DRUG ACTING ON CENTRAL NERVOUS SYSTEM

SEDATIVE-HYPNOTICS

Subject : Pharmacology-I
Code : BP404TP

Prepaed by
Ms. Shweta M. Pandya
Assistant Professor
B.Pharm, M.Pharm

Saraswati Institute of Pharmaceutical Sciences

Overview

- Introduction
- Historical Perspectives
- Classification: Sedative / Hypnotics
- Mechanism of action
- Barbiturates
- Benzodiazepines
- Miscellaneous Hypnotics & Anxiolytics

Introduction

Sedative – Hypnotics

Sedative

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

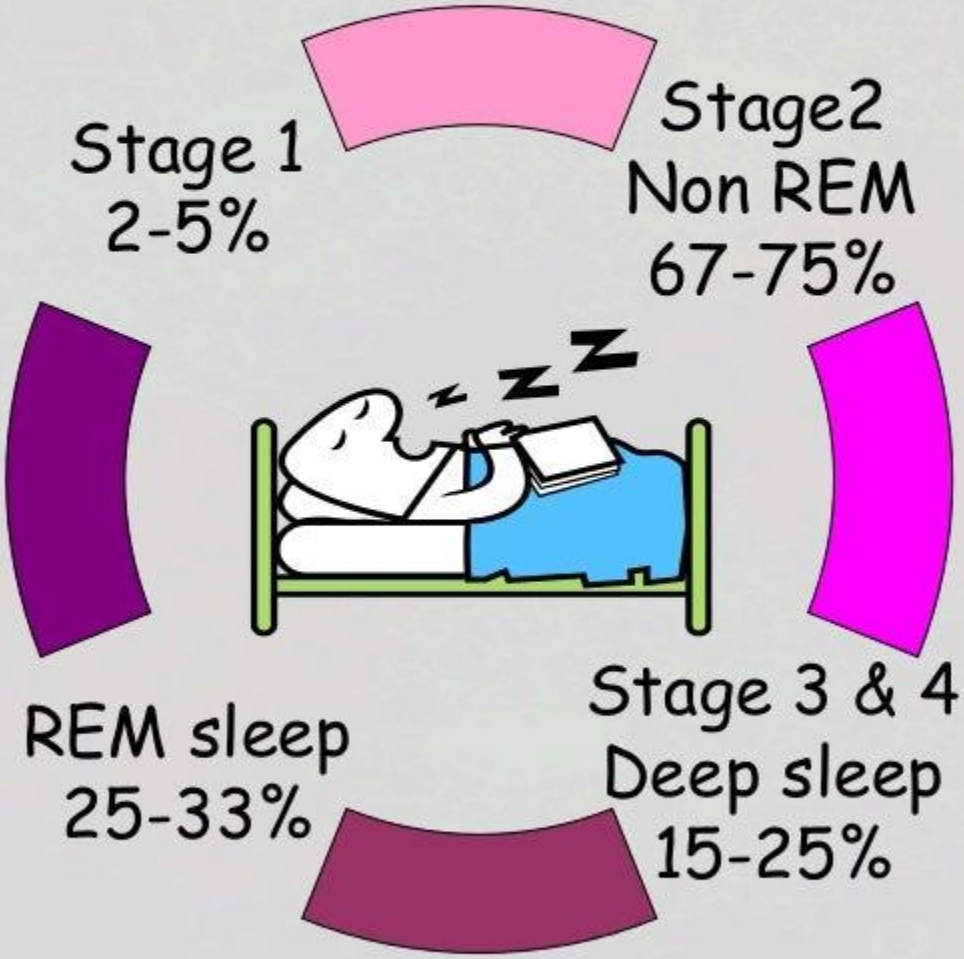
Hypnotic

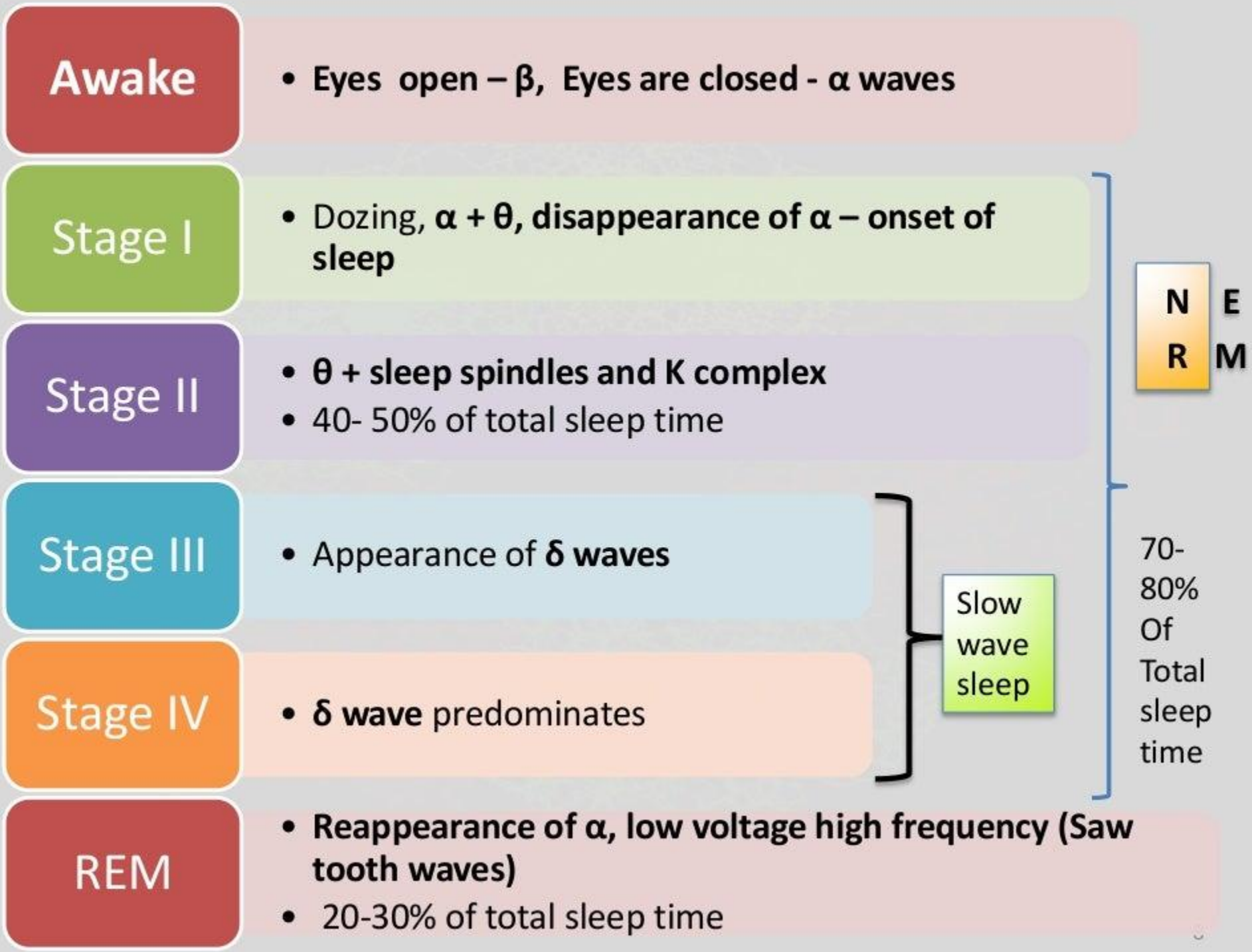
- A drug which produces sleep resembling natural sleep
- They are used for initiation and / or maintenance of sleep.
- Hypnotics in higher doses produce General anaesthesia.
- Site of action is on the midbrain and ascending RAS which maintain wakefulness.

