YU - MEDICINE
PASSION ACADEMIC TEAM

Central Nervous System

Sheet# 3 - Pharmacology

Lec. Title : Opioid Analgesics

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Opioid analgesics

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Alleviation of pain depends on its type;

1. Headaches or mild to moderate arthritic pain nonsteroidal anti-inflammatory agents (NSAIDs) are effective.

2. Neurogenic pain responds best to anticonvulsants, tricyclic antidepressants (for example, *amitriptyline*), or serotonin/norepinephrine reuptake inhibitors (for example, *duloxetine*) rather than NSAIDs or opioids.

3. However, for severe or chronic malignant pain, opioids are usually the drugs of choice

1- نتيجة مرض inflammation & prostaglandin formation
بنعالجه بNSAID مثل somatic pain على الجسم مثل آلام
المفاصل والعضلات وآلام الأعصاب .

2_for visceral pain the opioid now is effective to chronic cases more than acute.

- **Natural**
  - Morphine
  - Codeine
- **Semisynthetic**
  - Hydromorphone
  - Hydrocodone
  - Oxycodone
  - Oxymorphone
- **Synthetic**
  - Fentanyl
  - Meperidine
  - Methadone
  - Tapentadol
  - Tramadol

_sleep relive pain

_زمان كانو يسمو هاي الأدوية narcotic analgesic

كانوا يحكو انه المسكنات هاي بتخفف الألم لانه بتحفز النوم والنوم بشكل عام يسكن الالم وزمان حكو انه الـ morphine

وإخوانه بسكنو الألم وبنومو ولكن احنا الان بحاجة لتسمين الألم دون السبب بالنوم ومن هون صرنا نعطي ال opioid

بجرعات ما بتأدي إلى النوم ولا بتفقد المريض وعيه ولهيك صار اسمها Opioid analgesic not narcotic analgesic

_meperidine=loperamide & diphenoxylate

ويستخدم بعلاج ال diarrhea

_potency for meperidine to morphine =1/10

وبالتالي نحتاج إلى جرعة كبيرة منه مقارنة بالموظفين

صنعو من meperidine 3 أدوية :

1_fentanyl. 2_loperamide. 3_diphenoxylate

_Potency of meperidine 1/10 But fentanyl 50_100 potent as morphine.

_meperidine is less constipating But loperamide and diphenoxylate are more constipating from morphine.

_meperidine is different from morphine :

_1المورفين بيعمل miosis لل pupil

Meperidine بيعمل mydriasis

2_morphine constipating, meperidine less constipating

3_morphine more potent, meperidine (1/10 to morphine)

