CNS Pharmacology- mid

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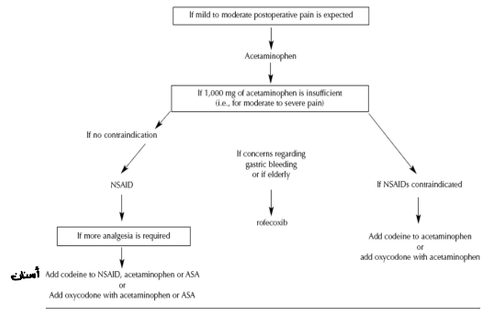
Lectures 1 & 2
Opioids

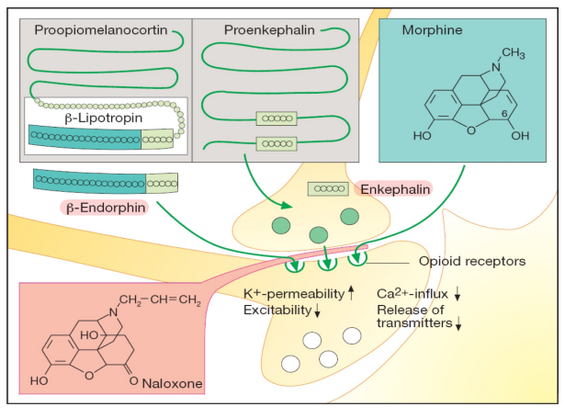
Opioids

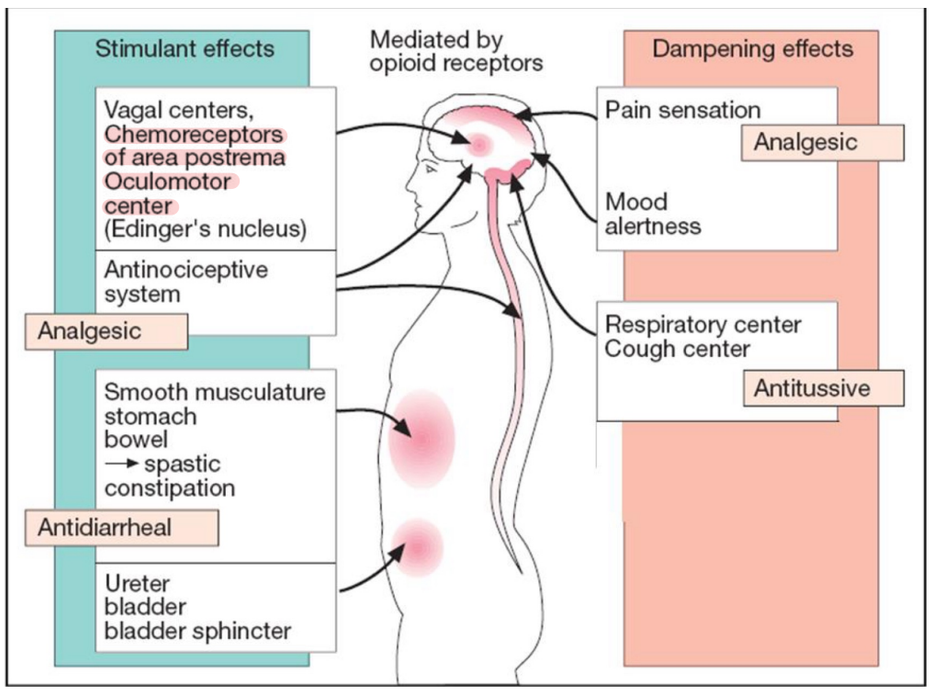
-pain → induced by the release of histamine, serotonin, PGs, bradykinins… that activate pain signaling

-analgesic ladder →

weak pain	moderate pain	very strong pain
Non opioid	weak opioid	strong opioid
+- adjuvant	+- non opioid	+- non opioid
	+-adjuvant	+- adjuvant



