Pharmacology

CNS

Sheet No

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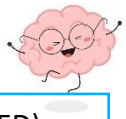
بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

This sheet was written based on both lectures (sec1/ recorded + sec2)

Welcome to our first pharmacology lecture in this semester!



Words in *BLUE ITALIC* are ADDITIONAL for clarification (NOT REQUIRED)

****Here are some of the CNS pharmacology topics that we will take:**

-Opioids or Narcotics (We'll start with this topic in this lecture)

-Hypnotic and anxiolytic drugs

-Local and general anesthesia

-Anticonvulsants

-Alzheimer drugs

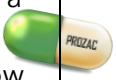
-Antipsychotics (such as drugs used for psychosis, bipolar mania, and schizophrenia)

-Antidepressants

-Drug abuse and misuse (this topic is very important in understanding opioids, hypnotics, and anxiolytics)

INTRODUCTION

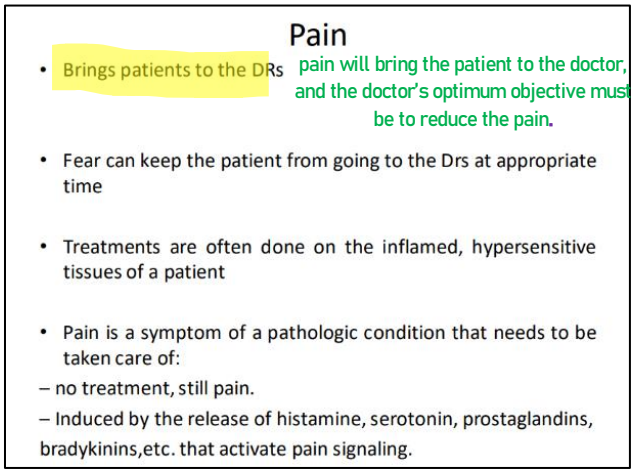
Drugs were found by experimentation or by accident more than being designed, so **many drugs we use we don't really know how they work and their mechanism of action**. For example, when we know that a certain drug is an antidepressant, we don't really know how it really produces this anti-depression, Prozac for instance is an SSRI antidepressant (selective serotonin reuptake inhibitor), **BUT** we don't really know how it works (the brain map is not yet clear and until now CNS is not well understood), because CNS is a dilemma, difficult, deep and complex specially in pharmacology and physiology, even if attempts are made to simplify it. No one can enter the human mind and truly understand the mechanisms of drug effects. Another example: we can use a lot of drugs to treat schizophrenia (such as alpha 2 agonists, dopamine 2 antagonists or agonists, and SSRIs), these drugs have different mechanism of actions BUT all cause the same effect. Mechanisms of actions of drugs are all expected in science and not real.



Extra information: primarily dopamine antagonists are used to treat schizophrenia, however there are some partial agonists such as Aripiprazole which can be also used, but main drugs are dopamine antagonists.

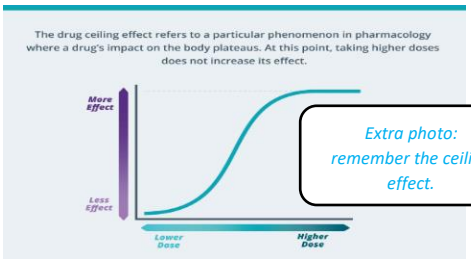
Pain management

It is an important and long-way topic, and you as doctors should know how to deal with pain. There are **many types of pain** such as inflammatory pain, post-surgery pain and cancer pain. Inflammatory pain which is a moderate pain that can result from inflammatory processes such as rheumatoid arthritis or gout and can be alleviated by **NSAIDs**, as inflammation induces many forms of pain by prostaglandins and other mediators.



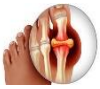
- NSAIDs reduce pain, inflammation, and fever. Examples are naproxen, celecoxib, diclofenac, and ibuprofen.
  Their ceiling effect reaches moderate pain (even diclofenac, which is the strongest NSAID, its maximum activity treats only moderate pain).

Also, there are **different thresholds of pain**: mild, moderate, moderate-severe, and severe pain. You as a doctor will deal mainly with moderate to severe pain.
For example, cancer pain which is a very bad chronic severe pain or post-surgery pain which is acute moderate-severe pain, in this case we **cannot use NSAIDs** that we used for moderate inflammatory pain even with maximum tolerated dose of ibuprofen or diclofenac because pain is higher than their ceiling effect, hence the idea of a drug that enters the brain and pain center and **INTERRUPTS THE PERCEPTION OF PAIN** has emerged, which are OPIOIDS. These are MAGICAL drugs that don't have ceiling effect and treat strong pain, no matter how severe it is. Severe pain doesn't respond to neither NSAIDs nor steroids.



