SEDATIVE AND HYPNOTICS

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SEDATIVE:

- A drug that reduces excitement, calms the patient (without inducing sleep)
- Sedative in therapeutic doses are anxiolytic agents
- Most sedatives in larger doses produce hypnosis(trans like stage in which subject become passive and highly suggestible)
- Site of action is on limbic system which regulates thought and mental function.

- HYPNOTIC
- A drug which produces sleep resembling natural sleep
- They are used for initiation and/or maintenance of sleep.
- Hypnotics in higher doses produce general anaesthesia.
- Site of action is on the midbrain and ascending RAS which maintain wakefulness.

Dose Dependent Action

SLEEP

BASICS:

- Sleep is a naturally recurring state characterized by
  1. Reduced or absent consciousness
  2. Relatively suspended sensory activity
  3. Decreased ability to react to stimuli
  4. Easily reversible
  5. Inactivity of nearly all voluntary muscles

FUNCTIONS OF SLEEP

- **Energy Conservation** :decrease in metabolic rate and body temperature
- **Restoration and Recovery** : increased anabolic hormones, decreased catabolic hormone
- Ecological **Hypotheses** of predator avoidance
- **Memory** Reinforcement and consolidation
- Synaptic and **Neuronal** Network Integrity

- The sleep-wake cycle, is regulated by **two separate biological mechanisms** in the body, which interact together and balance each other.

1)Circadian rhythm(Process C)

2)Sleep-wake homeostasis(Process S)

1)Circadian rhythm (Process C)

- Process C regulates the body's internal processes and alertness levels , which is governed by the internal biological or circadian clock.

- The body's built-in circadian clock, which is centred in the hypothalamus organ in the brain, is the main mechanism that **controls the timing of sleep**, and is independent of the amount of preceding sleep or wakefulness

- This internal clock is coordinated with the day-night / light-dark cycle over a 24-hour period, and regulates the

- **Body's sleep patterns**
- **Feeding patterns**
- **Core body temperature**
- **Brain wave activity**
- **Cell regeneration**
- **Hormone production**

- 2)Sleep-wake homeostasis(Process S)

➢ Sleep-wake homeostasis, or Process S, the accumulation of hypnogenic (sleep-inducing) substances in the brain, which generates a homeostatic sleep drive

➢ Sleep-wake homeostasis is an internal biochemical system that operates as a kind of timer or counter, generating a homeostatic sleep drive or pressure to sleep and regulating sleep intensity.

➢ It effectively **reminds** the body that it needs to sleep after a certain time, and it works quite intuitively:

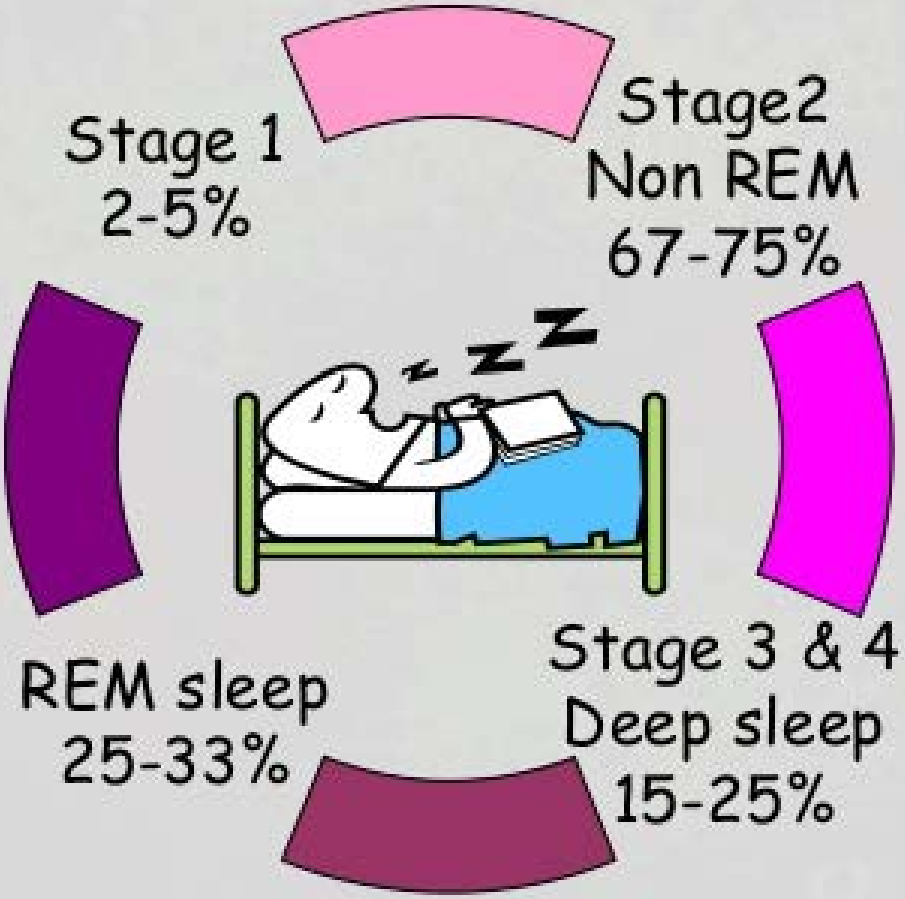
STAGES OF SLEEP

- The human body goes through stages of sleep when we lay down to rest, and interference with the sleep cycle can cause tiredness and irritability the following day.

- Science has discovered two distinct types of sleep, known as

    1. Rapid eye movement (REM) sleep
    2. Non-REM sleep.

Stages of Sleep



5 STAGES OF SLEEP

Stage 1(non-REM sleep)

- This sleep occurs in the first moments after you have laid your head down on your pillow and closed your eyes. The **eyes move slowly** and **muscle movement ceases.**

- Sleeper can be easily awakened by noise or other disturbances as she drifts in and out of sleep.

Stage 2(non-REM sleep)

- In this stage of sleep, the person is actually asleep and the sleeper is **not aware of surroundings**.

- Body temperature drops, breathing and heart rate are regular, and eye movements decrease significantly or are non-existent.

- Brain waves slow down, though there may be bursts of activity.

Stage 3 (non-REM sleep)

- This is deep sleep, characterized by even slower brain waves and less sporadic bursts of brain wave activity.
- Breathing slows and muscles relax.
- Sleepers are hard to awaken during this stage. Children sometimes **wet the bed** during this stage of sleep.

Stage 4 (non-REM sleep)

- This is the deepest sleep and is characterized by very slow brain waves and no sporadic bursts of brain wave activity.

- As with Stage 3 non-REM sleep, sleepers are hard to wake up. tissue repair takes place during this stage of sleep.

- Hormones will be released to assist with growth and development

- Once the sleeper reaches stage four (about an hour after sleep begins) they **then travel back up through** stages **three, two and one.**

Stage 5 (REM sleep)

- The REM stage is the sleep during which we dream. It is characterized by rapid eye movements even though the eyes are closed.
- Breathing is rapid, irregular, and shallow.
- Heart rate and blood pressure increase.
- Arms and leg muscles experience a type of paralysis that keeps people from acting out their dreams.
- some may talk or walk during REM sleep.

SLEEP HORMONES

- Sleep brain hormones are:

  Serotonin---which is produced during the day

  Melatonin---which is produced at night.