4_meperidine _ يصنع منه ثلاث ادوية ليعوضو مشاكله 😎

methadone مثل المورفين من ناحية analgesic

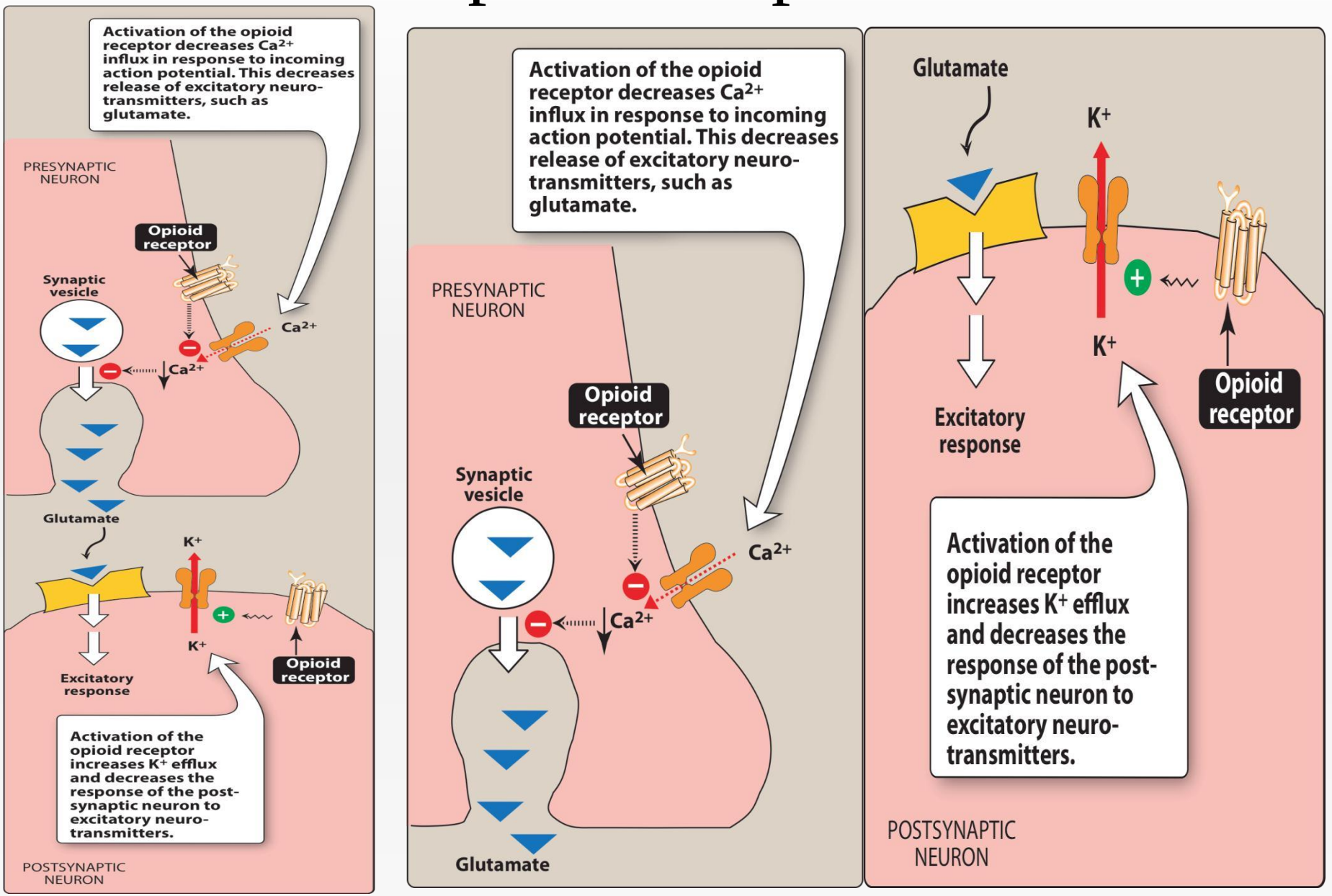
لكن الميزة الي بتميزه عن المورفين اذا المريض كَانو ياخذه وبعدين اتوقف ال withdrawal manifestation بتكون قليلة

Opioid receptors

Receptor subtype	Functions
μ (mu)	**Analgesia** **Sedation** **Inhibition of respiration** **Slowed gastrointestinal** Modulation of hormone and neurotransmitter release
δ (delta)	**Analgesia** Modulation of hormone and neurotransmitter release
K (kappa)	**Analgesia** Psychotomimetic effect Slowed gastrointestinal transit

(mu)u=supra spinal في كل أجزاء الدمج من فوق
Kappa_k=dorsal horn of spinal cord
المورفين بشتغل بشكل رئيسي على النوع الأول لكن بيعمل شغلة بنسميها
Euphoria (false sense and happiness)
dysphoria =abnormal mood بتعمل اشي اسمه kappa لكن
analgesic دورها مش قوي ك delta =
neurotransmitter لكن تأثيرها قوي عالهرمون و
the most important one is (Mu)

Opioid receptors



in presynaptic :opioid close the ca+2 channel and prevent release of glutamate.

