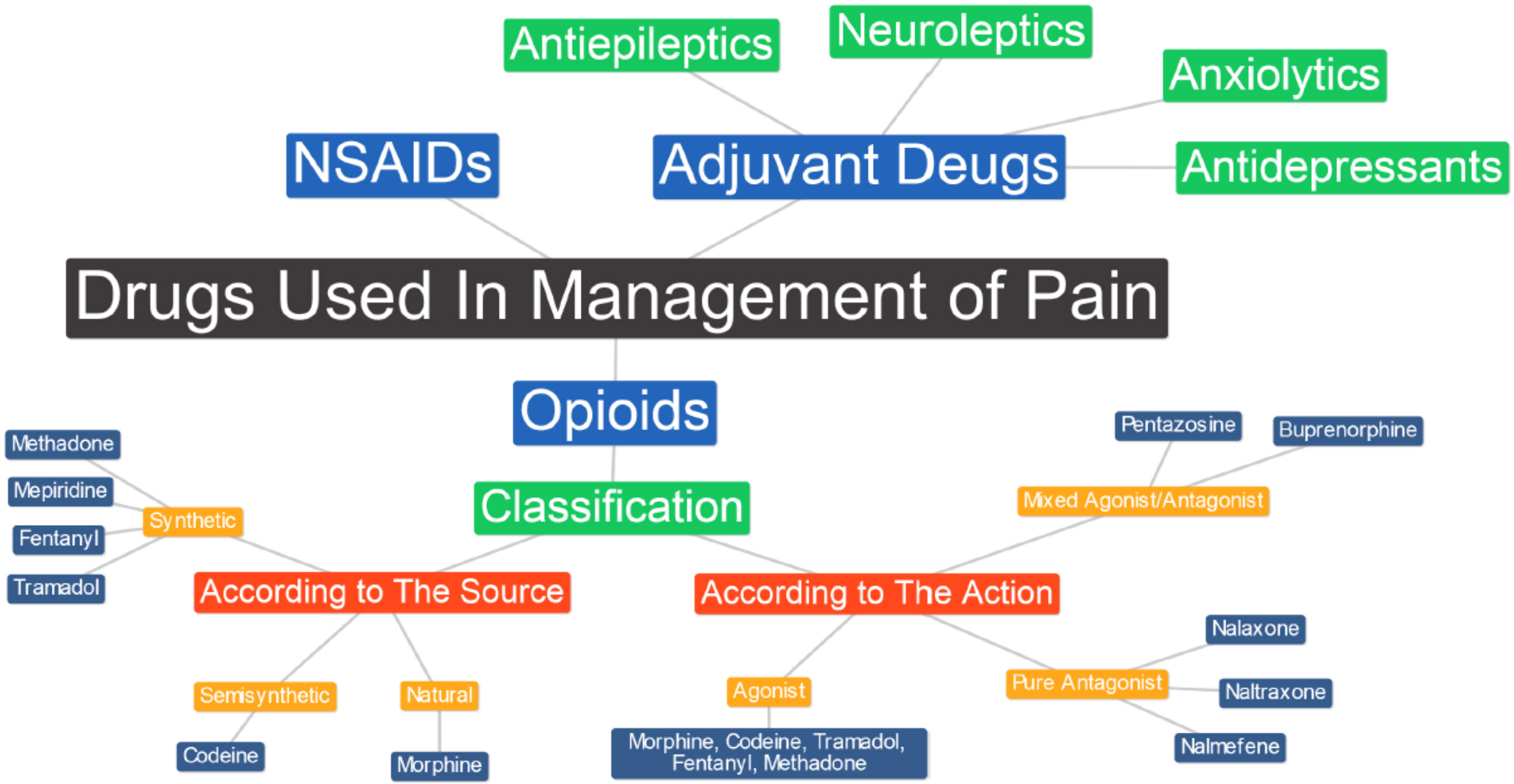
Lecture 5

Drugs used in management of the pain

Objectives:

- Categorize the different classes of drugs used to relieve pain
- Detail on the mechanism of action, pharmacokinetics and pharmacodynamics effects of morphine and its synthetic derivatives
- Hints on the properties and clinical uses of morphine antagonists

- Additional Notes
- Important


Drugs Used In Management of Pain
NSAIDs
Adjuvant Deugs
Antiepileptics
Neuroleptics
Anxiolytics
Antidepressants
Opioids
Classification
According to The Source
Synthetic
Methadone
Mepiridine
Fentanyl
Tramadol
Semisynthetic
Codeine
Natural
Morphine
According to The Action
Agonist
Morphine, Codeine, Tramadol, Fentanyl, Methadone
Mixed Agonist/Antagonist
Pentazosine
Buprenorphine
Pure Antagonist
Nalaxone
Naltraxone
Nalmefene

Mind Map

OPIOID RECEPTORS

- Mu (μ)
- Delta (δ)
- Kappa (k)

→ Substantial parallels between μ and δ receptors and dramatic contrasts between μ /δ and k receptors

