بسم الله الرحمن الرحيم

DOPAMINE SCIENTIFIC TEAM

Anxiolytics & Hypnotics (Pt.1)

MID | Lecture 3

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

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Reviewed by: Almothana Khalil

PHARMACOLOGY

رحلة اليقين مع سورة يس

بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ

وَإِن نَّشَأْ نُغْرِقْهُمْ فَلَا صَرِيخَ لَهُمْ وَلَا هُمْ يُنقَذُونَ ﴿٤٣﴾ إِلَّا رَحْمَةً مِّنَّا وَمَتَٰعًا إِلَىٰ حِينٍ ﴿٤٤﴾

فلما خاطبهم الله تعالى بالقرآن، وذكر حالة الفلك، وعلم تعالى أنه سيكون أعظم آيات الفلك في غير وقتهم، وفي غير زمانهم، حين يعلمهم صنعة الفلك البحرية الشراعية منها والنارية، والجوية السابحة في الجو، كالطيور ونحوها، والمراكب البرية مما كانت الآية العظمى فيه لم توجد إلا في الذرية، نبَّه في الكتاب على أعلى نوع من أنواع آياتها فقال: {وَآيَةٌ لَهُمْ أَنَّا حَمَلْنَا ذُرِّيَّتَهُمْ فِي الْفُلْكِ الْمَشْحُونِ} أي: المملوء ركبانا وأمتعة. فحملهم الله تعالى، ونجاهم بالأسباب التي علمهم الله بها، من الغرق، ولهذا نبههم على نعمته عليهم حيث أنجاهم مع قدرته على ذلك، فقال: {وَإِنْ نَشَأْ نُغْرِقْهُمْ فَلَا صَرِيخَ لَهُمْ} أي: لا أحد يصرخ لهم فيعاونهم على الشدة، ولا يزيل عنهم المشقة، {وَلَا هُمْ يُنْقَذُونَ} مما هم فيه.

{إِلَّا رَحْمَةً مِنَّا وَمَتَاعًا إِلَى حِينٍ} حيث لم نغرقهم، لطفا بهم، وتمتيعا لهم إلى حين، لعلهم يرجعون، أو يستدركون ما فرط منهم.

Pre-Studying Notice

- Most of the original content was read by the professor.
- Points that he mentioned either additionally or in other sites than originally in the slides have been added in congenial.
- Some annotations throughout the file are added to indicate the importance of a point.

• دعواتكم

Codeine – Partial agonist of μ-receptors

- Refer to modified 2 – slide *18,* first.
- In addition to what was mentioned, codeine is no longer used for postpartum women due to the risk of respiratory failure in the neonate, where codeine is transferred to the neonate by breast milk.
- The problem in codeine, although being a partial agonist, is that it is transformed into morphine by CYP2D6 enzyme, whose gene is present as more than 2 alleles in around 13.5% of the Jordanian population, making codeine dangerous not because of the drug itself, but due to the morphine metabolite that can depress respiration, especially in neonates.

Tramadol

- Analgesic action mechanism
  - Not fully understood
  - Weak affinity for μ-opioid receptor
  - Inhibition of norepinephrine reuptake

    → α2-adrenoreceptor activation

    → act synergistically with tramadol's opioid receptor activation

    → analgesia
- Advantage
  - Less respiratorpsychomotor recoveryy depression, nausea, vomiting, constipation
  - Rapid
- Moderate pain treatment : as effective as morphine
- Severe pain treatment : less effective than morphine

Tramadol

- Tramadol is a partial agonist for μ-receptors, only a small amount of the drug binds to μ-receptors as it has weak affinity towards the receptor as a drug.
- It also inhibits the reuptake of noradrenaline (norepinephrine), so it increases the amount of free noradrenaline circulating in the brain, improving plasticity.
- It's also an agonist for α-2 receptors (this is considered a controversial statement according to Dr. Malik, but he says it's logical), which leads to a decrease in the sympathetic tone (remember, α2 receptors decrease the sympathetic tone when activated). Since that automatically leads to less stress, we can use it in pain management.
- The exact analgesic mechanism of Tramadol is unclear, but we do know that all of its previous mechanisms are synergistic with each other to produce an analgesic effect.