وبالتالي العصب الي فوق مش رح ينقل الإشارات ورح يصير عصب ضعيف وما فيه conduction

المورفين والاوبيود بفتحو للكالسيوم لل post synaptic neuron

_لما البوتاسيوم يخرج من الخلايا العصبية بصير فقدان للايونات الموجبة من داخل الخلية وبالتالي بتزيد السالبية داخل الخلية hyperpolarization

- The analgesic properties of the opioids are primarily mediated by the μ receptors; however, the Ќ(kappa) receptors in the dorsal horn also contribute.

- For example, *butorphanol* and *nalbuphine* primarily owe their analgesic effect to K-receptor activation.

- The enkephalins interact more selectively with the delta receptors in the periphery.

_لما تتعرض لضربة عالراس الدماغ بفرز مادة ال enkephalins
لحتى يسكن الالم

Morphine

Has diverse effects:

- Analgesia,
- Drowsiness,
- Mood changes,
- Respiratory depression,
- Reduced GI motility,
- Vomiting,
- Endocrine and ANS changes.

Pharmacological Actions of morphine

Analgesia:

- ***without the loss of consciousness*** (raising the pain threshold at the spinal cord level and altering the brain's perception of pain).

- Patients treated with *morphine* are still aware of the presence of pain, but the sensation is not unpleasant.

- However, when given to an individual free of pain, its effects may be unpleasant and may cause nausea and vomiting.

_يستخدم في الآلام المزمنة والنستمرة لفترات طويلة
_بحالة اخذ المورفين من دون وجود ألم ماذا يحصل؟
رح يصير عنا اعراض للمورفين غير ال analgesic
سواء vomitingاو nausea
_ممنوع إعطاء المورفين لشخص يعاني من acute abdominal pain
as right renal colic or apendicitis
_ممنوع إعطائه المورفين لانه بعمل تسكين للألم وممكن تتفجر الزائدة ويموت المريض بدون ما يحس المريض .
واذا بدنا نعطي لهذا المريض فبنعطيه antispasmodic

- **Euphoria:** may be caused by disinhibition of the ventral tegmentum.

- **Respiration:** respiratory depression by reduction of the sensitivity of respiratory center neurons to carbon dioxide. This occurs with ordinary doses of *morphine* and is accentuated as the dose increases until, ultimately, respiration ceases.

- **Emesis:** directly stimulates the chemoreceptor trigger zone that causes vomiting.

_euphoria: false sense of happiness

_ممنوع إعطاء المورفين لمريض الازمة

_ممنوع إعطاء المورفين بحالة ال close head injuries

_المورفين بيعمل على زيادة ال co2وبالتالي بعمل Cerebral vasodilationولما يزيد ال diameter للاوعية بالدماغ رح يصير ترشيح للسوائل ويعمل edema وبالتالي رح يزيد intracranial pressure

- فبينتج عنه صداع وتشوش بالرؤية لانه لما يزيد الضغط بالمخ رح يزيد الضغط عالعصب البصري ويعمل blurred vision.
- _في الجرعات العادية للمورفين قد يحدث vomiting
- لكن بالجرعات العالية لا يعمل vomiting
- لأنها بتعمل depress for vomiting center.
- _يمكن استخدام المورفين ك antithesis

- **Depression of cough reflex:** Both *morphine* and *codeine* have antitussive properties. The receptors involved in the antitussive action appear to be different from those involved in analgesia.

- **Miosis:** The pinpoint pupil, characteristic of *morphine* use, results from stimulation of μ and kappa receptors (excites the Edinger-Westphal nucleus of the oculomotor nerve, which causes enhanced parasympathetic stimulation to the eye). There is ***little tolerance to this effect.***

Codeine = له مستقبل خاص فيه بال cns
في ال cough center called codeine receptor
_codeine more potent from morphine antitussive
_codeine is methyl morphine.
_CYP4502D6 is responsible for convert codeine to morphine.
_لكن الانزيم مش موجود عند كل الناس بس وجوده مهم لحتى ال codeineيشتغل .
_جرعة codeineبتكون قليلة عند استخدامه ك antitussive
مقارنة مع استخدامه ك analgesic.
كيف بقدر اعرف اذا الشخص عنده تسمم من المورفين لما يصل المستشفى من خلال ال pinpoint pupil
بكون ضيقة جدا مثل راس الدبوس(وطبعا بالحرعات العادية بصير عنده pinpoint pupilوحتى بعد ما يوقف الإدمان بضل تأثير المورفين و وجود pinpoint pupil

- **Gastrointestinal tract:**

produces constipation **(**by decreasing the motility and increasing the tone of the intestinal circular smooth muscle. Also, increases the tone of the anal sphincter).

