بسم الله الرحمن الرحيم

DOPAMINE SCIENTIFIC TEAM

Analgesics & Sedatives (Pt.1)

MID | Lecture 1

﴿إِنِّي تَوَكَّلْتُ عَلَى اللَّهِ رَبِّي وَرَبِّكُمْ ۚ مَّا مِن دَابَّةٍ إِلَّا هُوَ آخِذٌ بِنَاصِيَتِهَا ۚ إِنَّ رَبِّي عَلَىٰ صِرَاطٍ مُّسْتَقِيمٍ﴾

Written by: Mazen Nashash
Huthaifa Khuraisat

Reviewed by: Omar Ibrahim

PHARMACOLOGY

رحلة اليقين مع سورة يس

بِسۡمِ ٱللَّهِ ٱلرَّحۡمَٰنِ ٱلرَّحِيمِ

وَءَايَةٞ لَّهُمُ ٱلۡأَرۡضُ ٱلۡمَيۡتَةُ أَحۡيَيۡنَٰهَا وَأَخۡرَجۡنَا مِنۡهَا حَبّٗا
فَمِنۡهُ يَأۡكُلُونَ ٣٣ وَجَعَلۡنَا فِيهَا جَنَّٰتٖ مِّن نَّخِيلٖ
وَأَعۡنَٰبٖ وَفَجَّرۡنَا فِيهَا مِنَ ٱلۡعُيُونِ ٣٤ لِيَأۡكُلُواْ مِن ثَمَرِهِۦ
وَمَا عَمِلَتۡهُ أَيۡدِيهِمۡۖ أَفَلَا يَشۡكُرُونَ ٣٥

أي: {وَآيَةٌ لَهُمُ} على البعث والنشور، والقيام بين يدي الله تعالى للجزاء على الأعمال، هذه {الْأَرْضُ الْمَيْتَةُ} أنزل الله عليها المطر، فأحياها بعد موتها، {وَأَخْرَجْنَا مِنْهَا حَبًّا فَمِنْهُ يَأْكُلُونَ} من جميع أصناف الزروع، ومن جميع أصناف النبات، التي تأكله أنعامهم.

{وَجَعَلْنَا فِيهَا} أي: في تلك الأرض الميتة {جَنَّاتٍ} أي: بساتين، فيها أشجار كثيرة، وخصوصا النخيل والأعناب، اللذان هما أشرف الأشجار، {وَفَجَّرْنَا فِيهَا} أي: في الأرض {مِنَ الْعُيُونِ}.

جعلنا في الأرض تلك الأشجار، والنخيل والأعناب، {لِيَأْكُلُوا مِنْ ثَمَرِهِ} قوتا وفاكهة، وأدمًا ولذة، {و} الحال أن تلك الثمار {مَا عَمِلَتْهُ أَيْدِيهِمْ} [وليس لهم فيه صنع، ولا عمل، إن هو إلا صنعة أحكم الحاكمين، وخير الرازقين، وأيضا فلم تعمله أيديهم] بطبخ ولا غيره، بل أوجد الله هذه الثمار، غير محتاجة لطبخ ولا شيّ، تؤخذ من أشجارها، فتؤكل في الحال. {أَفَلَا يَشْكُرُونَ} من ساق لهم هذه النعم، وأسبغ عليهم من جوده وإحسانه، ما به تصلح أمور دينهم ودنياهم، أليس الذي أحيا الأرض بعد موتها، فأنبت فيها الزروع والأشجار، وأودع فيها لذيذ الثمار، وأظهر ذلك الجنى من تلك الغصون، وفجر الأرض اليابسة الميتة بالعيون، بقادر على أن يحيي الموتى؟ بل، إنه على كل شيء قدير.