The Benefits of Tramadol over Morphine

- Although Tramadol is only effective for moderate pain relief, this downside is alleviated by it also not sharing any of the downsides of other, strongly μ-receptor specific drugs, such as constipation, vomiting, and especially addiction.
- So how did people get addicted to Tramadol? People would use a much higher-than-required dose, so even though tramadol is weakly specific for μ-receptors, increasing the dose can get the sought-for effect and thus cause addiction.
- Responsible authorities later recognized tramadol's addiction potential and took action.
- Additional facts the doctor mentioned: (1) Tramadol cannot be used to treat addiction, and (2) it also has an anti-shivering effect.

Anxiolytic and Hypnotic drugs

Anti-stress Sleep-inducing

- **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) .**

Stress Management

- Stress is basically the continuous activation of our sympathetic nervous system, which is controlled by the limbic system, through different neurotransmitters (adrenaline, serotonin).
- We combat stress through exciting sympathetic inhibitors, most importantly GABA. This leads to CNS Depression (which is also the effect of alcoholic drinks, to be expanded upon in another lecture)
- The two main drugs that we will be talking about in this lecture that help with stress are: **Benzodiazepines and Barbiturates.**
- Their mechanism of action is focused on binding to an allosteric site: they bind to the GABA-gated chloride channel, increasing the affinity of GABA towards the receptor, which leads to one of two (very different!) things:

- Barbiturates: Prolong the duration of the opening of the chloride channel
- Benzodiazepines: Increase the frequency of the opening of the chloride channel

- Both drugs lead to increased Chloride permeability, which leads to hyperpolarization, which leads to less rapid firing, which leads to less activation of the sympathetic nervous system. **The end result? Less stress!**

Benzodiazepines

- **Are the most widely used anxiolytic drugs.**
- **have largely replaced barbiturates because they are safer and more effective.**

- **MOA:**

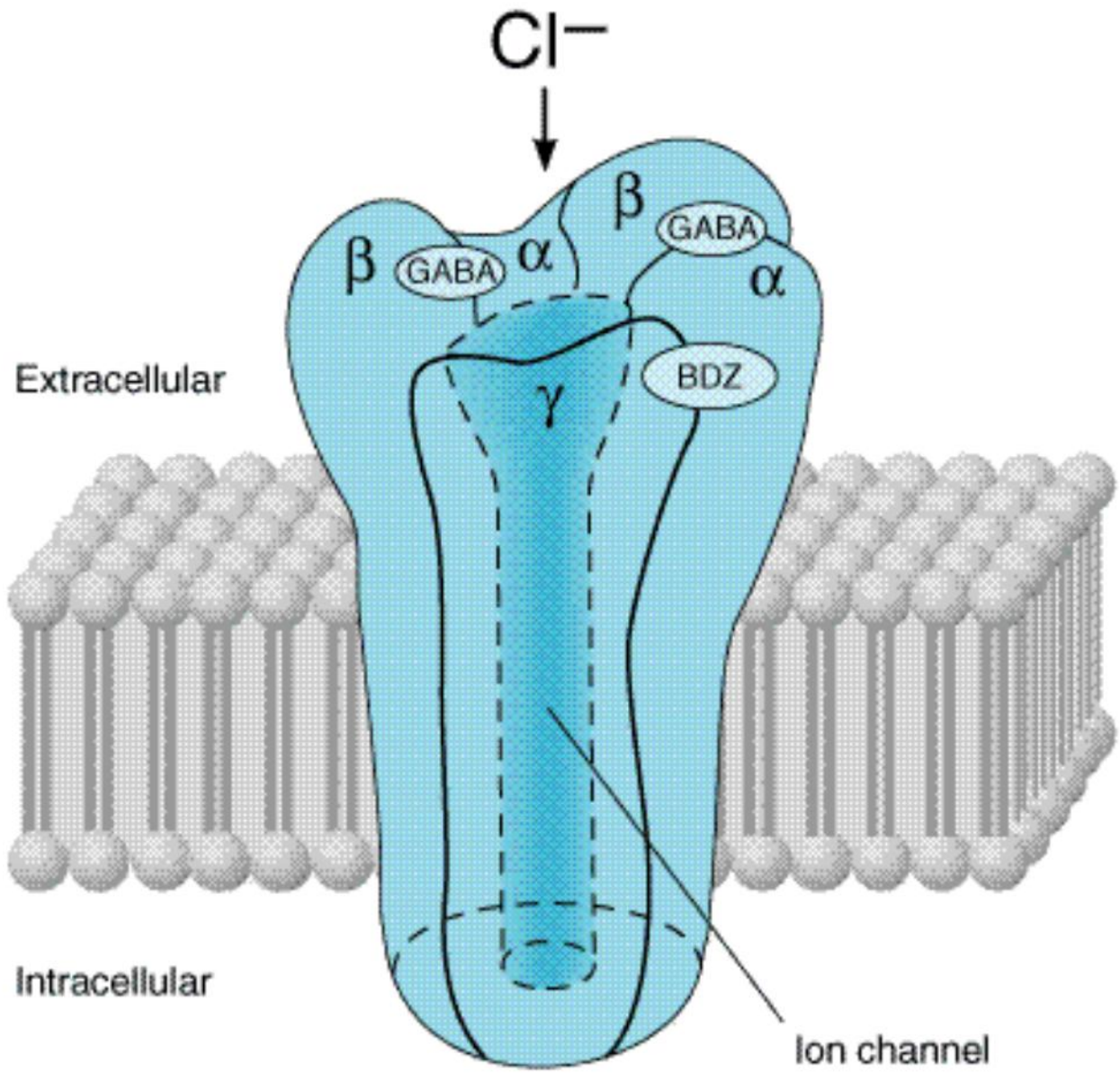
  Benzodiazepines enhances the affinity of GABA receptors for gamm-aminobutyric acid (GABA) receptors.

