CNS
Doctor 2021

Pharmacology

Modified (3)

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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 (Tramal)

- Widely used, but its usage is restricted due to addiction.
- It decreases the amount of norepinephrine, similar to clonidine, which is also used in pain management and is related to the cardiovascular system.
- Tramadol is not a pure receptor agonist; instead, it acts as a partial agonist with different mechanisms of action. It interferes with norepinephrine release and is associated with the NMDA receptors, which are involved in substance P. Therefore, Tramadol exhibits **mixed actions**, which is why it is used in clinic for various types of pain that may not respond to opioids.
- Tramal or Tramadol has multiple mechanisms of action (MOA).
- It somehow decreases the sympathetic system, which is associated with neurological pain.
- Not all opioids are effective for neurological pain. In cases where neurological pain does not respond to opioids, partial agonists like Tramal are used.
- It’s effective in treating the moderate pain.

Naloxone

Naloxone is a general antidote for opioids. Its half-life is approximately one hour, whereas morphine has a half-life of around four hours. When dealing with a patient with opioid toxicity, who has used opioids like heroin or oxycodone, or any opioid-like drug except for fentanyl (which has a half-life of 30 minutes or less), the drug will still occupy the receptors even after naloxone administration.

To counteract this, we may administer antagonist drugs that target the **μ-opioid receptors**. Additionally, placing the patient on a **mechanical ventilator** may be necessary.
Such a patient, who lacks tolerance, dependence, or addiction, is referred to as a **naive patient.** To ensure optimal half-life, naloxone may need to be administered multiple times in order to have parallel effect of the opioid's half-life.

- The management of opioid toxicity is of utmost importance.

Management of addicted patient (Toxicology) - Not required !

In the case of addicted patients, their opioid receptors are down-regulated due to chronic drug use. Consequently, if they experience an overdose, there is a significant amount of opioids circulating in their system.
When an addicted patient exhibits signs of respiratory depression, administering naloxone is contraindicated. This is because the quantity of available receptors is already low, and these receptors are inhibitory in nature. If all remaining receptors are blocked by naloxone, the patient may become comatose.

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

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) .**

Anxiolytic drugs are the first drugs prescribed in different doses between males and females, other than hormone-based, they are known as **gender prescriptions**. This is because stress levels can vary between men and women.

Please understand that when we mention stress in the context of treatment, we are specifically referring to **chronic stress/ idiopathic**. Chronic stress is caused by problems in the limbic system, which is a part of our brain. It is important to differentiate this type of stress from everyday stressors like difficult exams or other common challenges we experience in our daily lives.. Stress is regulated by two key factors: GABA and Serotonin. These neurotransmitters play a role in controlling the sympathetic tone through the limbic system. Stress occurs when the levels of GABA or serotonin decrease. Consequently, stress is treated using the following approaches:

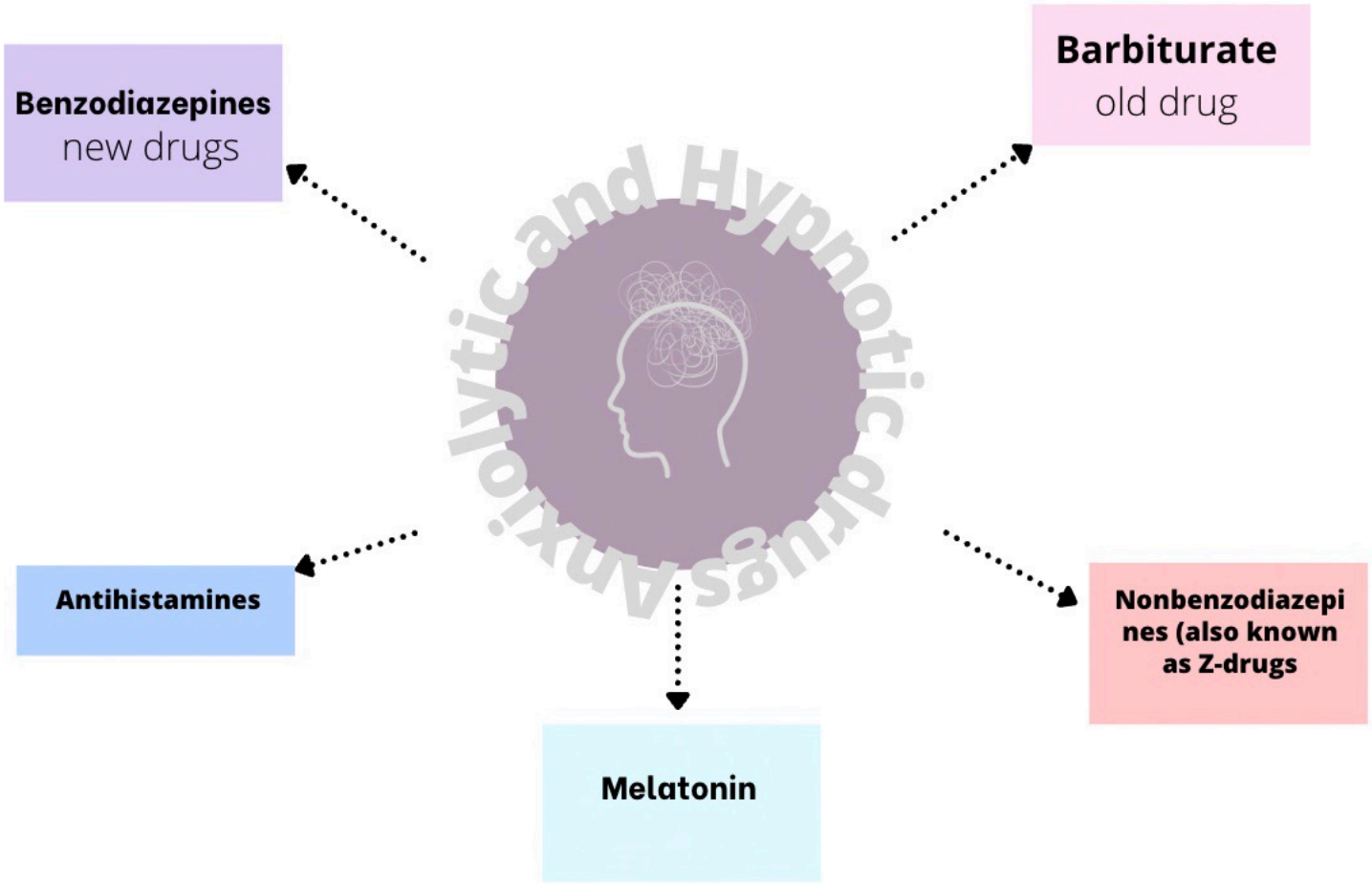
1. Benzodiazepines→ GABA receptors activators.
2. SSRI (Selective Serotonin Reuptake Inhibitors)→ increasing serotonin levels in the brain or activating 5-HTA receptors can effectively reduce stress.

Relationship between Anxiety and insomnia

After the anxiolytic effect, there is a hypnotic effect, which is achieved through an inhibitory mechanism in the body. Previously, it was believed that all anxiolytic agents also had hypnotic properties. However, this is not entirely true, as insomnia is achieved through a different mechanism related to **Melatonin** secretion. Melatonin plays a role in sleep and arousal regulation. It activates GABA receptors and affects sleep, promoting sleep enhancement and inhibiting wakefulness. That's why we turn off lights when we want to sleep, as it stimulates the release of melatonin.
Melatonin enhances GABA release in a specific area that is distinct from the one responsible for anxiety. However, both anxiety and insomnia share a common pathway involving GABA release.

- this is called **tissue specific receptor activity** refers to the phenomenon when the same agent (such as GABA) produces different effects depending on the specific tissue or organ it acts upon.

Anxiolytic and Hypnotic drugs



Barbiturates

- They exert their action by binding to GABA receptors and so potentiate the GABA action on the chloride channel opening (prolonging the opening duration). The binding site is distinct from that of benzodiazepines.