- If you are happy during the day and sleep soundly at night, then your brain hormones are **well balanced**.

SEROTONIN:

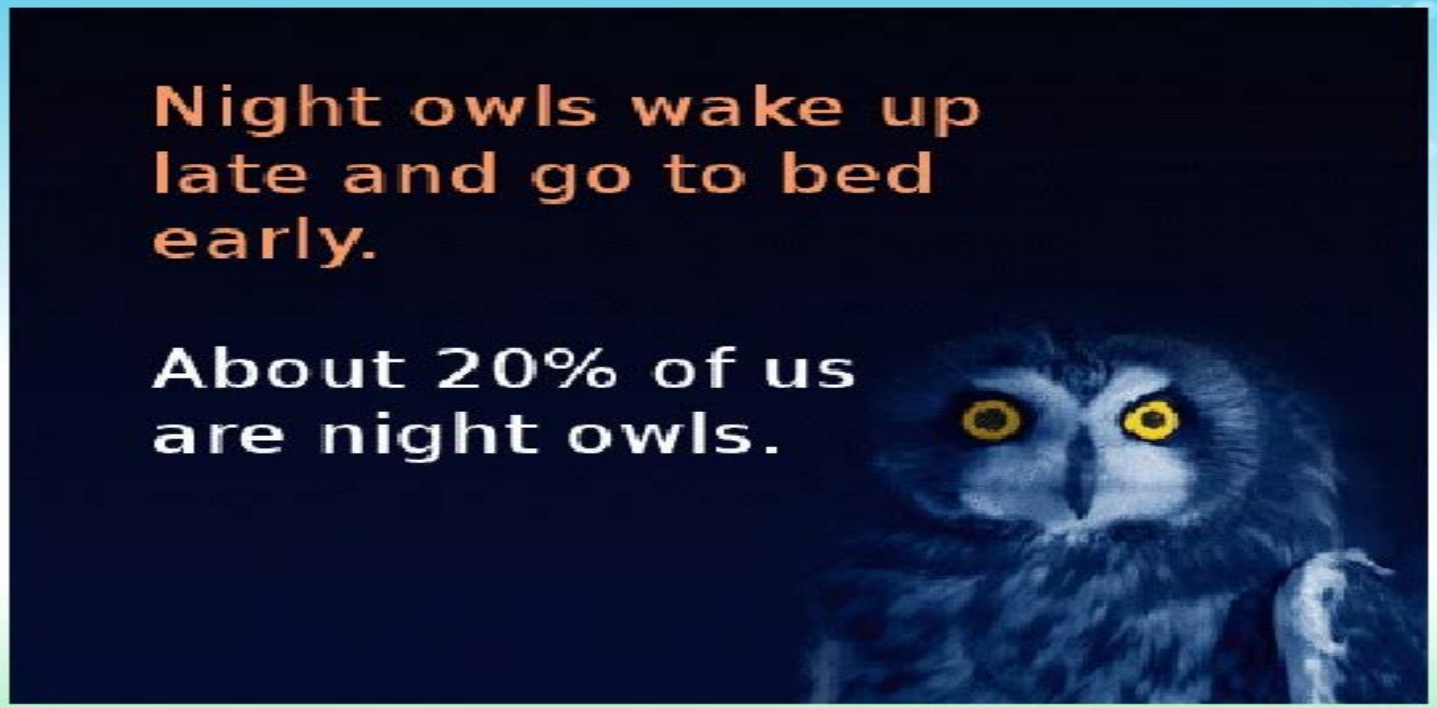
- **Serotonin ("happy hormone**")is secreted in the central nervous system.

Function of serotonin:

- Regulating moods, appetite, sleep

The lack of Serotonin causes

- Anxiety
- depression
- insomnia
- irritability



MELATONINE:

- Melatonin is produced from Serotonin during low light conditions and is produced naturally when darkness falls.

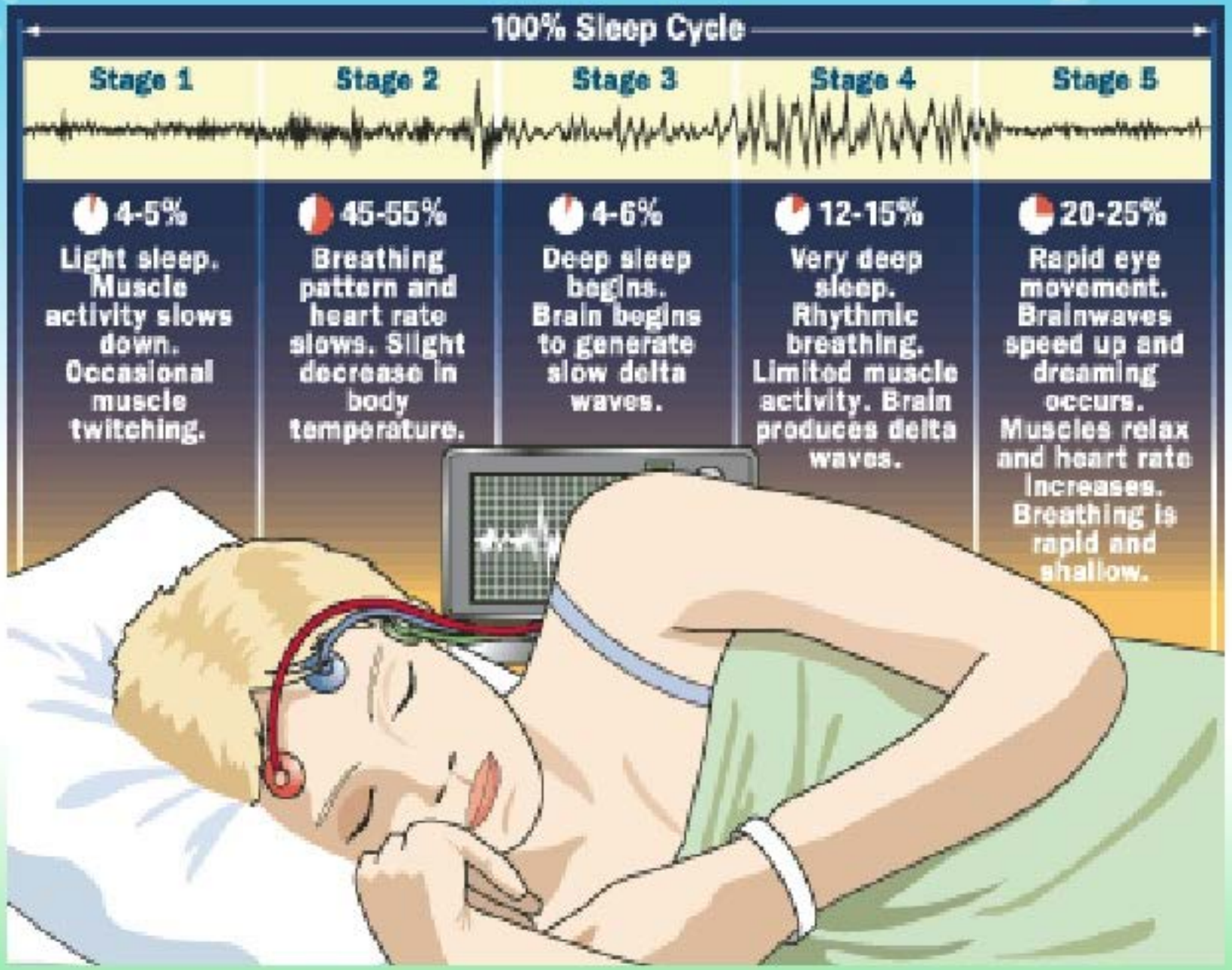
- Melatonin is secreted by the Pineal Gland.