Extra photo: remember the ceiling effect.

-Gout pain may reach severe pain, but it is considered a moderate pain and it is inflammatory in origin.



-Post-surgery pain: strong pain after surgeries, for example: hip or knee replacement surgery, open heart surgery (example: CABG).

The oldest drug in history is **morphine**, it was the first opioid isolated from the opium poppy tree in 1804, the poppy extract is full of opioids and the most important opioid is morphine, and at that time phytotherapy or plant therapy was replaced by pharmacology or drug therapy (the first isolated compound historically was morphine being the only active substance). After that in 1832, aspirin was chemically synthesized, so morphine and aspirin were the first two drugs to be found.

Morphine or any opioid such as fentanyl enter the CNS and bind to receptors called mu receptors or morphine receptors, these receptors:

1- **Increase the threshold** toward the pain.

2- **Change perception** toward the pain.

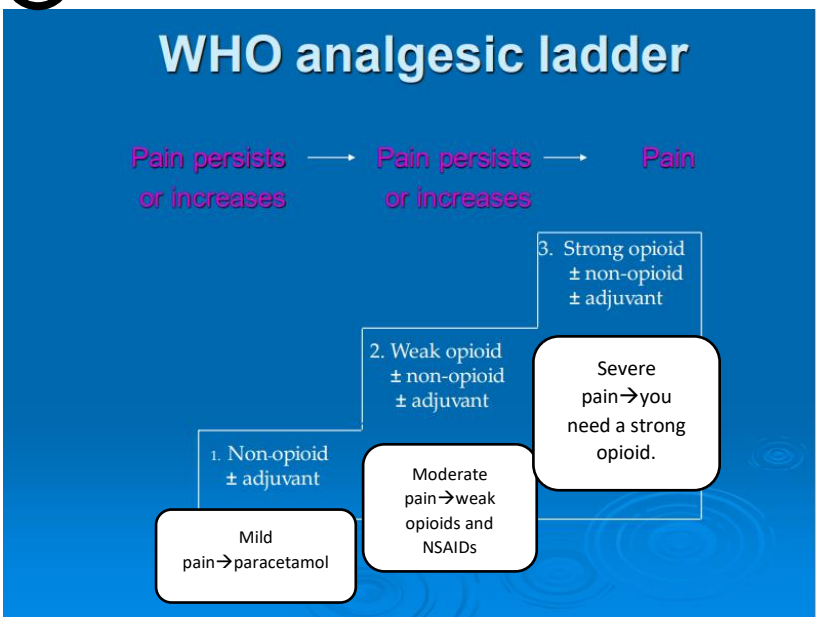
Pain threshold is the minimum intensity at which a person begins to perceive or sense a stimulus as being painful.

This interference with the brain has produced two major problems worldwide:

1- When these drugs enter the CNS, they will bind to a lot of other unwanted receptors other than the targeted receptors (not related to pain relief) producing **side effects** such as EUPHORIA.

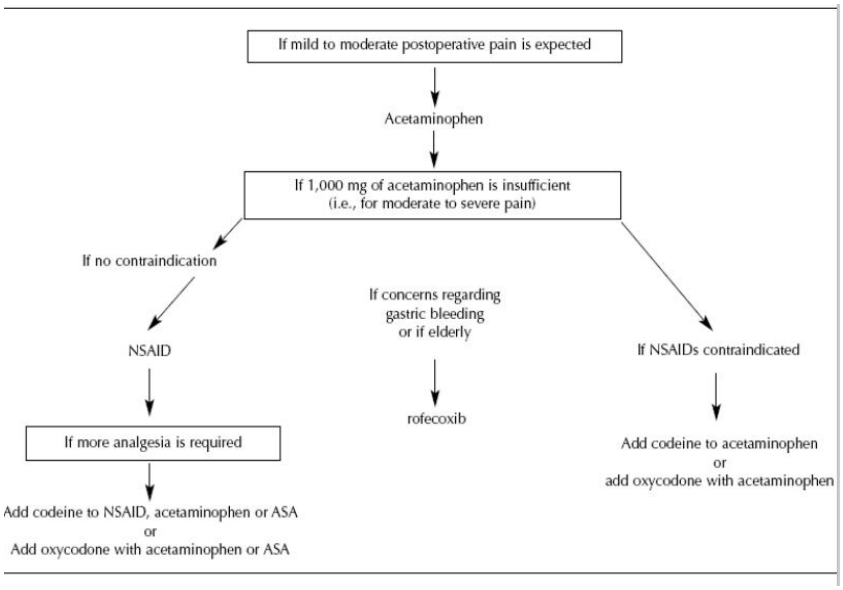
2- These drugs cause **ADDICTION**, this is a serious worldwide problem that you as a doctor must be aware of. In Britain, 1% of its population is addicted to opioids such as Morphine and Heroin, which is a very high percentage. In Jordan, we are relatively more protected because these drugs are more expensive, and we only have weaker forms here in Jordan.