  GABA is the major inhibitory neurotransmitter in the CNS.

- **Binding of GABA to its receptors triggers the opening of chloride channel, which leads to an increase in the chloride conductance.**

- **The influx of chloride ions causes a small hyperpolarization that moves the postsynaptic potential away from its firing threshold and thus inhibits the formation of action potentials.**

- **Benzodiazepines bind to GABA receptors resulting in a more frequent opening of adjacent chloride channels specific, high affinity sites on the cell membrane, which are separate from but adjacent to the receptor for GABA.**


Cl−
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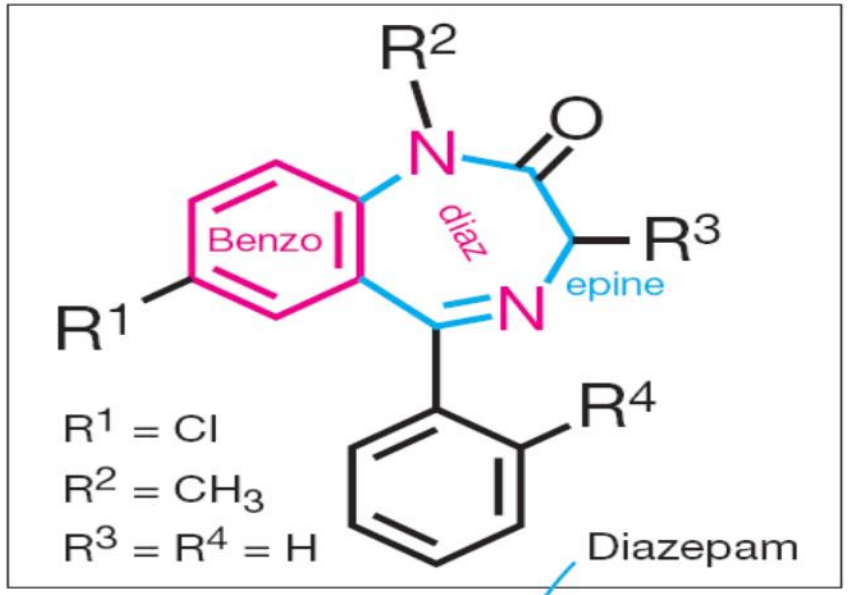
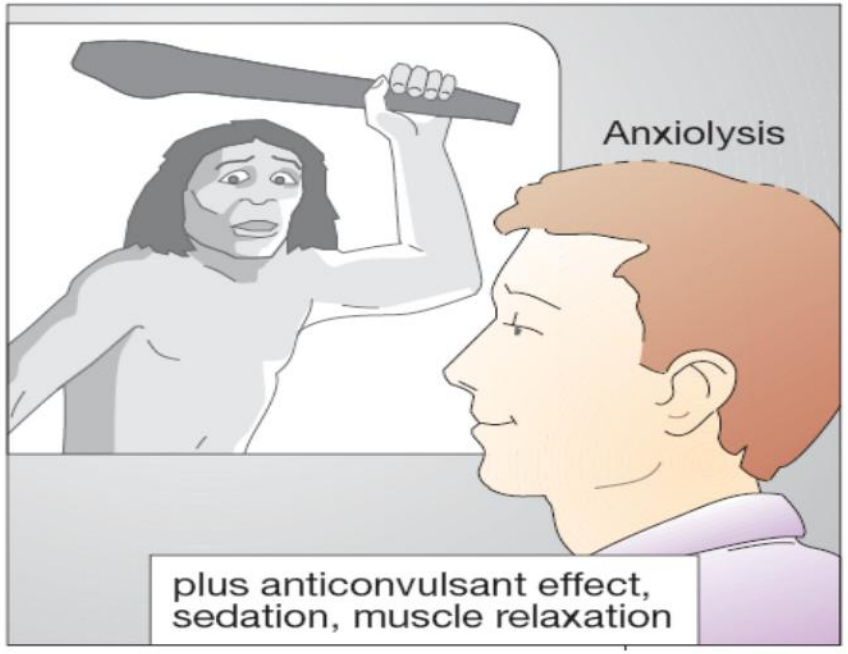
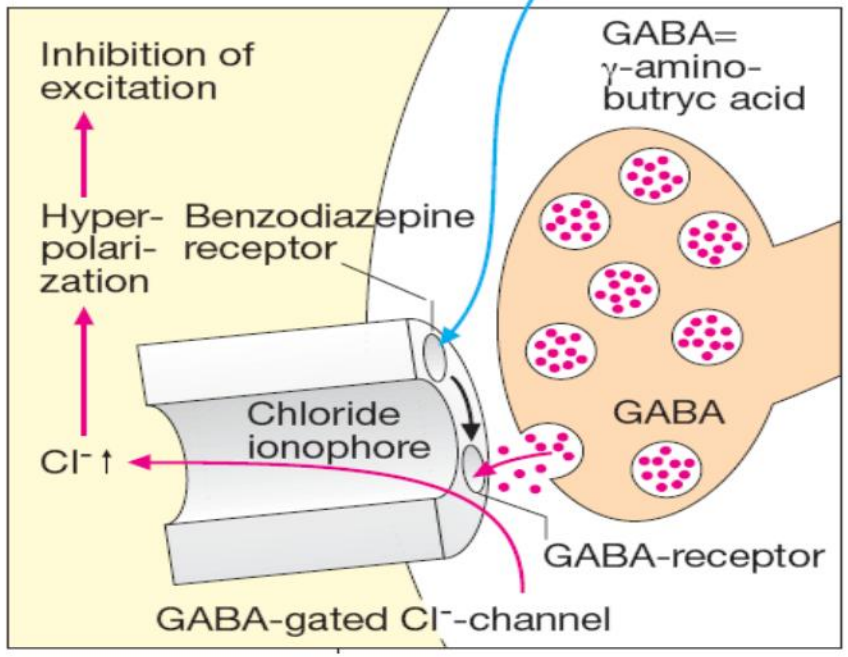