  In addition they can block excitatory glutamate receptors.
- Their action summarized in:

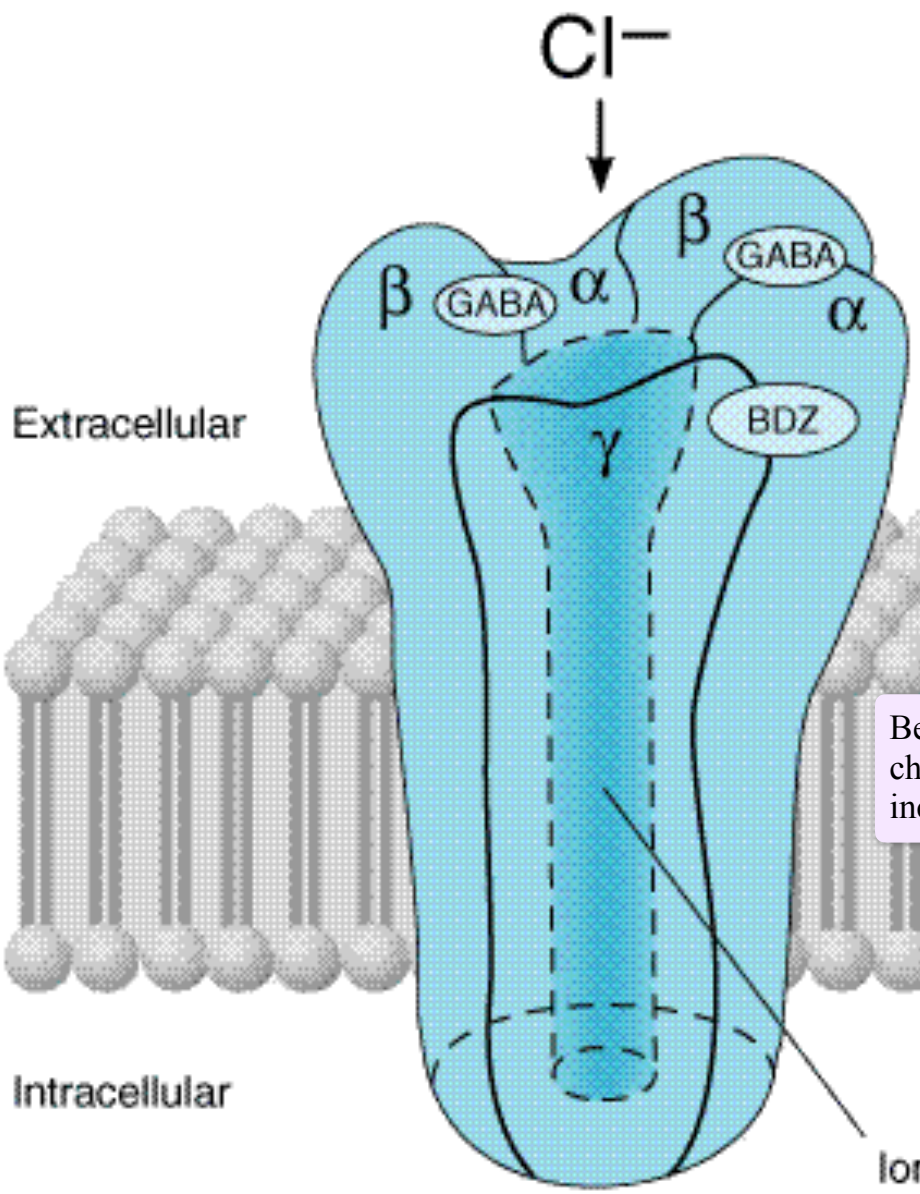
A. Depression of the CNS: at low doses they produce sedation, and high doses they cause hypnosis.

   → Anxiolytic

   thus it is useful as anesthetic. The selection of barbiturate is strongly influenced by the desired duration of action.

   The ultra short barbiturate such as thiopental are used intravenously to induce anesthesia.

GABA receptor complex



The influx of Cl^- ions leads to hyperpolarization.