Function of Melatonin

1.Synchronization of the biological clock

2. As an antioxidant.

3. It increases Killer T cells of the immune system.


100% Sleep Cycle
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
4-5%
Light sleep. Muscle activity slows down. Occasional muscle twitching.
45-55%
Breathing pattern and heart rate slows. Slight decrease in body temperature.
4-6%
Deep sleep begins. Brain begins to generate slow delta waves.
12-15%
Very deep sleep. Rhythmic breathing. Limited muscle activity. Brain produces delta waves.
20-25%
Rapid eye movement. Brainwaves speed up and dreaming occurs. Muscles relax and heart rate increases. Breathing is rapid and shallow.

BARBITURATES

CLASSIFICATION

Long acting

- Phenobarbitone (used in Epilepsy and Neonatal jaundice)

Short acting

- Butabarbitone
- Phenobarbitone

Ultra short acting

- Thioopentone (Anesthesia)
- Methohexitone

BARBITURATES

- All derivatives of Barbituric acid.
- Depressants of the central nervous system (CNS) that impair or reduce the activity of the brain by acting as a Gamma Amino Butyric Acid (GABA) potentiators
- Categorized as hypnotics and also called “downers”
- Produce alcohol like symptoms such as impaired motor control (ataxia), dizziness, and slower breathing and heart rate.

HISTORY

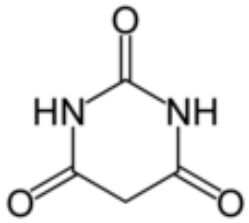
- Barbituric acid was first created in 1864 by a German scientist named **Adolf von Baeyer**. It was a combination of urea from animals and malonic acid from apples.

- Its first derivative utilized as medicine was used to put dogs to sleep but was soon produced by Bayer as a sleep aid in 1903 called Veronal.

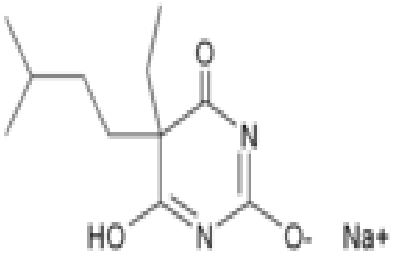
- Prescribed as sedatives, anesthetics, anxiolytics, and anti-convulsant.

- Also popular and abused in pop culture because of their alcohol like effects.

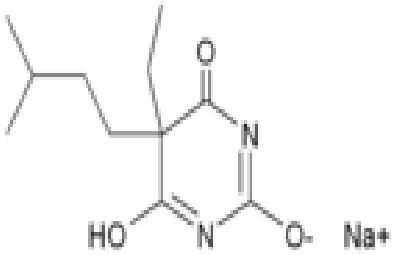
TYPES



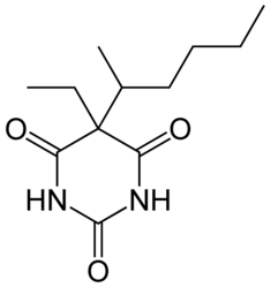
Barbituric Acid



Amobarbital

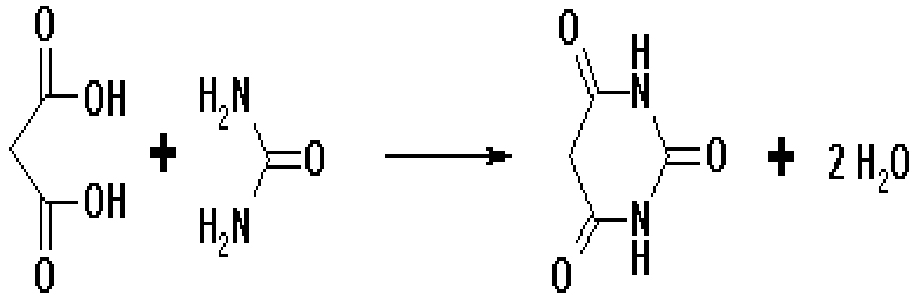


Phenobarbital



Pentobarbital

SYNTHESIS



Malonic Acid Urea Barbituric Acid

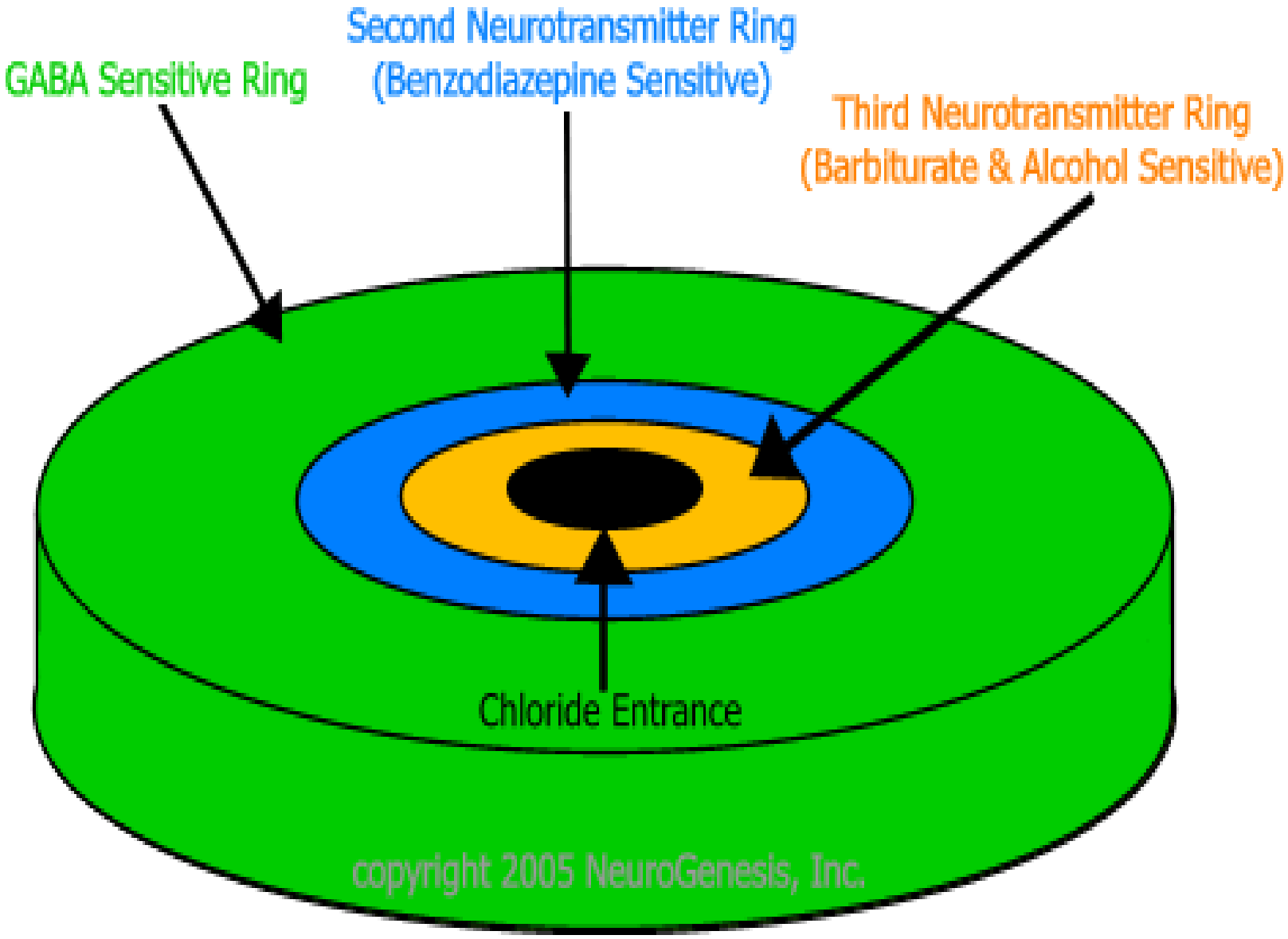
- Barbituric acid is synthesized by a condensation reaction that results in the release of H2O (dehydration) and the heterocyclic pyrimidine