Pain

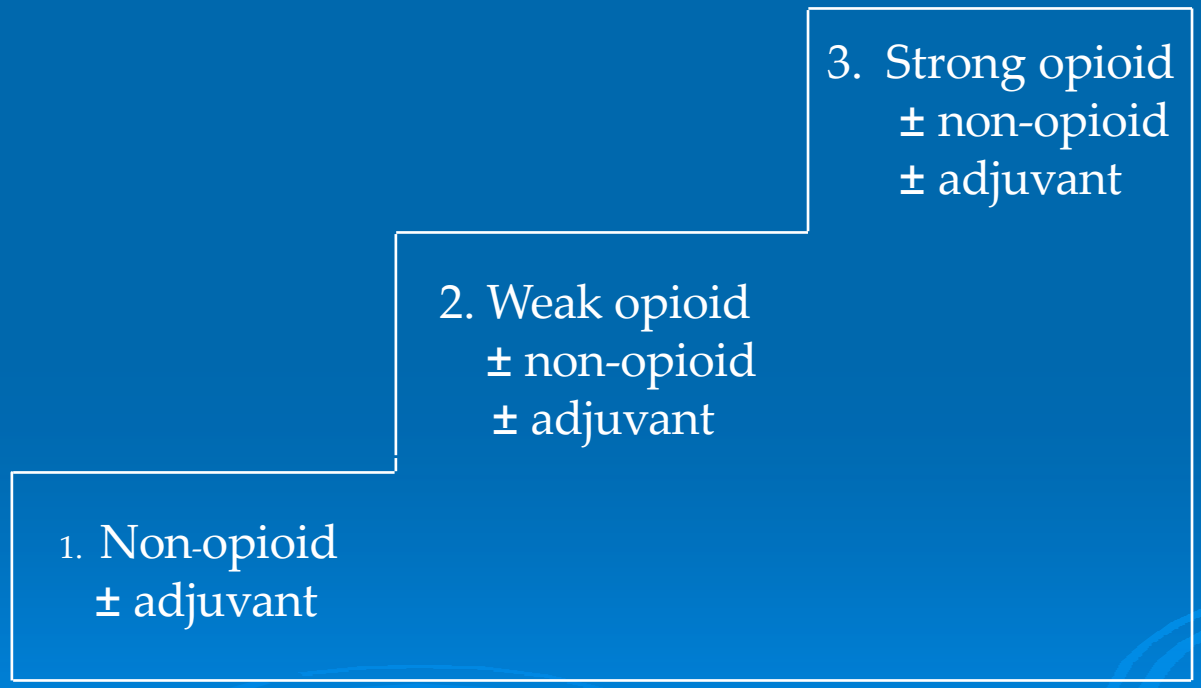
- Brings patients to the DRs
- Fear can keep the patient from going to the Drs at appropriate time
- Treatments are often done on the inflamed, hypersensitive tissues of a patient
- Pain is a symptom of a pathologic condition that needs to be taken care of:

– no treatment, still pain.

– Induced by the release of histamine, serotonin, prostaglandins, bradykinins,etc. that activate pain signaling.

