Dr. Malek Zihlif

CNS - Pharmacology

lecture 3 - Click here to watch the lecture we used to write this!

Slide's info are in BLACK

Edits are in RED

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Peripherally Acting Opioid

- Opioid receptor – outside central nerve system
  - Peripherally acting opioid agonist

    → analgesia without CNS side effect
- Loperamide
  - μ-opioid receptor agonist
  - Does NOT cross blood-brain barrier *extra*; this fact can be abused by taking very large doses!
  - Treatment : inflammation-induced hyperalgesia (As this pain type usually relieved by NSAID's, Loperamide is only used for diarrhea)
  - Relieve diarrhea

Anxiolytic - مهدئ and Hypnotic - منوّم drugs

In this section, we're still trying to depress the CNS but now for different reasons and not analgesia.

- **Anxiety is unpleasant state of tension and fear that seems to arise from unknown source. Sympathetic over activity (*without a known cause)·***

- **The symptoms of severe anxiety are similar to those of fear (such as tachycardia, palpitation, insomnia, restlessness, nervousness ..) and involve sympathetic activation.**

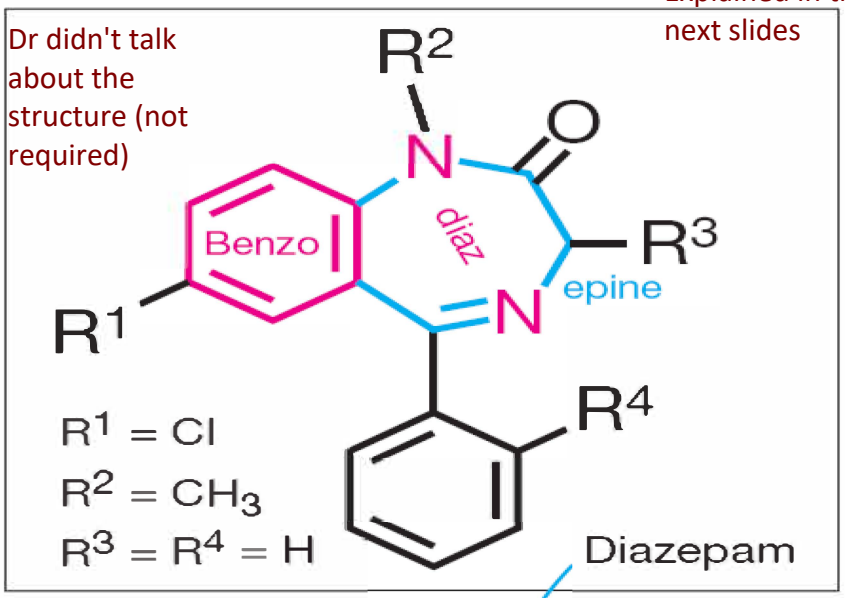
- **Severe anxiety may be treated with anti-anxiety drugs and/or some form of behavioral and psychotherapy.**

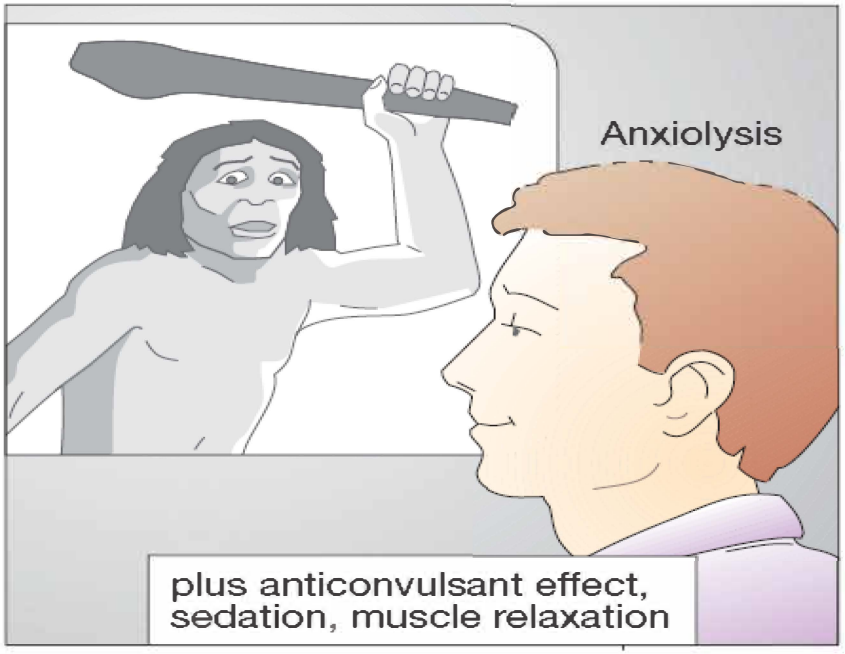
- **Because all of the anti-anxiety drugs also cause sedation (At low doses) and hypnotic (sleep-inducing)(At high doses), the same drugs often function clinically as both anxiolytic and hypnotic.**

