overdosage/Describe opioid antagonists

Pain:-

Pain is defined as an unpleasant subjective sensation that is a consequence of complex neurochemical processes in the peripheral and central nervous system. Pain can be either acute or chronic .

As it is a subjective sensation, the physician must rely on the patient's perception and description of pain.

Analgesics : These are the drugs which relieve pain without loss of consciousness.

Alleviation of pain depends on its type, and different therapies are effective as analgesics.

- **Headache or mild to moderate arthritic pain:** NSAIDs –like Ibuprofen, Diclofenac
- **Severe visceral or chronic malignant pain**, opioids--- like MORPHINE--- are the drug of choice.
- **Neuropathic pain:** Responds to Pregabalin, Gabapentine & Amitriptyline, carbamazepine.

To discover better analgesic drugs for chronic pain, many compounds are under study.

- Agents blocking Capsaicin receptors.
- Lidocaine & Mexilitine (Block tetrodotoxin resistant sodium channels)
- Ziconotide: (blocker of N-type calcium channels).
- Tetrahydrocannabinol (Acts on CB1 receptors)
- NMDA receptor antagonists & Nicotinic analogs.

Production of pain: includes **Nociception & Emotional reaction** associated with pain (crying, weeping).

A. Nociception: consists of following components :

- **Generation at nociceptor level:** Pain stimuli like injury, heat, acid, inflammation (noxious stimuli—which produce some degree of tissue damage)stimulate nociceptors/pain receptors--- free nerve endings
- **Spinal cord input:** The primary afferent neuron in periphery carries pain signals to dorsal horn of SC
- **Synapses with secondary neuron** via Glutamate & other NT like neuropeptide
- **Transmission to Medulla & Pons**
- **Perception at ventral caudal thalamus**. -

B: Emotional reaction associated with pain at cortical level--- crying, weeping.

Opium: Opium, the source of Morphine is obtained from poppy, Papaver somniferum & P album. When unripe poppy seed pod is incised , a white substance exudes, which dries to a brown gummy substance called opium. It contains 2 groups of alkaloids.

Phenenthrene series (Morphine 9-14% **,** Codeine 0.5-2%, Thebain0.2-15)

Benzyl isoquinoline series (Papaverine 0.8-1% **,** Noscapine 3-10%, Narcine0.2-0.4%)

ENDOGENOUS OPIOID PEPTIDES;Morphine like substances released in regions of CNS concerned with modulation of pain. They are derived from precursor proteins.3 main families

1.Endorphins
2.Enkephalins (Metenkephalins & Leu-enkephalins).
3. Dynorphins-- Dynorphin A Dynorphin B & α and β Neoendorphin.

Affinity of endogenous opiode peptides for opiod receptors

Mu Recep[tors: Endorphins> Enkephalins> Dynorphins
kappa receptors : Enkephalins> Endorphins & Dynorphins
Delta receptors: Dynorphins> >Endorphins &Enkephalins

Importance of Endogenous Opioid Peptides

- Important role in Nociception. Painful stimuli can evoke their release & diminish sensation of pain.
- Opioids promote release of Endogenous Opioid Peptides, in addition to effect on specific receptors,
- Acupuncture may release endogenous opioid peptides to produce analgesia; is under studies.
- Dynorphin levels rise in dorsal horn after tissue injury & inflammation.

Dynorphin A has pro-nociceptive activity & may produce hyperalgesia through bradykinin receptors.
dynorphin A also binds to NMDA receptors.

OPIOIDS: Opioids include natural alkaloids of opium, their semi- synthetic derivatives, synthetic drugs & natural endogenous opioid peptides that bind to opioid receptors & produce Morphine like effects, which can be blocked by Naloxone.

They are also called **opioid analgesics** as they relieve pain, or **Narcotic analgesics**– relieve pain; induce sleep. **Prototype drug is Morphine**. Primary use is to relieve intense pain, resulting from injury, surgery or chronic disease like cancer metastasis.Wide spread availability has led to abuse of agents with **Euphoric effects.**

OPIATE: Specifically describes **natural alkaloids of opium. ie morphine, codeine & thebaine .**

MORPHINE

Prototype drug of opioids Isolated from crude opium by SURTURNER in **1803,** he named it **morphine** after Morpheus-- Greek god of dreams.

Chemical Structure: An **alkaloid.** It is a **phenanthrene derivative** contains four fused rings.

PhK: ROA: oral, S/C, I/M , I/V, rectal suppositories, also by Epidural /Subarachanoid route

Absorption: Well absorbed from GIT. F 30 % due to variable, extensive Hepatic First Pass Metabolism . So oral doses are much higher than parenteral doses.

Distribution: Rapidly distributed to all tissues, including CNS. Crosses placenta.

Metabolism: In liver mainly by glucuronidation .90%metabolized to morphine-3 -glucuronide (M3G)

- 10%→ active metabolite morphine-6- glucuronide (M6G), 4-6 times more potent than morphine
- M3G & M6G are polar, poorly cross BBB. CNS uptake is enhanced by co-administration of **Probenecid** / **inhibitors of P –glycoprotein reverse transporter.**
- **So effects of active metabolites should be considered:** In renal impairment/ after prolonged use of high doses:M3G can produce **Seizures**. M6G can produce **prolonged & enhanced opioid action.**

Excretion: Mainly as glucuronides / some unchanged drug -in urine. **DOA:** 4-6hrs

MOA OF OPIOIDS/ MORPHINE

Opioid agonists (Morphine) act at multiple sites & inhibit synaptic activity, they produce their effects by:

1. **Binding to specific opioid receptors** at multiple sites in spinal cord & brain regions involved in transmission & modulation of pain; also in the periphery.

2. ↑ release endogenous opioid peptides(endorphins, enkephalins & dynorphins) which are inhibitory to neurons by acting on different specific opioid receptors.