Benzodiazepines bind to specific sites on the GABA receptor complex, which are separate from the barbiturates and GABA binding site- **allosterically regulated,** it enhances the affinity between GABA molecule and the receptor.

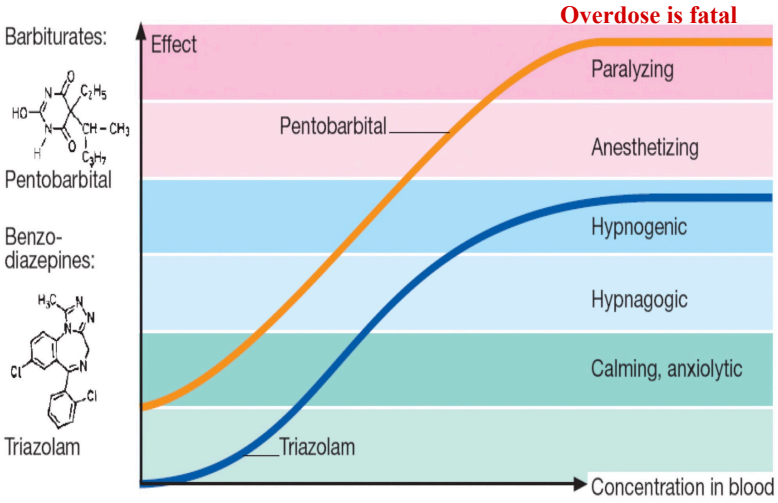
The GABA receptor complex consists of multiple subunits (α, β, γ), and the binding of benzodiazepines to different subunits can result in different effects.

Benzodiazepines enhance the **frequency** of channel opening, while barbiturates increase the **duration** of channel opening.

The duration of opening has a higher impact on the inhibitory effect exerted by these drugs.

Barbiturates have higher toxicity compared to benzodiazepines due to their mechanism of action. When taken in high doses, barbiturates not only bind to their specific sites on the GABA receptors but also displace the GABA molecules that are already bound. This competitive binding and displacement of GABA molecules by barbiturates further increase their inhibitory effect on the central nervous system → anesthesia → paralysis → death.

Pentobarbital is a Barbiturate.
Triazolam is a benzodiazepine.



Pentobarbital and Thiopental:

- Pentobarbital and Thiopental are examples of barbiturates.
- Thiopental is a short-acting barbiturate primarily used for the induction of anesthesia, particularly in resource-limited settings (poor areas).
- Thiopental is commonly employed for simple anesthetic procedures lasting less than half an hour, as it initiates the anesthetic effect within 30 seconds.
- Pentobarbital is used in Grand-mal epilepsy.

Propofol:

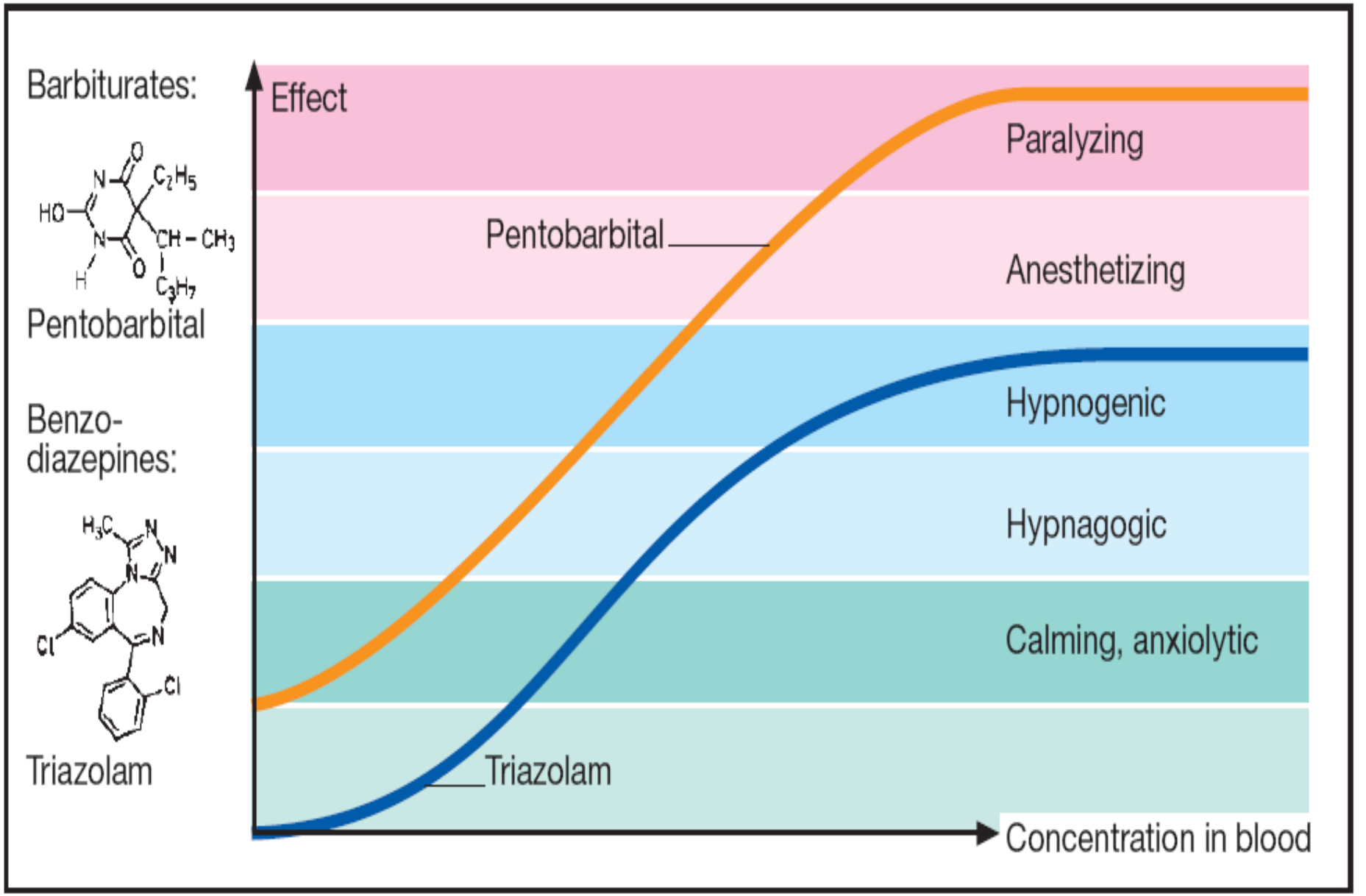
Propofol is another medication used for anesthesia induction and maintenance. Once the vial is opened, it is susceptible to contamination and bacterial growth (بخَمِّج). Therefore, it is generally recommended not to use propofol for more than one day after opening the vial.
It is not a barbiturate but belongs to a different class of drugs called intravenous anesthetics.

Temporary Impairment of Memory with Benzodiazepines:

- Benzodiazepines can produce temporary impairment of memory.
- This is because the function of memory and focus is associated with the neurotransmitter GABA, which is influenced by benzodiazepines.

- Overdose of Barbiturates is fatal ⇒ suicide, cause paralysis.
- An overdose of benzodiazepines is generally not lethal but can induce a state known as a (محبحب ماخد ١٢ حبة)

Hypnogenic refers to something that induces sleep, hypnagogic refers to the transitional state between wakefulness and sleep.



C. Concentration dependence of barbiturate and benzodiazepine effects

Barbiturates

B. Anticonvulsant: Phenobarbital (long-acting) is used in long-term management of tonic-clonic seizures, status epilepticus. Status epilepticus is a type of prolonged or continuous seizure activity that lasts for more than five minutes. The first-line treatment for status epilepticus is **benzodiazepines** because they work quickly.

Phenobarbital has been regarded as the drug of choice for treatment of young children with febrile seizure.

Also used in **Grand mal epilepsy, absence seizure.**

However, it can depress cognitive performance in children and the drug should be used cautiously.

C. Anxiety: barbiturates have been used as mild sedative to relieve anxiety, nervous tension and insomnia. (replaced by benzodiazepines).