These drugs can be intentionally manufactured with the aim of being addictive and euphoric, an example of this is a drug that is now spread in Jordan which is **Captagon**, which is a mixture of two risky drugs: 
Amphetamine and Theophylline (has combined **synergistic activity toward euphoria**, which means that Amphetamine alone does not cause euphoria or addiction, but Amphetamine with Theophylline will cause euphoria as both increase norepinephrine and dopamine. Amphetamine is a CNS stimulant was injected to horses to run faster. Theophylline is a xanthine derivative, CNS stimulant (cause CNS alertness), and a bronchodilator (xanthines are present in coffee and tea...). One of the other ways to manufacture drugs of abuse is to first take a hypoglycemic agent such as Amaryl sulfonylurea(glimepiride) followed by taking a mixture of caffeine and sugar rapidly. This will create euphoria sensation from the reward system of the brain, this is due to the sudden change of sugar concentration in the brain.



We use opioids whenever the patient has **strong pain**, BUT we don't have to forget that NSAIDs have a value, a lot of times we combine NSAIDs with opioids.

WHAT DRUG TO GIVE TO A PATIENT WITH PAIN?



Pain management depends on the severity of pain. If the patient experiences any pain (without knowing it's type):

1-Try firstly Acetaminophen for mild pain.

2-If Acetaminophen fails, try NSAIDs, if it fails and there is no contraindication give the patient both ibuprofen and paracetamol, if the patient has peptic ulcers, give him a selective NSAID such a Cerebrax/Celecoxib (cox-2 selective inhibitor).

3-If the patient is contraindicated or has a severe pain, **NOW** we try opioids, such as **CODEINE.**

Opioid analgesics:

1- All drugs in this category (around 10) 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.

- Endorphins and enkephalins are **endogenous opioids** that are responsible of natural balanced analgesia in our body by binding to receptors(mu receptors), even though science says that they don't really bind to receptors and it is unknown how they produce this analgesic effect.
- Copious secretion of endorphins prevent some dogs from feeling pain during attack(analgesic effect), so if a violent dog attack you, you won't benefit if you hit it, these types of dogs secrete both norepinephrine and endorphins during attack much more than human.

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

- **NO DRUG HAS A SINGLE EFFECT, EVERY DRUG HAS MULTIPLE EFFECTS**, this is due to two reasons:

1. Drug binding to **different kind of receptors with different AFFINITIES**, for example opioids can bind to muscarinic receptors or nicotinic receptors other than opioid receptors.
2. Drug binding to **same receptor in different tissues**, this will generate different effects according to different parts of our body, this is called TISSUE SPECIFIC RECEPTOR EFFECT or RECEPTOR ORGAN SPECIFIC EFFECT, that's why drugs can bind to the same receptor however in different parts of our body, producing therapeutic effect as well as side effects.
   - For example, opioids binding to the same type of receptors (mu receptors) with the same mechanism of action (opening potassium channels and closing calcium channels) will cause different therapeutic effects and functions:
   - If receptors are in GI tract: opioids cause decreased GI motility and **constipation** (side effect).
   - If receptors are in urinary bladder: opioids cause urinary retention (side effect), increase sphincter tone, and reduce the contractile forces of the uterus muscles, like anticholinergic effect.
   - If receptors are in CNS: opioids cause analgesic effect (therapeutic effect).