MECHANISM OF ACTION

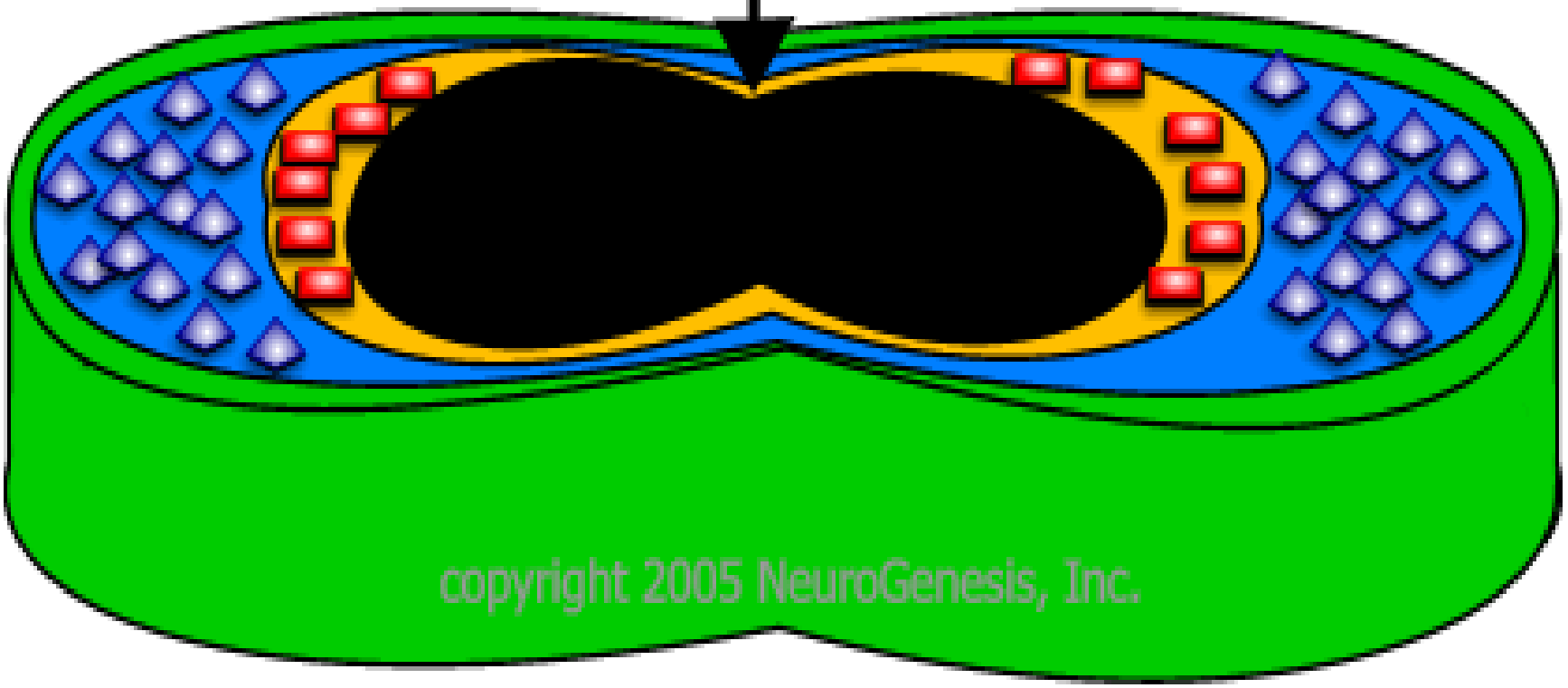
- Barbiturates potentiate the effect of GABA by binding to the GABA-A receptor at a nearby site and **increasing** the **chloride** flow through the channel.

- Glutamate performs the opposite effect from GABA restricting ion flow and increasing the transmembrane action potential of the neuron.

- By blocking this action Barbiturates serve to increase the duration of the receptor response to GABA and extend the depressed condition of the cell.


GABA Sensitive Ring
Second Neurotransmitter Ring
(Benzodiazepine Sensitive)
Third Neurotransmitter Ring
(Barbiturate & Alcohol Sensitive)
Chloride Entrance
copyright 2005 NeuroGenesis, Inc.

An excessive amount of external substances
that attach to the two inner rings can cause
the Chloride Channel to widen too much,
allowing an over-abundance of chloride to enter.



PHARMACOLOGICAL ACTION OF BARBITURATES

❖ **On CNS**

- Mild degree of sedation to general anaesthesia.
- Anticonvulsant effect
- Respiratory centre depression

❖ **On CVS**

- Hypotension
- Decrease heart rate
- Circulatory collapse

❖ **On Liver:**

- Enzyme induction,so increase metabolism of itself and other drugs.
- Stimulation of glucouronyl transferase.

❖ **On Kidney**

- Antidiuretc efffect (increase ADH)
- Decrease urinary output by depressing GFR

❖ **On Eye**

- No effect (normal dose)
- Miosis(Toxic effect)

❖ **On GIT**

- Constipation (on prolong use)

USES:

- Barbiturates have been use in the past to treat a variety of symptoms from **insomnia** and **dementia** to **neonatal jaundice**

- They have largely been replaced with drugs such as **benzodiazepine** due to their propensity for addiction and reduced effect over extended use

- Still widely used to treat most seizures including **neonatal seizures**

- Used when benzo class drugs fail or in underdeveloped countries

- **Cannot** be used for treatment of **absence seizures**

THERAPEUTIC USES

ANESTHESIA (THIOPENTAL, METHOHEXITAL)

- Selection of a barbiturate is strongly influenced by the desired duration of action.

- The ultrashort-acting barbiturates, such as thiopental, are used intravenously to induce anesthesia.

ANXIETY

- Barbiturates have been used as mild sedatives to relieve anxiety, nervous tension, and insomnia.

