

DRUGS OF ABUSE

OPIOID

شابتري سهل مش
صعب زي ما بقولوا
وفي معلومات بنعرفها
ومكررة ♥



by Noor Mansour

INTRODUCTION

مواد في النبات بون كاهينو زي 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

مواد صناعية أو شبه صناعية لها نفس تأثير opiates
الأروية المخدرة

□ **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**
علاوة على ما سبق من المختبر
→
- **Synthetic opioids** produced **completely by lab. synthesis**. Ex: **meperidine, methadone, diphenoxylate, fentanyl, propoxyphene**

Papaver somniferum, Opium poppy, common poppy Natural

نبته المورفين



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

- ✓ Nalbuphine,
- ✓ Pentazocine
- ✓ Butorphanol

التعريف

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

❖ **Partial agonists:**

- ✓ Buprenorphine

INTRODUCTION

* استخدامات opioids

- 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

* السرع انشي ١٧ بعد يوم
inhalation بعد يوم ٥/٥

Toxicodynamic

في 3 مستقبلات رئيسية في CNS :-

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

Receptor Stimulation

Mu (μ)

- Physical dependence الأدمان الجسدي والسحب
تثبيط السعال
نكس الميع
- Analgesia, sedation, cough suppression
- Respiratory depression اضطراب تأثير وهو تثبيط التنفس
- Dopamine release...euphoria → برفع الدوبامين وبجليل
بحس بالنشوة والسعادة لادمان نفسي

Receptor Stimulation

Kappa (κ)

Sedation, decreased respiration

Analgesia, decreased appetite

Miosis

تقلل الشهية

تضييق البؤبؤ

Delta (δ)

مضاد الاكتئاب

Analgesia, antidepressant properties

release of growth hormone

Dopamine released $\rightarrow \mu$ Receptor

Tolerance

لجذب هرمون النمو

زيت

ENDOGENOUS OPIOID PEPTIDES

له العواد الأفيونية الطبيعية، إلى جسمك بفرضها

- Three distinct families of peptides have been identified:
 - the **enkephalins**: bind to **delta** opioid receptor and is involved in **nociception** → يتلقى الألم بالأم
 - 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**

حتى تغرز

DEFINITIONS

يرتبط dopamine و euphoria مع ادمان نفسي

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

- Loss of control over drug use → فقدان القدرة على التحكم بالدواء
 - Compulsive drug use → استعمال قهري للشخص يستخدم الدواء حتى لو ماله
 - Continued use despite harm → يستمر بألفه بالرغم من الاضرار الهية
- الاجتماعية. الجسم يعود على الدواء → **Physical Dependence**

Stopping the drug leads to a withdrawal syndrome

- **Tolerance** لم اعرف ان الاعراض اذا توقفت عن
استخدام الدواء فجأة.

Less effect after prolonged use; dose escalation required

بعد فترة من الاستخدام الطويل ، نفس الجرعة لم تعد
تغطي نفس التأثير ولازم يرفع الجرعة ليحصل نفس
النتيجة.

Opiate Overview

center nervous system peripheral nervous system



- Receptors in CNS and PNS; linked to variety of neurotransmitters

- Analgesic effect

تسكين الألم

□ Inhibition of nociceptive information at points of transmission from peripheral nerve to spinal cord to brain
تمنع انتقال الإشارة الألم

- Euphoric effect

النشوة

□ From increased dopamine released in mesolimbic system
زيادة dopamine

- Anxiolysis Effect

تقليل القلق

□ From effect of noradrenergic neurons in locus ceruleus

CLINICAL EFFECTS

- Addicts use opioids for
 - Excitement, احساس بالحماس والانتعاش
 - Euphoria النشوة بسبب زيادة الدوبامين
 - Sensation of well-being that they produce احساس بالراحة النفسية والصدور
 - "flash" or "rush" or "high" الشعور السريع والقوي إلى بصير مباشرة به → إعطاء الجرعة مصوصاً (i.v. bolus) (ال)
- The rapid onset of these effects with an i.v. bolus....
activation of the mesolimbic dopamine system

□But dysphoria may occur....(kappa agonist)

↓
مشاكل مزاجية , قلق , عدم الراحة

TOXICOKINETICS OF OPIOIDS

□ Elimination

عملية glucuronidation و يتحول
إلى 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

في المرضى إلى عند ضم فشل أو تلف بالكبد
الأيام بطول مدة عمله لأن metabolism
يخسر عن طريق الكبد فيتراكم الدواء
و يوصل toxicity .

TOXICOKINETICS OF OPIOIDS

- Opiate metabolites are **excreted in the urine**, making **urine toxicology useful** → محللوا مخبر للبول فشان يفسفوا المتحاضيا.
- **Renal failure** also leads to toxic effects from accumulated drug or active metabolites (eg, **normeperidine**) إذا لشخص عده فشل كلوي رح كتر اكم الادوية normeperidine.
- Certain opiates (eg, **propoxyphene**, **fentanyl**, and **buprenorphine**) are **more lipid soluble** and can be **stored in the fatty tissues** of the body

و هذا بخلي مفعولها اطول بالجسم واهمها للتخلص منها.