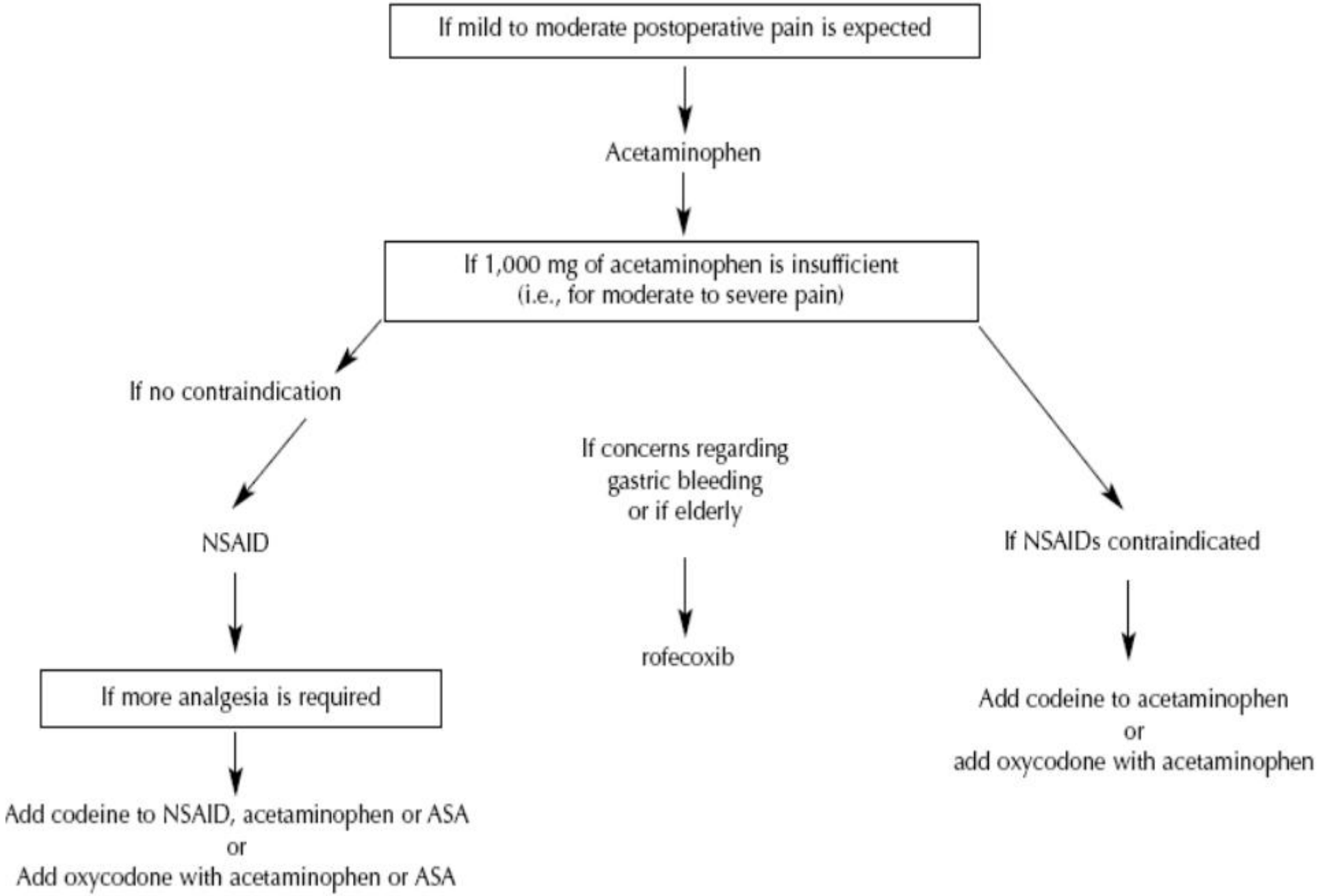
WHO analgesic ladder

Pain persists or increases → Pain persists or increases → Pain



The WHO Pain Ladder Concept

- Pain management follows a clinical stepwise approach to ensure the patient receives the appropriate treatment based on the pain intensity of their condition:
- **Step 1 (Mild Pain):** Managed primarily by **Paracetamol**.
- **Step 2 (Moderate Pain):** Managed with **NSAIDs** (Non-Steroidal Anti-Inflammatory Drugs). Common examples include **Ibuprofen**, **Diclofenac** (Voltaren), **Naproxen**, and **Celecoxib**.
- **Step 3 (Severe Pain):** When pain is agonizing and does not respond to previous steps, we move to **Strong Opioids**.
  - *Example:* A patient with **Stage 4 liver cancer** suffering from chronic, severe pain would require Step 3 intervention.


If mild to moderate postoperative pain is expected
Acetaminophen
If 1,000 mg of acetaminophen is insufficient
(i.e., for moderate to severe pain)
If no contraindication
NSAID
If more analgesia is required
Add codeine to NSAID, acetaminophen or ASA
or
Add oxycodone with acetaminophen or ASA
If concerns regarding
gastric bleeding
or if elderly
rofecoxib
If NSAIDs contraindicated
Add codeine to acetaminophen
or
add oxycodone with acetaminophen

Opioid analgesics

- All drugs in this category act by binding to specific Opioid receptors in CNS to produce effects that mimic the action of naturally occurring substances, called endogenous opioid peptides or endorphins.

- Exert their major effect by interacting with Opioid receptor in the CNS, and in other places such as GI tract and urinary bladder.

- Opioids cause hyperpolarization of nerve cells, inhibiting nerve firing, and presynaptic inhibition of transmitter release.

- Morphine causes analgesia, and patients treated with morphine are still aware of the presence of pain, but sensation is not unpleasant.

Opioid Analgesics: Indications

- Main use: to alleviate moderate to severe pain
- Cough centre suppression
- Treatment of diarrhea
- Balanced anaesthesia