Drug – Generally	MOA	Effect (wanted)	Side effects	Notes
Opioids (narcotics) Parent drug: morphine	- they are similar in structure to endogenous opioid peptides (endorphins). - like endorphins, they bind to a specific opioid receptor (μ), which is present in the CNS (& other sites- GI/ urinary system). - when binding to the receptor (μ), they cause: - increased K+ permeability (+ve out) -decreased Ca++ influx (+ve out) → less excitability (hyperpolarization) → less release of transmitters → less pain sensation 	**CNS** -stimulation of: -vagal centers -Antinociceptive system -dampening of: -pain sensation -mood -alertness →use: analgesic Sedative (not hypnotic) triangulation mood كتير لطيف **GI** -stimulation of: -smooth muscles of the bowel → spastic constipation →use: Antidiarrheal →keep in mind: here we use lopramide bc it doesn't cross the BBB (no CNS effect) **Respiratory** -dampening of: cough center →use: Antitussive →keep in mind: here we use codeine without the fear of respiratory depression, bc it's a partial agonist	**Respiratory** -dampening of the respiratory center →effect: elevated CO2 → death → the most dangerous SE **Renal** -stimulation of: sphincters →effect: water retention **GI** -constipation **CNS** -nausea & vomiting **-Euphoria** How? Depressing the nervous system → imbalance → reward system (dopamine) is unopposed → dopamine spikes زهزهة→ Addiction -**pupil constriction (miosis/ pin point)** VIP, why? -used to reveal addicts (no tolerance) **Skin** (Due to differences in perfusion) -Diaphoresis & flushing -itching	**Antidote:** Naloxone - t1/2 of Naloxone = 1 hr t1/2 of Morphine = 4 hrs ⇒ we need to close the pt 4 times Euphoria here is continuous جيدة غلط هيك → goood !! there is no such thing in real life 



Problems with repeated use of opioids	Explanation
Tolerance	**What?** Physiologic phenomenon resulting in progressive decline in potency of an opioid with continuous use **How?** By receptor (μ) desensitization **Exception:** constipation & pupil constriction
Physical dependence (=! addiction)	**What?** Physiologic state characterized by withdrawal symptoms upon abrupt discontinuation/ reduction of therapy. **Solution?** Tapering
Withdrawal symptoms	**When?** Depending on the drug t1/2 … After 4-5 times the t½ **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" Withdrawal is the opposite of every action 
Psychological dependence (Addiction) ↳ & Behavioral Syndrome	-the more euphoria, the more addiction (Fentanyl > heroin > morphine > codeine > oxycodone) -loss of control of drug use & continuous use despite SE - Story time: Fentanyl is not approved to be produced as tablets, due to fear of absorption & metabolism variation leading to intoxication (especially that it has a very narrow spectrum) The Mexican gangsters decided to produce ORAL Fentanyl and sell it to Americans … Now remember: 1. Fentanyl is highly euphoric (high chance addiction) 2. High metabolic variation (can be food dependent) → those 2 factors led to many cases of intoxication, represented by respiratory depression and death → 1 each 7 mins die in America due to Fentanyl toxication (this is why its called ZOOMBIE)
Hyperalgesia	

↳ Why?

After continuous use, 2 things happen :

1. Drug tolerance … Exogenous analgesic is less effective
2. Endogenous analgesics (Endorphins) are less produced + less effective due to ↓ # of receptors

⇒ most common scenario :