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**

معدل التخلص من الميثادون منخفض
معدل التخلص من الفنتاني مرتفع

Toxic Doses

الجرعة السامة تختلف حسب :-

- 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
خروج السم من الجسم
- Some newer fentanyl derivatives have potency up to 2000 times that of morphine
الأنواع الجديدة من الفنتاني أقوى بـ 2000 مرة من morphine

HISTORY

ع غالباً في حالات تسمم الأدوية ما يتقدّرنا هذه history ليس ؟

- In many case of opioid overdose....**impossible to obtain history** because of CNS depression, coma, lack of cooperation → المريض يكون غير متعاون
شواصة history ؟ ①
- History is important to direct the clinician to a better diagnosis....severity of the exposure, other toxicological syndromes or pathological processes (trauma, infection)
إذا المريض واعى important ②
- **If patient is conscious** it is imp. to determine...the type, amount of opioid, time and route of exposure, other medication, suicidal attempt → نوايا انتحارية ③
- Knowledge of the common street names may also be helpful

PHYSICAL EXAMINATION

فحوص

- ✓ **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** الأمعاء ما بتستغل
مشيح.
ارتخاء العضلات
- ✓ N.B: **Miosis** but may not be present if the patient is
hypoxic, or took sympathomimetics or anticholinergic
ما يهين عندهم تضييق للحين
- ✓ **With higher doses:** coma accompanied by respiratory
depression, and apnea often results in sudden death. بعوت فجأة
توقف التنفس
- Noncardiogenic pulmonary edema may occur

PHYSICAL EXAMINATION

التخافض درجة الحرارة

- ✓ Other common feature: **hypothermia & hyporeflexia**
لـ بتقل حركة العضلات
- ✓ **Seizures** are **not common** after opioid overdose but occur occasionally with certain compounds (eg, **codeine**, **dextromethorphan**, **meperidine**, **methadone**, **propoxyphene**, and **tramadol**)
يمكن يهيس seizures مع هـ
الادوية.
و بتلير مع هـ الفشل الكلوي
→
- ✓ 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
- ① □ Prolonged QT intervals and ② torsade de pointes have been reported with **methadone**... sudden ③ death
- The predominant cause of morbidity and mortality from pure opioid overdoses is: **respiratory compromise** → أهم 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
↪ آثار حقن الأبر بتدريج على الأدمان
- **Specific levels** not usually performed because of poor correlation with clinical effects → قياس مستويات الدواء بالدم ما يفيد غالباً.
حيث البول مفيد
- Qualitative screening of the urine is an effective way to confirm recent use (morphine, codeine..)
- But not all.....tramadol and fentanyl not detected
✗ حيث البول يكشف Codeine و morphine ليس ما يكشف
Fentanyl و tramadol.

PHYSICAL EXAMINATION

- **Opioid withdrawal syndrome:** اعراض الانسحاب :-
- Typical symptoms include: **anxiety**, **nausea**, **vomiting**, **diarrhea**, **abdominal cramping**, **insomnia** and **heightened sensation of pain**,
علامات مميزة :-
زيادة الحساسية بالألم
توسع العين
- Distinctive physical signs include **mydriasis**, **piloerection**.....self-limiting
قشعريرة (goose bumps)
حش مددين للحيه

CODEINE

- Codeine is 3-methylmorphine → مضافا methy group على morphine
- De-methylation produces morphine
- غير قانوني □ Illicit preparations found وإلا
 - combination of codeine and glutethimide (p.o) للشوة قوية زي الهيروين
 - 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

□ Fentanyl

□ Phenylpiperidine

تابع للمادة
المجموعه

□ Is a pure agonist

□ Used as analgesic

□ Less potent than morphine *meperidine أقوى من morphine*

□ Metabolized in the liver into

□ meperidinic acid &

□ normeperidine(active)

علينا اذا في مشاكل بالكبد جعل تراكم
للمادة الحادة الخفالة ويتعمل 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

antidote

بجمل مرضى الشبيه بالباركنسون ↓

PENTAZOCINE

- ❖ Introduced as an **analgesic in 1967** الأجبار 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®**. لتقليل 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

يعمل block μ Receptor
ويمنع النشوة

THERAPEUTIC APPROACH FOR DRUG ABUSE

1. Treat acute overdose:

- Symptoms, بجاني 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 اقل ال dose تدريجياً "وهكن اعطى"

علاج سلوكي ونفسي / دعم اجتماعي

opioid بديل .

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 → يساعد على التنفس
غيبوبة
- 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 الجهاز الهضمي

- **GI decontamination** may be extremely valuable in massive opioid ingestion within 1hr: عمية ن جبيرة خلال اول ساعة
- 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

مليناها غير



□ 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 الحسن الحريف بعد اعطاه Naloxone هذا تأكيد انه لنسمع افيووني.

■ The recommended initial dose is

■ 0.2-0.4 mg i.v for adults and

■ 0.01 mg/kg for children,

→ ما توقع الجرعات هذا بس لا قياضي اقداؤهم

■ Several doses may be given 2-3 min intervals

تكرار الجرعة كل 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
* اذا وصلنا الجرعة 10-20mg بدون استجابة ما يكون للسم 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
لا يجوز افراج المريض من المستشفى الا بعد مرور 3-4 ساعات من آخر جرعة Naloxone.
- Patients who breath normally does not need naloxone
اذا كان المريض يتنفس بشكل طبيعي لا يحتاج Naloxone.
- Assure a respiratory rate above 14 breaths per minute
- **NALMEFENE**.....longer duration of action (3-5 hours)

1-2 hours > naloxone ↙

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.
 Handwritten notes: "nausea & vomiting" with an arrow pointing to "N, V"; "لَوْنَر وَعَتَق" with an arrow pointing to "agitation, violence".
- 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 علاج حالات withdrawal

❖ 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 بقلل من الأعراض

❖ Psychological support دعم نفسي

FDA Approves First Non-Opioid for Withdrawal

في عام 2018 وافقت FDA على دواء Lucemyra لعلاج أعراض الانسحاب من الأفيون.

- 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.

الشعور
بالسوء

✳️ العلاج بـ Lofexidine يس لمدة الاسبوعين (١٤ يوم) ✳️

lofexidine يخفف أعراض الانسحاب بس ما يمنعها -

- 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 صيغ علاج بس ممكن يكون جزء من خطة العلاج.

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