Anxiolytic

- Anxiety is an unpleasant state of tension, apprehension, or uneasiness that arises from either a known or an unknown source
- Anxiolytic is an agent which decreases worriness manifested as the psychic awareness of anxiety which is accompanied with increased vigilance, motor tension, and autonomic hyperreactivity.

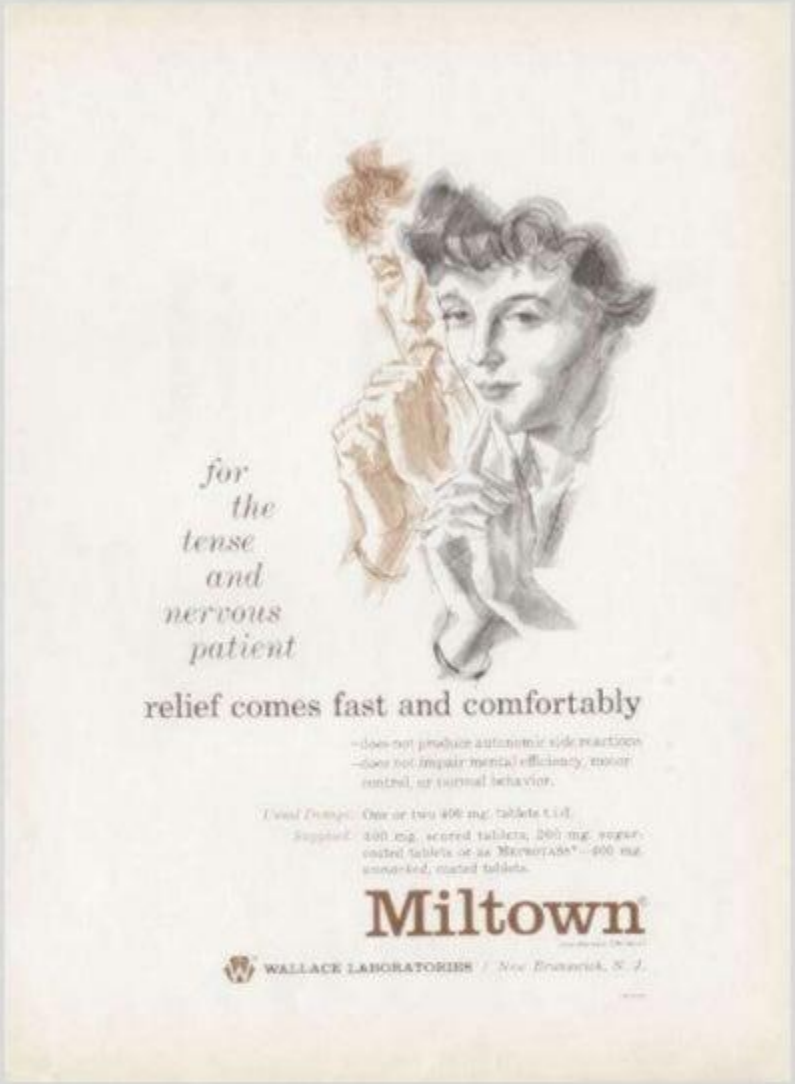
Stages of Sleep




Awake
• Eyes open – β, Eyes are closed - α waves
Stage I
• Dozing, α + θ, disappearance of α – onset of sleep
Stage II
• θ + sleep spindles and K complex
• 40- 50% of total sleep time
Stage III
• Appearance of δ waves
Stage IV
• δ wave predominates
Slow wave sleep
NREM
70-80% Of Total sleep time
REM
• Reappearance of α, low voltage high frequency (Saw tooth waves)
• 20-30% of total sleep time

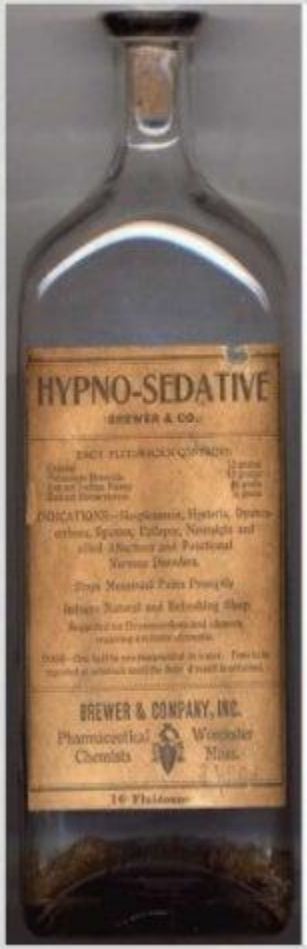
History

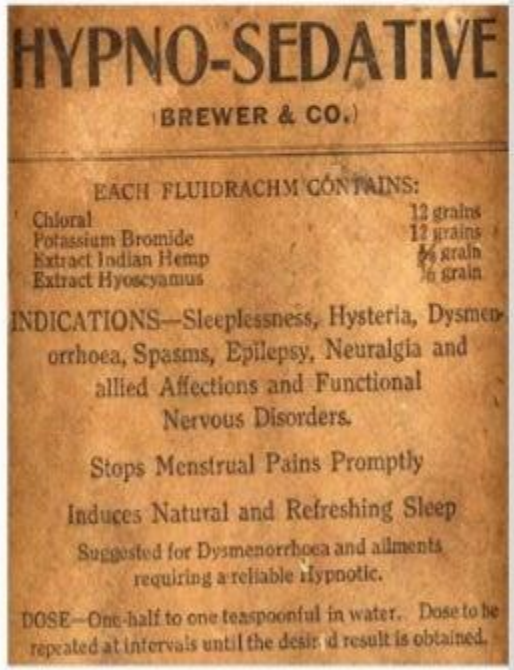

Why Count Sheep To Go To Sleep.
DID you ever tell anyone that you have trouble in sleeping? Notice how many people could tell you just how to get a good night's rest?
"Count sheep" says the old timer. "Relax your muscles" says another friend. You've had suggestions all the way from taking a warm bath to making your mind a blank, and they've all failed.
Yet there is a way for you to get a good night's sleep if your sleeplessness is due to a nervous condition. It's so pleasant—so easy that you can't afford to wait another day before trying it. About a half hour before you go to bed to-night, take a Dr. Miles' Effervescent NERVINE Tablet. Drop it into a glass of water. It makes a pleasant sparkling drink that quiets over-wrought nerves and permits sound, refreshing sleep.
You will find Dr. Miles' Effervescent NERVINE Tablets a pleasant relief for Nervousness, Sleeplessness due to Nervousness, Nervous Headache, Nervous Dyspepsia, Hysterical Conditions, Sea Sickness, Train Sickness, Auto Sickness and Minor Nervous disturbances. They are not narcotic, not habit-forming and do not depress the heart.
Use Trial Pkg. Coupon We invite you to try these modern tablets. Fill out the coupon on the inside back cover for a 15¢ trial package. Better still, get a $1.00 package at your drug store. If you're not satisfied, your druggist will refund your money.
Effervescent
DR. MILES
NERVINE
TABLETS


for the tense and nervous patient
relief comes fast and comfortably
Miltown
WALLACE LABORATORIES

