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A Systematic Review on Sedative and Hypnotics

Ganesh Anil Vitukade, Monika Niranjan Pawar, Abhishek Suryawanshi, Beautykumari Singh, Abhijit Shinde

Abstract: ***Sedative and hypnotic drugs are central nervous system depressants primarily used to induce calmness, reduce anxiety, and promote sleep. These medications include benzodiazepines, barbiturates, and various non-benzodiazepine sleep aids, each varying in their mechanism of action, efficacy, and safety profiles. Benzodiazepines, such as diazepam and alprazolam, enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABA-A receptor, resulting in sedative, anxiolytic, muscle relaxant, and anticonvulsant effects. They are commonly prescribed for anxiety disorders, insomnia, seizures, and muscle spasms. However, their use is associated with risks of tolerance, dependence, and withdrawal symptoms. Barbiturates, such as phenobarbital, were once widely used for their sedative and hypnotic properties but have largely been replaced by benzodiazepines and other safer alternatives due to their higher risk of overdose and dependence. Barbiturates enhance GABAergic transmission but also directly activate GABA receptors, leading to more profound central nervous system depression. Non-benzodiazepine sleep aids, including drugs like zolpidem, eszopiclone, and zaleplon, act on the benzodiazepine receptor site but have a different chemical structure. These drugs are often preferred for short-term treatment of insomnia due to their relatively lower risk of dependence and adverse effects compared to benzodiazepines.***

The pharmacokinetics of sedative and hypnotic drugs can be significantly influenced by patient-specific factors, including age, liver function, and concurrent use of other medications. For example, the metabolism of benzodiazepines can be inhibited by selective serotonin reuptake inhibitors (SSRIs) and certain antiulcer drugs, potentially leading to increased drug levels and heightened sedative effects. Additionally, enzyme-inducing antiepileptic drugs can accelerate the metabolism of these sedatives, reducing their efficacy.

I. CENTRAL NERVOUS SYSTEM

The nervous system is an intricate network that allows an organism to interact with its environment. Its functions are diverse, including signal circuits that facilitate thinking, language, emotions, learning, memory, and sensation.

The nervous system uses various neurotransmitters at different synapses, neuroeffector sites, and neuromuscular junctions. Examples include acetylcholine, norepinephrine, dopamine, serotonin, glutamate, gamma-aminobutyric acid (GABA), neuropeptides, hormones, and even nitric oxide.

Designing and developing drugs that can cross the blood-brain barrier (BBB) and target specific sites within the central nervous system (CNS) is a challenging and complex endeavours. Central Nervous system it is type of nervous system and the classification of nervous system is give as follows in fig.1

A. Classification

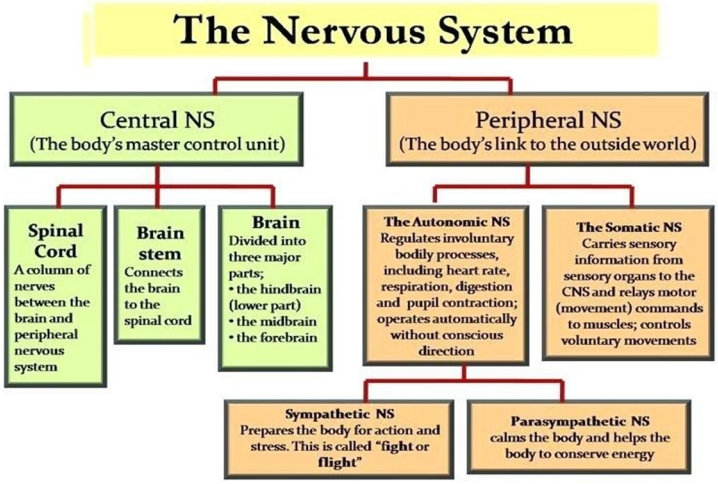


Fig. 1

II. SEDATIVES AND HYPNOTICS

Sedative and hypnotics both act on central nervous system. Sedative and hypnotic drugs reduce anxiety and produce a calming effect by inducing and maintaining sleep. These drugs are extensively used to treat various psychiatric disorders, including anxiety and insomnia. However, continuous use of currently available sedative-hypnotic therapies can lead to serious side effects, such as respiratory, digestive, and immune system dysfunctions, as well as deterioration of cognitive function, physical dependence, and tolerance.Most commonly sedative and hypnotics are use in the treatment of insomnia, which can also impair the vigilance of the psycho motor, but raise safety concerns.