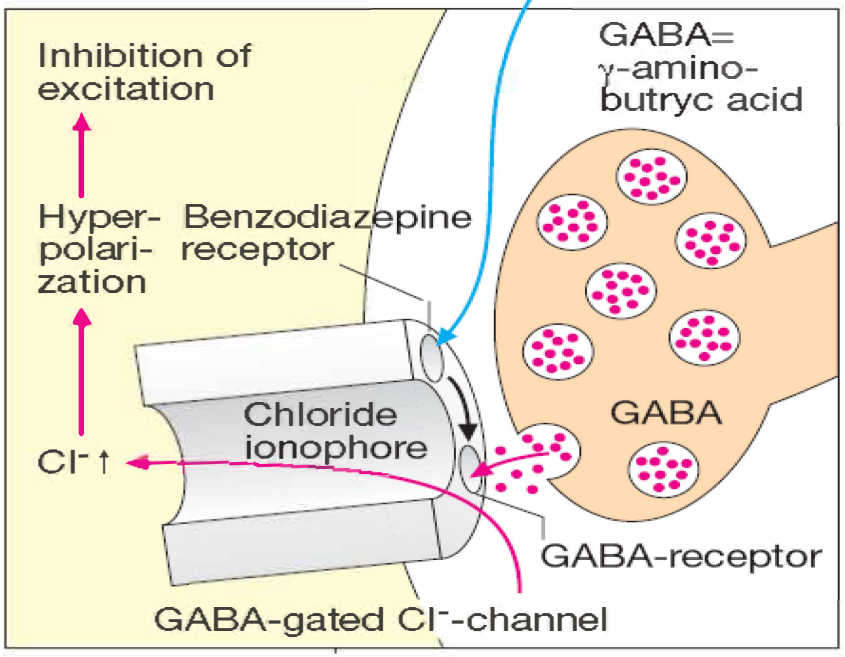
- **Please note that the anxiety we're talking about and trying to treat is IDIOPATHIC! These drugs shouldn't be taken for what we call "Everyday-stress" causes such as a hard exam or any other cause that we might face in our everyday life, even if that stress was for something that's worth stressing over or a major situation you're in! (Because they're addictive)**

Explained in the next slides

Dr didn't talk about the structure (not required)