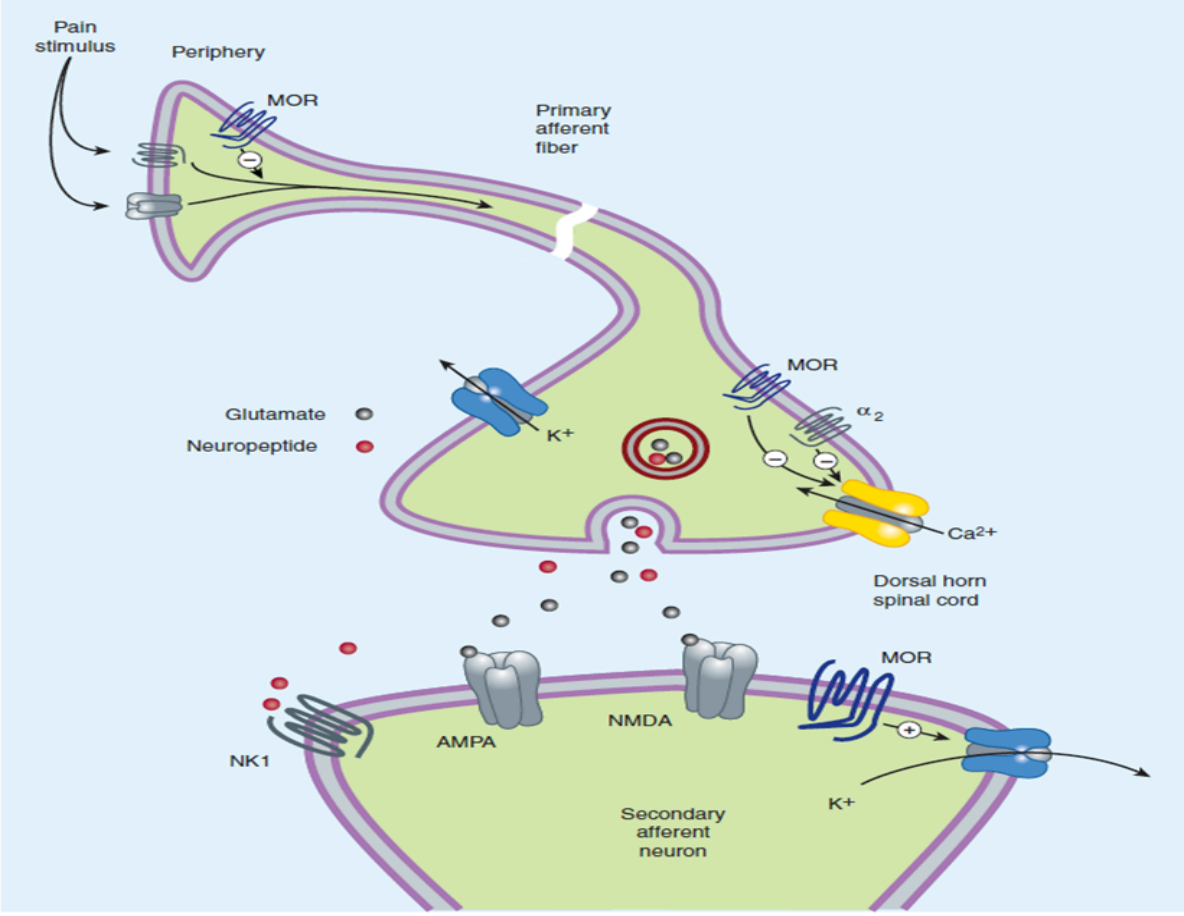
Opioid receptors : 3 major classes: μ (mu), κ (kappa) & δ (delta)**Sub Types:** μ_1, μ_2 , κ_1 , κ_2 , κ_3 , δ_1 , δ_2

Location: opioid receptors are located in:

a) CNS regions involved in transmission (ascending pathways) & modulation of pain (descending pathways) ie Dorsal horn of Spinal cord, Medulla/ Pons, Amygdla, Ventral caudate thalamus and Limbic system.

b) Periphery: -only μ (mu) receptors on primary afferent nerve fibers; also in Immune cells

MOA at Receptor Level:



Morphine & most agonists act primarily on μ (mu) receptors, some on kappa & Delta receptors

- All 3 types are GPCRs. They are coupled to $G_{i/q}$ proteins
- All inhibit Adenylyl cyclase
- They are associated with ion channels, ↓ presynptic Ca++ influx →↓ transmitter release . ↑ post synaptic K+ efflux (Hyperpolarization) & neuronal firing.

At <u>peripheral sensory nerve endings</u> : Activation of μ receptors, attenuates pain stimuli

At <u>presynaptic nerve terminals</u> <u>of nociceptive primary afferents</u> : Activation of μ receptors , close voltage gated Ca^{++} channels ---- <u>release of</u> **Glutamate & Neuropeptide**

Glutamate is main excitatory NT released from nociceptive nerve endings.

<u>At Postsynaptic level:</u> Activation of μ receptors **<u>opens K+ channels</u>**, which leads to:

- increased K+ efflux-----hyper-polarization
- response of post synaptic secondary afferent pain transmission neuron to excitatory neurotransmitter→inhibitory effect.

Inhibition of dorsal horn nociceptive processing: Opioids activate μ receptors, inhibit an inhibitory GABAergic interneuron, which normally inhibits descending pain inhibitory neurons at several sites

So the **pain inhibitory neuron is indirectly activated→ enhanced inhibition of nociceptive processing in dorsal horn of spinal cord--overall ↑analgesic effect.**

<u>Action at κ (kappa) receptors</u> in lamina I & II of dorsal horn ↓ release of substance P→Modulation of perception of pain in spinal cord----direct analgesic effect on spinal cord. {This is **<u>useful clinically-</u>**-- direct application of opioids to spinal cord produces analgesia without adverse effects (Respiratory depression, nausea, vomiting, sedation) produced by supraspinal actions of systemic opioids).