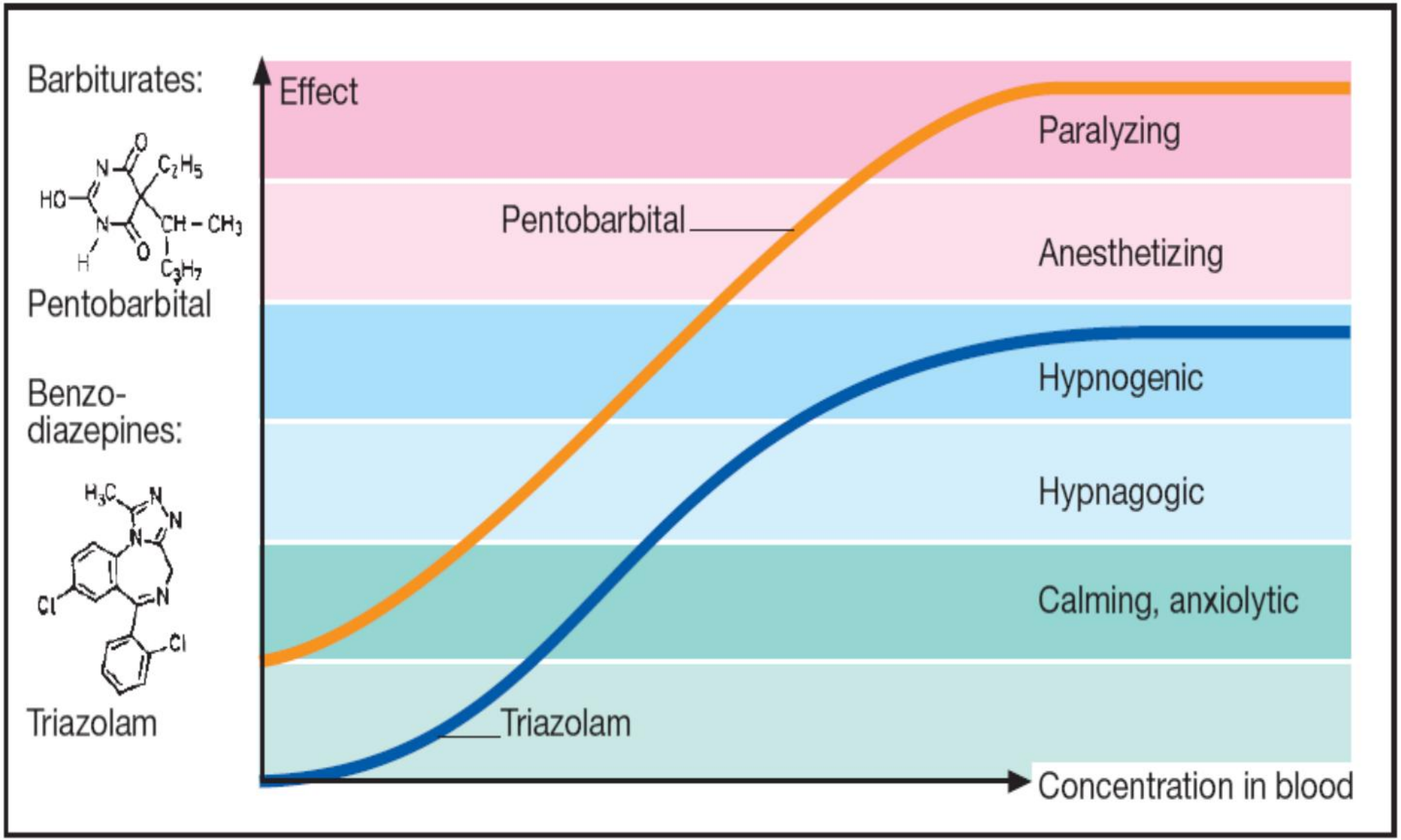
Benzodiazepines vs Barbiturates

- There's three types of barbiturates in markets right now: Pentobarbital, Phenobarbital, and Thiopental
- For Benzodiazepines, there are much more: Lorazepam, Diazepam, Temazepam, Clonazepam, etc.
- The main difference between Benzodiazepines and Barbiturates in terms of their use case is mainly the safety of their use; as you can see in the *graph (next slide),* barbiturates can eventually lead to paralysis and death, which is why they are no longer used. That's one of the reasons they're widely used for suicide; they give a calm and easy death. Additionally, unlike Diazepines, they don't have a "lag-dose" phase (where the dose is ineffective), the starting dose is anxiolytic.

Benzodiazepines are much safer; the different doses go as follows:

- "Lag-dose" (no effect): <1 mg
- Anxiolytic effect: 1 mg
- Hypnogenic: 2 mg or higher (ceiling of benzodiazepine effect)

- Benzodiazepine toxicity is relatively safe due to the ceiling effect, but for barbiturates, it can be lethal.
- Barbiturates are no longer used as anxiolytics/hypnotics, but they have other effects that will be discussed later.