History

- **Sedatives (before development of barbiturates)**
  - Since antiquity, alcohol beverages and potions containing laudanum and various herbals have been used to induce sleep.
  - Morphine was used for quick management of aggressive patients
    In 1800: most widely used sedative in asylums
  - In 1857: Bromide was the first agent to be introduced specifically as a sedative and soon thereafter as a hypnotic





History

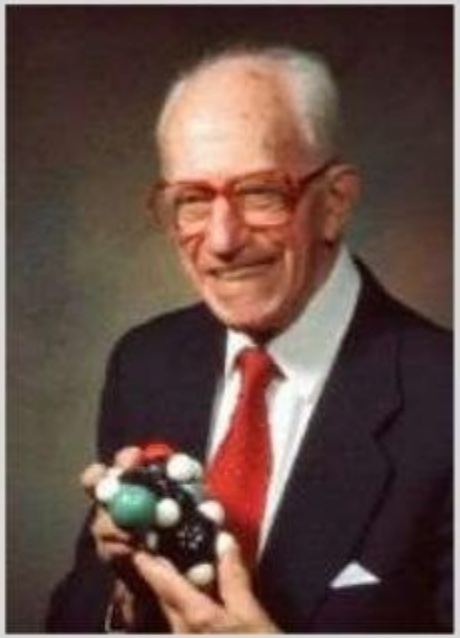
- **1864: Barbiturates** were introduced
  - Barbiturates were widely diverted from medical use and used on the street in the 60s where they were called "downers" and sold under a variety of different names.
  - Barbiturates had a low therapeutic index and were often used for suicide.

Baeyer, discoverer of barbiturates

Marilyn Monroe died of barbiturate overdose in 1962

History

- **By 1990s, barbiturates replaced by benzodiazepines**
  - 1961: introduction of chlordiazepoxide
  - **Sternback is credited with the invention of** *chlordiazepoxide*, *diazepam*, *flurazepam*, *nitrazepam*, *clonazepam*, and *trimethaphan*

