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Opioids

I. General Opioid Class Principles

Mechanism of Action (MOA)

- **Receptor Binding**: All drugs in this category bind to specific Opioid receptors(μ ,kappa and delta)in the CNS to produce effects that mimic endogenous opioid peptides or endorphins.
- **Location**: They exert their major effect by interacting with receptors in the CNS, GI tract, and urinary bladder.
- **Cellular Electrical Changes**:
  - **Increased Potassium (K^+) Permeability**: Causes K^+ to leave the cell, leading to hyperpolarization and inhibited nerve firing.
  - **Decreased Calcium (Ca^{2+}) Influx**: Prevents the release of excitatory neurotransmitters.
- **Functional Result**: Decreased excitability and transmission in the brain's pain centers, medically known as Analgesia.
- **Dual Action**: Opioids directly reduce pain signal intensity (damping) and stimulate the anti-nociceptive system (endogenous pain-inhibitory pathways).

General Clinical Effects & Side Effects

- **CNS**: Mood damping, sedation, powerful euphoria, and anxiolytic (anti-stress) effects.
- **Respiratory**: Suppression of the respiratory center in the brainstem; this is the primary cause of death in overdose.
- **The Eye**: Pupil constriction (**Miosis**) resulting in "Pinpoint Pupils," a classic tell-tale sign used by emergency doctors to identify toxicity or addiction.
- **GI & Urinary**: Nausea, vomiting, chronic spastic constipation, and urinary retention.
- **Vascular/Skin**: Histamine release (especially with Morphine) causes vasodilation, flushing, diaphoresis, and intense itching.

II. Neurobiology of Addiction & Tolerance

1. Euphoria and Brain Equilibrium

- **Dopamine Myth**: While opioids increase dopamine in the nucleus accumbens, dopamine alone does not explain euphoria.
- **Brain Network Theory**: Euphoria results from a complex imbalance across the entire neural network, involving Serotonergic, Dopaminergic, Noradrenergic, and GABAergic systems.
- **Vulnerability**: Addiction is defined as seeking happiness through a drug-induced state. Only a few patients become addicted due to **Pharmacogenetics** (genetic risk) and **Psychological Predisposition** (escaping trauma).

2. Tolerance, Dependence, and Addiction Definitions

- **Tolerance**: A physiologic phenomenon resulting in a progressive decline in the potency of an opioid with continued use.
- **Dependence**: A physiologic state characterized by withdrawal symptoms (Abstinence syndrome) upon abrupt discontinuation or reduction of narcotic therapy; it is independent of tolerance.
- **Addiction**: A psychological behavioral syndrome manifested by drug-seeking behavior, loss of control over drug use, and continued use despite adverse effects.
- **Hyperalgesia Paradox**: Chronic use can activate excitatory pain pathways (Central Sensitization), making the patient more sensitive to pain despite increasing doses.

III. Opioids☺

Morphine (Strong)

Feature	Details and Clinical Rules
Uses	• Alleviates severe pain (cancer). • Dramatically relieves dyspnea in acute pulmonary edema. • Treatment of diarrhea. • Supplemental sleep aid with hypnotics. • **Past:** MI workload reduction via vagal-induced bradycardia/hypotension.
Kinetics	• Lipophilic drug with high tissue penetration. • Half-life: 1–4 hours; Activity: 4–5 hours.
Metabolism	• Phase 2 (glucuronidation) produces **M6G** (active agonist) and **M3G** (inactive; contributes to myoclonus and confusion).
Dosing Rules	• Usually dosed 4x/day. • **Pain Flare**: Give 1/6 of total daily dose as an extra dose. • **Breakthrough Injection**: Usually 3–5 mg.
Warnings	• Avoid in renal failure (metabolites accumulate). • Avoid in asthma/severe allergies due to histamine release.

Fentanyl (Strong)

Feature	Details and Clinical Rules
Potency	**100 times more potent** than morphine.
Kinetics	Very fast onset; half-life 20–30 min; activity lasts ~45 min.