1) *Sedative:* Sedative is a drug that reduces excitement and calms the brain without inducing sleep, though drowsiness may be produced.
2) *Hypnotic:* Hypnotic is a drug that induces and/or maintains sleep, similar to normal arousable sleep.

The sedatives and hypnotics are more or less CNS depressants with somewhat differing time action and dose-action relationships. Hypnotics given in high doses can produce general anaesthesia. Thus, sedation—hypnosis—general anaesthesia may be regarded as increasing grades of CNS depression. Anxiety is a feeling of fear, confusion, or tension that arises from the expectation of an imagined or unreal threat. The most common drugs used to treat anxiety are benzodiazepines.

A. *Classification*

1) Barbiturate – e.g. – barbital, phenobarbital, secobarbital, pentobarbital
2) Benzodiazepines-e.g.- diazepam, chlorzepoxide,
3) Miscellaneous- e.g.- glutethimide

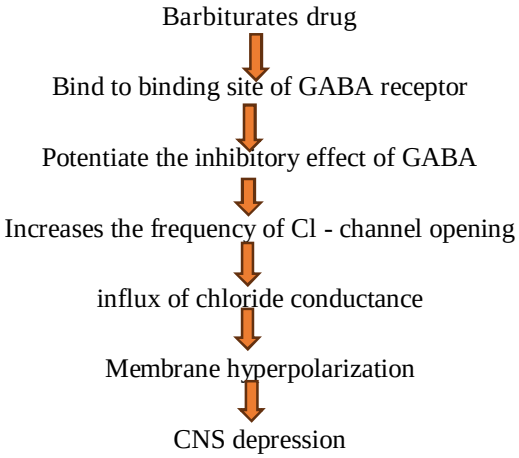
B. *Barbiturates*

Barbiturates are derivatives of barbituric acid (malonyl urea) that have been modified. Barbituric acid itself isn't a hypnotic, but when alkyl or aryl groups are added to its C5 position, the resulting compounds become hypnotics. If the oxygen at the C2 position is replaced with sulphur, it produces thiobarbiturates, which are more lipid-soluble and thus more potent. Barbiturates have different levels of lipid solubility: the more soluble they are, the more potent they are (effective in smaller doses) and the shorter their duration of action. Barbiturates do not dissolve in water, but their sodium salts do, creating a highly alkaline solution.Various indications given by barbiturates over the past 120 years , including insomnia, psychiatric disorders, anaesthesia, alcohol withdrawal, seizures, and elevated intracranial pressure.

III. CLASSIFICATION OF BARBITURATES

Based on duration of action:
Ultrashort acting (15min) e.g. - Thiopental
Short acting (2-4 hrs) e.g.- pentobarbital
Intermediate acting (4-6 hrs) e.g.-amobarbital
Long acting (6-8 hrs) e.g. - phenobarbital

A. *Mechanism of action*



Benzodiazepines are a class of drugs that act upon BZD receptors in the central nervous system. The receptor is a protein comprised of 5 transmembrane subunits, which collectively shape a chloride channel. Gamma-aminobutyric acid it has 2 types of receptor GABA A & GABA B receptors, GABA A is ligand gated ion channel type of receptor, and GABA b it is g-protein coupled type of receptor. Benzodiazepine drug which binds with the binding site of the Gamma-aminobutyric acid and after binding its Increases the frequency of Cl - channel opening after the opening influx of chlorine is occurs. And further hyperpolarization process is occur. And drug which depress the central nervous system.

B. Structure Activity Relationship

Barbituric acid served as the foundation for numerous formulations patented by Bayer. Because it has low lipophilicity, barbituric acid does not naturally affect the central nervous system (CNS). However, a lipophilic derivative of barbituric acid, called barbital (5,5-diethylbarbituric acid), was developed and successfully used to induce sleep in dogs.