Therapeutic effect: the chief and desired action of a drug

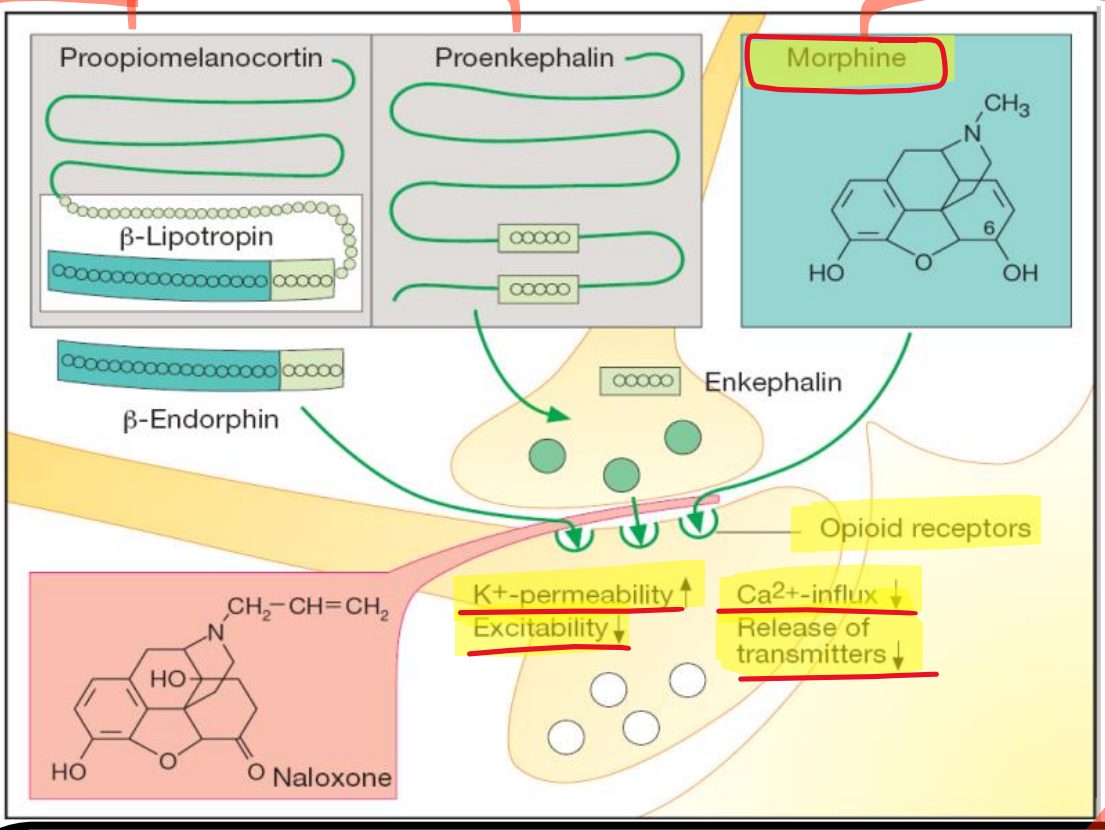
3- Opioids cause hyperpolarization of nerve cells *(by opening post synaptic K channels)* **thus inhibiting nerve firing** (increase threshold of firing)**, and presynaptic inhibition of transmitter release** *(by inhibiting presynaptic Ca channels).*

- Hyperpolarization of nerve cell→no action potential→no pain sensation (analgesic effect)

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

- **THERE IS NO DRUG LIKE MORPHINE**, what distinguishes it is its ability to **change perception of pain**, that's means it can change the patient's thoughts about pain; there is pain but the patient is pleasant! If you ask the patient about the location of the pain, he will point to it, but if you ask him whether he feels it, he will answer no! This is very weird! That's why most cancer patients are given morphine because it changes their interpretation of pain. The patient's perception of pain is important, if it is positive perception, this encourages the patient to take this medication (there is a psychological interference).

Mechanism of Action:



Endogenous opioids: endorphins and enkephalins

Exogenous opioids: such as Morphine (narcotics prototype).

Both endogenous and exogenous opioids bind to their receptors as agonists, this will cause:

1- Increase in potassium permeability (more opening of potassium channels→more potassium efflux) *(On Postsynaptic neuron)* thus hyperpolarization and decreased excitability.

2- Decrease calcium influx which will decrease neurotransmitters release *(On Presynaptic neuron)*.

Result: no action potential→ no pain sensation→ very strong analgesic effect without a ceiling effect.