ORL-1 — Nociception receptor, Antagonizes dopamine transport

- Anatomical distribution in brain, spinal cord, and the periphery
- All of them are typical G-protein coupled receptors

CLASSIFICATION OF OPOIDs

According to their specificity of action on receptors	μ -receptor agonists	Morphine, Codeine, heroin
	k -receptors agonists	Pentazocine
According to agonistic/antagonistic actions	Agonists	Morphine, Codeine, Pethidine, Methadone
	Mixed	Pentazocine
	Pure antagonist	Nalaxone, Naltraxone
According to their source	Natural	Morphine
	Semisynthetic	Heroin
	Synthetic	Pethidine, Methadone

Drugs used in management of pain

NSAIDS

* The first class used for controlling the pain.
* Work at the site of tissue injury to prevent formation of nociceptive mediators.
* Decrease opioid side effects .
* They neither cause tolerance or dependence.
* Has a ceiling effect to analgesia .

Opioids

Opium is derived from the juice of the opium poppy,Papaver somniferum.

The natural products includes morphine ,codeine , papaverine and thebaine.

Opiates are drugs derived from opium and semisynthetic and synthetic derivatives .

Opioids refer to opiates and endogenous opioid peptides ,e.g. B-endorphin.

Adjuvant drugs

Modify the perception of pain and remove concomitants of pain such as anxiety, depression.

E.g.

Anxiolytics

Neuroleptics

Antidepressants

Antiepileptics

WHO Pain Ladder?

1 **Mild Pain**
Nonopioid ± Adjuvant
Aspirin, Acetaminophen, NSAIDs...

2 **Moderate Pain**
Opioid ± Nonopioid ± Adjuvant
Codiene, Hydrocodone, Oxycodone...

3 **Severe Pain**
Opioid ± Nonopioid ± Adjuvant
Morphine, Hydromorphone...

Morphine

MoA	• Pre synaptic (bind to opioid receptors coupled with Gi → ↓ AC (Adenyl cyclase) & cAMP → ↓ voltage-gated Ca^{2+} → ↓ excitatory transmitters) . • Post synaptic (bind to post synaptic → ↑ opening of K channels → ↓ neuronal excitability)
P.D.	• Analgesia (Acute & Chronic). • Euphoria. • Respiratory depression (elevate CO_2 conc). • depression of cough reflex (antitussive "dry cough"). • ↑ CRTZ → Nausea & vomiting (stimulate chemoreceptors). • Pin point pupil. • Release Histamine from Mast cells. • On GIT :↑ in tone ↓ motility → sever constipation → ↑ pressure in the biliary muscle + contrction of the biliary sphincter → contraction of gall bladder.
Tolerance Dependence	○ Tolerance → (you take - you need more) • Rapid 12-24h • constipation and pupil size don't develop tolerance ○ Dependence → (you stop - you face symptoms) • withdrawal effect. • End of 8-10 days "physiological" • End of months & years "craving"
P.K.	• T ½ short = 2-3 h • slowly and absorbed orally • Given by IM, IV, SC. • Metabolized by Glucuronic acid. • Cross Placenta & BBB. • Undergoes enter-hepatic recycle .

Morphine

Indication	• Control pain → mostly Visceral . • Acute pulmonary edema → histamine leads to vasodilation of veins • Myocardial infarction. • Heart failure → non painful condition (relive distress)
ADRs	• Constipation. • Respiratory depression. • Itching. • Nausea & vomiting. • Constricted pupil. • Sedation. # CRINCS = doesn't mean anything.
C.I.	• Head injury (increase intracranial pressure) • Pregnancy • Bronchial asthma. • Biliary colic. • Elderly (renal clearance and liver metabolism deteriorate with age). • MAOIs. • Infant, neonates → b/c before 15 days of birth glucuronic acid didn’t form yet.

DRUGS	PD	USES	ADES
Codeine weak analgesic	• m agonist • Causes less dependence than morphine	Used in mild and moderate pain, cough, diarrhea	_____
Tramadol can be given orally More oral bioavailability	• Synthetic, m agonist • metabolite of Tramadol more potent than codeine • less potent than morphine • Inhibits NE and 5HT reuptake	Mild - moderate acute & chronic visceral pain And During labor	• Seizures (not in epileptics) • Nausea , Dry mouth, Dizziness, Sedation • Less adverse effects on respiratory & C.V.S
Pethidine	• Synthetic more effective k (Kaba) agonist • Less analgesic, constipating, depressant on fetal respiration than morphine • No cough suppressant effect • Has atropine like action (sm. relaxant)	• As in morphine but not in cough & diarrhea • Used in obstetric (pregnant) analgesia (No ↓ resp.) • Used in severe visceral pain; renal & biliary colics (sm. relaxant) • has better Preanaesthetic medication action	• Tremors, Convulsions, Hyperthermia, Hypotension • Blurred vision, Dry mouth, Urine retention • Tolerance & Addiction
Fentanyl	• Synthetic, m agonist, more potent than pethidine & morphine	• Analgesic supplement during anesthesia, (IV or intrathecal) To induce & maintain anesthesia in poor-risk patients [stabilizing heart.] • In combination with droperidol as NEUROLEPTANALGESIA • In cancer pain & severe postoperative pain; (transdermal patch changed every 72 hrs).	• Respiratory depression (most serious) • CV effects are less. • Bradycardia may still occur
Methadone	• Weaker synthetic μ- agonist • In non addicts, it causes tolerance & dependence but not as severe as that of morphine; t½ 55 h	Used to treat opioid withdrawal	_____