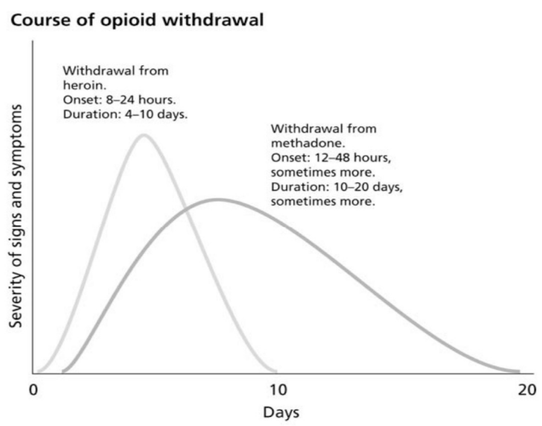
Cancer pts on palliative medication take opioids for a long time → Hyperalgesia

↳ otherwise, opioids are used for a short time (3-7 days) ⇒ less chance of tolerance & hyperalgesia

⇒ Solution : opioid rotation

Which is … using another opioid with an extra MOA → Strong : Methadone / NMDA blocker
→ Weak : Tramadol / Inhibits the reuptake of serotonin & norepinephrine

Opioid	General describtion	Drugs
Strong	-used for severe pain & have more euphoretic effect → more addiction - بنكتبوا بوصفة زهرية ... و اللي بحملها يعتبر مدمن -associated with the 5 problems mentioned previously	- morphine - mepiridine - methadone - fentanyl - oxycodone - heroin (no longer a drug)
weak	-used for moderate to severe pain -are partial agonists → less effect & less side effects (still have euphoretic effect on high doses) -less associated with the 5 problems - بنكتبوا بوصفة طوارئ	- codeine - tramadol

Strong opioid	MOA	Use	SE
Morphine / prototype	-acts on the opioid receptor (μ) -**Forms**: -tablets -oral solution (for pts that cant swallow / not for children) -pump (given to out pts, they press the pump when the feel the pain) **metabolism** -has 2 biologically active metabolites 1. morphine 6- glucuronide → Binds to the opioid μ receptor 2. morphine 3- glucuronide -Causes SE: myoclonus (seizures) & confusion → both metabolites are excreted renally -t1/2 is 1-2 hrs	**Main use** Analgesia -it induces sleep (but isn't a hypnotic), so used to supplement the sleep- inducing properties of hypnotics. **Other uses** -Antidiarrheal -was used to treat acute pulmonary edema associated with left ventricular failure.	-general opioids side effects -specific side effects are associated with the **accumulation of metabolites** (Morphine 3g). This metabolite is usually excreted sufficiently by kidneys & cause no problems. → BUT, this isn't the case in renal insufficiency pts → solution: use **Hydromorphone** Same effect, less metabolite acc. & SE
Mepiridine / pethidine	-acts on the opioid receptor (μ) -**Forms:** -injectable	-since its injectable & not socially well known to cause euphoria … we prefer using it to stay away of addiction. **Obstetric labor** - the least opioid crossing the placenta → least effect on fetus (respiratory depression) **Shivering (post anesthetia)** -How? By acting on opioid receptor kappa (k) - Although we previously said that opioids cause hypothermia (weird right?)	-general opioids SE **metabolite accumulation (normepiridine)** -causes: CNS hyper excitability Subtle mood changes Tremors Multifocal myoclonus (seizures) -when? In repeated large doses (250 mg/ day) + renal insufficiency (use Hydromorphone)
Methadone	-acts on opioid receptor (μ) -blocks NMDA receptor -what does that mean? Reduces neuronal excitability → reduces pain -reduces reuptake of serotonin & dopamine  	-used to treat ***difficult to treat pain***, especially when morphine failed. **used for chronic pain/ opioid addiction** -Why? - the secret lies in methadone being less prone to Tolerance. - less prone to tolerance = less prone to hyperalgesia & dependence (withdrawal) -How? -tolerance is a result of the peaks & troughs of a drug -Methadone has longer t1/2 (at least 1 day) + slower onset of action → sustained concentration & less ups and downs (less fluctuations) → less tolerance → less withdrawal symptoms & hyperalgesia -Methadone clinics are specialized in voluntary treatment of addiction using methadone -remember: use in hyperalgesia is called → **Opioid rotation** **Depression & fibromyalgia** - NMDA receptor antagonism have an antidepressant effect. -fibromyalgia (generalized body pain) is associated with NMDA receptor over reactivity. → however, there are better NMDA blockers for depression & fibromyalgia than an opioid	
Fentanyl (zombie)	-acts on opioid receptor μ -**Forms:** -patches (sustained release) -shouldn't be oral (remember the gangster story)	**Emergency (work fast, finish fast)** **Balanced anesthesia** -what does that mean? -in surgeries, we cant use pure anesthetic agents الا و... pts enter stage 4 of anesthesia (nearly coma) -So, we mix anesthetics with analgesics -why is Fentanyl the best analgesic to use? -It is strong enough (x100 efficacy of morphine) -It lacks a ceiling effect (the more you give, the more you get an effect… there is no ceiling) -It is fast enough … we don't want the opioid side effects (like vomiting) to persist after surgery.	
Oxycodone	-acts on opioid μ receptor **-Form:** oral	- it has a longer t1/2 tan morphine → supposed to have less addiction effect بس طلع ما بفرق	