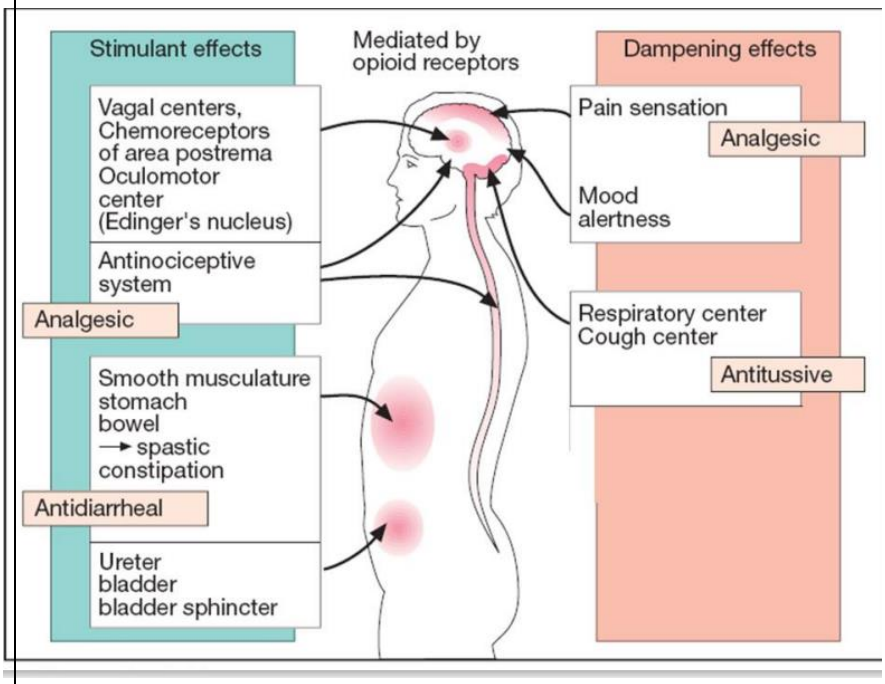
EFFECTS MEDIATED BY OPIOID RECEPTORS:

These are the desired effects.

Dampening pain sensation causing analgesic effect (used for moderate to severe pain)

Dampening mood alertness, opioids are not hypnotic drugs but have a **SEDATIVE EFFECT** (sleepy effect), not a strong effect and usually does not sleep you alone but is useful in post-surgical cases because they are analgesics and sedative.

Stimulate antinociceptive system causing analgesic effect (therapeutic effect).



Most crucial side effect:

Dampening of Respiratory center: becomes less responsive to Co2 levels, thus with increasing dose, there is increased dampening and respiratory suppression, which unfortunately leads to death. This is because as respiration decreases, Co2 increases which should stimulate the respiratory center in normal situations to increase the rate of breathing, but if the patient has overdosed on an opioid, the respiratory center will be less responsive to increasing Co2 levels thus continued respiratory suppression and death. This effect can occur on ordinary doses, but it is not dangerous except in elderly patients because their CNS is weaker than adults' CNS, however in overdoses it becomes life threatening.

Pupil constriction (Pinpoint pupils).

The importance of pinpoint pupil is during the evaluation of an obtunded patient, in which if an obtunded patient had pinpoint pupils upon examination, this suggest that opioid overdose was the cause of respiratory suppression.

2 MAIN treatable SIDE EFFECTS: spastic Constipation and urinary retention:

THE FIRST SIDE EFFECT outside CNS **of ANY OPIOID IS CONSTIPATION**, constipation is a more powerful and more common side effect than urinary retention, ALMOST ALL PATIENTS WILL HAVE CONSTIPATION on chronic use, that's why we treat it.

We can use opioids as an **anti-diarrheal** drug as it causes constipation. In this case we need an opioid that does not cross the blood brain barrier to avoid addiction, which is Loperamide (anti diarrheal).

Suppression of cough center: we can use opioids to suppress persistent cough, for example **codeine** is an antitussive drug as it inhibits cough center.

Why codeine but not morphine? Because it is a partial agonist which are drugs that does not produce the maximum full activity, but they produce half of the activity when binding to receptors. (To prevent full activation of opioid receptor thus avoiding addiction and less side effects) (Revacod: trade name of codeine)

Also, codeine used in dental pain that's not responsive to NSAIDs such as Ibuprofen (which is the preferred NSAID for tooth pain due to great penetration around and beneath teeth), because codeine has higher efficacy than ibuprofen. Remember the ceiling effect.

