

شابتر سهل مش
صعب زي ما بقولوا
وفي معلومات بنعرفها
ومكررة

DRUGS OF ABUSE

OPIOID



by Noor Mansour

INTRODUCTION

دواء = من النبات بدون تهيج = morphine, codeine

□ **Opiates**: a group of naturally occurring compounds derived from the opium poppy

□ **Opioids**: the class of drugs that includes all synthetic and semisynthetic drugs that mimic the actions of the opiates

أدوية المخدرة

مواء، مخدرات اصطناعية الـ
Opiates نفس تأثير

□ **Narcotics**: group of drugs with actions that mimic those of morphine (can cause the classic triad of respiratory depression, miosis, and decreased mental status)

INTRODUCTION

- They are subdivided into **natural, semisynthetic, synthetic and mixed agonist/antagonist subclasses**
- ***Natural opium agonists:*** morphine and codeine
- ***Semisynthetic:*** heroin, hydromorphone, oxymorphone, oxycodone
↳ *مُنْتَجَاتٌ فِي المختبر*
- ***Synthetic opioids*** produced **completely by lab. synthesis.** Ex: **meperidine, methadone, diphenoxylate, fentanyl, propoxyphene**

Papaver somniferum, Opium poppy, common poppy *Natural*

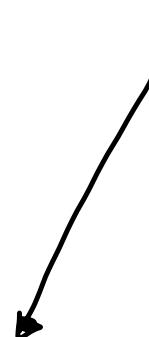
نبات المورفين



❖ *Opioids with **mixed agonist-antagonist** properties include:*

- ✓ Nalbuphine,
- ✓ Pentazocine
- ✓ Butorphanol

المحبطة



.....have agonist activity at some receptors and antagonist activity at other receptors:

❖ *Partial agonists:*

- ✓ Buprenorphine

INTRODUCTION

*Opioids اسکیواٹز

- Opioids are commonly used clinically as **analgesics** and **anesthetic agents**.....
غير قانوني
- But also available illicitly as **drugs of abuse**
- Absorption may occur via **parenteral**, **oral**, or **inhalational routes**

اسرع اسپی م بعد ین
oral بعديه inhalation

Toxicodynamic

-: CNS في عصبية مي 3 لى رئيسيات

- The opioids exert their pharmacologic effects by interacting with 3 specific receptors in the CNS.....mu, delta, kappa
- All three mediate analgesia
- The μ -receptor activation plays major role in the respiratory depression and slow GI transit
- μ
□ κ -receptor activation also slows gastrointestinal transit and seems to be involved in sedative actions
- δ
□ δ -receptor activation may play a role in the development of tolerance

Receptor Stimulation

Mu (μ)

Physical dependence
الإدمان الجسدي

والصعب
تنبيه المخال

Analgesia, sedation, cough suppression

Respiratory depression

انهيار تنفس وهو تنبيه التنفس

Dopamine release...euphoria

↑ برفع الدوبامين وجليل
السعادة (ادمان نفسي)
تحسن بالنشوة

نحسن امتحان

Receptor Stimulation

Kappa (κ)

Sedation, decreased respiration

Analgesia, decreased appetite

Constricts pupil

نَفْلُ الْمُسْكِيَّةِ

Delta (δ)

مُغَارِبُ الْأَعْنَابِ

Analgesia, antidepressant properties

release of growth hormone

Dopamine released $\rightarrow \mu$ Receptor

Tolerance

ENDOGENOUS OPIOID PEPTIDES

لـهـ الـوـادـ الـأـفـوـنـيـهـ الـمـيـنـيـهـ إـلـيـ إـنـجـلـزـ بـعـرـجـ ماـ

- Three distinct families of peptides have been identified:
 - the **enkephalins**: bind to delta opioid receptor and is involved in nociception → **بتـنـفـ الـأـفـسـاحـ بـلـعـ**
 - the **endorphins**: produced by hypothalamus and pituitary gland produce **analgesia and well-being** (during exercise, crying, spicy food consumption...), bind to mu receptor
 - and the **dynorphins**: bind to kappa receptor and are implicated in analgesia, appetite regulation, control the circadian rhythm

DEFINITIONS

يرتبط بـ dopamine و euphoria → ادمان نفسي

- **Psychological Dependence** (also dependence, abuse)

- Loss of control over drug use → فقدان القدرة على التحكم بالدواء في نفسه.
- Compulsive drug use → اسعال مفهوي (السته) يستهلك الدواء حتى لو لم يجده ضروري.
- Continued use despite harm → يستمر بالرغم من الضرر للحياة.

- **Physical Dependence** → ايجيم بتعود على الدواء

Stopping the drug leads to a withdrawal syndrome

- **Tolerance** لـ اعراض اعراض اذ ان وقف عن استخدام الدواء مجاہ:

Less effect after prolonged use; dose escalation required

بعد فترة من الاستخدام المفهوي، نفس الجرعة لفترة → تضاعف نفس التأثير ولازم يرفع الجرعة ليحصل نفس النتيجة.