Little tolerance developing.

It can also increase biliary tract pressure due to contraction of the gallbladder and constriction of the biliary sphincter.

Morphine and opioid produce constipation_نتيجة تأثيره = على الأعصاب الواصلة للجهاز الهضمي

_Mu & kappa receptors are located in central and GIT.

_ولذلك ال meperidine وأولاده الثلاثة بشتغلو على ال Mu & kappa الموجودة عالاعصاب الواصلة للجهاز الهضمي فبتعمل(spasm)

_وهذا ال constipation الناتج من ال opioid ما بصيرله tolerance ورح يستمر حتى بعد التوقف

- **Cardiovascular:** no major effects on the blood pressure or heart rate except at large doses, when hypotension and bradycardia may occur. Because of respiratory depression and carbon dioxide retention, cerebral vessels dilate and increase CSF pressure. (= contraindicated in individuals with severe brain injury).

- **Histamine release:** causing urticaria, sweating, and vasodilation (= contraindicated in asthmatics)

_ما بيحدث تأثير على ال cardiovascularالا بالجرعات الكبيرة وبينتج عنه hypotension

_لانه المورفين من أشهر أشهر أشهر)حكاها ٣مرات للأمانة (ال histamine release👇👇

بخلي histamine يفرز بكثرة والهيستامين بعمل vasodilation

- **Hormonal actions:**

1. Inhibits release of gonadotropin-releasing hormone and corticotropin-releasing hormone,
2. Decreases the concentration of luteinizing hormone, follicle-stimulating hormone, adrenocorticotropic hormone.
3. Testosterone and cortisol levels decrease.
4. Increases growth hormone release and enhances prolactin secretion.
5. Increases antidiuretic hormone (leads to urinary retention).

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

_Morphine lead to asphyxia neonatorum
And relaxation of uterusبآخر الولادة
meperidine_بنقدر نعطيه أثناء الولادة لانه ما باثر عال uterus
👉 contractionركز عليها كثير
##ممنوع إعطاء المورفين أثناء الولاد🤰🤰

Therapeutic uses

- **Analgesia**
- **Treatment of diarrhea**
- **Relief of cough (***Codeine* has greater antitussive action than *morphine)*
- **Treatment of acute pulmonary edema:** Intravenous *morphine* dramatically relieves dyspnea caused by pulmonary edema associated with left ventricular failure possibly by its vasodilatory effect.

Pyramid & diphenoxylate in treatment of traveler diarrhea.

_Heart failure :left side Heart failure يؤدي لتراكم الدم في ال pulmonary vein وبالتالي ارتاح السوائل منه وتحول الرئة إلى اسفنجة ملانة ماء.

المورفين يعمل على توسيع ال veinsوبالتالي يقلل من pulmonary edema ويزيد من ال Cerebral edema

_Morphine indicate in cardiac asthma

_Morphine contraindicate in bronchial asthma.

Pharmacokinetics

- Absorption of *morphine* from the gastrointestinal tract is ***slow and erratic (****Codeine* is well absorbed when given by mouth)
- Significant hepatic first-pass metabolism (therefore, intramuscular, subcutaneous, or IV injections produce the most reliable responses).
- **Distribution:** *Morphine* rapidly enters all body tissues, including the fetuses of pregnant women (should not be used for analgesia during labor)
- Only a small percentage of *morphine* crosses the blood-brain barrier (despite *fentanyl, methadone*, and *heroin*, which readily penetrate into the brain).