C. Concentration dependence of barbiturate and benzodiazepine effects

Benzodiazepines

- **They do not have analgesic action nor antipsychotic, but they exhibit the following actions:**

A. Reduction of anxiety (anxiolytic), at low doses.

They are useful in treating the anxiety that accompanies some form of depression and schizophrenia.

These agents should not be used to alleviate the normal stress of everyday life, and should be reserved to sever anxiety.

Our sympathetic system is activated daily, so everyday stress is normal.

Should be used for short periods of time because of the addiction potential.

The addiction here starts because of physical dependence (after 2nd or 3rd week of taking the drug, you start to develop tolerance), since benzodiazepines are in a sense agonists for GABA, they affect the limbic system, melatonin, sleep, etc. This means we should taper the drug instead of stopping it abruptly.

If you do stop the medicine abruptly, you will end having withdrawal symptoms that are the same as the problem you were treating initially (extreme stress if you were treating stress, insomnia if you were using the drug to put the patient to sleep), this leads to psychological dependence, which leads to the addiction in the end. This entire process is called “benzodiazepine dependance syndrome” in medicine, which is not due to euphoria.

Side note:
People get addicted to the euphoric effect of benzodiazepines through coupling it with Alcohol

Bridging Therapy for Anxiolysis

- To prevent the occurrence of “benzodiazepine dependence syndrome”, benzodiazepines should not be used more than 2-3 weeks, and serotonin is used instead to induce GABA activity.
- We use SSRIs, or SNRIs, or Buspirone (serotonin receptor agonist; will be discussed in lecture 4B) since they take 4-6 weeks to reach maximum activity.
- We start the patient on benzodiazepines and SSRI together so that when the 2-3 weeks end, SSRI/alternative is already active, and we can stop benzodiazepines.
- So, this is what the treatment plan for a patient with anxiety should look like:
  - Weeks 1-3: Patient takes SSRIs and Benzodiazepines together
  - Week 4: We start cutting off Benzodiazepines through tapering
  - Weeks 5-6: The SSRIs start taking their effect and treating the patient’s anxiety

