

CNS

Doctor 2021



Pharmacology Sheet (4)

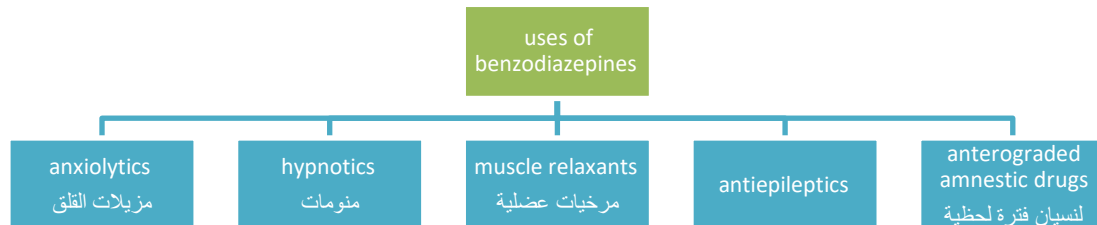
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(اللهم علمني ما ينفعني و انفعني بما علمتني و زدني علمًا، ربِّ اشرح لي صدري و يسر لي أمري و احل عقدة من لساني يفقهوا قولي)

الدكتور مالك بحكيكم اربطوا الأحزمة في عدد لا بأس به من الأدوية بس الأمور سهلة بإذن الله...بسم الله نبدأ
In this lecture we will discuss 5 uses of benzodiazepine:



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.

Severe 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) .

BENZODIAZEPINES

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

So these drugs will relieve stress, what types of stress are we're talking about? actually its long term , chronic , schizophrenic , depression , post traumatic and idiopathic stress

What about everyday stress ? you have to competent with it

(يَا أَيُّهَا الَّذِينَ آمَنُوا اصْبِرُوا وَصَابِرُوا وَرَابِطُوا وَاتَّقُوا اللَّهَ لَعَلَّكُمْ تُفْلِحُونَ)

COMPARISON OF THE DURATIONS OF ACTION OF THE BENZODIAZEPINES

Long acting	Intermediate acting	Short acting	Ultra-short acting
1-3 days diazepam	10-20 hrs Lorazepam	3-8 hrs Triazolam	1-3 hrs Remimazolam (new very important drug)
flurazepam	Alprazolam	Oxazepam	
Clorazepate	Bromazepam		
Chlordiazepoxide	Estazolam		
Quazepam	Temazepam		

Memorize the highlighted ones 😊

The difference between them is in pharmacokinetics , and clinical uses. DOA here isn't accurate because this family is lipophilic so we have what's called redistribution of drug .

From google : redistribution refers to the change in the plasma drug concentration which is significant enough to cause alteration/termination of drug action.

As the doctor said what happens here that the drug will be absorbed very fast and distributed through blood to the brain after certain period of time it will be redistributed to adipose tissue 😊

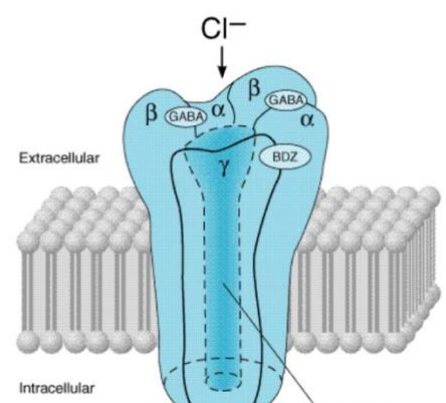
الدكتور حكى هاد المثال من الإعجاز النبوي للي بحب يرجع يسمعه بالمحاضرة :
شفاء عرق النساء ألية شاة أعرابية تذاب ثم تجزأ ثلاثة أجزاء ثم يشرب على الريق في كل يوم جزء
صحيح ابن ماجه : المصدر | الألباني : المحدث | أنس بن مالك : الراوي
صحيح : خلاصة حكم المحدث | 2805 : الصفحة أو الرقم

MECHANISM OF ACTION(MOA):

Benzodiazepines enhances the affinity of GABA receptors for gamma-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.

Now let's discuss each use :

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

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

In this case we give the long acting for less than 3 weeks , they target the limbic system due to their high affinity to **alpha 2** subunit.

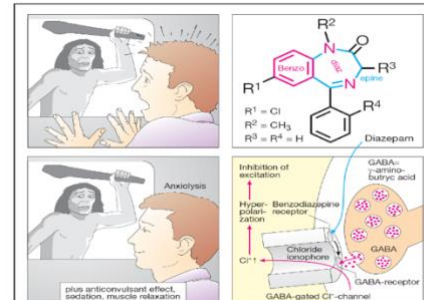
They are useful in treating the anxiety that accompanies some form of depression and schizophrenia.