Morphine with methyl group or acetyl group بصير
lipid soluble امتصاصه افضل لانه رح يصير

Adverse effects

- Severe respiratory depression occurs and can result in death
- Vomiting
- Dysphoria
- Allergy-enhanced hypotensive effects.
- The elevation of intracranial pressure, particularly in head injury, can be serious.

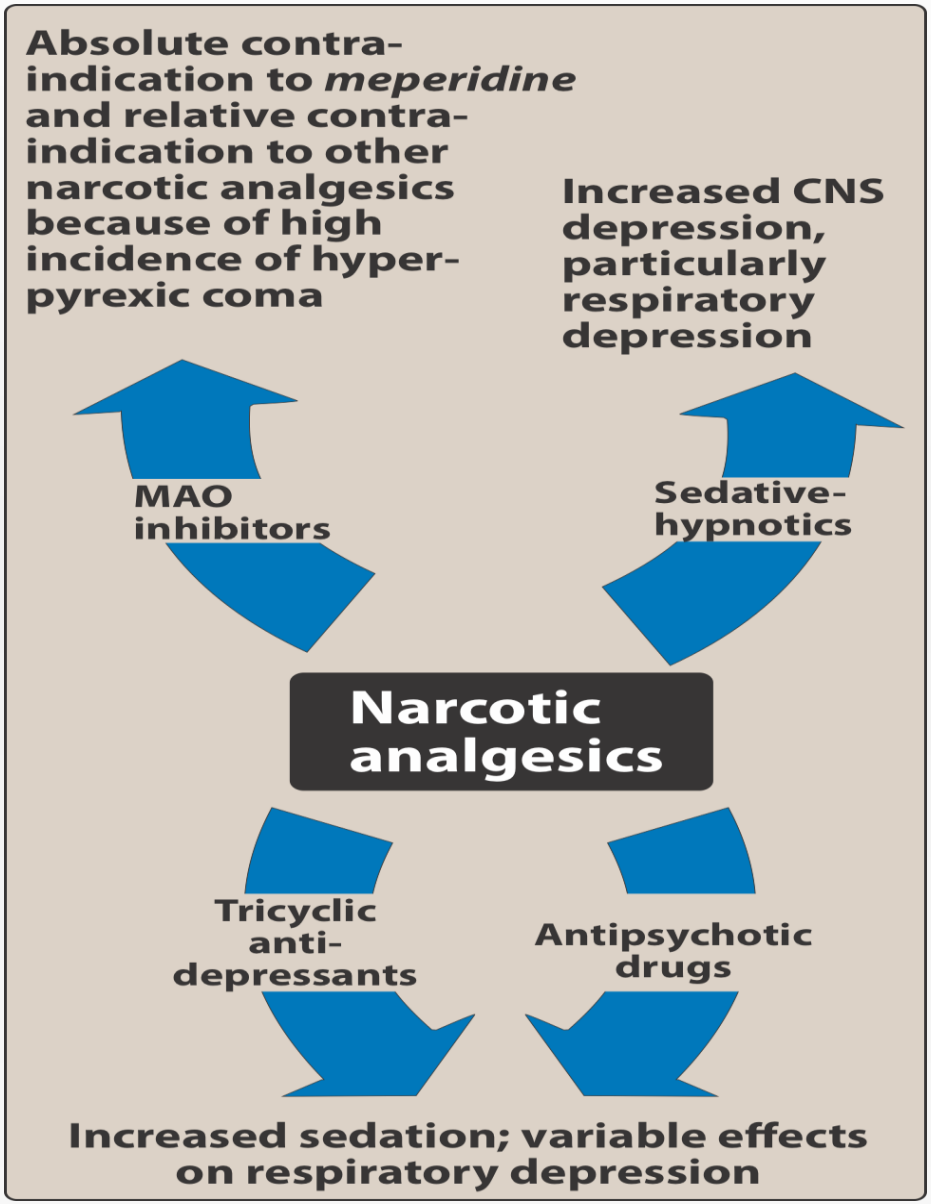
- Acute urinary retention in benign prostatic hyperplasia.
- Patients with adrenal insufficiency or myxedema may experience extended and increased effects from the opioids.
- *Morphine* should be used with cautiously in patients with bronchial asthma or liver failure.
- **Drug interactions:** The depressant actions of *morphine* are enhanced by phenothiazines, monoamine oxidase inhibitors, and tricyclic antidepressants