SSRI: selective serotonin reuptake inhibitor

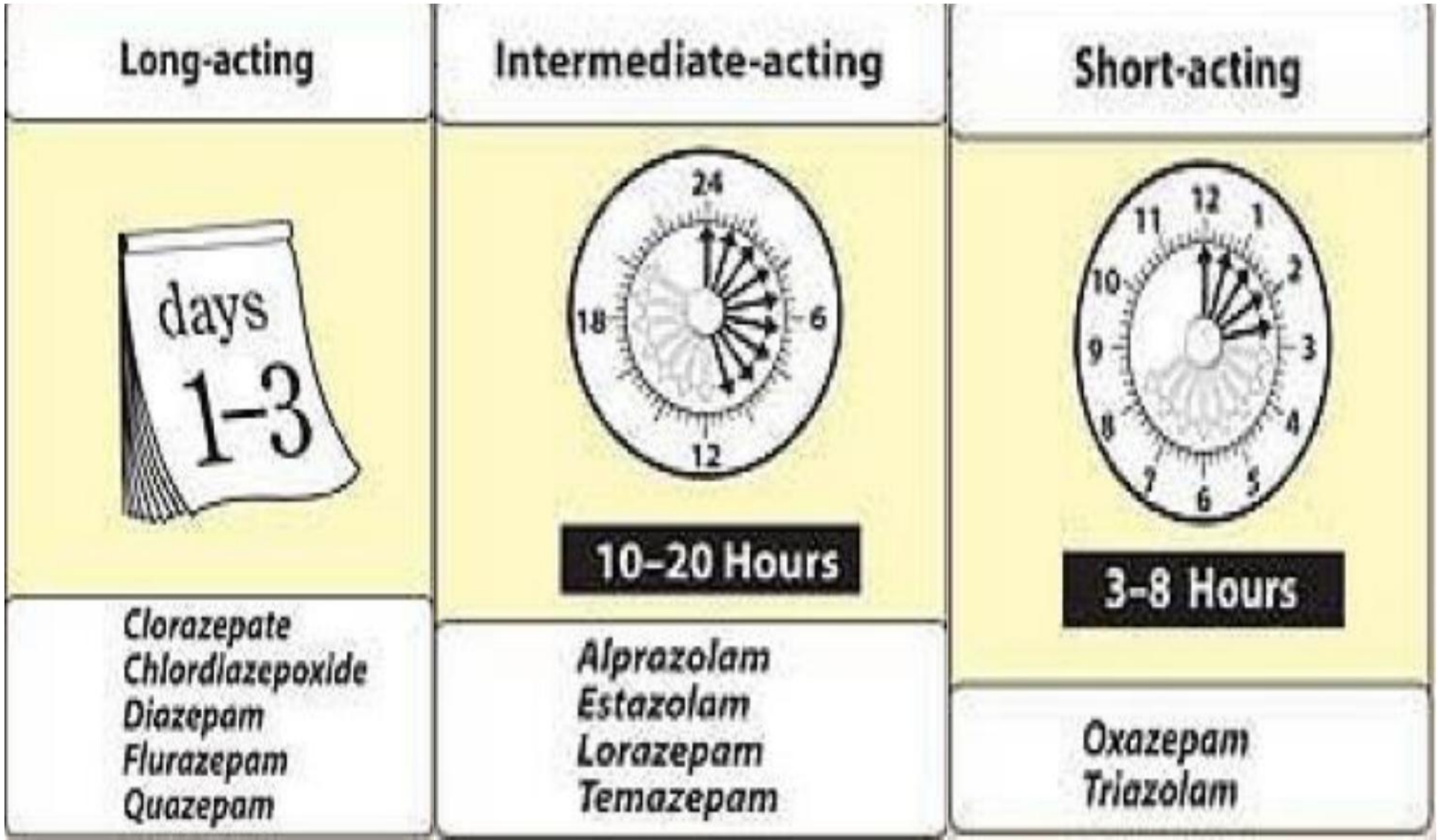
Benzodiazepines

- Physiological and physical dependence can developed if high doses of the drug are given over a prolonged period.
- Sudden withdrawal of benzodiazepines results in withdrawal symptoms, and tension.
- Benzodiazepine withdrawal syndrome is caused by stopping benzodiazepines or during dosage reduction.
- Because of the long half-lives of some of the Benzodiazepine withdrawal symptoms may not occur until a number of days after discontinuation of therapy
- Withdrawal symptoms including confusion, anxiety, agitation, insomnia, and tension.
- Over dose

Flumazenil is the only benzodiazepine receptor antagonist available for clinical use. The drug is available by IV administration only. Onset is rapid but duration is short, with a half-life of about one hour.

COMPARISON OF THE DURATIONS OF ACTION OF THE BENZODIAZEPINES

See next slide



Types of Benzodiazepines – Anxiolytics

- Long-acting (1 day or more): If you are treating chronic stress, you want to use long-acting benzodiazepines, for the same reason we use methadone: less tolerance, less dependance, less peaking, easier tapering. Memorize diazepam & flurazepam.

Other types are more used as hypnotics (discussed in *slide 24*):

- Intermediate-acting (8-12 hours)
- Short-acting (2-3 hours)

- **The longer acting benzodiazepines, such as Diazepam, are preferred with anxiety that may require treatment for prolonged periods of time.**

- **The anti-anxiety effects of the Benzodiazepines is less subject to tolerance than the sedative and hypnotic effects.**

- **Tolerance is decreased responsiveness to repeated doses of drug-occur when used for more than one to two weeks.**

  cross tolerance exists among this group of agents and has been associated with a decrease in GABA receptors density.

IMPORTANT

B. **Muscular relaxant: at high doses relax the spasticity of skeletal muscles probably by increasing presynaptic inhibition in the spinal cord.**

Diazepam is useful in the treating a muscle spasm such as occur in muscle strain, and in treating spasticity from degenerative disorder such as multiple sclerosis.

It can be used in herniated discs to relief the stress on nerves.

C. Sedative and hypnotic: all Benzodiazepines used to treat anxiety have some sedative properties and some can produce hypnosis. However, not all are useful as hypnotic agents.