Opioid Analgesics: Indications

- Main use: to alleviate moderate to severe pain
- Cough center suppression
- Treatment of diarrhea
- Balanced anesthesia

Opioids are used in what is called "Balanced anesthesia" in which giving opioids causes a dampening effect that decreases the dose requirement of other used anesthetics. Meaning that the use of analgesics has changed from single-agent anesthesia (high dose that increases the number of deaths) to multiple-agent anesthesia (lower dose from each agent).

Extra: balanced anesthesia is anesthesia produced by smaller doses of two or more agents considered safer than the usual large dose of a single agent.

Opioid Analgesics: Side effects

- **Euphoria**
- **CNS depression**
- **Nausea and vomiting**; due to:
  1- Interference between brain centers that are stimulated by these drugs (cough and respiratory center) in a way that also affects the vomiting center.
  2- *Stimulation of chemoreceptor trigger zone (CTZ) which contains receptors that detect emetic agents in the blood and relays that information to the vomiting center, which is responsible for inducing the vomiting reflex.*
- **Respiratory depression:** Overdose can cause CO2 retention and acidosis, might lead to death.
- **Urinary retention**
- **Diaphoresis** *(excessive sweating)* **and flushing**.
- **Pupil constriction (miosis)**; *due to central stimulation of Edinger Westphal Nucleus, which contains a group of parasympathetic preganglionic cells that innervate the ciliary muscle and the pupillary constrictor.*

*****Overdose → pinpoint pupil**

- **Constipation**; *due to:*
  1- Spasmodic non-propulsive contractions of intestinal smooth muscles.
  2- Increase intestinal water absorption
- **Itching**; *due to histamine release.*

Repeated Use of Morphine

1- Physical/ Physiological Dependance

Morphine changes the relationship between neurotransmitters (e.g. glycine, endorphins , enkephalins, nicotine, dopamine, serotonin, NE, acetylcholine, etc.) and affects the connectivity between neurons. As a result, it causes a change in the brain system and direct it to other functions.

يغير من منظومة الدماغ حيث يؤثر على العلاقة بين النواقل العصبية و يغير من طبيعة عملهم فيما بينهم

Leads to

2-Withdrawal Syndrome

- *Chronic administration of opioids reduces endogenous production of endorphins and epinephrine. Following sudden withdrawal, there is an immediate deficiency of endogenous opioids with rebound elevation of norepinephrine release.*
- Resolved by tapering the dose gradually.

3-Tolerance

- Chronic use leads to downregulation and desensitization of receptors. As a consequence, a reduction in the activity of the agonist occurs. If we want to have the same desired effect, we need to increase the dose gradually BUT keep an eye on ELDERLY because they are more prone to overdose and respiratory depression.
- Happens to all mentioned effects (side and normal effects) except miosis and constipation.
- Happens mainly to drugs that exhibit agonism. For example (for clarification): Salbutamol/ Ventolin, which is a beta 2 agonist, aka rescue drug, is supposed to be used only if we need it because TOLERANCE develops FASTLY!

4-Psychological Dependance

- Also referred to Addiction
- Caused by taking a single dose (morphine and heroin are addictive from just one dose).
- If anyone seeks to experience the feeling of euphoria and takes a pill, then it will cause addiction right away BUT if the drug was taken for therapeutic use (analgesia) then addiction would happen in only 0.3% of cases! So here, we repeat that opioids CHANGE PERCEPTION OF FEELING and its effect depends on many factors and is affected by different situations.
- Even though morphine can give you ultimate happiness, DO NOT try it!!!

REMEMBER..

-Physical dependence leads to withdrawal syndrome

-Tolerance leads to hyperalgesia

5-Hyperalgesia

- *Hypersensitivity to pain and extreme response to it.*
- Due to tolerance (hyperalgesia can be avoided by increasing the dose GRADUALLY) and is also considered of withdrawal signs.

Leads to

Withdrawal Reactions

Acute Action	OPPOSITE	Withdrawal Sign
Analgesia		Pain and irritability
Respiratory Depression		Hyperventilation
Euphoria		Dysphoria and depression
Relaxation and sleep		Restlessness and insomnia
Tranquilization (calmness)		Fearfulness
Decreased blood pressure		Increased blood pressure
Constipation		Diarrhea
Pupillary constriction		Pupillary dilation
Hypothermia		Hyperthermia
Drying of secretions		Lacrimation, runny nose
Flushed and warm skin		Chilliness and "gooseflesh"

❖ Important Terms you SHOULD know:

- **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 (Withdrawal syndrome) / *dependence leads to it.*
- Dependance is independent of tolerance/ *not the same terms.*

- **Addiction**:

Psychological & behavioral syndrome manifested by drug seeking behavior, loss of control of drug use, and continued use despite adverse effects.