Opiate Overview

center nervous system peripheral nervous system

1

1

- Receptors in CNS and PNS; linked to variety of neurotransmitters
- Analgesic effect نَسْكِينَ الْأَلْجَعَ

الاسْكِنْدَرِيَّةُ

□ تمنع انتقال Inhibition of nociceptive information at points of
الانتهاء انتشاره من المحيط العصبي إلى المخ

□ Euphoric effect المُنْتَهَى

- زیاده From increased dopamine released in mesolimbic system

□ Anxiolysis Effect تقليل القلق

From effect of noradrenergic neurons in locus ceruleus

CLINICAL EFFECTS

- **لما ينافس المدرجين بالاستهلاك المفرط**
 - **أحساس بالحماس والانتعاش** الحماس بسبب زيادة الدوبامين
 - **Euphoria** الشعور بالسعادة النفسية والهدوء
 - **Sensation of well-being that they produce** الحماس بالرائحة النفيسة والصدف
 - **"flash" or "rush" or "high"** السعور، السريع والشعور إلى التيار معاً (I.V. bolus)
 - The rapid onset of these effects with an i.v. bolus.... activation of the mesolimbic dopamine system
-But dysphoria may occur....(kappa agonist)

متداول مذكورة، فلفرع من المراجعة

TOXICOKINETICS OF OPIOIDS

□ Elimination

بَعْدُ، glucuronidation تُحول
inactive compounds

- Most opioids are **metabolized by hepatic conjugation** to inactive compounds that are excreted readily in the urine
- All opioids have a **prolonged duration** of action in patients with **liver disease** (eg, cirrhosis) because of impaired hepatic metabolism....drug accumulation and opioid toxicity

المرجع إلى عنصر فشل أو تليف الكبد
الـ Opioids يطول دورة حمله لأن metabolism
جدير عن طريق الكبد يتجدد في الدورة
- toxicity

TOXICOKINETICS OF OPIOIDS

- ▢ Opiate metabolites are excreted in the urine,
making urine toxicology useful → مخلوٰن للبول هنّان → يكشفوا المَتَّهِفِي.
- ▢ **Renal failure** also leads to toxic effects from accumulated drug or active metabolites (eg, **normeperidine**) اذا لُكْفِرْتُمْ عَنْ فَشْلِ كَلْوَيٍّ لِحَكْرَامِ الْأَرْدَرِيَّةِ ، normeperidine.
- ▢ Certain opiates (eg, propoxyphene, fentanyl, and buprenorphine) are more lipid soluble and can be stored in the fatty tissues of the body

وَصَنْدِيقَةٌ مُفْعَلَةٌ أَعْوَدَ بِالْجَسْمِ وَأَعْصَبَ لِلتَّقْلِيفِ
هُنَّا.

TOXICOKINETICS OF OPIOIDS

- ❑ Most of these drugs have large volumes of distribution (3–5 L/kg)
- ❑ The rate of elimination is highly variable, from 1–2 hours for **fentanyl** derivatives to 15–30 hours for **methadone**
 - ↳ **methadone** ↓ rate of elimination
 - ↳ **fentanyl**

Toxic Doses

ايجريعة المسمومة بحسب :-

- The toxic dose varies widely, depending on the specific compound, the route and rate of exposure, and tolerance to the effects of the drug as a result of chronic use

نحو المربع

- Some newer fentanyl derivatives have potency up to 2000 times that of morphine

الانواع الجديدة واتحاداتها اقوى بـ morphine ٢٠٠٠ مره

HISTORY

ع غالباً في حالات تسمى opioid ما يقدر ناحية history ليس ؟

- In many cases of opioid overdose.....**impossible to obtain history** because of CNS depression, coma, lack of cooperation → **المرifer يمكن الحصول عليه** → **history** **لبيان الحادث**
- History is important to direct the clinician to a better diagnosis.....severity of the exposure, other toxicological syndromes or pathological processes (trauma, infection)
ادلة المرifer وain important
- If patient is conscious it is imp. to determine....the type, amount of opioid, time and route of exposure, other medication, suicidal attempt → **نوابا انتهازية**
- Knowledge of the **common street names** may also be helpful

PHYSICAL EXAMINATION

مُحول

- ✓ **Mild to moderate overdose:** lethargy is common, miosis ← "pinpoint" pupils. BP and HR are decreased, bowel sounds are diminished, and the muscles are usually flaccid الإعصابات المترتبة على العصب المحي
- ✓ N.B: **Miosis** but may not be present if the patient is hypoxic, or took sympathomimetics or anticholinergic ذابح عينه تهنيق العين
- ✓ **With higher doses:** coma accompanied by respiratory depression, and apnea often results in sudden death. بجات مفاجأة الموت
- **Noncardiogenic pulmonary edema** may occur