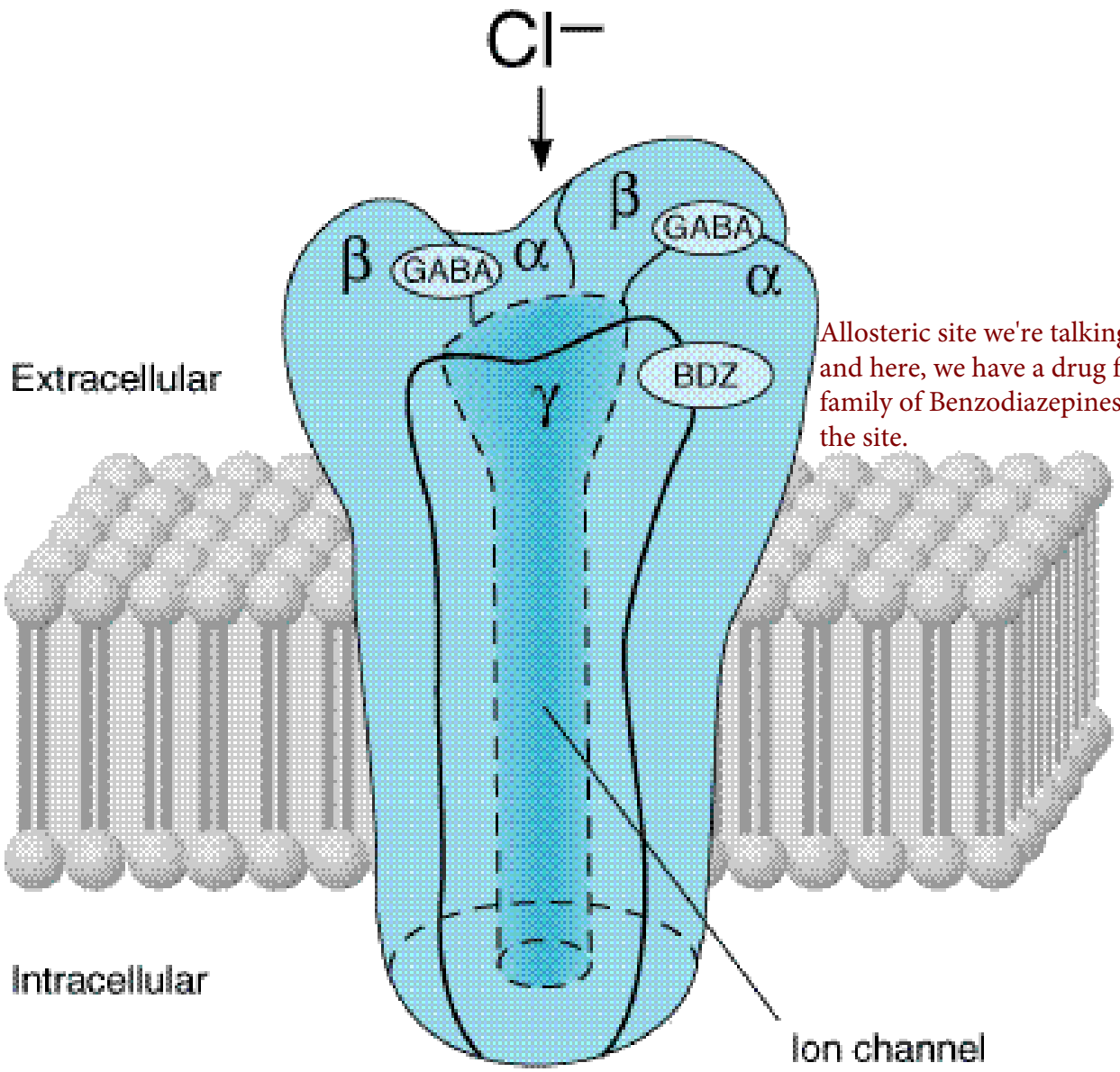




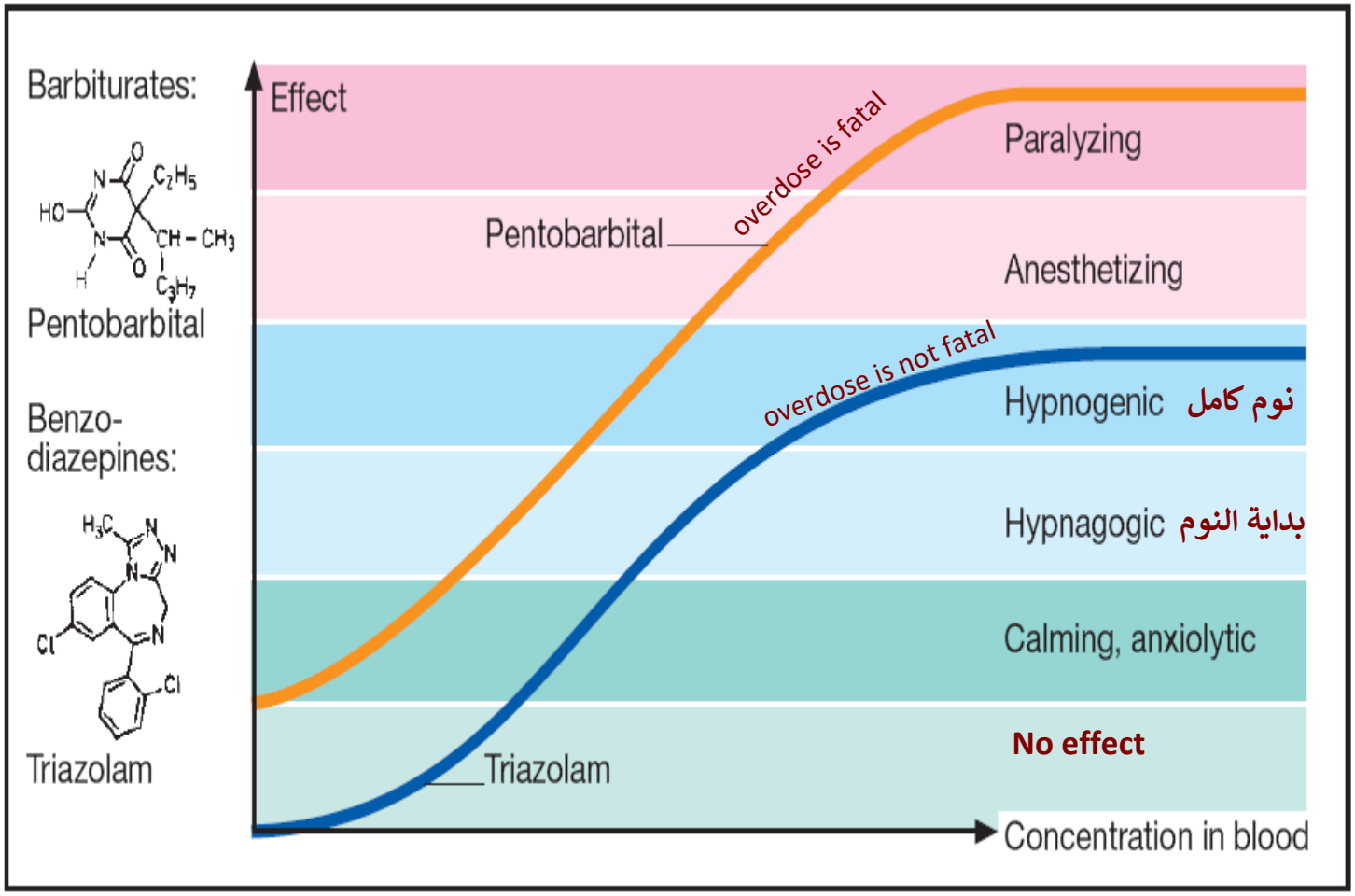
GABA = gamma amino butryc acid (The main inhibitory neurotransmitter in the CNS), binds to "GABA-Gated Chloride channel" and as the name implies, this binding will cause chloride ions to enter the neuron causing it to hyper-polarize thus inhibition of excitation.

On that same "GABA-Gated chloride channel", there's an allosteric binding site, agonistic binding of this site strengthens the binding of GABA on its receptor on the same channel causing 2 things:
1) Increased frequency of opening for that channel
2) Increased time in the opened state
Both of these will cause more chloride exiting, more hyper-polarization and at the end more inhibition of excitement.
This inhibition of excitement is the cause of "Anxiolysis", and at further levels (with increased dosage) is hypnagogic, and then hypnogenic ..

This is the target of the drugs we're talking about today; Benzodiazepines and Barbiturates.



Allosteric site we're talking about; and here, we have a drug from the family of Benzodiazepines bound to the site.



C. Concentration dependence of barbiturate and benzodiazepine effects

Pentobarbital is a Barbiturate.

Triazolam is a benzodiazepine.

In case of benzodiazepines, an overdose will cause your patient to become fearless (The effect now is the removal of any inhibitory activity in the CNS; (The Inhibitory activity we are talking about is what prevents us from doing an action by thinking of the consequences of doing it!)) IMPORTANT:

Overdose of Barbiturates will kill you - suicide
Overdose of Benzodiazepines won't kill and will cause the state called - محبجب (ماخذ 8-12 حبة)

Note how benzodiazepines can't give an effect beyond sleep, does that mean that it's safe? NO and we'll talk about its adverse effect later. Barbiturates on the other hand are more potent as it causes calming effect on the smallest of doses, to as far as paralysis on large doses; which means that an over dose of a barbiturate will KILL your patient! In fact its used in a lot of suicide cases that we even stopped using most of them these days.

Extra; the drugs that are still used in these days:

Phenobarbital is an anti-epilyptic drug used for children

Thiopental is a short-acting barbiturate for the induction of anesthesia.

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.**

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 forms of depression (Accompanied with irritability and anxiety) and schizophrenia (with the positive episodes).

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

severe anxiety might present as panic attacks or constant state of anger, constant palpitation, sweating.. (again, without a known cause).