Morphine – Drug interactions

- Rare

- Mostly about the depressant actions with:

- MAO inhibitors
- Tricyclic antidepressants (TCAs)
- Sedative hypnotics
- Antipsychotic drugs



_ممنوع إعطاء المورفين مع الأدوية الي بتعمل sedation
_ال meperidineبيعطي metabolite called normeperidine بيعمل تشنجات .
_المورفين بقلل درجة الحرارة اما meperidine بزيد درجة الحرارة

Tolerance and physical dependence

- **Tolerance to:**

1. The respiratory depressant,
2. Analgesic,
3. Euphoric, and
4. Sedative effects.

- **However, tolerance usually does not develop to the**

1. Pupil-constricting and
2. Constipating effects of the drug.

- **Physical and psychological dependence** readily occur with *morphine* and with some of the other agonists.
- Withdrawal produces a series of autonomic, motor, and psychological responses (begins 6-10 h. after the last dose)

Tolerance to all effect except (constipation and miosis) يستمر حدوثهن

Opiate withdrawal syndrome

Stage I: Up to 8 hours

Anxiety

Drug craving

Stage II: 8–24 hours

Anxiety

Insomnia

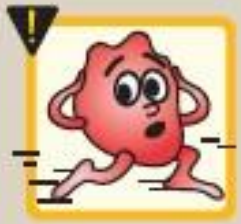
GI disturbance

Rhinorrhea

Mydriasis

Diaphoresis

Stage III: Up to 3 days



Tachycardia

Nausea, vomiting

Hypertension

Diarrhea

Fever

Chills

Tremors

Seizure

Muscle spasms

_withdrawal manifestation:
Increase sedation, anxiety, craving to it

_عند علاج الإدمان :
_1تقليل جرعات المورفين
_2تعويض المورفين بشيء يكون opioid بس تكون withdrawal manifestation اله اقل مثل methadone or buprenorphine

Fentanyl

- Very potent analgesic (100-fold of morphine) → used in anaesthesia.
- Very lipophilic
- Rapid onset and short duration of action (15 – 30 min), less than morphine
- Uses:
  - **Anaesthesia** (pre-aesthetic and induction and maintenance of anaesthesia) for its analgesic and sedative effects
  - **Analgesia**, postoperative pain and during cardiac surgery because it has no effect on myocardial contraction

_اذا استخدمنا ال fentanyl as transdermal patch
رح تتأخر ال onset of actionوال durationرح تطول .

_بنقدر نعطيه بعد العملية اذا كان oralولكن ال transdermal
patch is contraindicationبعد العمليات

Fentanyl

- Sublingual tablet
- Oral buccal tablets: mainly used for a breakthrough pain in cancer patients tolerant to opioids:
- Epidurally–combined with local anesthetics for labor and postoperative pain
- Intrathecally – analgesia
- Injection (IV): anaesthesia and analgesia
- Transdermal film (patch): Should not be used used for acute and postoperative pain
  - Onset of action is delayed at least 12 hours and the offset is prolonged.

Methadone

- Synthetic, orally effective opioid
- Approximately equal in potency to *morphine*
- Induces less euphoria
- Has a somewhat longer duration of action
- **Mechanism of action:** are mediated by μ receptors.
- Increases biliary pressure and is also constipating

_ Methadone _long duration تفيد في الإدمان مشان
withdrawal of methadone less severity وبضل لوقت
طويل الأعراض تاعته

- **Therapeutic uses:** analgesic, in the controlled withdrawal of dependent abusers from *heroin* and *morphine*.

- *Methadone* causes a withdrawal syndrome that is milder but more protracted (days to weeks) than that of other opioids.

- **Adverse effects:** can produce physical dependence like that of *morphine*.