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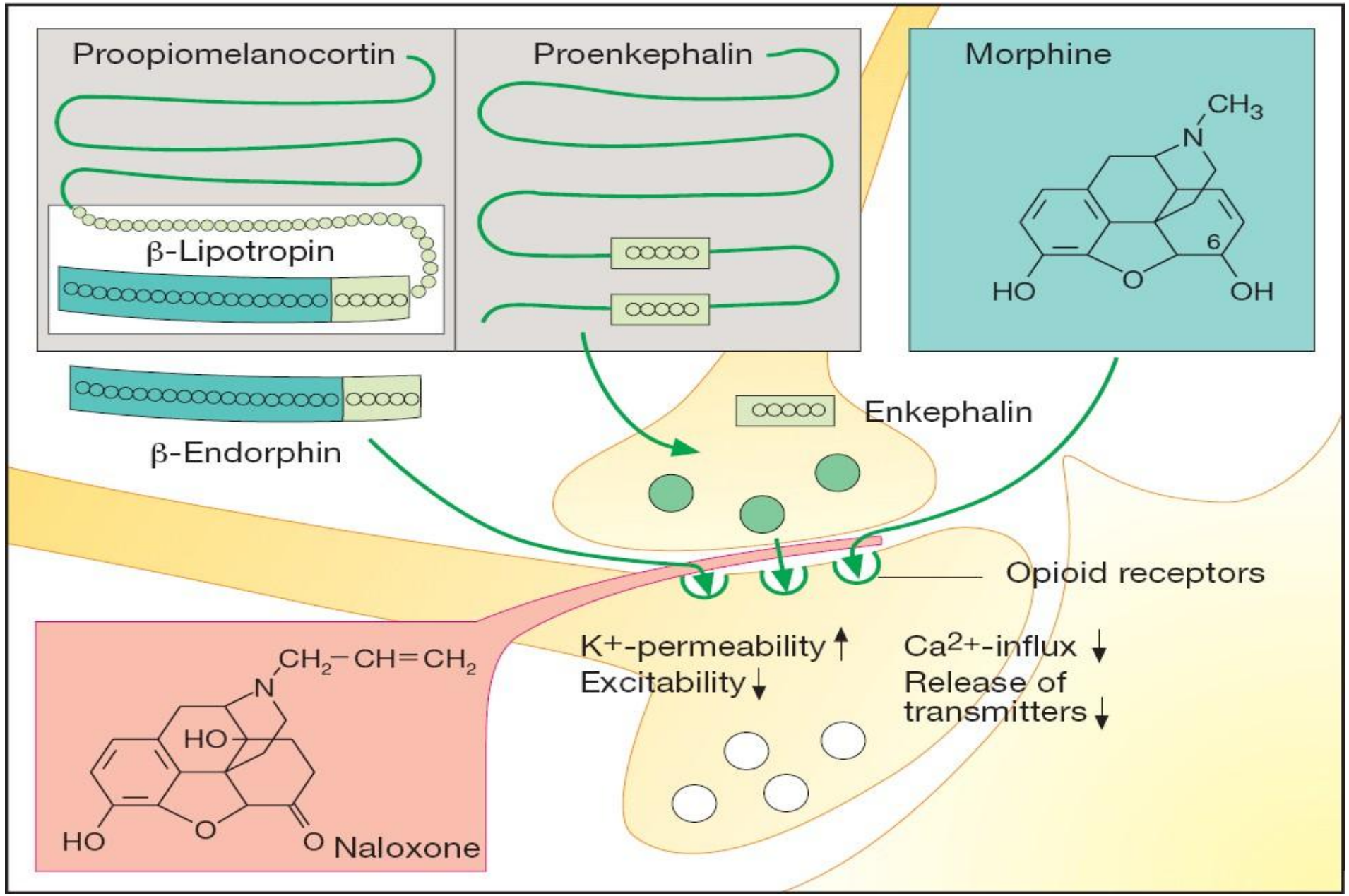
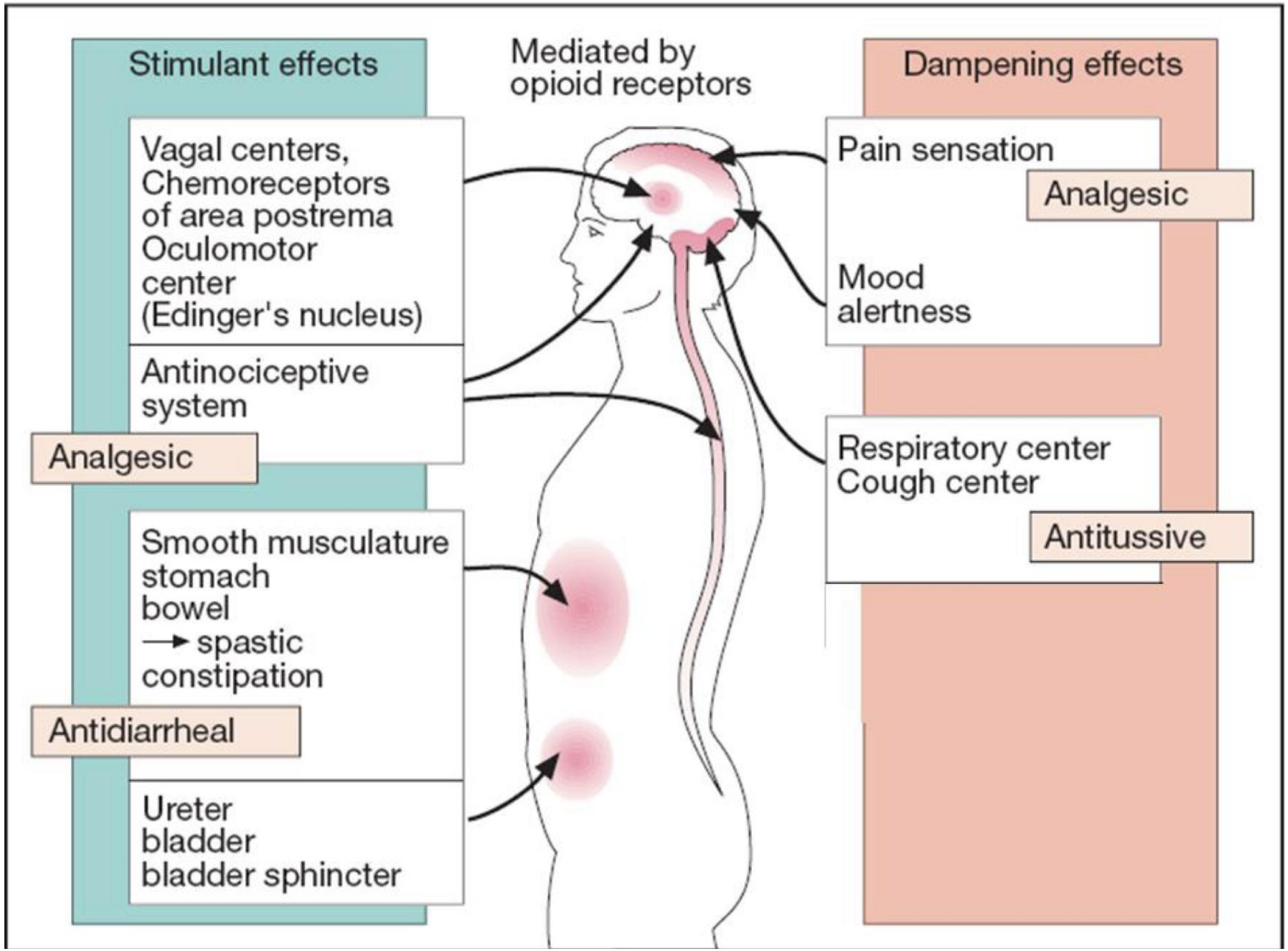
See next slides.....