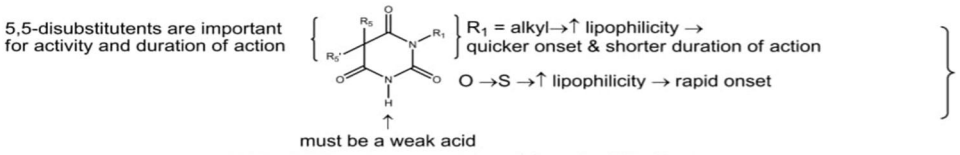


Fig. 2

Main drug of Barbiturates is barbituric acid (2,4,6 trioxohexahydro - pyrimidine) .is give in fig 2nd ,Substitution occurs at following position:

- Position 1st
- Position 2nd

It has less CNS depressant property but substitution at various positions gives various compounds with sedatives and hypnotic property.

- At 5th Position

- Replacement of hydrogen atom of 5th position by alkyl group increases ability of the drug to cross Blood Brain Barrier (BBB) and increases activity of drug .

Example: Phenobarbitone

- Further Increase in branching of this alkyl chain at 5th position increases lipophilicity, thus potency increases and duration of action decreases.

- At 1st position

- If CH3 is present at 1st position instead of H , then it increases lipophilicity which increases potency and duration of action decreases. Example: Methylphenobarbitone.

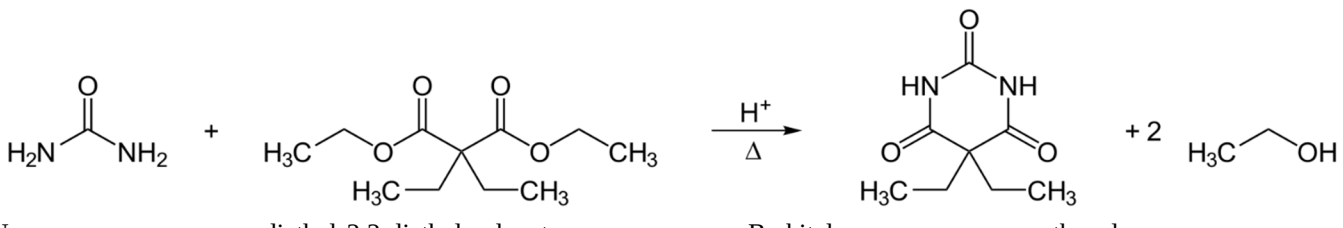
- At position 1st and 3rd replacement of H atom by alkyl group at only one nitrogen increases its Activity , but replacement on both the nitrogen decreases the activity.

- at position 2nd and 3rdouble bond is essential for the activity of the drug.

C. Synthesis of Barbiturate Drug:

Example - Barbital

Fig 3rd



Urea diethyl-2,2-diethylmalonate Barbital methanol

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IV. PHARMACOKINETICS

A. *Absorption*

1) *Phenobarbital:* It's quickly absorbed, reaching peak concentration in 2 to 4 hours. In adults, about 90% of the dose is absorbed, but this is lower in newborns.
2) *Methohexitone:* Its plasma levels were studied in children aged 2-7 years after rectal and intramuscular administration, and in younger children after intravenous injection.

B. *Distribution*

1) *Thiopentone:* It rapidly distributes into tissues. For volunteers, it has a distribution half-life (α) of about 2.8 minutes and (β) half-life of about 48.7 minutes.

C. *Metabolism*

1) *Methohexitone:* Primarily metabolized in the liver, with less than 1% excreted unchanged in urine.
2) *Phenobarbital:* Metabolism is slow, resulting in stable concentrations with steady dosing. Around 20-40% is excreted unchanged in urine, while the remainder undergoes slow liver metabolism.

D. *Elimination*

1) *Phenobarbital:* Approximately 25% is excreted unchanged in urine. Its renal excretion can be enhanced through methods like osmotic diuresis or urine alkalinization.
2) *Other Barbiturates:* Except for phenobarbital, most barbiturates are extensively metabolized rather than excreted unchanged in urine. Inchildren , a shorter half time duration occurs due to increased clearance The half-life of phenobarbital decreases by approximately 4.6 hours/day on long term administration.

E. *Pharmacodynamics*

Barbiturates are drugs that affect the brain and nervous system, causing sedation, hypnosis (sleepiness), and even anaesthesia.