- When used as hypnotics, they suppress REM sleep more than other stages. However, most have been **replaced** by the **benzodiazepines.**

THERAPEUTIC USES

ANTICONVULSANT: (PHENOBARBITAL, MEPHOBARBITAL)

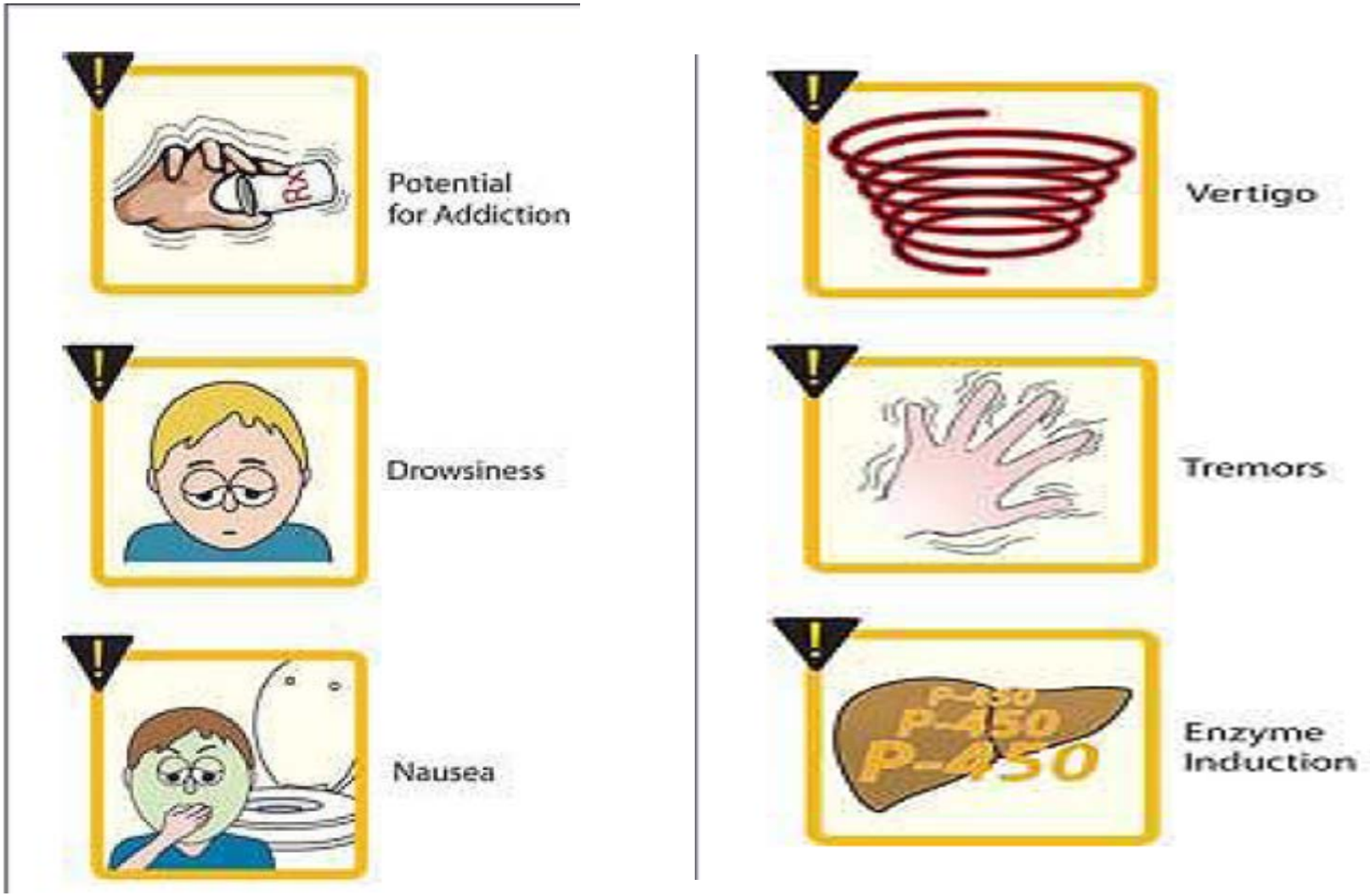
- Phenobarbital is used in long-term management of tonic-clonic seizures, status epilepticus, and eclampsia.

- Phenobarbital has been regarded as the drug of choice for treatment of young children with **recurrent febrile seizures**.

- Phenobarbital can depress cognitive performance in children, and the drug should be used cautiously.

- Phenobarbital has specific anticonvulsant activity that is distinguished from the nonspecific CNS depression.

ADVERSE EFFECTS



Tolerance:

- Repeated administration of Barbiturates.
- The tolerance is due to increase in its own metabolism, as well as adaptation of the cells in CNS.
- Tolerance with barbiturates develops for all effect except that for **anticonvulsant action.**

Drug Dependence

- Development of addiction is also common after repeated use of barbiturates.
- Withdrawal syndrome occurs after 12- 16 hrs and is characterized by **anxiety**, **restlessness**, **tremors**, **nausea**, **vomiting** .
- Drug is withdraw mostly trough the tappering method.

SYMPTOMS OF WITHDRAWAL

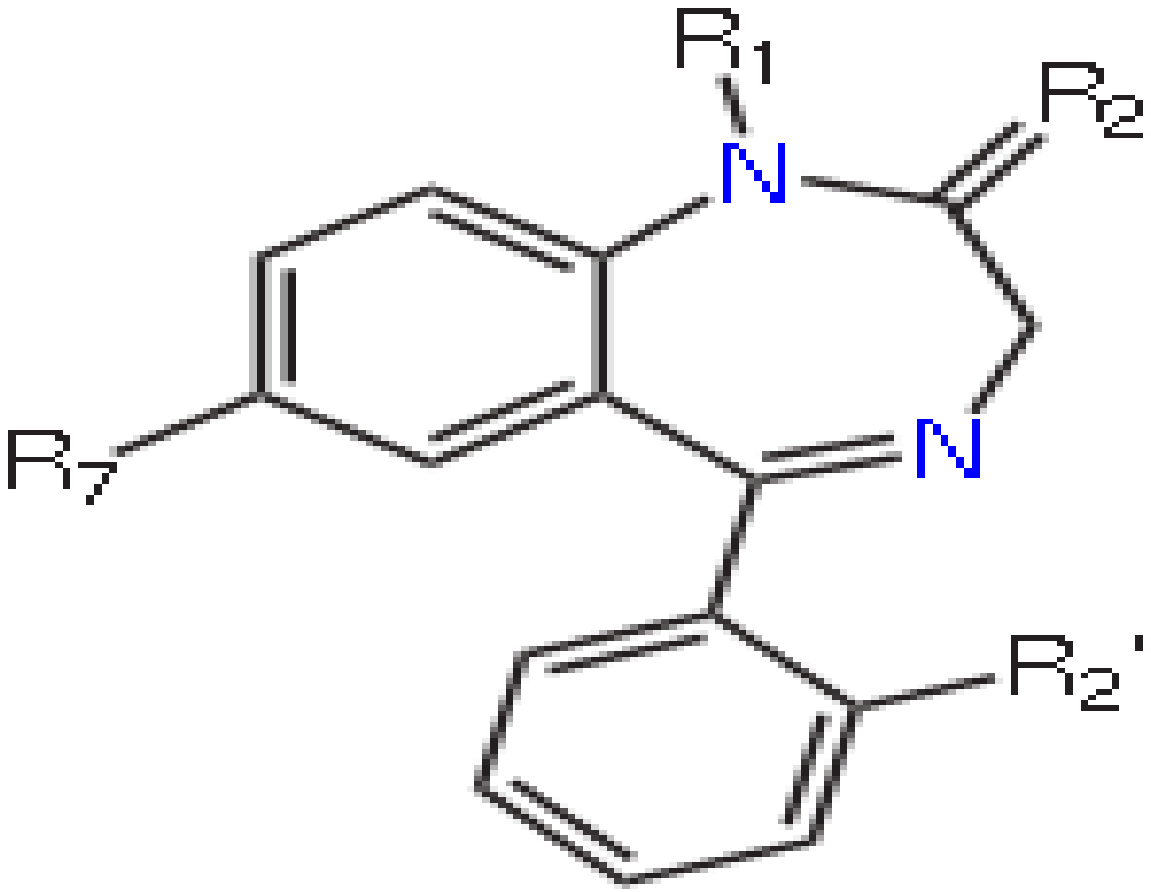
- Tremors
- Difficulty in sleeping
- Agitation
- Hallucinations
- High temperature
- Seizures.