PHYSICAL EXAMINATION

انفاس دفعه اکاراجه

- ✓ Other common feature: **hypothermia & hyporeflexia**
لے بنتقل حرارة العضلات
- ✓ **Seizures** are **not common** after opioid overdose but occur occasionally with certain compounds (eg, **codeine**, **dextromethorphan**, **meperidine**, **methadone**, **propoxyphene**, and **tramadol**) مع شبیه **seizures** **مثلاً يمکن ان تحدث** **اللذة**.
و بنابراین **الغثيان** **و انتفاذه** **الحادي**.
- ✓ Seizures may occur in patients with **renal compromise** who receive **repeated doses of meperidine** owing to accumulation of the metabolite **normeperidine**

Mortality/Morbidity

tricyclic antidepressant

- **Cardiotoxicity** similar to that seen with TCA due to severe **propoxyphene** intoxication
- [⌚] Prolonged QT intervals and [⌚] torsade de pointes have been reported with **methadone**...sudden [⌚] death
- The predominant cause of morbidity and mortality from pure opioid overdoses is: **respiratory compromise** → [⌚] اهم سبب للوفاة

DIAGNOSIS

The triad strongly suggests **opioid poisoning:**

- ✓ **Coma (CNS depression),**
- ✓ **Pinpoint pupils (miosis)**
- ✓ **Respiratory depression**
- ✓ The patient quickly awakens with NALOXONE

antidote for narcotic
drugs

DIAGNOSIS

- **Needle tracks marks** is suggestive of addiction
→ أثر لفون الأجهزة على الأدمان
- **Specific levels** not usually performed because of poor correlation with clinical effects
حالات صنور الدواد بالله → ما يغير حالات:
خزع البول يغير
- Qualitative screening of the urine is an effective way to confirm recent use (morphine, codeine..)
- But not all.....tramadol and fentanyl not detected
* خزع البول يكشف عن morphine و Cocaine و بس ما يكشف عن Fentanyl و Tramadol

PHYSICAL EXAMINATION

- **Opioid withdrawal syndrome:** اعراض اخراج المخدرات :-
- Typical symptoms include: **anxiety, nausea, vomiting, diarrhea, abdominal cramping, insomnia** and **heightened sensation of pain**,
ارتفاع
العلامات المميزة :-
ارتفاع = احساس بالالم
تعس العين
- Distinctive physical signs include **mydriasis, piloerection.....self-limiting**
تشنج معدودين للعيان
(Goosebumps) قشريرة

CODEINE

- Codeine is 3-methylmorphine → مهاجماً morphine المجموعة الميثيلية
- De-methylation produces morphine
- Illicit preparations found orally
- combination of codeine and glutethimide (p.o)
■ produce euphoria as heroin
- Possess analgesic and antitussive properties
- Less potent than morphine Codeine أقوى من morphine
- Tolerance doesn't develop rapidly

MEPERIDINE (Pro drug)

- Its structure is similar to

نحوه
كابع
Fentanyl

نحوه
كابع
Phenylpiperidine

- Is a pure agonist
- Used as analgesic
- Less potent than morphine

Meperidine is less potent than morphine

- Metabolized in the liver into

نحوه
كابع
meperidinic acid &

نحوه
كابع
normeperidine(active)

طيننا اذا في متناول الكبد بعمل ترجم
لما في ارادت الخفالة ويتصل toxicity

MPTP

- Meperidine analog
 - N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
(MPTP)
 - Associated with severe form of parkinsonism
 - reversed by the administration of
 - L-dopa and carbidopa

بحدوث مرض شبيه بباركنسون

antidote

PENTAZOCINE

- ❖ Introduced as an analgesic in 1967 الالجخار غير المشروع
- ❖ It was frequently encountered in the illicit trade
- ❖ An attempt at reducing the abuse of this drug was made with the introduction of Talwin Nx®. تقليل سوء الاستخدام
- ❖ This product contains a quantity of antagonist (naloxone) sufficient to counteract the morphine-like effects of pentazocine if the tablets are dissolved and injected

↙ Receptor μ block جمل
و يمنع النشوة

THERAPEUTIC APPROACH FOR DRUG ABUSE

1. Treat acute overdose:

- Symptoms, بعالي الاعراض
- Antagonists \rightarrow Naloxone

2. Management of withdrawal symptoms:

- Administration of drug to suppress acute withdrawal followed by gradual reduction in dose

3. Long-term rehabilitation

اقلل الى дose تدريجياً ومهن اعطي $\overbrace{\text{اعطى}}^{\text{اعطى}}$ بديل.