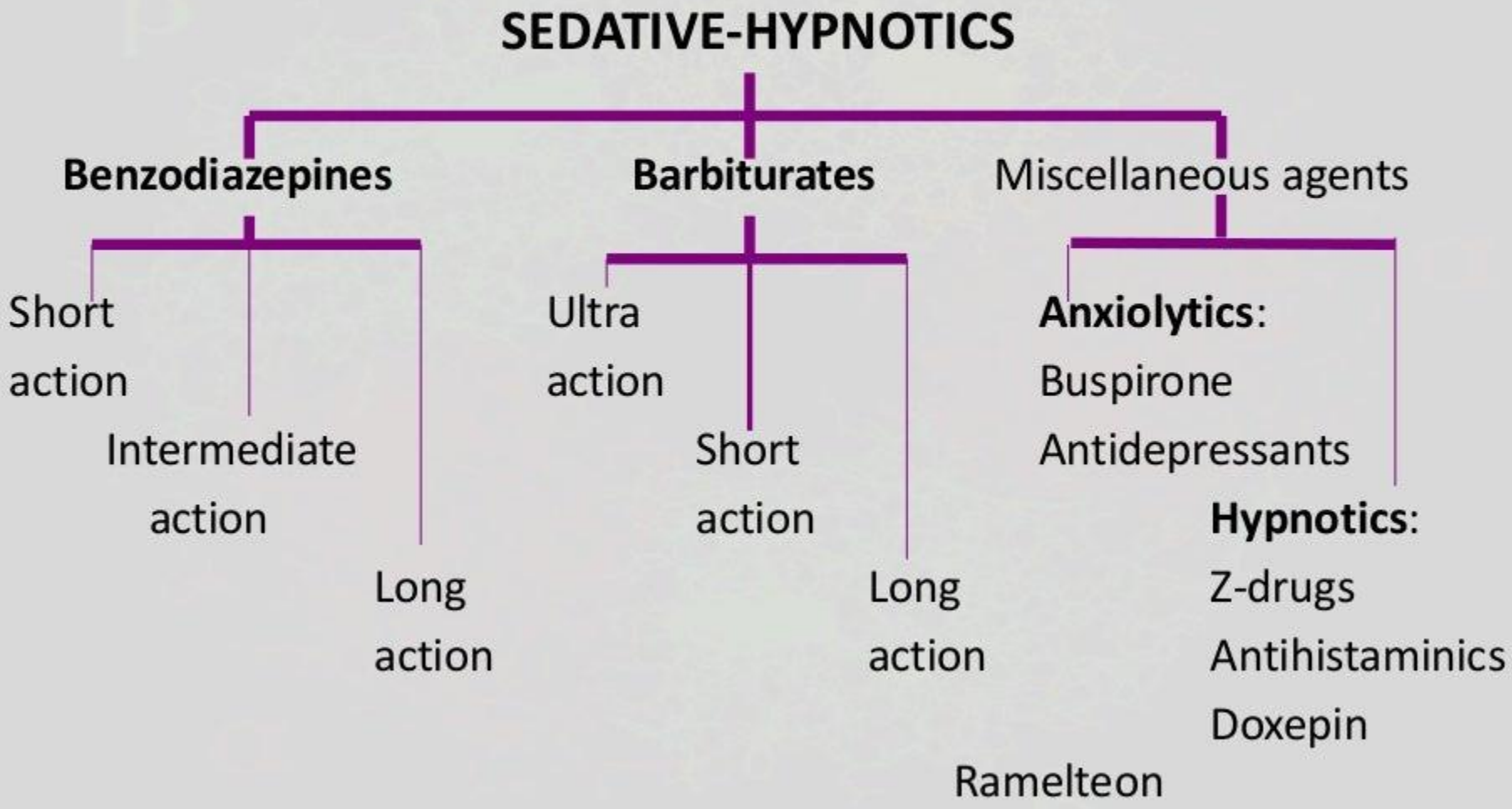


Leo Sternback

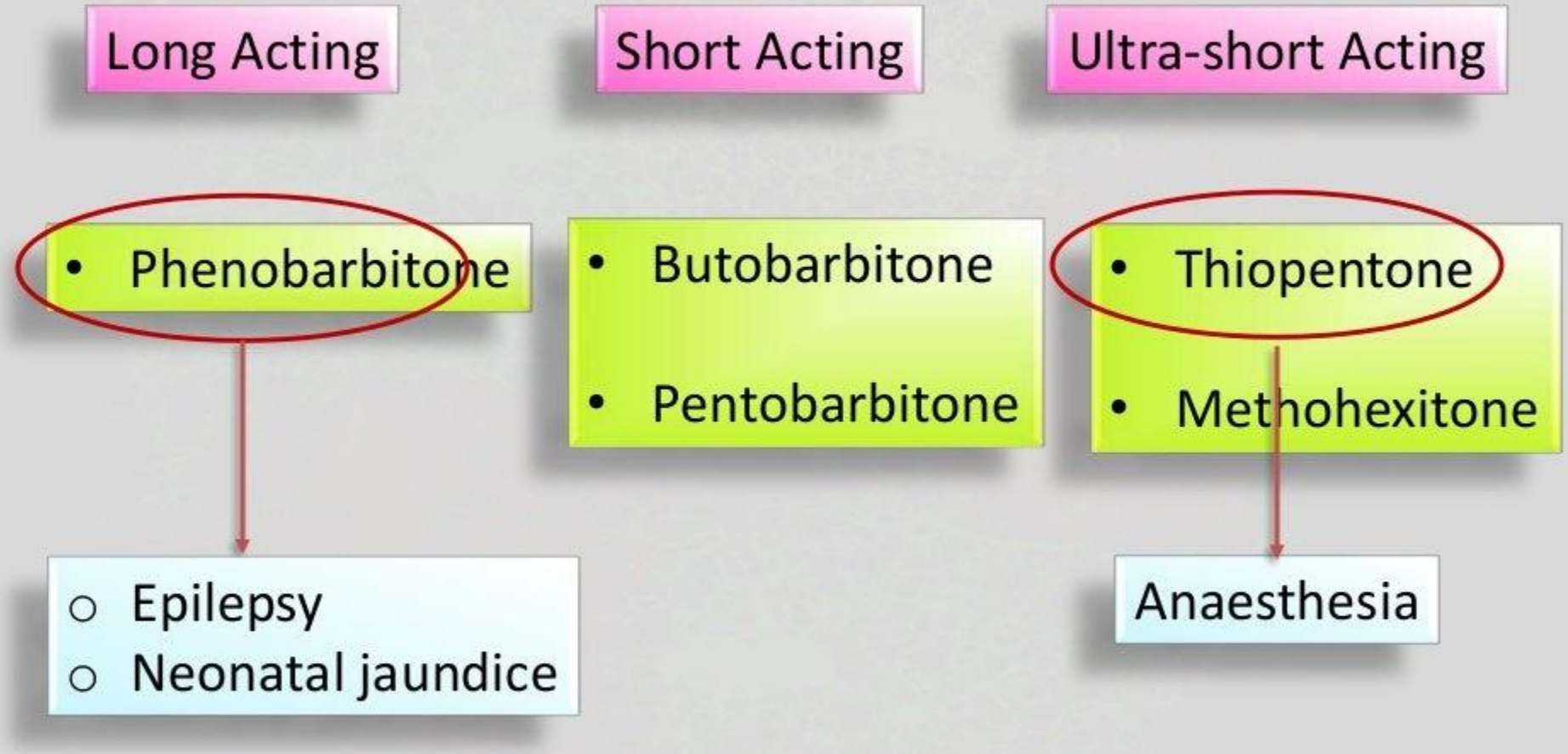
History

- **Others and Z Drugs**
  - **Methaqualone** (Quaalude) and **meprobamate (**Miltown) were used in the 60s as "non barbiturate tranquilizers".
    - **1951:** Methaqualone was synthesized in India as an antimalarial
    - 1965: the most commonly prescribed sedative in Britain
    - 1972: the sixth-bestselling sedative in the USA
    - discontinued in 1985, mainly due to its psychological addictiveness and recreational use
  - **Z drugs:** now replacing the BDZs; can be targeted to specific symptoms, insomnia and anxiety.

SEDATIVE-HYPNOTIC DRUGS



Barbiturates



Benzodiazepines
a/c to Duration of Action

Short acting

- Triazolam
- Oxazepam
- Midazolam

Intermediate acting

- Alprazolam
- Estazolam
- Temazepam
- Lorazepam
- Nitrazepam

Long acting

- Diazepam
- Flurazepam
- Clonazepam
- Chlordiazepoxide

Benzodiazepines a/c to Indications

Hypnotic

- Diazepam
- Flurazepam
- Nitrazepam
- Alprazolam
- Temazepam
- Triazolam

Antianxiety

- Diazepam
- Chlordiazepoxide
- Oxazepam
- Lorazepam
- Alprazolam

Anticonvulsant

- Diazepam
- Lorazepam
- Clonazepam
- Clobazam

Miscellaneous agents

Z Drugs

- Zolpidem
- Zopiclone
- Zaleplon

Melatonin receptor agonist

- Ramelteon

Others

- Antidepressants
- Antihistaminics

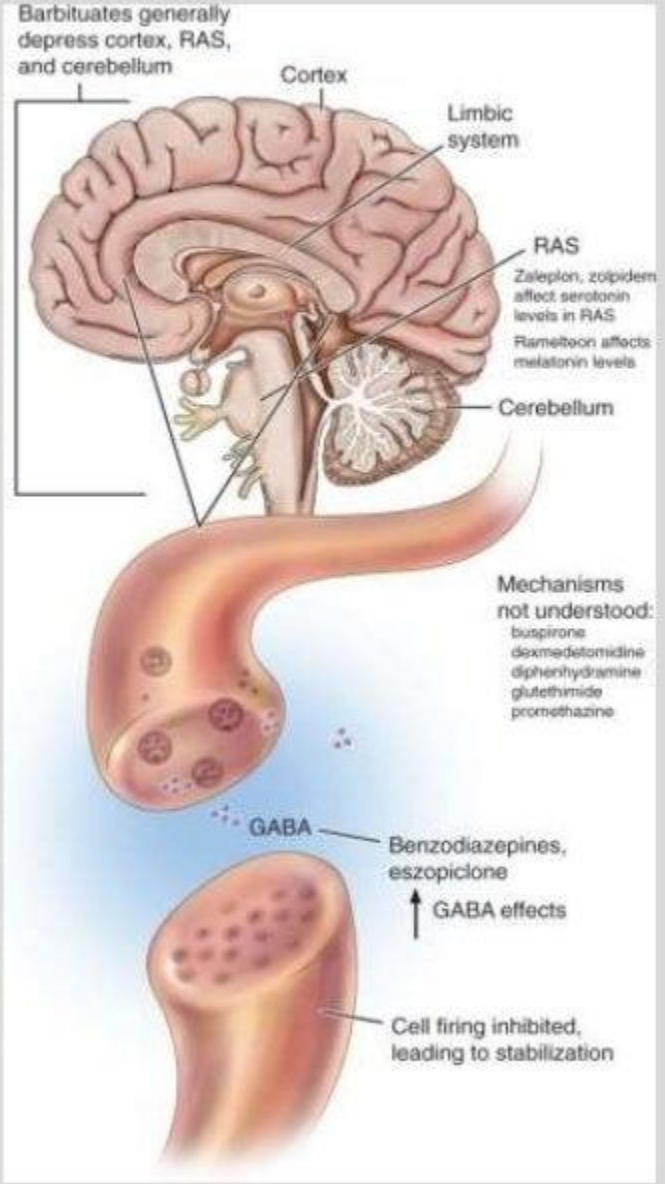
Site of Action

- Midbrain (RAS) - Wakefulness
- Limbic system - Thought & mental functions
- Medulla - Muscle relaxation
- Cerebellum - Ataxia