Heroin

- Does not occur naturally.
- It is produced by diacetylation of *morphine*, which leads to a three-fold increase in its potency.
- Its greater lipid solubility allows it to cross the blood-brain barrier more rapidly than *morphine*, causing a more ***exaggerated euphoria*** when the drug is taken by injection.
- It has no accepted medical use in the United States

The heroin is morphine +2 acetyl group
high lipid soluble وهاي الشغلة بتخليه

Codeine

- The analgesic actions of *codeine* are due to its conversion to morphine
- Whereas the drug's antitussive effects are due to *codeine* itself.
- Has a higher oral effectiveness.
- *Codeine* shows good antitussive activity at doses that do not cause analgesia
- At commonly used doses, the drug has a lower potential for abuse than *morphine*, and it rarely produces dependence.
- *Codeine* produces less euphoria than *morphine*.

Codeine _methyl morphine _ لهيك امتصاص عالي بحالة ال oral

_وبسبب الاختلافات بين الناس لما تاخذ ال codeineممكن يصير استجابة وممكن لا

Other agonists

- Oxycodone: For moderate to severe pain

Twofold more effective than morphine

Orally, could be used in combination with aspirin and paracetamol

- Oxymorphone:

More potent than morphine (parentrally; orally

- Hydromorphone:
  - 8-10 more potent than morphine
  - Hydromorphine in patients with renal dysfunction: less accumulation of active metabolies however some metabolites can cause CNS side effects (preferable over morphine for those patients).

Mixed Agonist-Antagonists and Partial Agonists

- Drugs that stimulate one receptor but block another are termed mixed agonist-antagonists.
- The effects of these drugs depend on previous exposure to opioids.

1. In individuals who have not recently received opioids; mixed agonist-antagonists show agonist activity and are used to relieve pain.
2. In the patient with opioid dependence, the agonist-antagonist drugs may show primarily blocking effects that is, produce withdrawal symptoms.

- ***Examples; Pentazocine, Buprenorphine, Nalbuphine***

_فيه ادوية تعمل عال Mu antagonist وفي ادوية عال kappa agonist as :pentazocine & nalbuphine & “Buprenorphine”😮

_كيف بقدر احددها:

_1على حسب المريض اذا كان مدمن عال opioid as morphine وهذا Mu agonist واعطيته هاي الأدوية بصير يعمل withdrawal لانه رح يسكر ال receptor بوجه المورفين .

_2اذا كان المريض مش مدمن هون هاي الأدوية بتشتغل ك kappa agonist وبعمل analgesic effect.