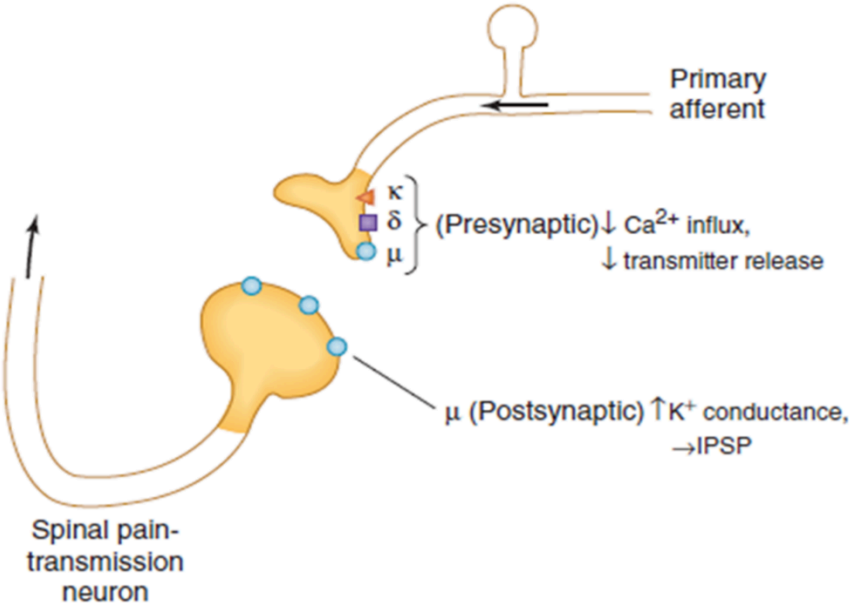


FIGURE 31–2 Spinal sites of opioid action. The μ, κ, and δ agonists reduce excitatory transmitter release from presynaptic terminals of nociceptive primary afferents. The μ agonists also hyperpolarize second-order pain transmission neurons by increasing K^+ conductance, evoking an inhibitory postsynaptic potential (IPSP). (Reproduced,

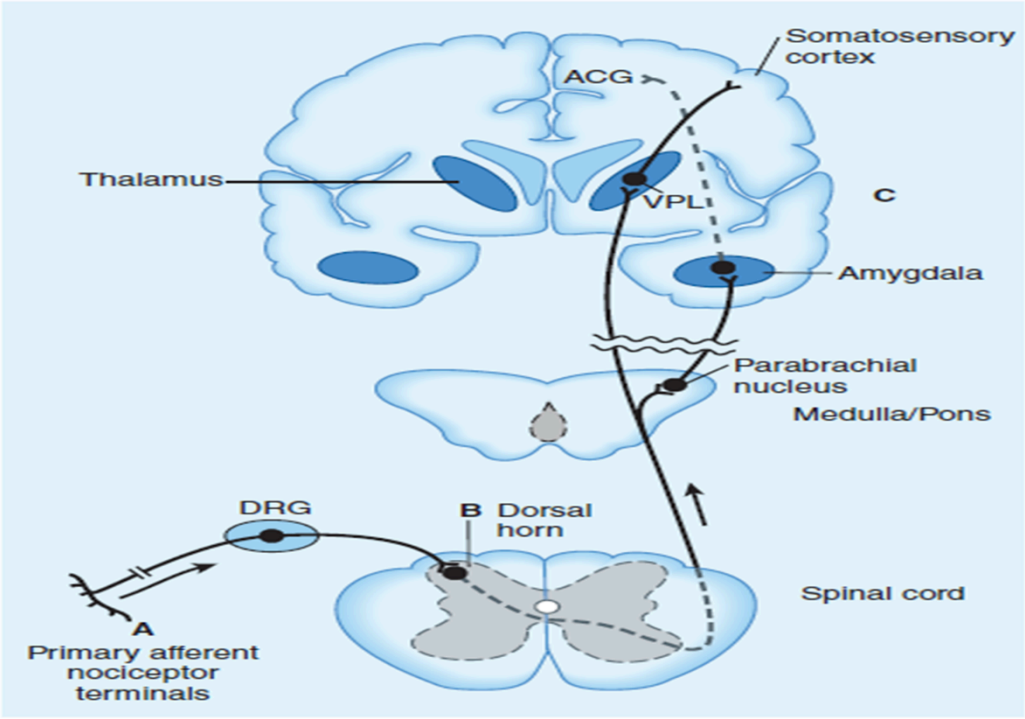
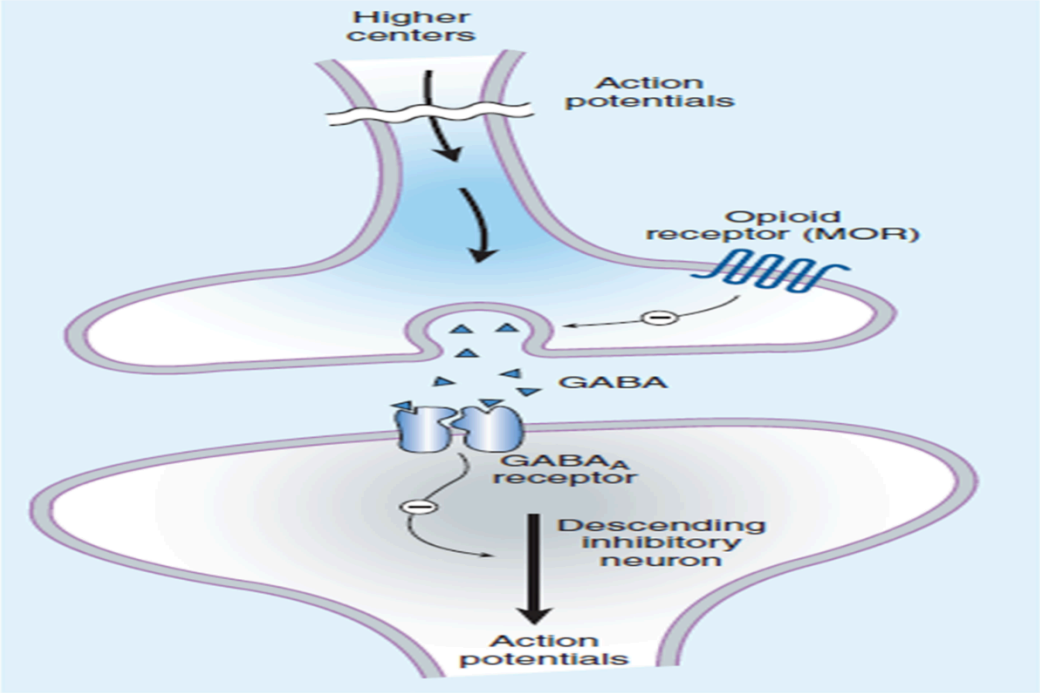


FIGURE 31–2 Putative sites of action of opioid analgesics.