✓ Effect : Limbic system > Midbrain RAS

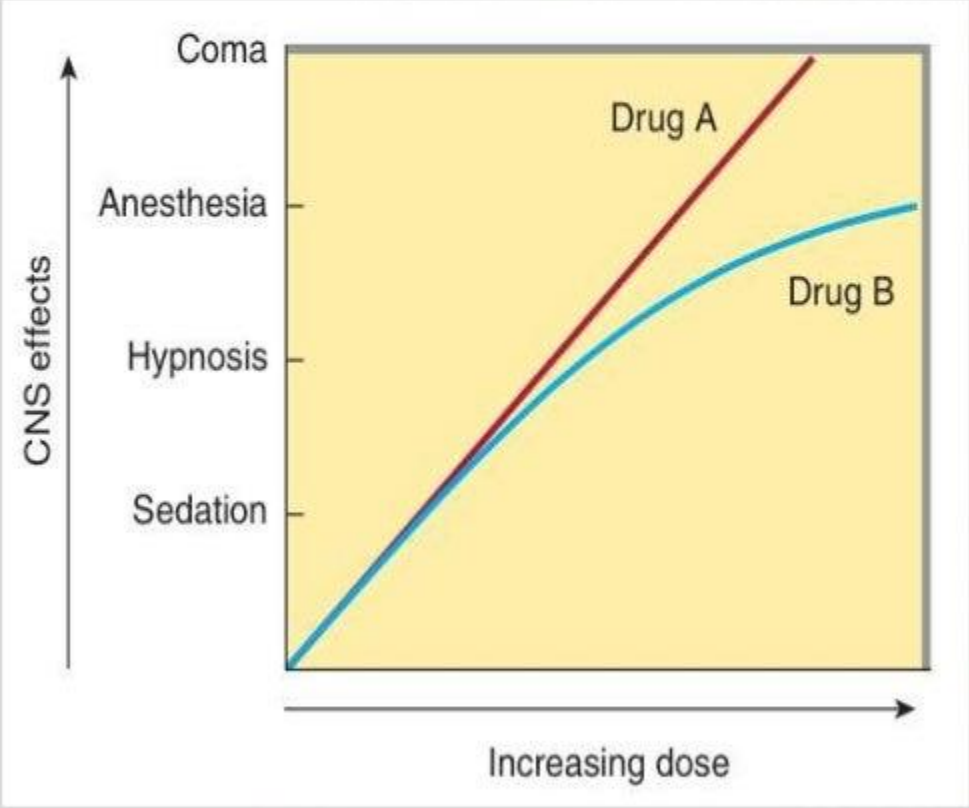
⇓

- Therapeutic dose ⇒ Anxiolytic > Sedative
- Higher dose ⇒ Depress RAS → Sedative & hypnotic effect



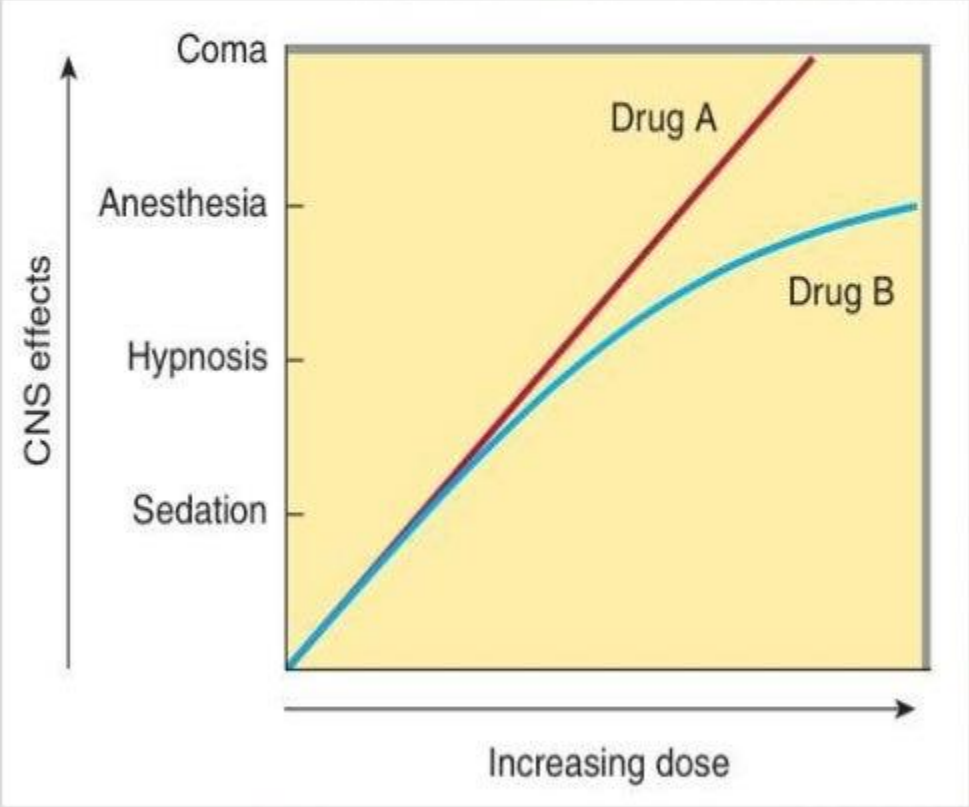
Dose Dependent Action

Dose-response curves for two hypothetical sedative-hypnotics



- Drug A:
  - An increase in dose higher than that needed for hypnosis may lead to a state of general anesthesia.
  - With higher doses, the drug will depress the respiratory and vasomotor centers which leads to coma.
  - Drug A is an example of alcohol and barbiturates.
- Drug B:
  - needs greater doses to achieve CNS depression.
  - Drug B is an example of benzodiazepines and newer hypnotics.

Dose-response curves for two hypothetical sedative-hypnotics



- Drug A – Barbitutates
  - Steeper DRC
  - Narrow margin of safety
- Drug B – Benzodiazepines
  - Flatter dose response curve
  - Greater margin of safety

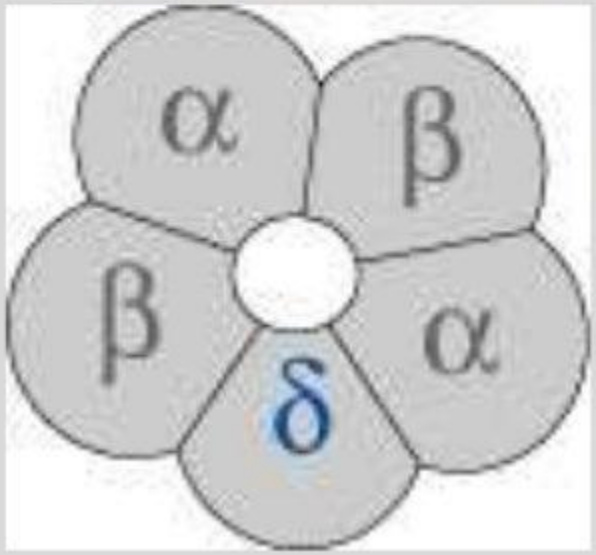
Mechanism of Action

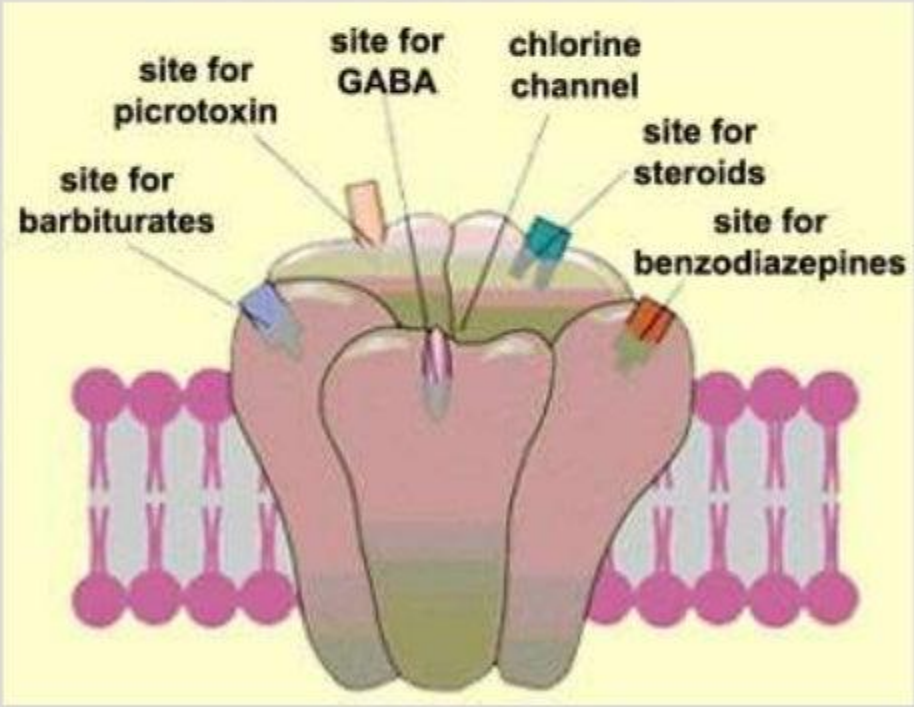
MOLECULAR PHARMACOLOGY OF THE GABA RECEPTOR