Stimulant effects
Mediated by opioid receptors
Dampening effects
Vagal centers, Chemoreceptors of area postrema Oculomotor center (Edinger's nucleus)
Antinociceptive system
Analgesic
Smooth musculature stomach bowel → spastic constipation
Antidiarrheal
Ureter bladder bladder sphincter
Pain sensation
Analgesic
Mood alertness
Respiratory center Cough center
Antitussive

The μ-Opioid Receptor System

- The **μ-opioid receptors** in the human body were not originally designed for drugs such as **morphine or fentanyl**. These receptors are part of a natural physiological system whose purpose is to bind the body's own **endogenous opioid peptides**, which regulate pain perception and produce feelings of well-being.
- **Endogenous Opioid Peptides:** The body naturally produces opioid-like substances, mainly **endorphins** and **enkephalins,** these molecules act as **natural agonists of μ-opioid receptors**, meaning they bind to these receptors and activate them. When they bind, they reduce pain perception and contribute to sensations of comfort or euphoria.
- **Pharmaceutical Opioids:** Drugs such as **morphine, fentanyl, and other opioids** are **exogenous agonists**. They activate the same μ-opioid receptors but often with **greater potency and longer duration**, effectively mimicking and amplifying the body's natural pain-control system.
- **The Survival Role of the System:** This endogenous opioid system plays an important role in **survival during extreme stress or injury**. In situations such as a **fight-or-flight response**, the body can release large amounts of endorphins. This temporary surge reduces the perception of pain, allowing an individual or animal to continue functioning despite injury.
- For example, an animal involved in a fight may sustain injuries but **not immediately feel pain** because of the large release of endorphins. The pain becomes noticeable only later, after the stress response subsides.
- Humans possess the same biological system, but in many medical situations (such as **severe trauma, surgery, or advanced disease**) the body's natural endorphin release is **not sufficient to control pain**. In these cases, **pharmaceutical opioids are used to activate the same receptors and provide effective analgesia**.

Cellular Mechanism of Action

- When opioids bind to their receptors, they produce a **damping (depressing) effect** on the Central Nervous System (CNS) through two main electrical changes:
- **Increased Potassium (K^+) Permeability:** This causes K+ to leave the cell, leading to hyperpolarization.
- **Decreased Calcium (Ca^{2+}) Influx:** This prevents the release of excitatory neurotransmitters.
- **Result:** This leads to **decreased excitability** and **decreased transmission** in the brain's pain centers, medically known as **Analgesia**.
- Opioids are considered the most powerfull analgesics in medicine due to their unique pharmacological profile:
- **Central action:** they act directly on brain and spinal cord receptors.
- **No ceiling effect:** Unlike NSAIDs, opioids don't have a clear Emax or ceiling effect. This means there is no pre-determined limit to their effectiveness; as you increase the dose, the pain relief continues to increase, which is essential in for terminal palliative care.
- The reason behind this effect of opiods is that full opioid agonists can **fully activate μ-receptors once they bind,** so as the dose increases: dose ↑ → more receptors occupied → stronger signaling → more analgesia.

(Since these drugs can produce **maximal receptor activation**, the analgesic effect can keep increasing with dose (until toxicity occurs))

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Dual Effect on Pain Perception

- Opioids relieve pain through two main actions within the CNS:

1. **Damping of Pain Sensation:**

They directly reduce the intensity of the pain signal transmitted through the nervous system.

2. **Stimulation of the Anti-nociceptive System:**

They activate the body's endogenous pain-inhibitory pathways that suppress pain transmission.