SIDE EFFECTS

- Drowsiness
- Confusion
- Dizziness
- Trembling
- Impaired coordination
- Vision problems
- Grogginess(strong desire of sleep)
- Feelings of depression
- Headache

BENZODIAZEPINE

Benzodiazepine



GENERAL PROPERTIES OF BENZODIAZEPINES

- Benzodiazepines are compounds with **sedative**, **anxiolytic** and **anticonvulsant properties**.

- As the **dose is increased** the effects observed are first anxiolytic, followed by sedation, then hypnosis and finally unconsciousness with respiratory depression.

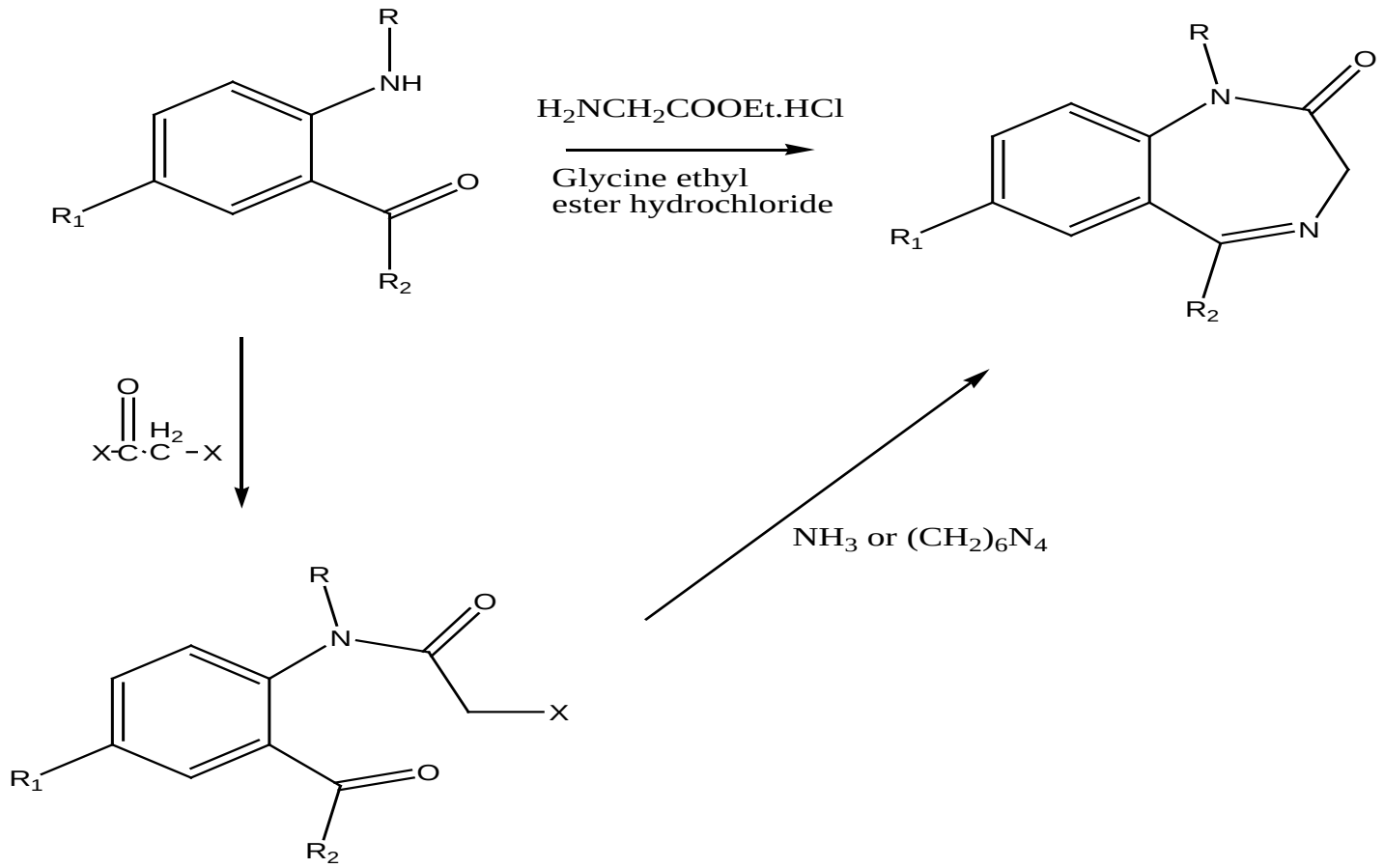
- First clinically useful benzodiazepine, chlordiazepoxide hydrochloride, was discovered in 1957.

History

- The first benzodiazepine, **chlordiazepoxid**e (Librium), was synthesized in 1955 by **Leo Sternbach** while working at Hoffmann–La Roche on the development of tranquilizers.

SYNTHESIS :-

The 2- amino aryl ketone is condensed with a bifunctional, two carbon fragment to give **1,4-benzodiazepin-2-ones**.



CLASSIFICATION

short acting

- Triazolam
- Oxazepam
- Midazolam

Intermediate acting

- Alprazolam
- Estazolam
- Temazepam
- Lorazepam

Long acting

- Diazepam
- Clonazepam
- Chlordiazeeroxide
- Flurazepam

MECHANISM OF ACTION

- Benzodiazepines act as GABA (aminobutyric acid) potentiators.

- They bind to BZ receptors on the GABA-BZ receptor complex, which allows them to allosterically modulate and enhance the activity of GABA.

- This results in increased hyperpolarization at target neurons, making them less responsive to excitatory stimuli.

PHARMACOKINETICS

- Oral route peak plasma concentration (1-3) hours
- Extensive protein binding
- Lipophilic, readily cross blood-brain barrier
- Distributed widely though out body
- Hepatic metabolism
- Many have active metabolites
- Biotransformation affected by liver disease, age, individual variation

PHARMACOLOGICAL ACTION

❖ Reduction in anxiety and agression

- BZD are useful in anxiety because of low risk of drug interactions, based on enzyme induction, high therapeutic index, slow elimination rate and a **low risk of drug dependence.**

- BZD in general, produce additive CNS depression when administered with other CNS depressant drug including ethanol.

- **Alprazolam** is specifically useful as an anxiolytic agent.

❖ Sedation and induction of sleep

- They induce sleep which is almost identical to normal sleep as the REM component is not suppressed.

❖ Reduction in muscle tone and co-ordination

- All BZD produce decrease in spontaneous motor activity in animals

- BZD exert inhibitory effect on polysynaptic reflexes and interneurones transmission and at high dose suppress transmission at the skeletal muscles.