- Pentameric transmembrane anion channel
- composed of five subunits α, β, γ and also δ, ε, π, ρ, etc.
  - there are six different α, four β, and three γ
- multiple BZD receptor subtypes
- Two $\alpha 1$ and two $\beta 2$ and one $\gamma 2$ subunits – most commonly expressed BZD receptor isoform

MOLECULAR PHARMACOLOGY OF THE GABA RECEPTOR

Ligand	Subunit
GABA	β
Barbiturate	α or β
Benzodiazepine	α / γ interface
Z-drugs	α1





GABA-A RECEPTOR Cl CHANNEL BINDING SITE LIGANDS

- Agonists
  - GABA: promotes Cl influx
  - Barbiturates: facilitates & mimics GABA action
  - Benzodiazepines: facilitate GABA action
  - Alcohol, Inhalational anaesthetics, propofol: open Cl channel directly
- Antagonists
  - Bicuculline: competitive antagonist at GABA Rc
  - Flumazenil: competitive antagonist at BZD site
  - Picrotoxin: blocks Cl channel non-competitively
- Inverse agonists
  - β-carbolines (DMCM – dimethoxyethyl-carbomethoxy-β-carboline): inverse agonist at BZD site
  - produce anxiety and seizures

Mechanism of Action

Barbiturates / Benzodiazepines

↓

Bind to **$GABA_A$ receptor** at different allosteric sites

↓

Facilitates GABA action

↓

Barbiturates increase **duration** & Benzodiazepines increase frequency of opening of Cl^- channel

↓

Membrane hyperpolarization

↓

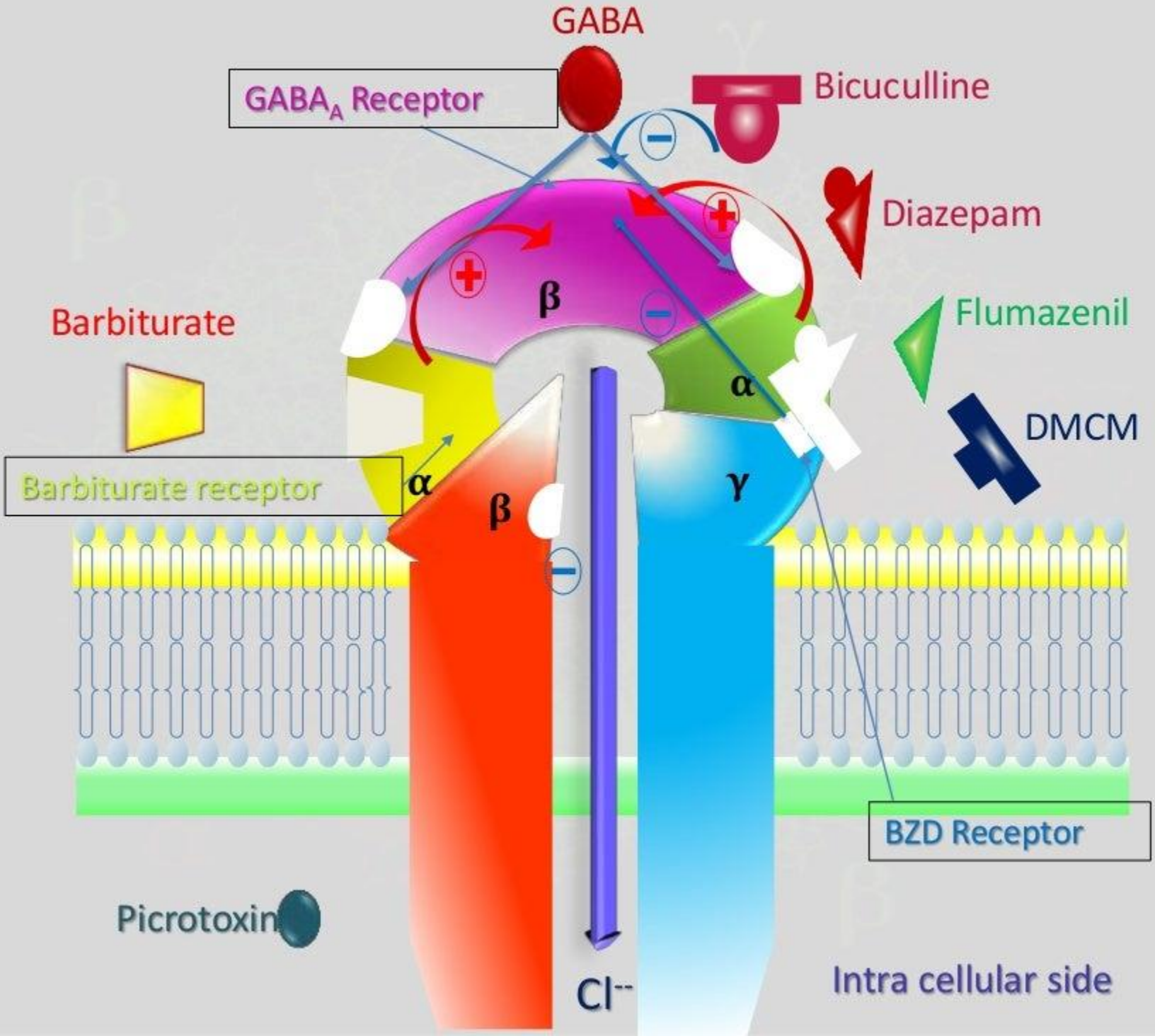
CNS depression

At **higher dose** Barbiturates can act as GABA **mimetic**

Mechanism of Action

- Benzodiazepines
  - increase frequency of opening of Cl^- channels induced by GABA (**GABA facilitatory action**)
  - increase binding of GABA to $GABA_A$ receptor

- Barbiturates
  - increase duration of opening of Cl^- channels induced by GABA (**GABA facilitatory action**)
  - at high conc.
    - can directly increase Cl^- conductance through Cl^- channels (**GABA mimetic action**)
    - inhibit Ca dependent release of neurotransmitters
    - depress glutamate induced neuronal depolarization through AMPA receptor
  - at very high conc. (anaesthetic doses)
    - depress voltage sensitive Na^+ & K^+ channels


GABA
GABA$_A$ Receptor
Bicuculline
Diazepam
Flumazenil
DMCM
Barbiturate
Barbiturate receptor
β
α
β
α
γ
BZD Receptor
Picrotoxin
Cl⁻⁻
Intra cellular side

Barbiturates

Pharmacokinetics

- well absorbed after oral administration and distribute throughout the body.
- Distribution and Duration of Action determined by Lipid Solubility
  - **More lipid soluble = fast onset & short duration of action, BUT…**
    - sequestered by body fat
    - and as brain levels fall, released slowly from fat cells back into blood
  - **Two-Phase Excretion Curve – 2 Half-Lives**
    - Rapid drop in blood level as drug is redistributed;
    - Released from body fat;

Pharmacokinetics

- All barbiturates redistribute from the brain to the splanchnic areas, to skeletal muscle, and, finally, to adipose tissue.
  - CNS effects are of thiopental are terminated by rapid redistribution of the drug from the brain to other highly perfused tissues (skeletal muscles)
- readily cross the placenta and can depress the fetus.
- metabolized in the liver, and inactive metabolites are excreted in urine.
- Alkalinization increases excretion ($NaHCO_3$)

Actions

- At low doses, produce sedation (have a calming effect and reduce excitement).
- At higher doses, cause hypnosis, followed by anesthesia (loss of feeling or sensation), and, finally, coma and death.
- Barbiturates do not raise the pain threshold and have no analgesic properties
  - may even exacerbate pain
- Barbiturates suppress the hypoxic and chemoreceptor response to CO2, and overdosage is followed by respiratory depression and death.
- Large dose cause circulatory collapse due to medullary vasomotor depression & direct vasodilatation.