It is important to balance the sedative effect needed at bedtime with the residual sedation (hangover) on awakening.

The three most commonly prescribed for sleep disorder are long-acting Flurazepam, intermediate-acting Temazepam, and short-acting Triazolam.

hypnotics should be given for only a limited time, usually less than 2 to 4 weeks.

Types of Benzodiazepines – Hypnotics

- Long-acting: For patients with irregular sleep, who wake up intermittently, we use long-acting benzodiazepines, such as **diazepam**.
- Intermediate-acting: For patients who sleep for a short period than wake up, we use **intermediate-acting** benzodiazepines.
- Short-acting (2-3 hours): For patients with regular sleeping patterns but who suffer in initiation of sleep, short-acting benzodiazepines such as **triazolam** are sufficient.

❖ Hangover is a problem, which is residual activity of hypnotics in daytime, especially after using long-acting benzodiazepines. This can be very annoying, so hypnotics must not be used unless truly necessary.

❖ This is why identifying the underlying cause of insomnia is essential, especially in long-term insomnia (>2 weeks), since prolonged use of hypnotics is devastating.

D. **Anticonvulsant: several Benzodiazepines have anticonvulsant activity and used to treat epilepsy and other seizure disorder.**

Antiepileptics will be discussed in detail; here we mean one case: **status epilepticus.**

Clonazepam is useful chronic treatment of epilepsy, whereas diazepam is the drug of choice in terminating grand-mal epileptic seizers. Either IV or as a suppository (PR)

Both drugs can be used, but diazepam is more common in acute episodes.

E. **Anterograde amnesia: Benzodiazepines does produce temporary impairment of memory.**

The short –acting agents are employed in premedication for endoscopic and bronchoscopic procedures such as angioplasty.

PK criteria

Long-acting compounds (e.g. flurazepam) may ensure that a patient will sleep through the night, they also may cause cumulative effects resulting in daytime sluggishness or drug hangover

Short-acting compounds (e.g. triazolam) avoid the hangover problem, but their use may be associated with early awakening and an increase in daytime anxiety

The professor skipped this

LONG-TERM INSOMNIA

Nonpharmacological treatments are important for all patients with long-term insomnia.These include

- Reduced caffeine intake
- Avoidance of alcohol
- Adequate exercise
- Relaxation training
- Behavioral-modification approaches, such as sleep-restriction and stimulus-control therapies.
- Nonpharmacological treatments for insomnia have been found to be particularly effective in reducing sleep-onset latency and time awake after sleep onset.

Benzodiazepines

- **Adverse effect:**

  (1) Drowsiness and confusion: the two most common side effects.

IMPORTANT **(2) Ataxia occurs at high doses and precludes activities that require fine motor coordination.**

IMPORTANT **(3) Cognitive impairment, can occur .**

(4) Triazolam often shows rapid development of tolerance, early morning insomnia, daytime anxiety.

- **Interaction and precautions:**

  (1) Used cautiously in treating patient with liver diseases.

  (2) Should be avoid with acute narrow angle glaucoma.

  (3) Alcohol and other CNS depressant enhance the sedative-hypnotic effect.

The professor skipped this

Features of withdrawal and dependence vary. Commonly there is a kind of **psychological dependence** based on the fact that the treatment works to reduce patients' anxiety or sleep disturbance and therefore they are unwilling to stop. If they do stop, there can be relapse, where original symptoms return.

Withdrawal of BDZs should be gradual after as little as 3 weeks' use but for long-term users it should be very slow, e.g. about 6–12 weeks. Withdrawal should be slowed if marked symptoms occur and it may be useful to substitute a long $t_{1/2}$ drug (e.g. diazepam) to minimize rapid fluctuations in plasma concentrations. **In difficult cases withdrawal may be assisted by concomitant use of an antidepressant.**

The professor skipped this

Sedative/Hypnotics

All of the anxiolytics/sedative/hypnotics should be used only for symptomatic relief.

****

All the drugs used alter the normal sleep cycle and should be administered only for days or weeks, never for months.

****

USE FOR

SHORT-TERM TREATMENT

ONLY!!

PHARMACOLOGY QUIZ LECTURE 3

رسالة من الفريق العلمي

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Corrections from previous versions:

Versions	# and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			