B: Action on brain circuits normally regulated by endogenous opioid peptides: Opioids promote release of Endorphins /Enkephalins / Dynorphins, which act on different specific opioid receptors. So a μ (mu) selective agonist may produce effects mediated by κ (kappa) & δ (delta) also; through these opiopeptides.



EFFECTS MEDIATED BY MAIN OPIOID RECEPTORS

μ (mu) receptors: Supraspinal, spinal & peripheral Analgesia, Sedation, Physical dependence, Respiratory depression, Slowed GI transit , Modulation of hormone & neurotransmitter release

Endogenous peptide affinity: Endorphins > Enkephalins > Dynorphins

κ (kappa): Supraspinal & spinal Analgesia, Sedation, Pupillary constriction, Slowed GI transit. Psychomimetic effects(Euphoria/ Dysphoria , Physical dependence). Modulation of hormone & neurotransmitter release. **Endogenous peptide affinity: Dynorphins >>Enkephalins & Endorphins**

δ (delta) receptors :Supraspinal & spinal Analgesia, Modulation of hormone & neurotransmitter release

Endogenous peptide affinity: Enkephalins > Endorphins > Dynorphins

Pharmacological Effects of opioids/ Morphine on CNS:.

A: Depressive Effects

- Analgesia
- Sedation & Mental clouding
- Hypnosis
- Respiratory Depression
- Cough Suppression

B: Stimulant (Disinhibitory) Effects

- Euphoria
- Miosis
- Vomiting
- Truncal Rigidity
- Bradycardia

C: Effect on body temperature

Depressive Effects of Morphine/ opioids

Analgesia: Opioids produce relief of pain. They are unique that they produce analgesia by affecting both the sensory & affective (emotional) components of pain. Perception of pain by brain is altered & it is not unpleasant.(NSAIDs have no significant effects on affective component).

- **Supraspinal & Spinal Analgesia** is produced via stimulation of μ (mu), κ (kappa) δ (delta) receptors
- **Peripheral Analgesia** is produced via stimulation of μ (mu), receptors only.

Sedation: Opioids produce Drowsiness & Mental clouding. No amnesia.

Hypnosis: Sleep induced more commonly in elderly than young. More marked with phenanthrene derivatives than synthetic opioids like Meperidine or Fentanyl. Both REM &NREM sleep pattern is disturbed

Pt. can easily be aroused from this sleep. Very deep sleep with other CNS depressants, as effect is potentiated.

Respiratory Depression: Morphine/opioids produce **dose related respiratory depression**

- It is due to inhibition of brain stem respiratory mechanisms.
- The alveolar PCO2 is increased, but response of respiratory centre neurons to ↑ PCo2 is decreased.
- Respiratory depression is influenced by painful stimuli; so may become marked when pain is relieved.
- Intolerable in pt with ↑ intracranial pressure (ICP), asthma , COPD & cor pulmonale.

Cough Suppressions: Depression of cough centre; Useful in pathological cough, & patients in whom ventilation is maintained via endotracheal tube. Accumulation of secretions, air way obstruction & atelectasis can occur.

B: Stimulant (Disinhibitory) Effects

Euphoria: Patients on opioids or I/V drug abusers, experience a pleasant floating sensation with ↓anxiety & distress, irrespective of the surrounding. This is due to disinhibition of ventral tegmentum .

Euphoria is the main component responsible for drug abuse Rarely dysphoria--- restlessness & malaise occurs.

Miosis: Constriction of pupil with all opioids, (except Meperidine; mydriasis due to anti-muscarinic effects).

Mech: Disinhibition /Stimulation of Edinger- Westpaul nucleus of occulomotor nerve---enhanced parasympathetic activity--- constriction of pupil; can be blocked by atropine.

Tolerance does not develop to miosis-- ---Pin point pupils are diagnostic of opioid addicts.

Miosis can be reversed by opioid antagonist Naloxone Miosis also helps for diagnosis of opioid overdosage; in other causes of coma, along with respiratory depression pupils are dilated

Nausea & Vomiting :Opioids produce nausea & vomiting ; due to:Activation of CTZ/ . Vestibular pathways may also be involved, as ambulation increases these effects.

Bradycardia: Opioids ↓HR due to disinhibition /stimulation of Vagal Nucleus.

Meperidine is Exception is ↑ HR due to anti-muscarinic effects.

Truncal Rigidity:↑ tone of large muscles of trunk by opioids, due to disinhibition at supraspinal level.

- ↑ tone--↓thoracic compliance---interference with ventilation.
- Most marked with I/V Fentanyl, Sufentanil, Alfentanil, Ramifentanil– highly lipid soluble.
- Combine NM blockers with opioids to overcome truncal rigidity, while preserving the analgesia.

Effects of opioids on body temperature: Homeostasis of body temperature is mediated in part by action of endogenous opioid peptides in brain. Experimentally administration of opioid agonists to anterior hypothalamus μ **(mu)** agonists produce **Hyperthermia**, **(kappa)** agonists produce **Hypothermia**

Peripheral Effects of opioids

1. Effects on GIT: Opioids produce **constipation, d**ue to activation of μ receptors in **Enteric nervous system, mainly in colon.** Tolerance does not develop. So addicts are severely constipated

Effect on Large bowel (colon) They inhibit pre-synaptic cholinergic nerves in sub mucosal & myenteric plexuses in colon.

- Large bowel propulsive peristalsis ↓ & tone is ↑.Prolonged colonic transit time --- ↑ fecal water absorption.
- This effect is useful in diarrhea, but adverse effect as constipation in cancer patients.

Effect on Stomach— Motility (rhythmic contraction& relaxation) may ↓.Tone (persistent contractions) may ↑. Gastric acid secretion is decreased .