F. *How Barbiturates Work*

GABA Receptor Activation: Barbiturates attach to GABA receptors in the brain. GABA is a neurotransmitter that calms neural activity.
Increased Chloride Conductance: This attachment allows chloride ions to enter neurons more easily. This process hyperpolarizes neurons, making them less likely to fire signals.
Glutamate Inhibition: Barbiturates also reduce the release of glutamate, which is an excitatory neurotransmitter.
Effects on Other Neurotransmitters: They can influence dopamine, serotonin, and acetylcholine systems in the brain.

G. *Pharmacological Action*

Barbiturates act primarily by enhancing the inhibitory effects of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABA-A receptor. Here's a breakdown of their pharmacological actions:

1) *GABA-A Receptor Modulation:* Barbiturates bind to specific sites on the GABA-A receptor complex, which is a ligand-gated chloride ion channel. This binding increases the duration of GABA-mediated chloride channel openings, leading to membrane hyperpolarization and inhibition of neuronal excitability.
2) *Central Nervous System Depression:* By enhancing GABAergic neurotransmission, barbiturates produce sedative, hypnotic, and anesthetic effects. These effects are dose-dependent, ranging from mild sedation to profound anesthesia.
3) *Anticonvulsant Properties:* Barbiturates can suppress seizure activity by increasing the threshold for neuronal firing and reducing the spread of epileptic discharges.
4) *Muscle Relaxation:* They exert a direct depressant effect on the spinal cord, resulting in relaxation of skeletal muscles.
5) *Respiratory Depression:* High doses of barbiturates can depress the respiratory center in the brainstem, leading to decreased respiratory rate and potentially respiratory arrest.
6) *Cardiovascular Effects:* Barbiturates can cause vasodilation and decrease cardiac output, particularly at higher doses.

H. Adverse Effects

1) *Respiratory Depression:* They can slow breathing, which can be dangerous.
2) *Dependence and Addiction:* They can lead to physical and psychological addiction.
3) *Cognitive Impairment:* They may affect thinking and memory.
4) *Overdose Risk:* Taking too much can be fatal.

Barbiturates are now less commonly used due to their potential for abuse and safer alternatives being available.

I. Pharmacokinetics Interaction

The binding of thiopentone to albumin is decreased in the elderly, resulting in higher free drug concentrations in older patients. In older adults, the binding of thiopentone to albumin is reduced, leading to higher levels of the free drug. Enzyme-inducing antiepileptic drugs (AEDs) like carbamazepine, phenytoin, phenobarbital, and primidone enhance the activity of various cytochrome P450 enzymes (CYP1A2, CYP2C9, CYP2C19, and CYP3A4), glucuronyl transferases (GT), and epoxide hydrolase, which speeds up the metabolism of other drugs.

J. Drug-Drug Interaction of Barbiturates

By taking systemic hormonal contraception drug causes contraceptive failure Barbiturates are restricted for pregnant and lactating women because abnormal development of fetus.When barbiturates are combined with other CNS depressants, such as benzodiazepines and opioids, they can cause oversedation and severe respiratory depression.Barbiturates should not be given with alcohol, alcohol increases the risk of overdose.

K. Benzodiazepines

Introduction

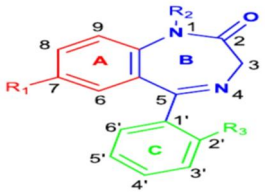
Benzodiazepines were first introduced into medical practice in the 1960s and quickly became widely used. The first benzodiazepine synthesized was chlordiazepoxide in 1957. These medications primarily treat anxiety disorders but can also serve as anesthetics in rare cases of severe conditions. Benzodiazepines act on specific receptors in the central nervous system, known as benzodiazepine receptors. Examples of benzodiazepines approved by the FDA include alprazolam, clobazam, chlordiazepoxide, and others.

They are among the most prescribed medications due to their effectiveness in alleviating anxiety and inducing relaxation. However, their use requires caution due to potential side effects and the risk of dependence if used long-term or in high doses.