- These effects are centrally mediated and are independent of sedative effect.

❖ Anticonvulsion effect

- Diazepam, Nitrazepam and Clonazepam possess antiepileptic activity of which diazepam is specifically useful in status epilepticus.

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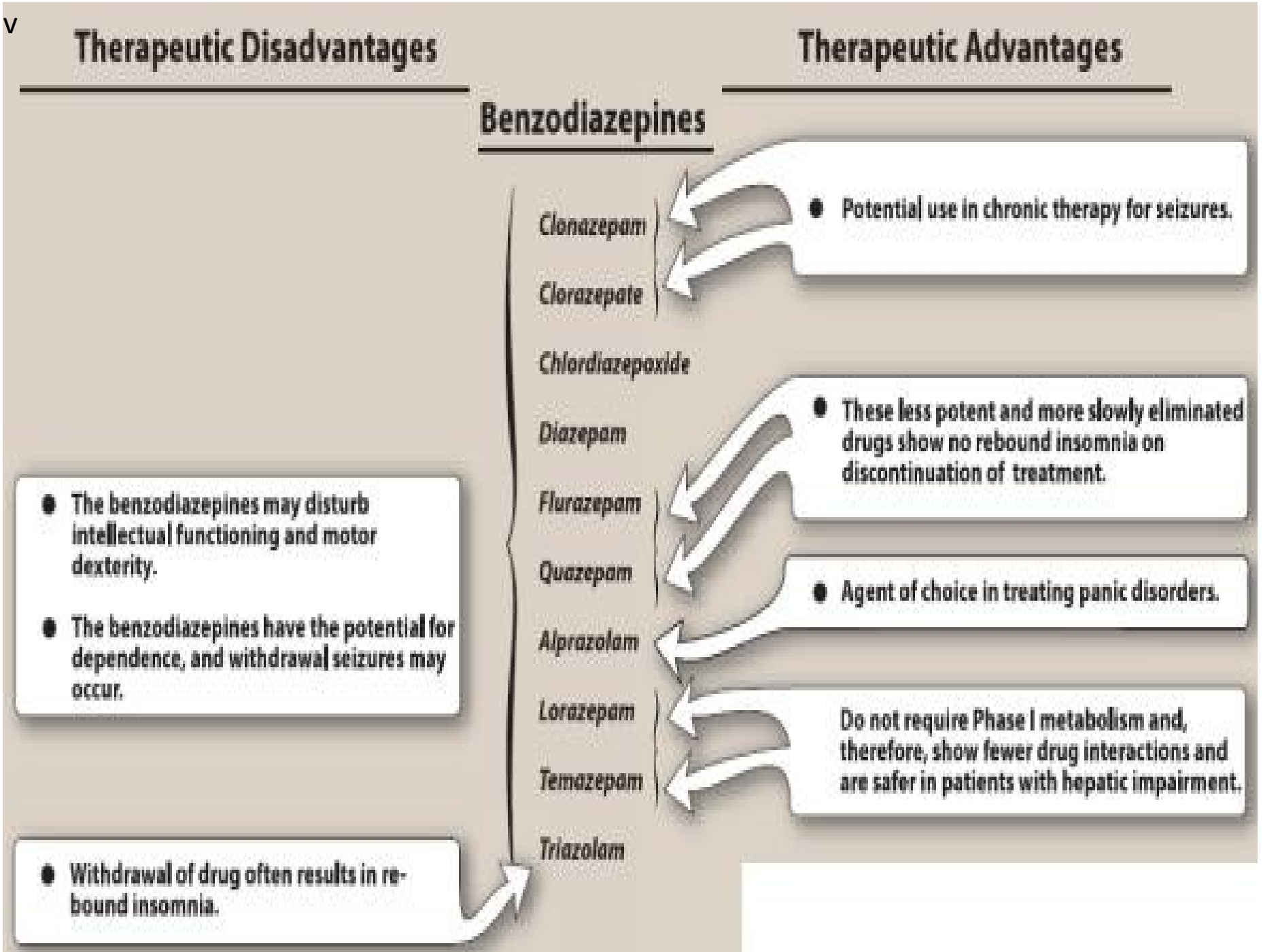
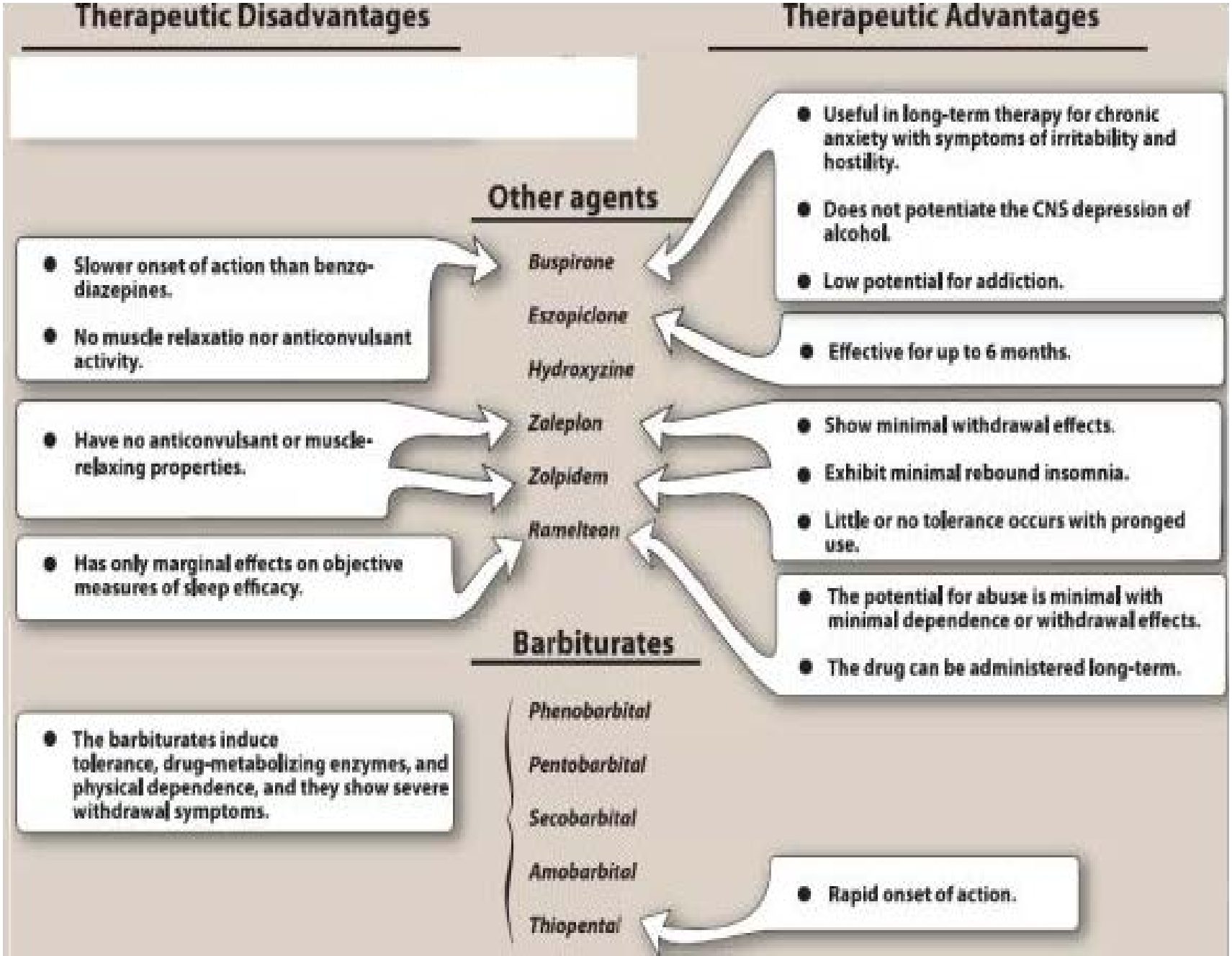