Opioids

علاج سلوكي ونفسى دفع اهتمام

FIRST AID MEASURES AND MANAGEMENT PRINCIPLES

□ ABC: Airway, Breathing, Circulation

- Profound CNS depression, apnea, impaired gag reflex suggest **endotracheal intubation** for airway control and protection against aspiration مُساعدة التنفس
- Patients with altered consciousness should receive intravenous **thiamine**, and **glucose**
- Treat seizures, hypotension, and noncardiogenic pulmonary edema if they occur

FIRST AID MEASURES AND MANAGEMENT PRINCIPLES

ازالة السموم من المعدة والجهاز الهضمي

- **GI decontamination** may be extremely valuable in massive opioid ingestion within 1hr: عمليات كبرى خلال أول ساعتين
 - Administer activated charcoal orally
 - Gastric lavage with large orogastric tube if needed
 - Consider whole-bowel irrigation after ingestion of sustained-release products
- **Enhanced elimination.** Large Vd of the opioids and availability of an effective antidotal treatment....no role!

FIRST AID MEASURES AND MANAGEMENT PRINCIPLES

حليناها على

□ Administration of antidote (**naloxone**)

- Is a short-acting competitive opioid antagonist considered in patients with respiratory depression or altered consciousness (no agonist properties)
- Complete resolution is diagnostic of opioid intoxication → اذا لحسن الحظ بعد اعطاء نالوكسون *Naloxone* صدأ تأثيره انه تسمى افيون.
- The recommended initial dose is
 - 0.2-0.4 mg i.v for adults and
 - 0.01 mg/kg for children,
- Several doses may be given 2-3 min intervals

مكرار الجرعة على 2-3 دقائق

FIRST AID MEASURES AND MANAGEMENT PRINCIPLES

- Also i.m, intranasal
- If up to 10-20 mg and still no response....not opioid intoxication $10-20 \text{mg} \rightarrow \text{ بدون استجابة مابين للكحول}$ \rightarrow opioid
- **Caution:** The duration of effect of naloxone (1–2 hours) is shorter than that of many opioids....do not release a patient who has awakened after naloxone treatment until at least 3–4 hours has passed since the last dose of naloxone $3-4 \text{ ساعات} \rightarrow$ لا يجوز افراج المريض \rightarrow نالوكسون \rightarrow \rightarrow نالوكسون \rightarrow نالوكسون \rightarrow نالوكسون
- Patients who breath normally does not need naloxone \rightarrow اذ اكأن المريض يتنفس بحاله طبيعية \rightarrow نالوكسون \rightarrow نالوكسون \rightarrow نالوكسون
- Assure a respiratory rate above 14 breaths per minute
- **NALMEFENE**.....longer duration of action (3-5 hours)

$1-2 \text{ hours} \rightarrow \text{ Naloxone} \rightarrow$

FIRST AID MEASURES AND MANAGEMENT PRINCIPLES

- Over-administration of naloxone can provoke acute withdrawal symptoms in opioid-dependent patients (N, V, agitation, violence), and this can complicate treatment
 nausea & vomiting *↓* *لوعة وعنة*
- If combined opioid and sympathomimetic intoxication administration of naloxone may cause life-threatening condition of sympathomimetic intoxication by removing the “protective” CNS depressant effect of opioid

Treatment of withdrawal syndrome in opioid abuser

❖ Pharmacological approach

- ❖ Two general approaches are commonly adopted
 - ❖ A longer-acting opioid, such as **methadone**....followed by a gradual reduction in dosage of the substitute drug
 - ❖ Use of various pharmacological agents, such as **clonidine** and/or a **benzodiazapine**.....will mitigate symptoms and signs of withdrawal

❖ Psychological support

withdrawal ملاجع

بقلل من الأعراض

دعم نفسي

FDA Approves First Non-Opioid for Withdrawal

لطفاً ارجوكمLucemyra دواعي FDA في 17 مايو 2018 . opioid is withdrawal

- May 17, 2018 → The FDA approved the first non-opioid drug, lofexidine hydrochloride (Lucemyra), to help treat symptoms of opioid withdrawal in adults.
- The FDA found the drug to be safe and effective in easing symptoms such as diarrhea, nausea, vomiting, anxiety, and an overall feeling of sickness that often keep patients from withdrawing from opioids.

العلاج بـ Lofexidine → العلاج بـ لوفيدين (14 يوماً)

لخفف اعراض الانسحاب بـ Lofexidine

- Lofexidine may ease withdrawal symptoms but may not completely prevent them. It is approved for treatment for only up to 14 days. It is not a treatment for opioid use disorder but can be used as part of a broader, long-term treatment plan for managing it, the FDA said in a news release.

هو من العلاج بـ لوفيدين. يكون جزءاً من خطة العلاج.

- <https://www.webmd.com/mental-health/addiction/news/20180517/fda-approves-first-non-opioid-for-withdrawal>