Weak opioid	MOA	Use	SE
Codeine	-partial agonist on the opioid receptor μ -metabolized by the enzyme CYP2D6 -morphine is one of its metabolites (addiction possobility)	-moderate to severe pain -dental pain (Tylenol= codeine + acetaminophen) -Antitussive (the strongest effect) -remember: codeine itself doesn't cause respiratory depression because it's a partial agonist	-associated with pharmacogenetics… -In the east, the enzyme CYP2D6 is more active due to gene duplication → problem: codeine acts more as morphine Example: Ethiopian breastfeeding woman in Canada was given codeine to alleviate postpartum pain… after a while, her baby died. -Ethiopian= eastern = active CYP2D6 = high morphine production -breastfeeding: morphine is lipophilic -baby died: due to sufficient dose of morphine to depress respiration & cause seizures
Tramadol	-weak affinity to μ receptor -inhibits norepinephrine reuptake (WDA effect) → α2 receptor activation (remember Clonidine?) → analgesia (but less effective than morphine for severe pain) ➔ Overall, MOA is not fully understood	- moderate pain **Advantages** -less chance of respiratory depression -less nausea, vomiting -less constipation -rapid acting	

Peripherally Acting Opioid

- Opioid receptor – outside central nerve system
  - Peripherally acting opioid agonist
    → analgesia without CNS side effect
- Loperamide
  - μ-opioid receptor agonist
  - Not cross blood-brain barrier
  - Treatment : inflammation-induced hyperalgesia
  - Relieve diarrhea

Lectures 3 & 4 & 5
Anxiolytics & Hypnotics

Anxiolytic and Hypnotic drugs

- **Anxiety is unpleasant state of tension and fear that seems to arise from unknown source.**
- **The symptoms of severe anxiety are similar to those of fear (such as tachycardia, palpitation) and involve sympathetic activation.**
- **Sever anxiety may be treated with antianxiety drugs and/or some form of behavioral and psychotherapy.**
- **Because all of the antianxiety drugs also cause sedation, the same drugs often function clinically as both anxiolytic and hypnotic (sleep-inducing) .**

Hypnotics & Anxiolytics → use & treat insomnia & Anxiety (Chronic Stress, not everyday Stress)

1] Mechanism of Sleep & Stress

A- Stress is controlled by the limbic System

Limbic → Sympathetic ⇒ Inhibition of Sympathetic = less Stress

*Note: GABA is under the control of Serotonin

- Serotonin ⊖ ⇒ Increase Serotonin effect ⇒ give Antidepressants [SSRIs]
- GABA ⊖ ⇒ Increase GABA effect ⇒ give 1] Benzodiazepines 2] Barbiturates