Classification

1) Short acting (t ½ <5h) Triazolam, oxazepam , Midazolam
2) Intermediate-acting (t½ 5_24 h) alprazolam _. Lorazepam clonazepam
3) Long acting (t½ >24h) clorazepate, Diazepam, flurazepam chloradiazepoxide

L. SAR of Benzodiazepines



structure of benzodiazepines is given in figure 4
substitution occur at following ring
Ring A- aromatic ring
Ring B – 1,4 diazepine ring
Ring C – phenyl ring

Fig 4

BDZ should present the following structural features for greatest anti-anxiety potency:

1) In ring "A" at 7th position, an electron-withdrawing group like Cl, Br, NO2, etc. is attached.by attached the electron-withdrawing group it increases the activity of the drug
2) Substitution on the 6,8,9th position it will decrees the activity of the drug and facilitate the elimination of the drug.
3) Addition or substitution In ring "b" at the position 1st methyl group is attached to thr nitrogen atom, by addition of methyl group at the 1st position it will increase the activity of the drug

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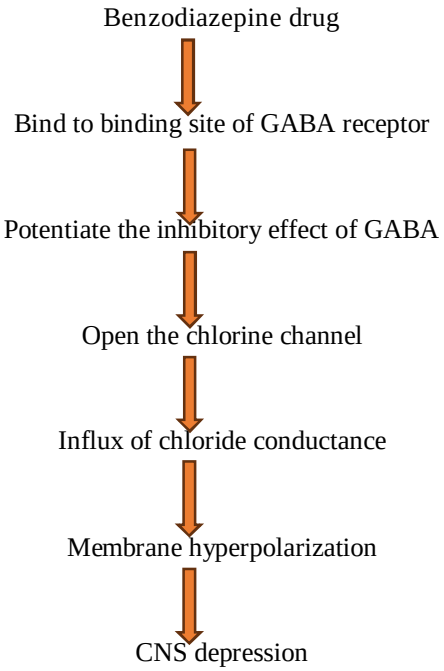
4) Replacement occurs at 2nd position by two hydrogen atoms at 2nd position which decreases the activity of the drug and medazepam drug is found and its is less potent then other
5) At 3rd position replacing one hydrogen atom with hydroxyl group lowers the activity of the drug and the facilitate the elimination
6) By addition a carboxyl function at position 3rd , clorazepate is found which enhance the duration of action.
7) Double bond between 4th and 5th position it is good for the activity of the drug and it is also essential.
8) At 5th position phenyl substitution is necessary for the activity and it causes the potent compound
9) Electronegative substituents like Cl or F are added at the ortho-position, and disubstitution in both ortho positions in ring C is done.
10) Derivatives with additional rings attached to the diazepine nucleus at positions 1st and 2nd are more active
11) By replacing the benzene ring with heteroaromatic ring (eg, pyrazole) compounds yielded. with interesting anxiolytic properties (eg, Ripazepam)

Mechanism of action
Mechanism of action



Benzodiazepines are a class of drugs that act upon BZD receptors in the central nervous system. The receptor is a protein comprised of 5 transmembrane subunits, which collectively shape a chloride channel. Gamma-aminobutyric acid it has 2 types of receptor GABA A & GABA B receptors, GABA A is ligand gated ion channel type of receptor, and GABA b it is g-protein coupled type of receptor. Benzodiazepine drug which binds with the binding site of the Gamma-aminobutyric acid and after binding its open the chlorine channel after the opening influx of chlorine is occurs. And further hyperpolarization process is occurred. And drug which depress the central nervous system.

M. Pharmacokinetics

1) *Absorption:* after the administration of the drug, the drug is absorbed into the GIT except clorazepate. Clorazepate which undergoes decarboxylation in gastric juice before absorption. Afte the administration by parenteral route diazepam and chlordiazepoxide will absorbed slowly and the absorption of lorazepam or midazolam after the administration of the drug into the IV route it has better absorption in comparison to the intramuscular route. benzodiazepine drug which has Midazolam drug that crosses the blood-brain barrier and give more absorption it is lipophilic in nature so the reason for the cross is the blood-brain barrier.

2) *Distribution:* The benzodiazepine binds to plasma protein and plasma protein binds of diazepam drug for greater in comparison to alprazolam and clonazepam. Plasma protein binding is approximately 70% for alprazolam, 85% for clonazepam, and 99% for diazepam is redistributed rapidly. concentration of BZD drug in CSF is equal to the drug in plasma
3) *Metabolism:* All benzodiazepines are metabolized by the liver. However, some benzodiazepines (i.e. - lorazepam, oxazepam, and temazepam) do not go through CP450 metabolism (Phase I metabolism), and are only metabolized via glucuronidation (Phase II metabolism).