- **Clinical Observation:**

Patients treated with opioids often report that **"the pain is still present, but it no longer bothers them,"** reflecting that opioids not only reduce pain intensity but also alter the **emotional perception of pain**.

Additional CNS and Clinical Effects

- Beyond killing pain, opioids exert several other significant effects on the patient:
- **Mood and Stress:** They cause **mood damping**, **sedation**, and have a strong **anxiolytic (anti-stress)** effect.
- **Cough Suppression:** They are potent **anti-tussives** (e.g., Codeine).
- **Mental State:** While they are not true hypnotics, they significantly calm and sedate the patient.

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The Lethal Risk: Respiratory Depression

- The most dangerous and life-threatening effect of opioids is the suppression of the **respiratory center** in the brainstem.
- **Overdose:** An excess dose of opioids leads to **severe respiratory depression**, which is the primary cause of death related to opiods overdosing.
- **The Fentanyl Crisis:** In recent years, the U.S. has seen a massive spike in mortality due to **Fentanyl overdose**, where the drug's extremley high potency leads to immediate respiratory failure.

Antidote and Clinical Examples:

- **The Antagonist: Naloxone** is the medical antidote (antagonist) for opiods. It is used to block opioid receptors and immediately reverse the effects of an opiod overdose, potentially saving the patient's life.

See next slides....

Opioid Analgesics: Side Effects

- Euphoria
- CNS depression
- Nausea and vomiting
- Respiratory depression
- Urinary retention
- Diaphoresis and flushing
- Pupil constriction (miosis)
- Constipation
- Itching

Major Side Effects of Opioids (Systemic View)

- Opioids affect nearly every system in the body. Clinically, these effects are categorized as follows:
- **Central Nervous System (CNS):** General depression leading to **sedation**, **euphoria** (which contributes to addiction), and the life-threatening **respiratory depression**.
- **The Eye (The "Miosis" Sign):** Opioids cause **pupil constriction**, resulting in **Pinpoint Pupils**. This is a classic, "tell-tale" sign used by emergency doctors to identify an opioid overdose or chronic addiction.
- **Gastrointestinal & Urinary: Nausea** and **vomiting** are common initially. Long-term use leads to chronic **constipation** and **urinary retention.**
- **Vascular & Skin (The Histamine Effect):** Opioids, especially **Morphine**, trigger the release of **histamine**. This causes **vasodilation**, **flushing**, and intense **itching**.
  - *Clinical Warning:* Avoid using Morphine in patients with a history of **severe allergies** or asthma, as the histamine release can worsen their condition.

If you encounter a patient with Pinpoint Pupils, Severe Constipation, and Slow Breathing, you should immediately suspect Opioid Toxicity.

Opioid Effects on the GI Tract: From Side Effect to Therapy

- Opioid receptors are highly concentrated in the **gastrointestinal (GI) tract**. When opioids bind to these receptors, they utilize the same cellular damping mechanism (**Increased Potassium permeability** and **decreased Calcium influx)** leading to **decreased excitability** of the intestinal nerves
- **Functional Result:** This leads to a significant **decrease in intestinal motility** (the speed at which food moves through the gut) eventually causing constipation.
- **Clinical Application:** While **constipation** is a notorious side effect for patients taking morphine for pain, we strategically use this effect to treat **diarrhea**.
  - *Example:* **Loperamide** (Imodium) is an opioid that acts primarily on GI receptors to provide a potent **anti-diarrheal effect**.

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The Phenomenon of Tolerance

- **Tolerance** occurs when the body becomes accustomed to the drug, requiring higher doses to achieve the same effect. However, tolerance does not develop equally across all symptoms:
- **High Tolerance:** Patients quickly build tolerance to the **euphoria**, **sedation**, and even the **respiratory depression**.
- **The Exception (Constipation):** Interestingly, the body almost **never develops tolerance to constipation**.

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The Neurobiology of Euphoria and Addiction

- **Euphoria**—often described by patients as an intense, pleasurable "high"—is the primary driver of opioid abuse.
- **The Classical vs. Modern View of Euphoria:**

➢ **The Old Explanation:** Opioids bind to **u-receptors**, which directly stimulate the **Reward System**, leading to a massive release of **Dopamine** in the brain's nucleus accumbens.

➢ **The Modern "Brain Network" Theory:** Current neuroscience suggests the brain operates in a state of **equilibrium** involving multiple neurotransmitter systems: **Serotonergic, Dopaminergic, Noradrenergic, and GABAergic,** this theory states that opiods not only increase dopamine release, however they **imbalance the whole brain's equilibrium** causing that euphoric effect, so while dopamine is a key player, it isn't the whole story.