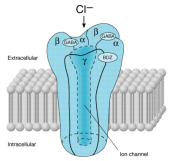
B- Sleep is controlled by Melatonin

Awakeness is controlled by Histamine & orexin ⇒ give antihistamine / orexin to treat insomnia

Melatonin
- (+) → GABA ⇒ Increase GABA effect to treat insomnia ⇒ Same drugs
- (-) → Orexin

2] GABA in Sleeping vs. Stress

General MOA for GABA:



Activates Cl^- channel → Cr influx → Hyperpolarization → Depression of the CNS → Sleep / Calm ⇒ The major inhibitory NT in the CNS

Notes about the Cl^- channel:

1] Composed of 4 Subunits → 2α, 1β, 1λ
- Binding to α_1 = Hypnosis
- Binding to α_2 = Anxiolytic

2] Tissue specific → different between Sleep center & Stress center (Ex. We have 2 isoforms of α Subunit)

↳ For this reason, The drug will need a higher dose to cause hypnosis, than anxiolytic.

3] Types of insomnia we are going to treat

A- Sleep onset insomnia ⇒ Trouble in falling asleep ⇒ use a Short acting hypnotic ... it peaks When the pt. wants to start sleeping

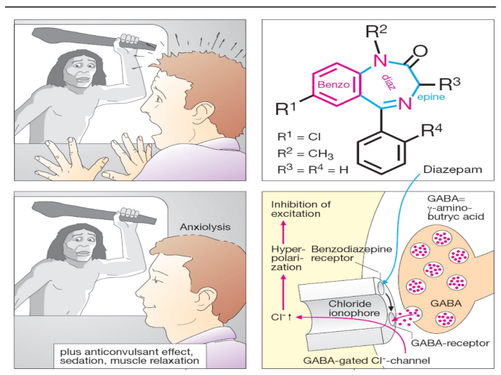
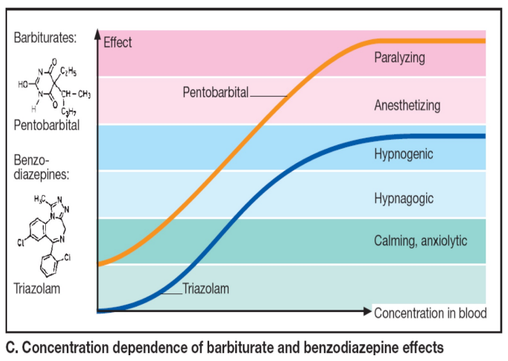
B- Early morning insomnia ⇒ Waking up to early & can't go back to sleep ⇒ use an intermediate acting Hypnotic ... it peaks When the pt. is about to wake up

C- Sleep maintenance insomnia ⇒ Trouble in Staying asleep (frequently wakes up) ⇒ use a long acting Hypnotic ... maintains high dose all night

COMPARISON OF THE DURATIONS OF ACTION OF THE BENZODIAZEPINES

Long-acting	Intermediate-acting	Short-acting
days 1-3	10–20 Hours	3–8 Hours
Clorazepate, Chlordiazepoxide, Diazepam, Flurazepam, Quazepam	Alprazolam, Estazolam, Lorazepam, Temazepam	Oxazepam, Triazolam