Therapeutic Disadvantages
Therapeutic Advantages
Benzodiazepines
Clonazepam
Clorazepate
Chlordiazepoxide
Diazepam
Flurazepam
Quazepam
Alprazolam
Lorazepam
Temazepam
Triazolam
Potential use in chronic therapy for seizures.
These less potent and more slowly eliminated drugs show no rebound insomnia on discontinuation of treatment.
Agent of choice in treating panic disorders.
Do not require Phase I metabolism and, therefore, show fewer drug interactions and are safer in patients with hepatic impairment.
The benzodiazepines may disturb intellectual functioning and motor dexterity.
The benzodiazepines have the potential for dependence, and withdrawal seizures may occur.
Withdrawal of drug often results in re-bound insomnia.

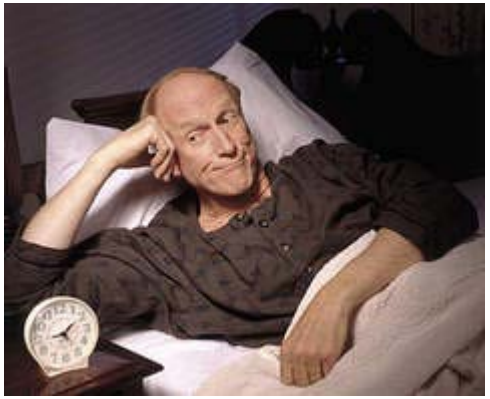

Therapeutic Disadvantages
Therapeutic Advantages
Other agents
Buspirone
Eszopiclone
Hydroxyzine
Zaleplon
Zolpidem
Ramelteon
Barbiturates
Phenobarbital
Pentobarbital
Secobarbital
Amobarbital
Thiopental
Slower onset of action than benzodiazepines.
No muscle relaxatio nor anticonvulsant activity.
Have no anticonvulsant or muscle-relaxing properties.
Has only marginal effects on objective measures of sleep efficacy.
The barbiturates induce tolerance, drug-metabolizing enzymes, and physical dependence, and they show severe withdrawal symptoms.
Useful in long-term therapy for chronic anxiety with symptoms of irritability and hostility.
Does not potentiate the CNS depression of alcohol.
Low potential for addiction.
Effective for up to 6 months.
Show minimal withdrawal effects.
Exhibit minimal rebound insomnia.
Little or no tolerance occurs with pronged use.
The potential for abuse is minimal with minimal dependence or withdrawal effects.
The drug can be administered long-term.
Rapid onset of action.

USES:

- Anxiety and panic
- Seizures (convulsions)
- Insomnia or trouble sleeping.
- General anaesthesia
- Sedation prior to surgery or diagnostic procedures
- Muscle relaxation
- Acohol withdrawal
- Nausea and vomiting
- Depression
- Panic attacks

SIDE EFFECT

- Feeling of depression
- Loss of orientation
- Headache
- Sleep disturbance
- Confusion
- Irritability
- Aggression
- Excitement
- Memory impairment



WITHDRAWAL SYMPTOMS

- Anxiety
- Trouble sleeping
- Restlessness
- Muscle tension
- Nausea
- Blurred vision
- Sweating,
- Nightmares
- Depression,
- Muscle coordination problems
- Muscle twitching
- Hallucinations
- Delusions
- Ringing in the ears

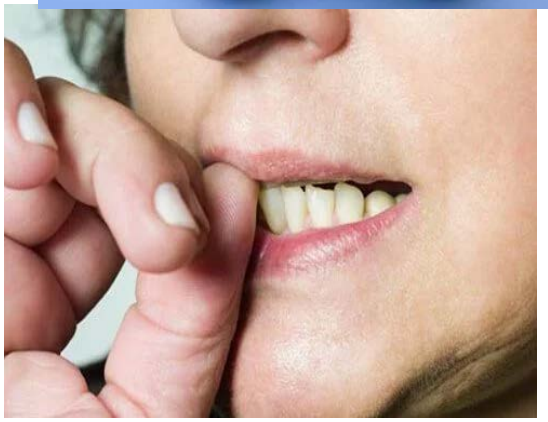
CONTRAINDICATION

- The FDA classifies benzodiazepines as pregnancy **categoryD**, which means that benzodiazepines can potentially cause fetal harm if administered to pregnant women.

- Benzodiazepines **enter breast milk** and can cause lethargy and weight loss in the newborn.. Therefore, they should not be used in **nursing mothers**.

OVERDOSE SYMPTOMS

- Confusion
- Slurred speech
- Loss of muscle control
- Trouble thinking or talking
- Unconsciousness
- Low blood pressure
- Slow or shallow breathing
- Seizure
- Cardiac arrest



RESEARCH TOPICS

- The use of benzodiazepines and related drugs (Z drugs) is associated with a modestly increased risk of Alzheimer's disease, according to a recent study from the University of Eastern Finland.

Benzodiazepines are associated with increased risk of Alzheimer's disease

Date: August 13, 2018

Source: University of Eastern Finland

Summary: The use of benzodiazepines and related drugs (Z drugs) is associated with a modestly increased risk of Alzheimer's disease, according to a recent study.

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RELATED TOPICS

Health & Medicine

- Alzheimer's Research
- Healthy Aging
- Controlled Substances
- Chronic Illness

Mind & Brain

- Alzheimer's
- Disorders and Syndromes
- Caregiving
- Addiction

FULL STORY

The use of benzodiazepines and related drugs (Z drugs) is associated with a modestly increased risk of Alzheimer's disease, according to a recent study from the University of Eastern Finland. The risk increase was similar with both benzodiazepines and Z drugs regardless of their half-life. The results were published in *Acta Psychiatrica Scandinavica*.

Even though the increased risk for Alzheimer's disease was small in this study, the threshold for prescribing benzodiazepines and related drugs should be high enough due to their several adverse effects and events, such as falls. These medications are commonly used for sleep problems, but their effectiveness for this indication diminishes over weeks or months. However, the risk of

Research suggests benzodiazepine use is high while use disorder rates are low

News & Events

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Science Highlight

October 18, 2018

Benzodiazepines, such as sedatives and sleeping aids, are often used for the short-term treatment of anxiety and insomnia. While benzodiazepine use is highly prevalent among U.S. adults, public health experts have not known what proportion of benzodiazepine users misuse them or meet criteria for benzodiazepine use disorders. A recent analysis suggests that benzodiazepine use disorders are relatively rare among the adults who use benzodiazepine medications, even if they are misusing them.

Contact Press Office

301-443-6245
(8:30-5:30 ET)
media@nida.nih.gov

Resources for the Media

THANK YOU