Feature	Details and Clinical Rules
Primary Use	• **Titration**: Ideal intraoperatively because it wears off by the time the patient wakes. • Augments anesthesia to reduce toxic general anesthetic doses.
Forms	• Jordan: Patches (sustained 48-hour release). • Sublingual and oral tablets.
Safety	Dosed in **micrograms (mcg)** due to narrow therapeutic index.

Meperidine (Pethidine) (Strong)

Feature	Details and Clinical Rules
Mechanism	Binds to μ and **Kappa r**eceptors; has anticholinergic effects.
Potency	1/10th the potency of morphine (5mg morphine =~50mg meperidine).
Main Uses	• **Labor**: Least likely to cause fetal respiratory distress. • **Shivering**: Best drug; lowers shivering threshold in hypothalamus via kappa receptors.
Toxicity	• **Normeperidine**: Accumulation causes tremors, myoclonus, mood changes, and **seizures**.
Constraints	Use for maximum 3 days. Avoid in renal failure.

Methadone

Feature	Details and Clinical Rules
Mechanism	μ agonist + **NMDA receptor blocker** + Monoaminergic reuptake inhibition.
Kinetics	**Longest half-life** (9–36 hours); dosed **1 time per day**.
Uses	• **Addiction**: Milder peaks reduce euphoria; treats physical dependence. • **Rotation**: Best drug for patients with hyperalgesia due to NMDA activity. • **Pain**: Effective for neuropathic pain.

Oxycodone (Strong)

Feature	Details and Clinical Rules
Profile	"Brother of morphine"; oral only; 2–3x/day.
Clinical Note	Less euphoria/tolerance than morphine; high addiction risk (common in USA).

Codeine (Weak Opioid)

Feature	Details and Clinical Rules
Drug Class	Partial μ -agonist with a "**ceiling effect**".
Uses	• **Antitussive** (cough suppressant). • Moderate pain like toothaches.
Metabolism	Converted to morphine via **CYP2D6**.
Genetics	**13.5% of Jordanians** are ultra-metabolizers (>2 alleles).

Tramadol (Weak Opioid)

Feature	Details and Clinical Rules
Mechanism	Weak μ affinity + **NE reuptake inhibition** → alpha 2 adrenoreceptor activation →act synergistically with tramadol's opioid receptor activation→ analgesia.
Advantages	Less respiratory depression, nausea, and constipation; rapid psychomotor recovery. -Moderate pain treatment : as effective as morphine -Severe pain treatment : less effective than morphine

Loperamide (Peripheral)

Feature	Details and Clinical Rules
Mechanism	Peripheral μ agonist; **does not cross blood-brain barrier**.
Clinical Uses	Treatment of diarrhea and inflammation-induced hyperalgesia.

Hydromorphone (Strong)

Feature	Details and Clinical Rules
Indication	Preferred over morphine for patients with **renal failure**.
Potency	Higher potency than morphine; not present in Jordan.

"قويّ التوكل لا يُهزم؛ والله إذا كلَّف أعان"

IV. High-Yield Rules and Withdrawal Signs

- **The WHO Ladder**: Step 1 (Paracetamol) → Step 2 (NSAIDs) → Step 3 (Strong Opioids).
- **No Ceiling Effect**: For full agonists, analgesia continues to increase with dose until toxicity.
- **Tolerance Pattern**: Tolerance develops for euphoria and respiratory depression; **never** for constipation or miosis.
- **Antidote**: **Naloxone** is the immediate antagonist for reversing opioid overdose.

Acute Actions vs. Withdrawal Signs

Acute Action (Drug Effect)	Withdrawal Sign (The Opposite)
Analgesia	Pain and irritability
Respiratory Depression	Hyperventilation
Euphoria	Dysphoria and depression
Relaxation and sleep	Restlessness and insomnia
Constipation	Diarrhea
Pupillary constriction (Miosis)	Pupillary dilation
Flushed and warm skin	Chilliness and "gooseflesh"
Drying of secretions	Lacrimation, runny nose

"اللهم إني أستودعك ما قرأت وما حفظت وما تعلمت، فردّه عند حاجتي إليه، إنك على كل شيء قدير"

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