- First Phase: Many drugs break down into active parts called N-desalkylated metabolites. But some drugs like triazolam, alprazolam, and midazolam are exceptions.
- Second Phase: Next, the drugs go through a process called hydroxylation, often creating another active form.
- Third Phase: Finally, the drugs combine with a substance called glucuronic acid in a process known as conjugation.

Most benzodiazepines are processed in the liver by enzymes CYP3A4 and CYP2C19. However, lorazepam is different because it skips the enzyme step and directly combines with glucuronic acid. This makes lorazepam suitable for people with liver

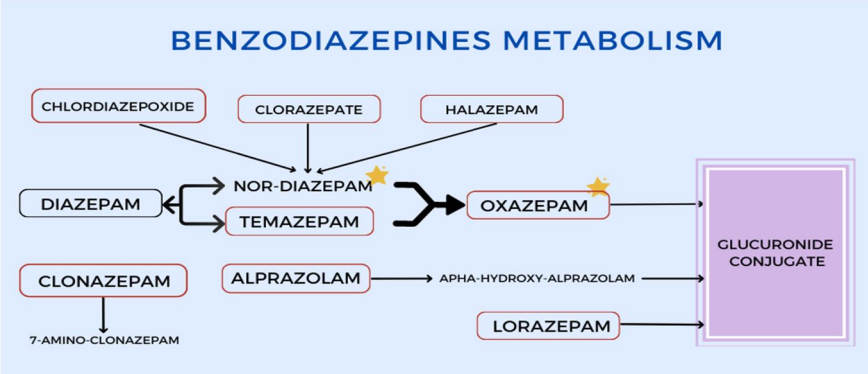


Fig 5

4) *Elimination:* Benzodiazepines are mainly removed from the body by the kidneys. Diazepam creates active by-products like oxazepam, temazepam, and desmethyldiazepam, which make its effects last longer. In older people and those with kidney problems, these drugs stay in the body longer.

N. Pharmacodynamics

Benzodiazepines (BZDs) enhance the function of a specific receptor in the brain known as the GABA-A receptor. This receptor is a type of protein complex that acts as a gateway for chloride ions when activated by the neurotransmitter GABA (gamma amino butyric acid). GABA is widespread in the brain and plays a crucial role in calming neuronal activity by reducing excitability.

The GABA-A receptor consists of five subunits made up of different proteins. It typically includes two α subunits, two β subunits, and one γ subunit. Each receptor complex has two binding sites for GABA but only one for benzodiazepines, located where the α and γ subunits meet. Specifically, certain α subunit isoforms (variants) contain a histidine residue that binds strongly to benzodiazepines, while others do not interact with these drugs.

When benzodiazepines bind to their specific site on the GABA-A receptor, they cause a change in the receptor's shape. This alteration enhances the ability of GABA to bind to its own sites on the receptor. As a result, the chloride channel opened by the receptor allows more chloride ions to enter the neuron, leading to hyperpolarization. This process ultimately enhances the inhibitory effect of GABA throughout the central nervous system, producing a calming or sedative effect.

V. PHARMACOLOGICAL ACTION

Benzodiazepines (BZDs) exert their pharmacological actions primarily through interaction with the gamma-aminobutyric acid type A (GABA-A) receptor in the central nervous system. Here's a breakdown of their key pharmacological actions.

1) *Anxiolytic Effects:* Benzodiazepines are effective in reducing anxiety by enhancing GABAergic neurotransmission in key brain regions involved in anxiety regulation
2) *Sedative and Hypnotic Effects:* Benzodiazepines induce sedation and sleepiness by modulating GABAergic neurotransmission in the reticular activating system.
3) *Muscle Relaxant Properties:* Benzodiazepines reduce muscle tone and spasticity by enhancing GABA-mediated inhibition in the spinal cord and brainstem.

4) *Anticonvulsant Effects:* Benzodiazepines prevent seizures by increasing GABAergic inhibition, thereby reducing neuronal excitability.
5) *Amnesic Effects:* Benzodiazepines can cause anterograde and retrograde amnesia, affecting memory formation and retrieval processes.
6) *Tolerance and Dependence:* Long-term use of benzodiazepines can lead to tolerance, requiring higher doses for the same effect, and dependence, with withdrawal symptoms upon discontinuation.
7) *Withdrawal Syndrome:* Abrupt cessation of benzodiazepines can lead to a withdrawal syndrome characterized by anxiety, insomnia, and potentially severe symptoms
8) *Clinical Applications:* Benzodiazepines are used clinically for various conditions including anxiety disorders, insomnia, acute seizures, and as adjuncts in anesthesia.
9) *Pharmacokinetics and Metabolism:* Understanding the pharmacokinetics and metabolism of benzodiazepines is essential for optimizing their clinical use and minimizing adverse effects.