Therapeutic Uses: Barbiturates

- **Anesthesia:**
  - The ultra–short-acting barbiturates, such as *thiopental:* used IV to induce anesthesia
  - but have largely been replaced by other agents.
- **Anticonvulsant:**
  - *Phenobarbital* is used in long-term management of tonic–clonic seizures
  - can depress cognitive development in children and decrease cognitive performance in adults, and it should be used only if other therapies have failed.
  - *Phenobarbital* is used for the treatment of refractory status epilepticus

Therapeutic Uses: Barbiturates

- **Sedative/hypnotic:**
  - Barbiturates have been used as mild sedatives to relieve anxiety, nervous tension, and insomnia.
  - However, the use of barbiturates for insomnia is no longer generally accepted, due to their adverse effects and potential for tolerance.
- **Hyperbilirubinemia** and **kernicterus** in the neonates (increase glucouronyl transferase activity).

Adverse effects

- drowsiness, impaired concentration, and mental and physical sluggishness
- The CNS depressant effects of barbiturates synergize with those of *ethanol.*
- Hypnotic doses of barbiturates produce a drug "hangover" that may lead to impaired ability to function normally for many hours after waking.

Adverse effects

- Barbiturates induce cytochrome P450 (CYP450) microsomal enzymes in the liver.
  - Therefore, diminishes the action of many drugs that are metabolized by the CYP450 system.
- Barbiturates are contraindicated in patients with acute intermittent porphyria (because of increased heme synthesis)
  - Increase activity of hepatic gamma amino levulinic acid synthetase ALA □ synthesis of porphyrin

Adverse Effects

- Chronic use results in development of tolerance
  - Metabolic tolerance
    - Occurs with phenobarbital
    - Induces its own metabolism
    - Decreases CNS response to the drug itself
- Abrupt withdrawal from barbiturates may cause
  - tremors, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium, and cardiac depression
  - Death may also result from overdose

Benzodiazepines

Pharmacokinetics

- lipophilic
- rapidly and completely absorbed after oral administration
- distribute throughout the body and penetrate into the CNS
- Redistribution occurs from CNS to skeletal muscles& adipose tissue (→ **termination of action**)
- The longer-acting agents form active metabolites with long half-lives.

Metabolism

- All Benzodiazepines are metabolized in the liver
  - Phase I: (liver microsomal system)
  - Phase II: glucouronide conjugation and excreted in the urine.
- Many of Phase I metabolites are active: Increase elimination half life of the parent compound , cumulative effect with multiple doses.
- EXCEPTION: No active metabolites are formed for (LEO) Lorazepam, Estazolam, Oxazepam.
- Cross placental barrier during pregnancy and are excreted in milk (Fetal & neonatal depression)

Actions

- Reduction of anxiety
  - At low doses, the benzodiazepines are anxiolytic
  - reduce anxiety by selectively enhancing GABAergic transmission in neurons having the α_2 subunit in their $GABA_A$ receptors
  - thereby inhibiting neuronal circuits in the limbic system of the brain
  - The antianxiety effects of the benzodiazepines are less subject to tolerance than the sedative and hypnotic effects.

Actions

- Sedative/hypnotic
  - All benzodiazepines have sedative and calming properties
  - some can produce hypnosis (artificially produced sleep) at higher doses
  - The hypnotic effects are mediated by the α_1-$GABA_A$ receptors.

Actions

- Anterograde amnesia
  - Temporary impairment of memory with use of the benzodiazepines
  - mediated by the α_1-$GABA_A$ receptors.
  - The ability to learn and form new memories is also impaired.

Actions

- Anticonvulsant
  - Several benzodiazepines have anticonvulsant activity.
  - This effect is partially, although not completely, mediated by α_1-$GABA_A$ receptors.

- Muscle relaxant
  - At high doses, the benzodiazepines relax the spasticity of skeletal muscle
  - by increasing presynaptic inhibition in the spinal cord, where the α_2-$GABA_A$ receptors are largely located.

Dependence

- Psychological and physical dependence can develop if high doses are given for a prolonged period.
- Abrupt discontinuation results in withdrawal symptoms
  - confusion, anxiety, agitation, restlessness, insomnia, tension, and (rarely) seizures
- Benzodiazepines with a short elimination half-life, such as *triazolam,* induce more abrupt and severe withdrawal reactions than those seen with drugs that are slowly eliminated such as *flurazepam*

Adverse Effects

- Drowsiness and confusion: Most common AE
- Ataxia occurs at high doses
- Cognitive impairment (decreased long-term recall and retention of new knowledge) can occur with use of benzodiazepines.
- Benzodiazepines should be used cautiously in patients with liver disease.
- Alcohol and other CNS depressants enhance the sedative–hypnotic effects of the benzodiazepines.
- Administration in third trimester can result in “floppy-infant syndrome”

Therapeutic Uses: Benzodiazepines

Anxiety disorders

- Benzodiazepines are effective for the treatment of the anxiety symptoms secondary to
  - panic disorder, generalized anxiety disorder (GAD), social anxiety disorder, performance anxiety, posttraumatic stress disorder, obsessive–compulsive disorder, and extreme anxiety associated with phobias and anxiety related to depression and schizophrenia.
- The longer-acting agents, such as *clonazepam*, *lorazepam*, and *diazepam*, are often preferred in those patients with anxiety that may require prolonged treatment.
- For panic disorders, *alprazolam* is effective for short- and long-term treatment
- To control Alcohol withdrawal symptoms:
  - chlordiazepoxide, chlorazepate, diazepam & oxazepam

Sleep disorders

- decrease the latency to sleep onset and increase stage II of non–rapid eye movement (REM) sleep.
- Both REM sleep and slow-wave sleep are decreased.
- Commonly prescribed benzodiazepines for sleep disorders include
  - intermediate-acting *temazepam* and short-acting *triazolam*.
  - long-acting *flurazepam* is rarely used, due to its extended half-life, which may result in excessive daytime sedation

Amnesia

- The shorter-acting agents are often employed as pre- medication for anxiety-provoking and unpleasant procedures, such as endoscopy, dental procedures, and angioplasty.
- Midazolam is used to facilitate amnesia while causing sedation prior to anesthesia.

Seizures

- Clonazepam is used as an adjunctive therapy for certain types of seizures
- lorazepam and diazepam are the drugs of choice in terminating status epilepticus.
- Due to cross-tolerance, chlordiazepoxide, clorazepate, diazepam, lorazepam, and oxazepam are useful in the acute treatment of alcohol withdrawal and reduce the risk of withdrawal-related seizures.