Effect on Small intestine: Resting tone is ↑ with periodic spasms. ↓.Amplitude of non-propulsive contractions

2. Effects on Biliary Tract: Contraction of smooth muscles----Biliary colic

Sphincter of Oddi may constrict,reflux of biliary & pancreatic secretions ↑ plasma amylase & lipase levels**.**

3. Effects on CVS: Opioids ↓HR; due to stimulation of Vagal Nucleus No significant effect on cardiac rhythm , CO & ECG. Meperidine is exception– tachycardia due to anti-muscarinic effects.

Effect on Blood vessels & Blood pressure: Blood pressure is usually well maintained, may↓ if CVS is stressed and / or ↓ blood volume. Hypotension is due to peripheral arterial & venous dilation-- due to depression of VMC & histamine release

Effect on **cerebral Blood vessels :** only seen when PCO2 ↑--- cerebral BV dilate, ↑ blood flow & ↑ **ICP** so C/I in pts with head injury

4. Renal Effects : Both CNS (stimulation of ADH release by Mu receptors) & peripheral effects:

Depressed function due to ↓ Renal plasma flow, ↑ sodium re-absorption. Ureteral & UB tone may ↑ --

post-op urinary retention may occur & ureteral colic may worsen.

5. Effect on Uterus: ↓ tone **may prolong labor & may depress respiration of neonate.**

6. **Neuro –endocrines effects**: Opioids stimulate release of ADH, prolactin & somatotropin , ↓ release of LH.

7. Pruritis / Histamine release--- Morphine / opioids produce:

- Flushing & warming of skin, sometimes sweating
- Frequent Pruritis / Urticaria after parenteral administration. Intense pruritis over the lips may limit usefulness after spinal /epidural administration

Cause: Histamine release from mast cells. Stimulation of proprioceptive neural circuits in spinal cord & medulla

8. ACTION ON IMMUNE CELLS: **μ (MU)** receptors promote endogenous release of beta-endorphins by immune cells within injured & inflamed cells

Morphine/opioids modulate the immune system by effects on: Lymphocyte proliferation, Antibody production & Chemotaxis**; the leucocytes migrate to site of injury & release opiopeptides**, which help to ↓ **pain.**

Natural killer cells cytolytic activity & lymphocyte proliferative response to mitogens are usually inhibited.

OPIOIDS MAY ACT ON RECEPTORS AS:

Agonist: An opioid that activates a receptor, may be strong / moderate/ weak in action. Example: Morphine

Mixed Agonist-Antagonist: An opioid that activates one opioid receptor subtype but blocks the other type. Example: Buprenorphine

Partial Agonist: An opioid that activates a receptor to produce a submaximal response on full receptor occupancy& can block effects of a full agonist. Example: Pentazocine

Antagonist: A drug that blocks all or some opioid receptors. Example: Naloxone

CLASSIFICATION OF OPIOIDS

I: NATURAL/ SEMISYNTHETIC / SYNTHETIC OPIOIDS: Classified according to:

A. Spectrum of clinical uses: Analgesics, Anti-tussives , Anti-diarrheals , Anesthetics

B. Strength of analgesia: Strong, moderate & weak Analgesics.

C. Ratio of agonist to antagonist effects: Agonists, Mixed Agonists- Antagonists Partial agonists, & Antagonists.

D. Chemical groups: Phenanthrenes, Phenyl heptylamines, Phenylpiperidines, Morphinans

II: ENDOGENOUS OPIOPEPTIDES: Endorphins, Enkephalins &Dynorphins

Classification according to Clinical uses(Therapeutic Classification):

I. Analgesics (will be classified in detail)

II. Anti-tussives: Dextromethorphan, Codeine, Pholcodeine Levopropoxyphene

III. Antidiarrhoeals: Diphenoxylate, Diphenoxin, Loperamide

IV. Anesthetics: Morphine, Fentanyl, Alfentanil, Sufentanil

Classification of Analgesics; (Agonist – antagonist & Chemical Classification of opioids)

1. **AGONIST OPIOIDS**

a) **STRONG AGONISTS/ ANALGESICS**

Phenanthrenes: Morphine, Heroin, Hydromorphone , Oxymorphone**.**

Phenylheptylamines: Methadone

Phenylpiperidines: Fentanyl, Sufentanil, Remifentanil, Alfentanil, Meperidine (Pethidine).

Morphinans: Levorphanol

b) **MILD TO MODERATE AGONISTS:**

Phenanthrenes: Codeine, oxycodone, dihydrocodeine, hydrocodone.

Phenylheptylamines: Propoxyphene

Phenylpiperidines: Loperamide, Diphenoxylate, difenoxin.

2. **OPIOIDS WITH MIXED RECEPTOR ACTIONS / AGONIST-ANTAGONISTS :**

Phenanthrenes: Buprenorphine, Nalbuphine

Morphinans: Butorphanol

Benzomorphans: Pentazocine.

Miscellaneous: Tramadol, Tapentadol

3. **OPIOID ANTAGONISTS:**

Pure antagonists: Naloxone, Naltrexone, Nalmefene,

Weak agonists-antagonists: Nalorphine & levallorphan.

Analgesics combinations:

- Codeine, hydrocodone, oxycodone, propoxyphene in combination **with acetaminophen**
- Codeine& oxycodone in **combination with Aspirin**
- Hydrocodone is available in combination with **Ibuprofen**.

THERAPEUTIC USES OF OPIOIDS

1. **For Analgesia:** ***Morphine, Fentanyl*****, Meperidine,** ***oxymorphone, hydromorphone***
2. **Acute Pulmonary edema associated with LVF---*****Morphine***
3. **Use in General Anesthesia (GA) : for**
   - **Pre-anesthetic medication --*****Morphine, Meperidine,***
   - **Intra-operative: As adjunct to main GA/ spinal anesthesia:** ***Morphine***
   - **As primary component of GA:** ***Morphine, Fentanyl, Sufentanil, Alfentanil***
   - **Regional Analgesic – Epidural / Sub-arachenoid admin.--- Morphine & Fentanyl.**
   - **Post operative analgesia:** ***Morphine, Meperidine***
4. **Cough suppression:** ***Dextromethorphen, Codeine, Pholcodeine***
5. **For Diarrhea:** ***Loperamide, Diphenoxylate, Difenoxin***
6. **For relief of Shivering---** ***Meperidine(Pethidine)***

1. Use of Opioids for Analgesia: Relief of pain: Successful treatment of severe pain is challenging task. Pain should be adequately assessed. Match its severity to the appropriate therapy & evaluate its effectiveness. For a patient **in severe pain, use of opioids is the primary part of management.** Severe, constant, Visceral pain is relieved by opioid analgesics with high efficacy. Sharp, intermittent pain not controlled effectively.