A. Adverse Effects of Benzodiazepines

1) *Sedation and Drowsiness:* Benzodiazepines often make people feel sleepy and sluggish, which can make it hard to function normally or move well.
2) *Cognitive Impairment:* They can cause confusion, make it difficult to remember things, and make it hard to focus, especially in older people.
3) *Respiratory Depression:* Taking high doses or using benzodiazepines with other drugs that slow down the brain can slow breathing, which can be dangerous.
4) *Physical Dependence and Withdrawal:* Using benzodiazepines for a long time can make the body dependent on them. Stopping suddenly or reducing the dose quickly can lead to symptoms like anxiety, trouble sleeping, shaking, and even seizures.
5) *Impaired Coordination:* Benzodiazepines can make it harder to move smoothly, coordinate actions, and react quickly, which increases the risk of accidents.
6) *Paradoxical Reactions:* In some people, rather than calming them down, benzodiazepines can cause unexpected reactions like feeling agitated, aggressive, or losing inhibitions.
7) *Drug Interactions:* Benzodiazepines can interact with other medications, especially those that also affect the brain, leading to stronger effects or more side effects

B. Pharmacokinetic Interaction of Benzodiazepines

When opioids, such as oxycodone, are used together, there is a higher risk of side effects. Additionally, it's important to be aware of potential interactions that could affect how the drugs are processed in the body. When taking antidepressants like selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and fluvoxamine, they can slow down the breakdown of some benzodiazepines, like alprazolam and diazepam. This can result in higher levels of benzodiazepines in the body.
Antiulcer drugs: Cimetidine, an H2 blocker, can slow down the metabolism of benzodiazepines like diazepam and chlordiazepoxide. This can cause their levels to rise in the body, potentially leading to increased side effects.
Other benzodiazepines: Taking multiple benzodiazepines together, such as midazolam with others, can lead to pharmacokinetic interactions, potentially affecting how these drugs are processed in the body.

C. Miscellaneous Agents

Miscellaneous drugs of Sedatives and hypnotics are those which are not categorized in Benzodiazepines and Barbiturates.
Miscellaneous Drugs are classified as:

- Alcohols
- Amides
- Aldehydes

1) *Alcohols are Further Classified Into*

a) Meprobromate.
b) Ethchlorvynol.

2) Amides are Further Classified Into
a) Glutethmide.

3) Aldehydes are Further Classified Into
a) Paraldehyde.
b) Trichlofos sodium.

D. Mechanism of Action

The main mechanism of action of these miscellaneous drugs is that it binds to GABA 'A' receptor. After this binding it causes opening of chlorine ion channels which leads to chlorine influx.
This leads to CNS depression which causes sedation.

E. Pharmacokinetics

Glutethimide is unpredictably absorbed from the gastrointestinal tract, but peak serum concentrations generally occur within 1–6 hours following a therapeutic dose. Liver metabolizes glutethimide to form conjugated and unconjugated metabolites.

F. Pharmacodynamics

Glutethimide is like the barbiturates and is a hypnotic and sedative drug. It was introduced in 1954 as a safer alternative to barbiturates but was soon found out that it causes addiction and withdrawal symptoms.

G. Therapeutic Uses

1) Glutethimide: This induces sleep without respiratory depression.
2) Meprobromate: This is used as a skeletal muscle relaxant and a sedative and hypnotic.
3) Ethchlorvynol: This drug is used to manage insomnia. It is a short duration hypnotic.
4) Paraldehyde: Paraldehyde is used in the treatment of seizures and acts as an anticonvulsant.
5) Trichlofos Sodium: This drug is used as a sedative and hypnotic. This drug does not cause gastric irritation.