Opioid antagonists

Drugs	Indications	Extra info.
Naloxone	Respiratory depression caused by opioid overdose Reverse the effect of analgesia on the respiration of the new born baby	Pure opioid antagonist Precipitates withdrawal syndrome in addicts Effect lasts only for 2-4 hours
Naltrexone	-	Very similar to naloxone but with longer duration of action [t½=10h]

Summary

Drugs	Indications	Adverse Effects	Extra info.
Morphine	Pain Control: Cancer pain, severe burns, trauma. Acute Pulmonary Edema, Myocardial Ischemia Severe visceral pain; (BUT not in renal and biliary colics) Non painful conditions: HF	Sedation Respiratory depression Constipation Nausea and vomiting Itching Pupillary constriction	Tolerance & dependence develop rapidly. Crosses BBB Crosses placenta.
Codeine	Mild & moderate pain, Cough, Diarrhea	-	μ Agonist, Dependence < morphine
Tramadol	Mild, moderate acute & chronic visceral pain. During labor.	Seizures, Less adverse effects on respiratory & C.V.S	Synthetic, μ agonist Less potent than morphine
Pethidine	Obstetric Analgesia Severe visceral pain: (renal and biliary colics)	Tremors, Blurred vision, Urine retention Tolerance & Addiction	Synthetic kappa agonists LESS analgesic + LESS constipating + LESS fetal respiration effects THAN morphine. Has atropine like action
Fentanyl	Analgesic during anesthesia In combination with Droperidol as NEUROLEPTANALGESIA In cancer pain & severe postoperative pain	Respiratory depression CV effects are less Bradycardia may still occur	Synthetic μ agonist. More potent than pethidine & morphine
Methadone	Opioid Withdrawal	-	Weaker synthetic μ- agonist
Naloxone	Respiratory depression Reverse the effect of analgesia on the respiration of the new born baby.	-	Pure opioid antagonist Precipitates withdrawal syndrome in addicts Effect lasts only for 2-4 hours
Naltrexone	-	-	Very similar to naloxone but with longer duration of action [t½=10h]

MCQs

1. **Which of the following is an absolute contraindication to opioid use?**
   A. Closed head injury
   B. Myocardial infarction
   C. Acute pulmonary edema
   D. Biliary colic

2. **Which of the following is specifically will bind to K-receptor ?**
   A. Morphine
   B. Pentazocine
   C. Nalaxone
   D. Pethidine

3. **Psychological dependence of morphine will last for?**
   A. 8-10 days
   B. 2 weeks
   C. months to years
   D. 12 -24 hours

4. **An epileptic patient felt pain in the internal viscera, What is the drug that shouldn't be given to this patient?**
   A. Fentanyl
   B. Tramadol
   C. Pethidine
   D. Morphine

5. **Doctor prescribed to a patient with cancer pain a natural analgesic, that cause constipation as a side effect, What is most likely the drug?**
   A. Codeine
   B. Morphine
   C. Methadone
   D. Fentanyl

Answers: 1. A 2. B 3. C 4. B 5. B

6. **Patient with biliary colics have severe pain that is treated with one of the analgesic that work on Kappa receptors, Which of the following is the drug used by this patient?**
   A. Codeine
   B. Pethidine
   C. Fentanyl
   D. Methadone

7. **Which of the following is used as opiate receptor antagonist?**
   A. Naloxone
   B. Methadone
   C. Morphine
   D. Pathedine

8. **9 month patient crying due to sever pain treated with analgesic that is not morphine that might lead to respiratory distress due to?**
   A. Decrease P450 enzyme activity in infants
   B. Decrease conjugating of the morphine in infants
   C. Decrease Renal execration
   D. Impairment of the liver

9. **Patient coming to the ER complaining of severe body ache, insomnia, diarrhea, lacrimation, The doctor notice that the patient has miosis. Which of the following drugs could be given to this patient?**
   A. Fentanyl
   B. Morphine
   C. Naloxone
   D. Methadone

Answers: 6. B 7. A 8. B 9. D

MCQs

An analgesic that may lead to constipation, respiratory depression, is used to treat a patient with severe pain due to burning of his body.

1. What is the most likely drug that this patient treated with ?
    - Morphine

2. What is effect of this drug to the pupil?
    - Pinpoint pupil

3. What is the final effect on the GIT?
    - Increase in the tone of the muscles but with decrease motility.
    - Head injury → due to the vasodilation effect
    - Impaired pulmonary function.
    - Biliary colic
    - In infants

SAQs

Good luck!

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