Drugs working on GABA receptor

Drug	MOA	Use	SE	Notes
Benzodiazepines (zepams)	Binds allosterically to Cl- channels at the α2-BDZ site → Increases the affinity of **GABA** binding to the channel → Increases the frequency of channel opening → more Cl- influx → more CNS depression → Anxiolytic effect. *frequent opening = has a limit (ceiling) → maximal effect is hypnosis (whatever the dose is) Binds α1 subunit weakly → Hypnosis ** This is why the hypnotic dose is higher than the anxiolytic. & this is why only Benzo drugs with higher affinity towards α1 receptor can be used for hypnosis. (not all Benzo are Hypnotic… all are hypnogogic) **→ dual effect (advantage on Z drugs)**   C. Concentration dependence of barbiturate and benzodiazepine effects	- They have no analgesic nor antipsychotic actions **Anxiolytics** (at lower doses) - Again, not used for everyday stress -Example: treating anxiety that accompanies some form of depression and schizophrenia -less prone to tolerance -Diazepam → preferred bc of its long acting effect **Hypnosis** (higher doses) - Benzos with highest affinity to α1: Flurazepam/ long acting Lorazepam/ intermediate acting Medazolam/ short acting - choice of duration of action is dependent on the type of Insomnia. -to prevent tolerance → use for no more than 4 weeks **Muscle relaxants** (higher doses) -Diazepam is useful in treating normal muscle spasms + spasticity from degenerative disorders such as MS **Anticonvulsants** -Clonazepam → chronic treatment of seizures -Diazepam (IV) → drug of choice for terminating *status epilepticus,* a grand-mal epileptic seizures that stays for >10 mins. -This is an essential part of emergency kit **Anterograde amnesia** -means → temporary impairment of memory -used in minor medical procedures that do not require Anesthesia (ex: colonoscopy, stenting, brain surgeries) -use: 1. Anxiolytic dose (we don't want the pt. to sleep) 2. short acting Benzo	**Hangover** - A SE related to Hypnotic use - what does it mean? المريض بصحى مسطل a *hangover* pt. cannot do fine movements (like driving) - when does it happen? When the pt. wakes up, but is still under the effect of the remaining dose of Hypnotic. - Logically, long acting hypnotics (Flurazepam) & to a lesser extent intermediate acting (Lorazepam) are associated with *hangover.* - short acting hypnotics are less likely to cause hangover → this is why they are preferred… especially if the pt. has sleep onset insomnia. **Drowsiness & confusion** Most common **Ataxia (ترنح)** - At high doses - limits the abilities of fine motor coordination **Cognitive impairment** -using Benzodiazepines on the long term may affect the cognitive function & memory عشان هيك الطالب اللي بكون ماخده قبل الامتحان ما بتذكر اشي - Since they act on a receptor → long use = **-tolerance** **-physical dependence** **-withdrawal symptoms** (rebound) →symptoms: confusion, anxiety, agitation, insomnia… → Benzo withdrawal symptoms starts after the drug is diminished from body (depends on DOA). → withdrawal happens even in reduction of the dose … so, tapering must be for a long period (up to 6 months) → moreover, tolerance can happen during the usage of drug (mostly short acting/ Triazolam), due to frequent peaks and troughs. → what is practically done: A patient with insomnia/ anxiety is ideally given an antidepressant (SSRI)… BUT, antidepressants need 4 weeks to work… SO, we bridge the pt. on benzo until SSRIs start working. After 4 weeks, Benzo is stopped (with no withdrawal symptoms) & SSRI activity is sufficient.	- The most widely used anxiolytics - Have largely replaced Barbiturates, bc they are safer and more effective. -criminals use an overdose of benzo → they massively depress the sympathetic system and lose the feeling of fear بنسميه محبحب - Benzodiazepines themselves cannot cause Euphoria (effect is on GABA rather than dopamine) → no psychological dependence - But when taken with wine → euphoria **Antidote** Flumazenil/ IV … rapid onset & short t1/2 -Why do we need an antidote if the maximal (ceiling) effect is sleeping? Benzo taken with wine causes significant CNS depression → respiratory depression → death -t1/2 of Flumazenil = 1 hour → You need to dose the pt. more than once, depending on the DOA of the overdosed Benzo **Precautions & contraindications** - use cautiously in treating pts with liver disease - avoid in pts with acute arrow angle glaucoma - Alcohol & other CNS depressants enhance the sedative- hypnotic effect.
Barbiturates (barbitals)	Binds to the Cl- channel on a different binding site → increases the affinity to GABA → increases the duration of channel opening → massive Cl- influx → massive CNS depression * continuous opening = has no limit (no ceiling) → increasing the dose may have stronger effects than hypnosis	SE mostly come from the continuous opening of the Cl- channel … **Respiratory depression → death** By suppressing the hypoxic receptors that response to CO2 **Coma in toxic doses**	- Are no more used as hypnotics nor anxiolytics **Thiopental** Used to induce anesthesia in surgeries (Although not the best choice) **Pheno & Pento barbital** Used as anticonvulsants Phenobarbital is the drug of choice for treatment of young children with febrile seizures.	- Have suicidal misuse - No fear of tolerance because its not used for long periods ..
Z drugs (new BDZ receptor agonists) -Zolpidem -Zaleplon -Zopiclone	Bind to α1 subunit with a higher affinity than Benzo → better hypnotic activity However, cannot bind α2 subunit → No anxiolytic, anticonvulsant, or any other activity	**Alternative to Benzo** -Z drugs do not cause tolerance → allowed to be used for long periods to treat insomnia. **Zolpidem** -Available in Jordan -t1/2 = 2 hrs … meaning that, drug stays in the body for 2x4= 8 hours (a perfect sleep period) -use is around bedtime for early morning & sleep maintenance insomnia **Zaleplon & Zopiclone** -t1/2 = 1 hr … meaning that, it stays in the body for 4 hrs -use is directly at bedtime to initiate sleep in pts with sleep onset insomnia	**Hangover** Can happen, but much less than Benzo **Sleep walking & nightmares & agitations (هلاوس)**	- The most frequently prescribed hypnotic in the US - effect is gender dependent → higher activity in females… female dose is ½ - Approved by the FDA to be used for up to 7- 10 days الناس عم تستعملهم اكثر