Opioids are effective in pains like:

- Pain of myocardial infarction
- Pain due to Fractures
- Post operative pain
- Pain of cancer metastasis/ terminal illness pain: chronic use of opioids is required. There is development of tolerance & dependence. This should not be a barrier, they should be provided with best therapy to improve quality of life. Morphine, Pethidine, Fentanyl, Hydromorphone, may be used by different routes. Amphetamines increase analgesic effect of opioids.
- Labor pains: opioids used during labor , may delay labor& depress neonatal respiration. ***Meperidine (Pethidine)*** is preferred over ***Morphine***—less respiratory depressant for fetus
- Acute renal /biliary colic requires strong agonists, colic may worsen due to ↑smooth muscles tone, it can be overcome by enhancing the dose.

ROA: The opioids can be given by oral , S/C, I/M or I/V Inj & also following **Alternative Routes**

- Transdermal patch--- Fentanyl
- Intranasal route---- Butorphanol
- Buccal transmucosal route----Fentanyl lozenges /lollipop
- Rectal suppositories: Morphine & Hydromorphone
- Patient controlled analgesia--- I/V infusion device controlled by patient by pressing a button-- Morphine
- Epidura , Subarachanoid-- Morphine & Fentanyl. Direct application of opioid analgesics to spinal cord provides a regional analgesic effect with less A/E like respiration depression, nausea , vomiting & sedation**.**

2. Acute Pulmonary edema associated with left ventricular faiure:

I/V Morphine , with I/V Furosemide. Morphine provides remarkable relief by:

- **Reduced anxiety**– due to ↓ perception of shortness of breath
- **↓ cardiac preload,** due to reduced venous tone by histamine release
- **↓ cardiac afterload**, due to reduced PVR.
- Relieves painful myocardial ischemia

3. Use of opioids- in Anesthesia.

a**) Pre-anesthetic medication** —due to its sedative, anxiolytic & analgesic properties--- morphine, Pethidine

b) **Intra-operative** as adjunt to main GA--- morphine

c) As primary component of GA-- Fentanyl ---Used in cardio vascular or other surgery where minimal cardio vascular depression is aimed

d) Regional Analgesic – Epidural / Sub-arachenoid administration--- Morphine & Fentanyl..

e) Post operatively as analgesic--- -- Morphine, Pethidine

4. DIARRHEA: Loperamide, Diphenoxylate, Diphenoxin **(**phenylpiperidine derivatives**)** are used

They have more selective action on GIT & less on CNS.They activate μ - receptors in enteric nervous system.

Loperamide, Poor crossing of BBB. Negligible CNS effects, no analgesic effect & no abuse potential Available without prescription for Non- specific, Non-infectious diarrhea.

Dose: 2 tabs stat then one tab after each diarrheal stool.

Diphenoxylate: No CNS effects in therapeutic doses. CNS effects in high doses & there is abuse potential. Is a prescription opioids. It is used in combination with small quantities of Atropine to decrease abuse liability. Tablets contain Diphenoxylate 2.5mg & Atropine (0.025mg) Useful in Non- specific, Non-infectious diarrhea.

Difenoxin :Metabolites of Diphenoxylate. Similar to Diphenoxylate.

5. COUGH SUPPRESSION (Anti –tussive effect**)** --- Opioids are the most effective Anti –tussive, suppression of cough occurs at doses lower than used for analgesia. Dextromethorphan, Codeine, Pholcodine, Levopropoxyphene ,Noscapine may be used. Codeine has addictive potential.

Dextromethorphan: Preferred anti-tussive. No addictive potential. Less constipation C/I in children < 6 yrs.

D/I : High incidence of hyperpyrexic coma & hypertension with MAO inhibitors.

6. RELIEF OF SHIVERING: Meperidine ↓ shivering----through action on α_2 receptor subtype.

ADVERSE EFFECTS OF OPIOIDS : may be acute or chronic.

Acute A/E:

1. Dysphoria : restlessness & malaise
2. Respiratory depression
3. Nausea & vomiting
4. Raised intracranial pressure
5. Postural hypotension accentuated by hypovolemia
6. Constipation
7. Urinary retention
8. Itching around nose, urticaria (more frequent with parenteral & spinal administration
9. Drug interactions

Drug interactions:

- Sedative hypnotics: (Benzodiazepines, Barbiturates)↑ CNS depression, especially respiratory depression
- Antipsychotic tranquilizers;(Haloperidol, chlorpromazine): ↑ sedation. Variable effect on respiratory depression.↑ antimuscarinic & α adrenergic blockade on CVS.
- MAO inhibitors (Iproniazid, Tranylcypromine) are C/I; risk of Hyperpyrexic coma & Hypertension.
- Amphetamines ↑ analgesic effect.

Chronic Adverse Effects: When opioids are used/ abused for prolonged periods, there is development of:

1.**Tolerance, Physical dependence, addiction & Opioid induced hyperalgesia**

Tolerance: With frequently repeated therapeutic doses of Morphine or other opioids, there is **gradual loss of effectiveness.**To reproduce the original response a **larger dose is required..** Tolerance is generally manifested **after2-3 wks**, but use of ultra-potent opioids in peri-operative period may produce tolerance within hrs. Degree of tolerance may be up to **35 folds**. Degree of tolerance differs to various effects of Morphine

- **Minimal /No Tolerance**: Miosis, constipation, convulsions. Addicts have pin point pupils & constipation
- **Moderate Tolerance**: Bradycardia
- **Marked tolerance to:** Analgesia, euphoria, dysphoria, sedative & respiratory depressant effects, hypothermia, emetic, anti-diuretic, hypotensive & anti-tussive effects .