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

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

Actually after 3 weeks of taking these drugs the GABA receptors will be desensitized/ downregulated , so if you suddenly stop them the ptn will suffer from rebound anxiety , the ptn will conclude that he cant live without the drug anymore (psychological dependance), you will try to do tapering but the ptn isn't honest with you he's taking the drug anyway because of dependance.

The doctor said it's a global big issue called "Benzodiazepine dependence syndrome".



- The longer acting benzodiazepines (less tolerance , dependance and addiction) , 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.



Don't use them more than 3 weeks!

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

Someone will say why do we still use them ? why just we use SSRIs ?

Actually we have to do what's called " bridging therapy " , the idea is that SSRIs need around 6 weeks to start acting on the ptn , so we start a long acting benzodiazepine and buspirone until they work.

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

Over inhibition of limbic system , decreases motor signals going out of the CNS which decreases the muscle conductivity .

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.

Nowadays Its not used in this case that much, but its beneficial in certain cases of disc, when a muscle is pressing on nerve .
الدكتور حكي ما تستخدموه هون خوفًا من ادمان .
المرضى الي بالغالب بكونوا كبار سن و بصير بدهم الدوا عشان ما يعملوا عمليات.

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.

All hypnotics are anxiolytics but not all anxiolytics are hypnotics .

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

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

It depends on the case :

Induction of sleep —————> Triazolam. المريض مش قادر ينام لحاله يعني بس بده يدخل المرحلة الأولى من النوم و بعدين بكمل طبيعي

Interrupted sleep —————> lorazepam or bromazepam و المريض بنام ساعة و بصحى و بعدين ساعتين و بصحى و هكذا

Short duration sleep —————> Flurazepam ٤ ساعات المريض بنام عادي بس بصحى بعد ٤ ساعات يعني نومته اقصر من الحد الطبيعي

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

Again the zepams with high affinity to **alpha1** subunit are the ones which used as hypnotics .

The ones that works on **alpha2** will inhibit the limbic system according the dose but this wont lead to sleep , because sleep is related to melatonin which affect on GABA and go in pathways leading to sleep.

يعني ببساطة الادوية تبعت القلق الي بتشتغل على **ألفا ٢** لو تضل تزيد الجرعة ما رح تنام رح تهدى كثير بس ما رح تنام ، لازم يكون الدوا عنده قوة ارتباط عالية **بألفا ١** عشان يخليك تنام ...طيب مين هدول ؟ الي هم ال ٤ الي فوق 😊

CATEGORIES OF INSOMNIA

Not required

😊 للإطلاع فقط بس عشان يكون عندك فكرة إنه النوم عبارة عن مشكلة كبيرة بالمجتمعات الأخرى بس عنا عاد الكل بنام كويس

Transient insomnia	Short-term insomnia	Long-term insomnia
<ul style="list-style-type: none"> •Lasts <3 days •---Caused by a brief environmental or situational stressor. •---Respond to attention to sleep hygiene rules. •--- Hypnotics should be used at the lowest dose and for only 2-3 nights. 	<ul style="list-style-type: none"> •3 days to 3 weeks •--- Caused by a personal stressor such as illness, grief, or job problems. •---Sleep hygiene education is the first step. •---Hypnotics may be used adjunctively for 7-10 nights. •---- Hypnotics are best used intermittently during this time, with the patient skipping a dose after 1-2 nights of good sleep. 	<ul style="list-style-type: none"> •lasted for >3 weeks •---No specific stressor may be identifiable. •---A more complete medical evaluation is necessary in these patients, but most do not need an all-night sleep study.

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

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.

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

Clonazepam is useful chronic treatment of epilepsy (not for grand-mal now we have lamotrigine ,phenytoin, and carbamazepine) , whereas diazepam is the drug of choice in terminating grand-mal epileptic seizures.

Okay here we have 2 cases :

- 1) In case of seizure within a 5 minutes period, without returning to a normal level of consciousness between episodes that is called **status epilepticus**, we give IM or IV injection of diazepam.
- 2) In case of **febrile seizures** in babies we gave diazepam rectally , its not preferred due to its effect on brain.

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.