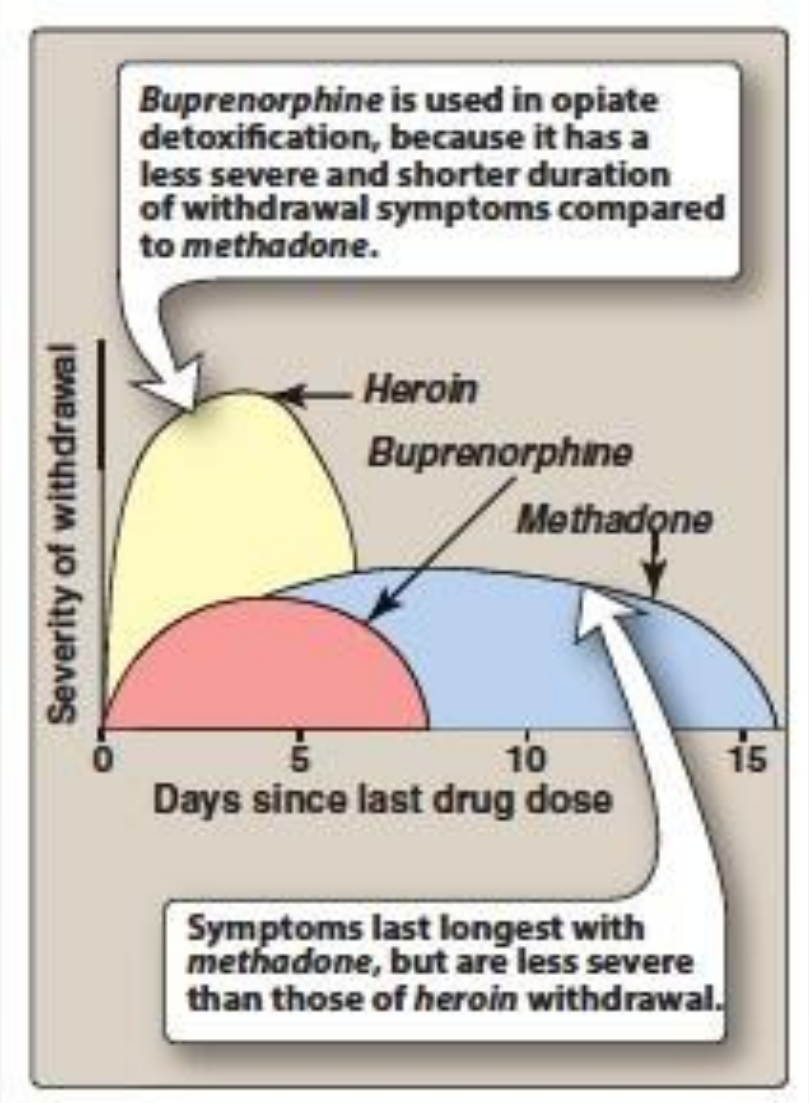
_Buprenorphine is a partial Mu agonist ركز عليها 👌 .

Buprenorphine

- MOA: **partial agonist at μ receptors,** forming strong bonds → long duration of action
- Incompletely reversible by naloxone
- Precipitate withdrawal in users of morphine or other full opioid agonists
- Side effects: little sedation, respiratory depression, hypotension, nausea and dizziness.
- Main use:

1. opioid detoxification: For opioid withdrawal: sublingual tablet or film, buprenorphine alone or with naloxone
2. analgesia for moderate to severe pain
   - Dosage forms for analgesia: I.V injection, sublingually and transdermal film

اذا زودنا الجرعة بصير antagonistفتستخدم لعلاج الإدمان



- Buprenorphine widely used opioid detoxification than methadone (has shorter and less severe withdrawal symptoms compared to methadone)
- Naloxone can be added to prevent the abuse of buprenorphine via IV administration

الميزة انه اعراض ال withdrawal ما رح تظل كتير مقارنة مع ال methadone

_ليش less severe?

Because it is partial agonist

_ليش short duration?

لانه مرتبط ب receptor بشكل قوي

buprenorphine_افضل من ال methadone في علاج الإدمان

Other analgesics - Tramadol

- μ-Opioid receptor weak agonist, centrally
- Weak inhibitor of norepinephrine and serotonin reuptake
- Analgesic for moderate to severe pain
- Only partially antagonised by naloxone
- Respiratory depression less than morphine
- Drug-drug interactions: antidepressants → selective serotonine reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and MAO inhibitors
- Anaphylactic reactions
- Associated with misuse and abuse

_tramadol May Increase level of serotonin and lead to serotonin syndrome.

_الترامادول اخف من المورفين ك analgesic

_الفرق بين addiction & poisoning:
_poising of opioid May lead to death مشان هيك بعطيه
I. V naloxone or oral naltrexone. على طول مثل antagonist
_ ٣علامات تدل على ال respiratory_ comatose: poisoning
depression _miosis.
_addiction
_بنعمل withdrawal للمادة الي ادمن عليها بالتدريج
طبعا ممكن يعمل hypertension & tachycardia مشان هيك بنستخدم
lafutidine or clonidine
_بستخدم substitute as buprenorphine or methodize لأنهم بقللو من الأعراض
_وبعد ما اخلص ال withdrawal تماما ممكن استخدم antagonist as naloxone

Antagonists

- 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 *heroin*, and precipitate the symptoms of opiate withdrawal.
- ***Naloxone, Naltrexone***