VI. CONCLUSION

By the above article, it can be concluded that sedatives and Hypnotics provide varied medicinal values and enhance the medical procedures by inducing sedation / calming effect.
while sedative and hypnotic drugs play a crucial role in managing anxiety, insomnia, and related disorders, their use must be carefully monitored to minimize risks of adverse effects, tolerance, and dependence. Further research and development of these medications continue to focus on enhancing their safety and efficacy profiles.
Sedatives and Hypnotics Drugs Are Immensely useful but the overdose factor should be taken care of as A Overdose of Sedatives and Hypnotics may lead to serious problems such as respiratory depression and can also be responsible for death.

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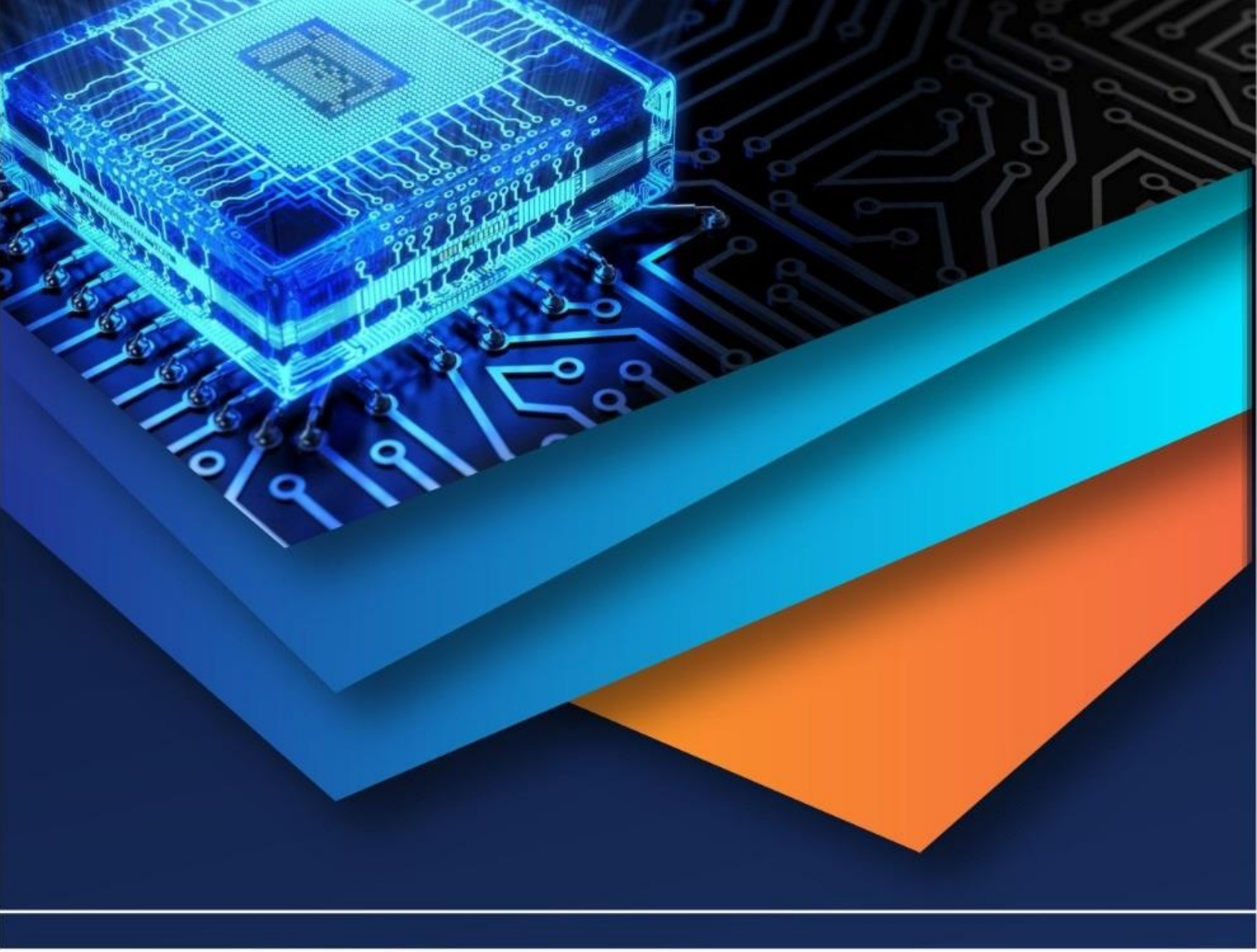

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