- **Dopamine Alone Is Not the Full Explanation:**
- A critical point to consider is that artificially boosting dopamine with agonists does not produce the same refined "euphoria" as opioids. For example, in **Parkinson's disease**, giving high doses of dopaminergic agonists can lead to what is clinically described as **"Mad Old Man Syndrome."** * This term describes a state of **uncontrolled, impulsive, or hyperactive behavior** rather than simple pleasure.
- This contrast proves that while opioids increase dopamine in a way that produces euphoria, excessive dopamine activity on its own creates extreme, **maladaptive behaviors**. Therefore, euphoria is the result of a **complex imbalance** across the entire neural network, not just a dopamine spike.

➢ Why is Opioid Euphoria So Dangerous?

- The danger lies in the **intensity** of the experience. Opioid-induced euphoria introduces the brain to a level of "happiness" or "pleasure" that is impossible to achieve through normal life activities (like eating or exercise).
- **Seeking Behavior:** The patient becomes psychologically attached to this new baseline and begins "seeking" the drug to reproduce a state that the brain now prefers over reality.

➢ Why Do Only Some People Become Addicted?

- If we give Morphine to 100 patients in a hospital for post-surgical pain, the majority will stop taking it once the pain is gone, but only few will become addicted. This is explained by two main factors:
- **Pharmacogenetics (Genetic Risk):** Some individuals are genetically predisposed to addiction. Their brain chemistry or receptor sensitivity makes them more "vulnerable" to the drug's addictive potential.
- **Psychological Predisposition:** A person's internal "willingness" or mental state plays a role. If a person is using the drug to escape psychological trauma or depression, they are much more likely to develop a behavioral tendency toward addiction.

➢ "Single-Dose" Attachment:

- A critical perspective in addiction medicine is that for a vulnerable individual, **a single intense euphoric experience** can be enough to develop addiction just after. That one moment of extreme pleasure creates a "craving" so strong that the patient spends the rest of their life trying to reproduce it. In this context, **Addiction is defined as seeking happiness through a drug-induced state.**

See next slides....

Repeated use of Morphine

- Psychological dependence
- Physical dependence
- Tolerance
- Withdrawal syndrome
- Hyperalgesia???????

The Narrow Window: Respiratory Depression and Genetics

➢ **Respiratory depression** is the most lethal complication of opioid use. Two main factors make it the leading cause of death:

1. **Pharmacogenetic Differences**

- Individuals vary genetically in how they **metabolize opioids and respond to μ-opioid receptors**. Variations in drug-metabolizing enzymes (e.g., CYP450) and receptor sensitivity can cause the **same dose** to produce mild effects in one person but **severe respiratory depression** in another.

2. **Narrow Therapeutic Index**

- Opioids have a **small margin between the therapeutic dose and the toxic dose**. A slight increase in dose can quickly shift the effect from **analgesia to life-threatening respiratory depression**, especially when drug potency or concentration is unknown (e.g., illicit opioids).

The Paradox of Hyperalgesia

➢ During long-term opioid therapy, a paradoxical effect may occur where **increasing opioid doses lead to increased sensitivity to pain instead of better analgesia**.

- **Mechanism:**

1. Central Sensitization (Activation of Pronociceptive Pathways)

Chronic opioid exposure can activate **excitatory pain pathways in the CNS,** this makes pain-transmitting neurons **more sensitive to stimuli**, lowering the pain threshold.

2. μ-Receptor Adaptation

Repeated opioid stimulation leads to **μ-opioid receptor desensitization and downregulation**, reducing the effectiveness of both **exogenous opioids and endogenous opioid peptides (endorphins and enkephalins)**.

➢ **Clinical Result:**

- Patients may experience **worsening or more diffuse pain despite increasing opioid doses**, creating a cycle of dose escalation (Pain ↑ → dose ↑ → neural adaptation ↑ → pain ↑ → dose ↑)
- At high doses, the **risk of respiratory depression becomes dangerously high** due to the narrow therapeutic margin.

See next slides....

Tolerance/Dependence/Addiction

- **Tolerance**

– Physiologic phenomenon resulting in progressive decline in potency of an opioid with continued use.

Dependence

– Physiologic state characterized by withdrawal symptoms upon abrupt discontinuation/ reduction of narcotic therapy.

- Abstinence syndrome
- Independent of tolerance

Addiction

– Psychological behavioralsyndrome manifested by drug seekin behavior, loss of control o drug use, and continued us despite adverse effects.

Withdrawal Reactions

See next slides.....

Acute Action

- Analgesia
- Respiratory Depression
- Euphoria
- Relaxation and sleep
- Tranquilization
- Decreased blood pressure
- Constipation
- Pupillary constriction
- Hypothermia
- Drying of secretions
- Flushed and warm skin

• Withdrawl Sign

- Pain and irritability
- Hyperventilation
- Dysphoria and depression
- Restlessness and insomnia
- Fearfulness
- Increased blood pressure
- Diarrhea
- Pupillary dilation
- Hyperthermia
- Lacrimation, runny nose
- Chilliness and “gooseflesh”

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Opioids: Analgesic Power, Tolerance, Dependence, and Addiction

1.The Concept of Agonism and Toxicity

- **Agonist drugs** (like Morphine) bind to receptors to produce a physiological response. However, all drugs follow the principle of **dose-dependent toxicity**.
- **Example:** Repeated use of **Beta-2 agonists** (like Salbutamol) in respiratory therapy leads to receptor **desensitization**.
- **The Opioid Parallel:** The same principle applies to opioids. Constant stimulation of **μ-receptors** leads to a decreased response, which we call **tolerance**.