Should be used for short periods of time because of the addiction potential. This is a different form of addiction, this is NOT related to Euphoria and rather to something called "Tranquilizing effect" - (calm and in a stable mood)

That's how people who take this for everyday stress like exams get addicted too

- **The longer acting benzodiazepines, such as Diazepam -aka- Valium, are preferred with anxiety that may require treatment for prolonged periods of time such as psychosis or depression. (As we said from the previous lecture -methadone for example- the longer the action the less withdrawal symptoms and the less tolerance occurs.**

- **The anti-anxiety effects of the Benzodiazepine is less subject to tolerance than the sedative and hypnotic effects. Because for anti-anxiety we use small doses (which makes it less viable to tolerance -the lower the dose the less the tolerance-)**

- **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.

COMPARISON OF THE DURATIONS OF ACTION OF THE BENZODIAZEPINES

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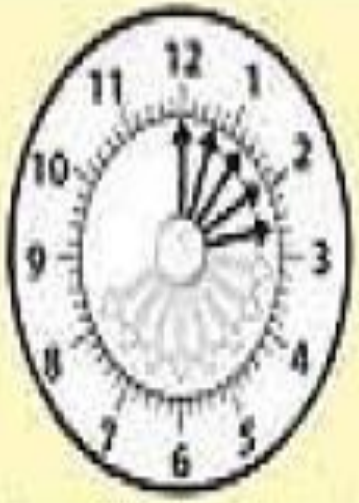
Long-acting	Intermediate-acting	Short-acting
	 **10–20 Hours**	 **3–8 Hours**
Clorazepate *Chlordiazepoxide* *Diazepam* *Flurazepam* *Quazepam*	*Alprazolam* *Estazolam* *Lorazepam* *Temazepam*	*Oxazepam* *Triazolam*

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.

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.

The idea here is "Potency", with increased dosage all of them will eventually cause hypnosis! BUT we cannot always give larger doses in the same tablet.

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

Hangover: is a state of headache similar to that of alcohol, these people can't perform fine motor movements (They shouldn't drive early in the morning if they're feeling this Hangover effect).

this is achieved by understanding the pharmacokinetics of the drug you're dealing with which will help us in dealing with its adverse reactions! (we'll focus on this in the upcoming slides).

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.

PK criteria PK stands for pharmacokinetics

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
Such case of benzodiazepines can be used for a patient that can fall asleep but keeps on waking up quickly without getting enough sleep, so we need to give him a drug that covers the whole period of sleep.

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
Such case of benzodiazepines can be used for a patient that cannot fall asleep but once they eventually do, they can sleep for 6-7 hours just fine. (Intermediate-acting drugs also cause no hangover just like short-acting)

So why don't we always give such drugs? Because of tolerance, what made your patient sleep today (the dose of it), won't make him sleep in the next week etc..)

CATEGORIES OF INSOMNIA

This is pharmacotherapy **(NOT REQUIRED)**

Transient insomnia	Short-term insomnia	Long-term insomnia
•Lasts <3 days •---Caused by a brief environmental or situational stressor. •---Respond to attention to sleep hygiene rules. Clean your bed, drink some milk, relax, دعاء النوم (YES ALL OF THIS HELPS) But if this didn't help, we give the following below •--- Hypnotics should be used at the lowest dose and for only 2-3 nights.	**•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 used for a maximum of 10 days •---- Hypnotics are best used intermittently during this time, with the patient skipping a dose after 1-2 nights of good sleep. tolerance prevention	**•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. We can't recommend these drugs for longer than 2 weeks, and a patient with such insomnia will need it for even more time.

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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, whereas diazepam is the drug of choice in terminating grand-mal epileptic seizers.

E. **Anterograde amnesia: Benzodiazepines does produce temporary impairment of memory. while under the effect, the patient will not remember what is happening around.**

This is very important for us, as we don't want a patient to remember things during procedure which might cause "Post traumatic depression"

The short –acting agents are employed in premedication for endoscopic and bronchoscopic procedures such as angioplasty and some dental procedures (especially when the patient is "dentophobic")

Benzodiazepines

- **Adverse effect:** That's why we don't use them except than when we need them

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

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

  (3) Cognitive impairment, can occur .

  (4) Triazolam often shows rapid development of tolerance, early morning insomnia, daytime anxiety. (Discussed in the next lecture)

- **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.