Here we gave high dose of triazolam that cause very high cns depression and affect the memory, I want the ptn to forget certain period of time (بعمله عملية)
و هو صاحي بدي إياه ينسى هاد الموقف

Students who use these drugs before exams will forget what they studied 😊

"تفقهوا قبل أن تسودوا"
"أخشوشنوا فإنَّ النعم لا تدوم"

BENZODIAZEPINES

- **Adverse effect:**

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

- (2) Ataxia occurs at high doses and precludes activities that require fine motor coordination. (you test it by drawing a line and ask the ptn to walk on it)

- (3) Cognitive impairment, can occur . (that's why we don't use them with children except in two situations : febrile seizures , and those who have dental phobia and I want them to forget the dental procedure)

Because of the 3 effects above the ptn shouldn't drive after taking these medications , because when you drive you need fine motor movement.

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

- **Interaction and precautions:**

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

- (2) Should be avoided with acute narrow angle glaucoma.

- (3) Alcohol and other CNS depressants enhance the sedative-hypnotic effect. (administration of alcohol with one of these drugs "bromazepam ,lorazepam ,diazepam" will cause euphoria that's why you may have person presented in the ER with bradycardia, or hypotension , or respiratory arrest due to overdose with one of these drugs, we differentiate between it and opioids by pinpoint pupil phenomenon)

- **antidote: Flumazenil**

BENZODIAZEPINES

- Physiological and physical dependence can develop if high doses of the drug are given over a prolonged period.

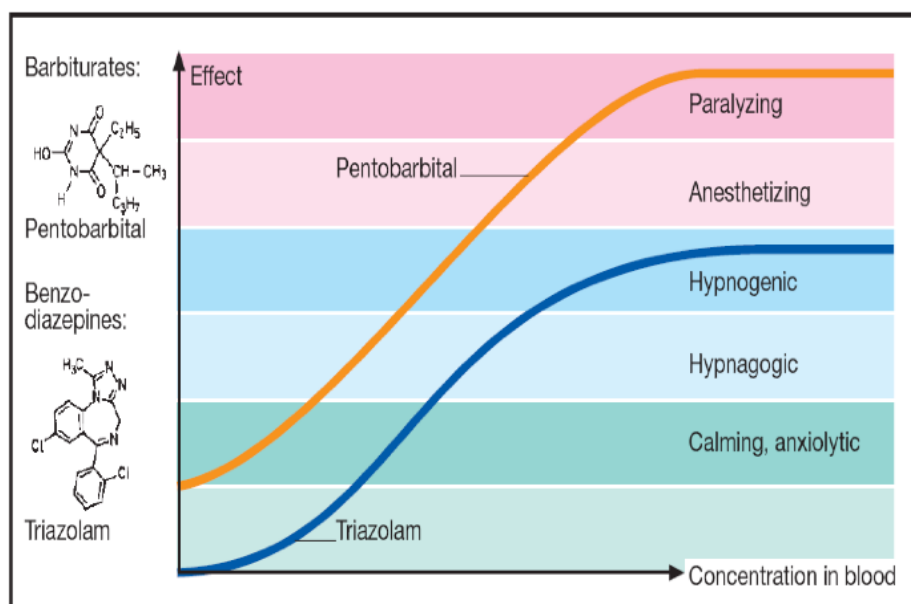
- Sudden withdrawal of benzodiazepines results in withdrawal symptoms, and tension.

- 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.

BUSPIRONE

- Is useful in treatment of generalized anxiety disorders, and has efficacy comparable to benzodiazepines.
- Its action is mainly mediated by serotonin (5HT) receptors (2 weeks to start working).
- The anxiolytic effects of buspirone may take more than a week to become established, making the drug unsuitable for management of acute anxiety states (not very effective in panic disorders).
- buspirone lacks anticonvulsant and muscle-relaxant properties of the benzodiazepines and causes only minimal sedation.
- The frequency of adverse effects is low, the most common effects being headaches, dizziness, nervousness.



C. Concentration dependence of barbiturate and benzodiazepine effects

Good luck 

(إِنَّ الْإِنْسَانَ خُلِقَ هَلُوعًا * إِذَا مَسَّهُ الشَّرُّ جَزُوعًا * وَإِذَا مَسَّهُ الْخَيْرُ مَنُوعًا * إِلَّا الْمُصَلِّينَ)

لا تنسوننا و المسلمين من صالح دعواتكم

وفقنا الله و إياكم لما يحب و يرضى

V2

Alpha 2 for anxiolytics , alpha 1 for hypnotics
الدكتور حكي اعكسوهم Changes in colors