Melatonin / hypnosis

Drug	Description	MOA	Use
Melatonin / Ramelton	- Melatonin is a natural hormone produced from the pineal gland & is responsible of the circadian rhythm & initiation of sleep - Circadian rhythm → con. Increase in the evening -Ramelton is a synthetic tricyclic analog of melatonin	- there 2 GPC receptors for melatonin: 1. MT1 → promotes the *onset of sleep* 2. MT2 → shifts the timing of circadian rhythm → melatonin & Ramelton bind both receptors	Acting on MT1 → used for sleep onset insomnia Acting on MT2 → used for jet lag insomnia لما حدا يسافر مكان عكس التوقيت

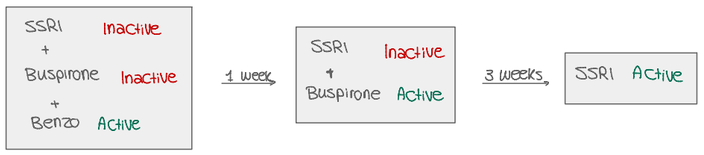
Orexin / hypnosis

Drug	MOA	Use	SE
Suvorexant	- Receptor antagonist for Orexin (OX1, OX2)	- treatment of insomnia	- somnolence - daytime sleepiness - sedation - headache - fatigue - dry mouth → SE are clear at high doses (above 20 mg)

Serotonin / Anxiety

Drug	MOA	Use	SE
Buspirone	- Serotonin (5 HT) receptor agonist - specifically 5 HTA1 receptor … which is responsible for the CNS depression function. → keep in mind: It needs 1 week to start working So, its not suitable for management of acute anxiety states or panic attacks	- useful in the treatment of generalized anxiety disorders … Has an efficacy comparable to benzo - Mostly used in bridging (for a short period) → Instead of giving benzo for 4 weeks - rarely used alone for a long period - can be used for a long period as a combination with SSRIs - used as an alternative to SSRI to regain sexual functions when lost due to serotonin syndrome. - lacks the muscle relaxant, anti convulsant effect of benzo	- frequency of SE is low → headache, dizziness, nervousness

* Bridging in the usage of SSRI , using benzo & Buspirone



Good luck