Opioids: Analgesic Power, Tolerance, Dependence, and Addiction

➢ **Tolerance** is defined as a decreased response to a drug after repeated exposure.

- **The Escalation:** A patient may start with **5 mg** of Morphine in Week 1. By Week 2, they may need **10 mg**, and by Week 3, **20–30 mg** to achieve the same level of pain relief.
- **The Mechanism:** This occurs due to the **downregulation** of **μ**-receptors and **neuroplastic changes** in the brain's signaling pathways.

➢ **Physical (Physiological) Dependence and Withdrawal**

- **Physical dependence** is a neuroadaptation where the brain and receptors adapt to the constant external supply of opioids.
- **Brain Plasticity:** The brain changes its "set point" in response to continuous stimulation.
- **Withdrawal (Absence) Syndrome:** If the drug is stopped abruptly, the body reacts violently. The symptoms are typically the **opposite** of the drug's original effects:
  - **Pain & Agitation:** Instead of analgesia and calm.
  - **Diarrhea & Hyperventilation:** Instead of constipation and respiratory depression.
  - **Mood Fluctuations:** Severe anxiety and depression.
- **Clinical Management:** To avoid this, doctors use **Tapering**—gradually reducing the dose- to allow the receptors to restore their natural balance safely.

Tolerance and Dependence

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Pregnancy and elderly

- If acetaminophen is insufficient, opioids are considered

- acceptable during pregnancy provided they are given for a short duration.

- Chronic opioid use can result in fetal dependence, premature delivery and growth retardation.

- In elderly

Opioid analgesics have an increased likelihood of more profound adverse effects as well as prolonged durations of action. Therefore it is best not to select an opioid.

If it is necessary, reduced doses must be utilized.

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Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities
Strong opioid agonists				
Morphine Methadone Fentanyl	Strong -receptor agonists	Analgesia relief of anxiety sedation slowed gastrointestinal transit	Severe pain adjunct in anesthesia (fentanyl, morphine) pulmonary edema (morphine only) maintenance in rehabilitation programs (methadone only)	First-pass effect duration 1–4 h except methadone, 4–6 h *Toxicity:* Respiratory depression severe constipation addiction liability convulsions
Hydromorphone, oxymorphone: Like morphine in efficacy, but higher potency				
Meperidine: Strong agonist with anticholinergic effects				
Sufentanil, alfentanil, remifentanil: Like fentanyl but shorter durations of action				
Partial agonists				
Codeine	Less efficacious than morphine	Like strong agonists weaker effects	Mild-moderate pain cough	Like strong agonists, toxicity dependent on genetic variation

Opioids

- Weak opioids
  - Codeine
  - Tramadol
- Strong opioids
  - Oxycodone
  - Morphine
  - Methadone
  - Fentanyl
  - Mepiridine
  - Heroin

Classification: Weak vs. Strong Agonists

- In practice, we categorize these substances into two main groups. Weak opioids, such as Codeine and Tramadol, are partial agonists towards neuroreceptors. They have a "ceiling effect," meaning they produce partial euphoria and partial respiratory depression. These are suitable for moderate to severe pain, like dental work, where ibuprofen fails but we want to avoid the high risk of full physical dependence.

- Strong agonists, on the other hand, have no ceiling effect. The "Big Five" in this category—Morphine, Oxycodone, Methadone, Meperidine (Pethidine), and Fentanyl—differ primarily in potency rather than efficacy. We rarely reach "maximum efficacy" because the patient would likely develop respiratory failure before that point.

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Potency and the "Zombie" Risk

- **The difference in potency among strong opioids is staggering. While Morphine is the standard, Fentanyl and Heroin are 100 to 200 times more potent (respectively). For perspective, if a Morphine dose is 5 mg, a Fentanyl dose must be measured in micrograms (mcg).**
- **This is why Fentanyl is often called a "zombie" drug on the streets. Because it is active in such tiny amounts, it is incredibly easy to overdose. In a medical setting, we use patches to strictly control the rate of entry into the bloodstream. However, when these micrograms are pressed into illegal tablets, the margin for error disappears.** Because of fentanyl's narrow safety margin, healthcare professionals must **carefully titrate doses and monitor patients**. Using excessive doses simply to suppress pain or agitation can be dangerous and potentially fatal.

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PHARMACOLOGY QUIZ LECTURE

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