Cross Tolerance-:A patient who develops tolerance to one opioid may be tolerant to other opioid, but this tolerance is incomplete. So one opioid may be substituted for another in chronic treatment of pain---**Opioid rotation** .

Mechanism of development of Tolerance: Mainly **pharmacodynamic,** persistent activation of mu- receptors plays a primary role. It may be due to:

- **Upregulation of cAMP system**
- **Failure of Receptor re-cycling**: For maintenance of normal sensitivity of μ (mu)- receptors, re-activation by endocytosis & recycling is required. Failure of Morphine to induce endocytosis & re-cycling of μ (mu)-receptors produces tolerance. Methadone, induces endocytosis & is used to treat opioid tolerance & dependence.
- **Receptor uncoupling**: Dysfunction of interactions b/w μ receptors & G pr second messenger system.

NMDA- receptor: Ketamine; antagonist of NMDA- receptor can block development of tolerance.

2.Opioid Dependence-

a. **Euohoria:** Indifference to stimuli & sedation, some abdominal effects linked to intense sexual orgasm specially when injected I/V, promote their compulsive use.

The above factors are strongly reinforced by development of physical dependence.

b. Physical Dependence- It develops on chronic administration of opioids; marked with strong mu-agonists. The presence of certain amount of drug is necessary in body fluids for the normal physical activities of life.

When the drug is withdrawn, or I/V Naloxone is given; Withdrawal or Abstinence syndrome results.

Signs & symptoms of Abstinence syndrome include: Rhinorrhea, Lacrimation, Yawning, Chills, Goose flesh(piloerection), Hyperventilation, Hyperthermia, Mydriasis, Muscular aches, Vomiting ,diarrhea, anxiety & hostility.

The time, intensity, duration of Abstinence syndrome depends upon the type of drug & its $t_{1/2}$.

- Drug with short $t_{1/2}$ -- Morphine& Heroin, severe S/S appear within 6-10 hrs of last dose, peak in 36-48hrs, mostly disappear by 5 days.
- Drug with longer $t_{1/2}$ -- Methadone, S/S appear slowly, are mild & several days are required to reach peak, may last for 2 wks, so methadone is used for detoxification of Morphine & Heroin addicts.

Mechanism of opioid Dependence:

- ↑ Dopamine concentrations in mesolimbic projection produces Euphoria, through mu receptors.
- The physical dependence, is due to interference with long term potentiation (LPT) at sites of convergence of dopamine & glutamate----- ventral tegmental area, nucleus accumbens or pre-frontal cortex

3: Addiction— *Addiction can develop after prolonged use of opioids.*

As defined by the American Society of Addiction Medicine addiction is a primary, chronic disease of brain reward, motivation, memory, and related circuitry.

Addiction is characterized by inability to abstain consistently, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response

Risk of inducing dependence & addiction is an important consideration in therapeutic use of opioid drugs.

Despite that risk, adequate pain relief should never be withheld. & Certain principles can be observed by the clinician to minimize problems presented by tolerance and dependence when using opioid analgesics:

• Establish therapeutic goals before starting opioid therapy. This tends to limit the potential for physical dependence. The patient and his or her family should be included in this process.

• Once an effective dose is established, attempt to limit dosage to this level. This goal is facilitated by use of a written treatment contract that specifically prohibits early refills and having multiple prescribing physicians.

• Consider using nonopioid analgesics whenever possible.

• Frequently evaluate continuing analgesic therapy and the patient's need for opioids.

Opioid induced hyperalgesia: Persistent administration of Morphine, Fentanyl& Remifentanil ↑sensation of pain---hyperalgesia. Spinal dynorphins & activation of bradykinin plays a role.

- **CONTRAINDICATIONS TO USE OF OPIODS**

1.Pure /full agonists should never be combined with weak partial agonists

Pentazocine C/I with Morphine as analgesia will↓& There is risk of withdrawal syndrome

2. Patients with Head injury: Risk of ↑ intracranial pressure, due to cerebral vasodilation.& ↑ blood flow

3. **Pregnancy.** If mother has been given Morphine; labor is delayed Depressed respiration of newborn , --- give I/V Naloxone to overcome the respiratory depression to newborn. Pethidine is preferred to Morphine Pregnant females using opioids chronically: The fetus may become dependent on opioids in utero. Withdrawal symptoms in early post-partum period--- irritability, shrill cry, diarrhea even convulsions.

4.Impaired pulmonary function: acute respiratory failure may occur **i**n pts with asthma, COPD corpulmonale

5.Impaired hepatic or renal function. Decreased clearance.

6.Endocrine diseases: Prolonged &↑ response in Adrenal insufficiency (Addison' disease) & Hypothyroidism

OPIOIDS OVERDOSAGE:

Diagnosis: Triad of Pinpoint pupils . Coma & Respiratory depression I/V Naloxone reverses coma

Treatment : Naloxone, a pure opioid antagonist I/V, short DOA: 1 – 2 hrs, so dose is to be repeated

- General supportive measures; specially ventilatory support.

Opioid Antagonists: Pure opioid antagonists: Naloxone, Naltrexone , Nalmefene. Morphine derivatives.

Naloxone: Used I/V, short DOA: 1 – 2 hrs , metabolized by glucuronidation

MOA: Competitive antagonist at opioid receptors. Blocks all 3 main types of opioid receptors.

High affinity for μ, lower for κ & δ receptors

Effects of Naloxone: Given I/V, in a morphine treated pt. completely reverse its effects in 1-3 minutes.

- In acute overdosage: Normalizes depressed respiration, level of consciousness, pupil size, bowel activity & awareness of pain. In an **addict it produces Abstinence syndrome**

Th. Uses of Naloxone: In acute opioid overdosage

- In opioid depressed newborn , if mother has been given Morphine during labor.
- Low dose naloxone used in treatment of adverse effects associated with I/V or subdural opioids; itching nausea & vomiting while sparing analgesia.(oral analogs are preferred---methylnaltrexone & alvimopan**)**

Naltrexone: Orally effective longer DOA: 48hrs..Useful in maintenance programs of abusers.. Can block effects of Heroin for 48 hrs .It also ↓craving for Alcohol in chronic alcoholics by ↑baseline β-endorphin release**.**

Nalmefene: Given I/V, longer DOA:8-10 hrs

METHYLNALTREXONE& ALVIMOP: Pure peripheral mu antagonists, do not enter CNS.