Nicotine leads to:

1- **Addiction;** because it causes small euphoria**.**
2- **Physical dependence;** that's why we notice a body change in smokers (e.g loosing weight). To avoid weight gain, ex-Smokers are advised to put بزر in their pockets (because now their appetite is no longer suppressed).

يعني كل ما يجوعوا ياكلوا من البزر بدل ما ياكلوا أشياء تانية قد تسبب لهم الزيادة في الوزن

BUT nicotine doesn't cause tolerance nor withdrawal symptoms.

- Anti-depressants
- Anti-schizophrenic drugs
- Anti-manic drugs
- Cortisone (makes the human body depends on exogenous source)

All DO NOT cause addiction (have no pleasant effect that drive the patient to be addicted toward it) though they have physical dependance and withdrawal symptoms.

Weeds

Marijuana

Cannabis

All cause Addiction

NO physical dependance/ tolerance/ withdrawal symptoms

اللهم صلّ على سيدنا محمد

-The most difficult type of psychological dependence is alcohol addiction which is a social addiction; في كل حدث بحياته بتلاقيه راح يشرب كحول, يعني يربطه بحياته بكل حالاته

Also, nicotine causes social addiction. That's why it's hard to take off alcohol and nicotine from addicts. Opioids' addiction is easier to deal with because their addicts take them secretly, so it's not linked to social life (but definitely they have higher risk on body).

الإدمان على الكحول و النيكوتين مرتبطين بالحياة, لذلك صعب ينسحبوا من المدمن, بينما المورفين يؤخذ سريًا و ليس مرتبط بأحداث الحياة

-Euphoria caused by opioids is much higher than by alcohol and nicotine.

Remember ..Euphoria is a SIDE EFFECT NOT AN EFFECT!

Opioids

1. Weak opioids

- Codeine
- Tramadol

2. Strong opioids

- Oxycodone
- Morphine
- Methadone
- Fentanyl
- Meperidine

USMLE Questions:

1- A 49-year-old female with a history of breast cancer comes to the office due to severe back pain. She took paracetamol and NSAIDs but continues to have severe pain. Upon examination, she has tenderness over several lumbar vertebrae. Neurologic examination is uneventful. The patient is prescribed oral morphine therapy. Which of the following is the most likely direct effect of this drug on the spinal cord neurons of this patient?

A. Activation of sodium-calcium exchange pumps

B. Blockage of voltage dependent sodium influx

C. Increased calcium influx into the cells

D. Increased chloride influx into the cells.

E. Increased potassium efflux out of the cells.

E: Correct. Opiate analgesics reduce pain by binding to mu receptors and inhibiting synaptic activity in the central nervous system. Activation of presynaptic mu receptors on the primary afferent neuron leads to closure of voltage-gated calcium channels and reduced excitatory neurotransmitter release. Binding to mu receptors on the postsynaptic membrane causes opening of potassium channels and membrane hyperpolarization.

2- A 52-year-old woman is diagnosed with metastatic breast cancer. She is managed with an opioid analgesic for bone pain that is well controlled during the first 6 days of treatment. The following week, the usual dose becomes ineffective and the patient reports nausea, itching, and constipation. Also, she is unable to walk or do her work due to the pain. The opioid dose is increased. Over the next few weeks, the patient would likely experience which of the following?

A. Euphoria

B. Increased Itching

C. Persistent nausea and vomiting.

D. Respiratory suppression

E. Urinary retention

F. Worsening constipation

F. Correct: Chronic opioid use leads to the development of tolerance to analgesic effects and most side effects, with the exception of constipation and miosis. To prevent bowel complications, it is recommended that patients be treated prophylactically with adequate fluid intake and daily laxatives.

(وَأَنْ لَيْسَ لِلإِنسَانِ إِلَّا مَا سَعَى، وَأَنَّ سَعْيَهُ سَوْفَ يُرَى، ثُمَّ
يُجْزَاهُ الْجَزَاءَ الأَوْفَى)

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