- Barbiturates are indeed a class of drugs that have been **used as antiepileptic** agents, since they enhances the inhibitory effects of GABA

Barbiturates

- **The Barbiturates were formally the mainstay of the treatment used to sedate the patient or to induce and maintain sleep.**

- **Today they have been largely replaced by the benzodiazepines because they induce tolerance, physical dependence and very severe withdrawal symptoms, and most importantly, their ability to cause coma in toxic doses.**

- **Short acting barbiturates such as Thiopental is still used to induced anesthesia.**

Adverse effects and interactions

a. **Respiratory depression: they suppress the hypoxic receptors that response to CO2, and overdosage is followed by respiratory depression and death.**

for many decades, barbiturates poisoning has been a leading cause of death among drug overdose.

b. **Enzyme induction: they induce the CYP450 microsomal enzymes in the liver, and thus interact with many drugs.**

c. **CNS effects: cause drowsiness, impaired concentration.**

d. **Drug hangover: hypnotic doses produce a feeling of tiredness after patient awake (many hours).**

e. **Physical dependence: sudden withdrawal may cause tremors and anxiety and weakness**

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 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.

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

These drugs do not typically produce euphoria by themselves. However, if benzodiazepines are used alongside alcohol, which is also a central nervous system depressant, the effects of benzodiazepines will be enhanced, potentially leading to euphoria.

- Regarding long-term usage of benzodiazepines, it is true that the body can develop tolerance to the medications over time. With continued use, the body may adapt and downregulate GABA receptors, which are the inhibitory receptors in the brain. This downregulation can lead to a decrease in the effectiveness of the medication and potentially result in a rebound effect. this is why these agents shouldn't be used more than 2-3 weeks.

- **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.

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.

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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.

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.**

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

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.

  (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.

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.

Recap

- Tramadol is an analgesic drug, It has a weak affinity for the μ-opioid receptor and inhibits the reuptake of norepinephrine. Tramadol provides pain relief by activating α2-adrenoreceptors and synergistically interacting with opioid receptors. It has advantages such as less respiratory depression, nausea, vomiting, and constipation compared to other opioids. Tramadol is effective in treating moderate pain but is less effective than morphine for severe pain. However, its usage is restricted due to the risk of addiction.

- Naloxone is a general antidote for opioid overdose. It works by targeting μ-opioid receptors and has a shorter half-life than opioids like morphine. In cases of opioid toxicity, naloxone administration may need to be repeated multiple times to counteract the prolonged effects of opioids. It is important to manage opioid toxicity carefully, and mechanical ventilation may be necessary for patients experiencing respiratory depression.

- Anxiolytic and Hypnotic drugs are used to manage anxiety and sleep disorders. Anxiety is a state of tension and fear, and severe anxiety can be treated with antianxiety drugs and psychotherapy. These drugs also have sedative properties, making them useful as hypnotics for sleep induction. Benzodiazepines are the most widely used anxiolytic drugs and enhance the affinity of GABA receptors for the neurotransmitter GABA, thereby promoting inhibitory effects in the central nervous system. They reduce anxiety, induce muscle relaxation, have sedative and hypnotic effects, and can be used as anticonvulsants. However, they should be used for short periods of time due to their addiction potential and tolerance development. Benzodiazepines can cause side effects such as drowsiness, confusion, ataxia, and cognitive impairment. Benzodiazepine withdrawal syndrome can occur if the drug is abruptly discontinued.

- Benzodiazepines have largely replaced barbiturates because they are safer and more effective as anxiolytic drugs. Barbiturates were once commonly used as sedative-hypnotic drugs but have been largely replaced by benzodiazepines due to their higher risk of adverse effects and overdose. Barbiturates act as central nervous system depressants by enhancing the inhibitory effects of the neurotransmitter GABA. They have sedative, hypnotic, and anticonvulsant properties. However, barbiturates are associated with a higher risk of toxicity, dependence, tolerance, and overdose compared to benzodiazepines. They are generally not recommended for long-term use and have a narrower therapeutic index, making them potentially more dangerous.