Alvimopan used for treatment of post operative ileus following bowel resection surgery.

Methylnaltrexone Ueful for constipation with late stage disease; without precipitating abstinence syndrome.

Weak agonists-antagonists: Nalorphine & levallorphan– used previously.

Different groups description

Strong Opioid Agonists:

Phenanthrenes: Morphine ,Hydromorphone , Oxymorphone**:** used for severe pain **Heroin (diamorphine , diacetylmorphine):**

- Produced by diacetylation of morphin , which makes it **3 times more potent than morphine**
- High affinity for μ receptors. It is **fast acting**.
- More lipid soluble, readily crosses BBB---- marked euphoria after I/M inj. So **strong drug of abuse**.
- Converted to morphine in body, DOA ½ than morphine.**Not used clinically , not a better analgesic**

Phenylheptylamines: Methadone Synthetic opioids Effective by oral, I/V , I/M , S/C , Spinal & Rectal route.

- Oral bioavailability < morphine. longer half life– 25-50 hrs
- Potency more than morphine---- **superior analgesic**.
- Agonist at μ receptors also at NMDA receptors & inhibits monoamines reuptake transporters.

Therapeutic uses of Methadone: Potent & clinically useful analgesic

- Used for **difficult to treat pain– neuropathic, cancer pain, when tolerance to Morphine has developed**.
- Used **for Detoxification & maintenance programs for morphine & Heroin addicts** --- withdrawal syndrome is mild but longer-- days to wks

A/E: Danger of respiratory depression, prolonged Qt interval--- may be fatal, if used with enzyme inhibitors

Phenylpiperadines: Fentanyl. One of the **most widely used** synthetic opioid.

- Strong μ receptor agonist, variable affinity for κ & δ receptors
- Fentanyl is 100 times more potent than morphine. Rapidly acting & short DOA 15-30 minutes.
- Given by I/V, Transdermal patch or Transmucosal route, Epidurally or intrathecally.

Sufentanil, Remifentanil, Alfentanil: Like Fentanyl but shorter DOA.

Sufentanil 5-7 times more potent than Fentanyl.
Alfentanil & Remifentanil less potent, rapid OOA & shorter DOA, metabolized by blood & tissue esterases.
Thrapeutic uses of Fentanyl : Cancer pain , tolerant to Morphine.

- As general anesthetic in patients with low cardiac reserve.
- For post operative analgesia

A/E: like other μ agonists. Muscular rigidity of abdomen & chest→Life threatening **hypoventilation**
Meperidine (Pethidine): Synthetic opioid, chemically Phenylpiperidine
High affinity for μ, also binds well to **κ receptors.** Actions similar to Morphine , but **has Antimuscarinic effects** , so produces mydriasis, tachycardia & negative inotropic effects on heart.

- Safer than Morphine in labor pains; less respiratory depression of neonate.
- **Its metabolite nor-meperidine can produce seizures in high doses / renal failure**.

MILD TO MODERATE AGONISTS:
Phenanthrenes: Codeine, oxycodone, dihydrocodeine, hydrocodone : Partial agonists, analgesic efficacy < Morphine. Codeine useful antitussive but potential for abuse.
Phenyl heptylamines: Propoxyphene: Chemically related to Methadone efficacy 50 % less than Codeine. Incidence of deaths so not used.
Phenylpiperidines: Loperamide, Diphenoxylate, Diphenoxin**. Used as antidiarrheal,(discussed with uses)**
OPIOIDS WITH MIXED RECEPTOR ACTIONS / AGONISTS-ANTAGONISTS :.
Buprenorphine: Potent & long acting. Given **sublingually to** avoid significant hepatic first pass effect.

- Slow release **transdermal patch** with one wk DOA also available
- **Partial μ agonist**, κ & δ antagonist .Dissociates slowly from μ receptors so long DOA 4-8hrs.
- It can antagonize effects of strong analgesics at μ receptors May precipitate abstinence syndrome .
- Its effects are resistant to reversal by Naloxone.
- Also binds to ORLI-1 receptors ---clinical significance not clear
- Used for **Detoxification & maintenance programs for opioid dependence**. Also ↓ **craving for alcohol.**
- A/E: Hallucinations, nightmares & anxiety. Severe respiratory depression on I/V admin specially with BZ

Pentazocine: κ receptor agonist & weak μ & δ receptor antagonist.

- Useful **for moderate pain , orally or parenerally**. Can precipitate withdrawal syndrome in Morphine addict , but does not antagonize the respiratory depression. Pentazocine produce different from of Withdrawal or Abstinence syndrome as compared to that produced by Morphine or other agonists.

Tramadol: A centrally acting analgesic A **weak μ receptor agonist**. **Moderate SERT inhibitor & weak NET inhibitor**-- ↓ Serotonin & Norepinephrine reuptake.. Partial reversal with Naloxone. **Useful adjunct with pure agonists in chronic neuropathic pain.** A/E: Seizures , risk of serotonin syndrome.
Tapentadol: Newer analgesic , μ receptor agonist , also inhibits NET--↓ Norepinephrine reuptake. Used as analgesic for moderate pain. Headache, Nausea & vomiting possible dependence.
N/OFQ system: A noval receptor ligand system; homologus to opioid peptides has been found recently; known as N/OFQ system

- The principle receptor is ORLI-1—orphanin opioid receptor like subtype-1.
- The principle ligand has been named NOCICEPTIN by one group & ORPHANIN FQ by the other.
- Nociceptin acts only on ORLI-1receptor , now called NOP
- N/OFQ system is widely expressed in CNS & periphery.
- Experiments have shown that it is implicated both in pro-nociceptive & anti-nociceptive activity & modulation of drug reward, learning, mood, anxiety, cough processes & Parkinsonism.