Muscular disorders

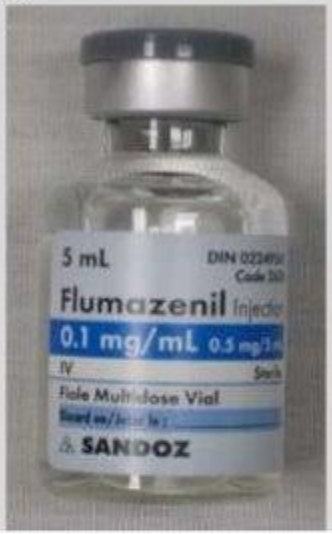
- Diazepam is useful in the treatment of
  - skeletal muscle spasms, such as occur in muscle strain
  - spasticity from degenerative disorders, such as multiple sclerosis and cerebral palsy

Advantages of benzodizepines over barbiturates

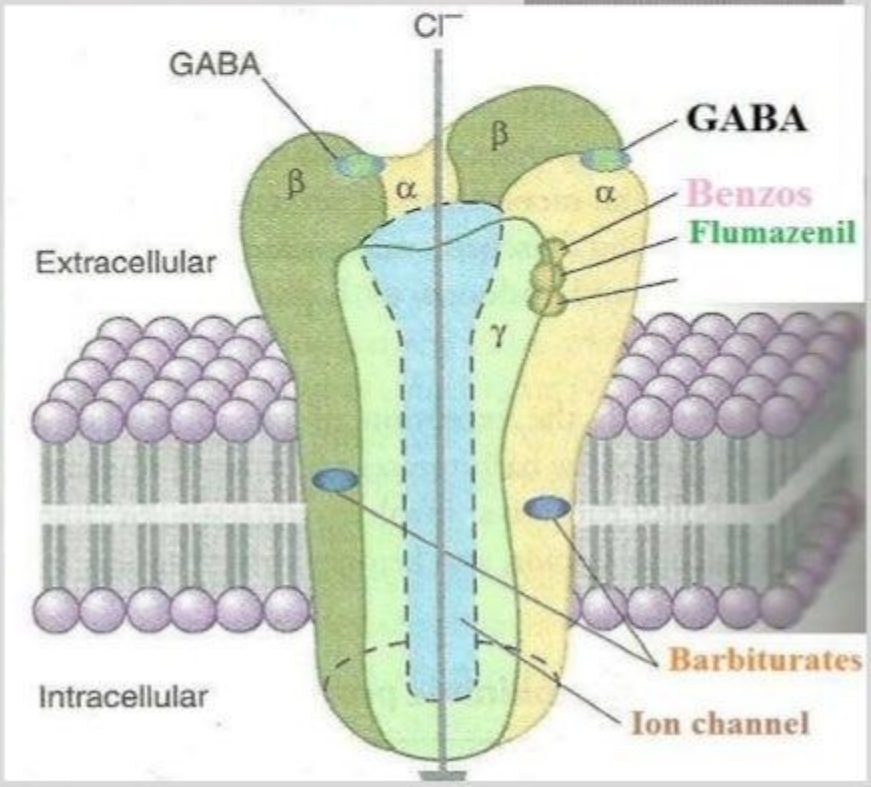
Benzodiazepines	Barbiturates
○ Less neuronal depression ○ High therapeutic index	○ More neuronal depression
○ No anaesthesia even at high doses ○ Patient can be aroused	○ Loss of consciousness, ○ Low margin of safety
○ No effect on respiration or cardiovascular functions at hypnotic doses	○ Cause respiratory and cardiac depression
○ No effect on REM sleep ○ Less distortion of normal hypnogram	○ ++ suppression of REM sleep ○ Withdrawal ⇒ rebound ↑ in sleep ○ Hangover

Benzodiazepines	Barbiturates
○ Abuse liability very low	○ Tolerance ○ Dependence
○ No hyperalgesia	○ Hyperalgesia (↑ Sensitivity to pain)
○ Amnesia without automatism	○ Amnesia with automatism ○ Loss of short term memory
○ Not enzyme inducers – Less drug interactions	○ Potent enzyme inducers – More drug interactions
○ Specific antagonist – Flumazenil	○ No antagonist available

Flumazenil: Benzodiazepine antagonist



- FDA approval in 1991
- MOA: A selective competitive antagonist of BZD receptors (BZ-1)
- Blocks action of Benzodiazepines and Z-drugs but not other sedative /hypnotics.
- Uses:
  - Acute BZD toxicity
  - reversal of BZD sedation e.g. after endoscopy



Other Anxiolytic Agents

- **Antidepressants**
  - Selective serotonin reuptake inhibitors (SSRIs) such as *escitalopram* or *paroxetine*) or
  - serotonin/norepinephrine reuptake inhibitors (SNRIs), such as *venlafaxine* or *duloxetine*
  - SSRIs and SNRIs have a lower potential for physical dependence than the benzodiazepines and have become first-line treatment for GAD

Other Anxiolytic Agents

- **Buspirone**
  - Acts as a partial agonist at the 5-HT_{1A} receptor presynaptically inhibiting serotonin release.
    - The metabolite 1-PP (1-(2-pyrimidyl-piperazine) has 2 receptor blocking action
  - Indicated for generalized anxiety disorders but takes 1 to 2 weeks to exert anxiolytic effects
  - no anticonvulsant or muscle relaxant properties
  - Advantages:
    - does not have sedative effects and does not potentiate CNS depressants
    - few side effects
    - relatively high margin of safety,
    - not associated with drug dependence
    - No rebound anxiety or signs of withdrawal when discontinued

Other Anxiolytic Agents

- **Propranolol** (□-blocker)
  - Use to treat some forms of anxiety, particularly when physical (autonomic) symptoms (sweating, tremor, tachycardia) are severe.

- **Clonidine (**□2-Adrenoreceptor Agonists)
  - used for the treatment of panic attacks
  - useful in suppressing anxiety during the management of withdrawal from nicotine and opioid analgesics

Other Hypnotic Agents

- **Z-drugs**: Zolpidem, Zaleplone, Zopiclone
  - not structurally related to benzo diazepines, but selectively bind to the benzodiazepine receptor sub- type BZ1.
  - do not significantly alter the various sleep stages and, hence, are often the preferred hypnotics
  - no anticonvulsant or muscle-relaxing properties.
  - shows few withdrawal effects, exhibits minimal rebound insomnia, and little tolerance occurs with prolonged use.

Other Hypnotic Agents

- **Ramelteon**
  - selective agonist at the MT1 and MT2 subtypes of melatonin receptors.
    - Melatonin is a hormone secreted by the pineal gland that helps to maintain the circadian rhythm underlying the normal sleep–wake cycle.
  - no direct effects on GABAergic neurotransmission
  - indicated for the treatment of insomnia characterized by difficulty falling asleep (increased sleep latency)
  - Advantages:
    - no effects on sleep architecture, no rebound insomnia or significant withdrawal symptoms,
    - minimal potential for abuse, and no evidence of dependence or withdrawal effects(can be administered for long term)

Other Hypnotic Agents

- **Antihistamines**
  - Some antihistamines with sedating properties, such as *diphenhydramine, hydroxyzine,* and *doxylamine,* are effective in treating mild types of situational insomnia.
  - However, they have undesirable side effects (such as anticholinergic effects) that make them less useful than the benzodiazepines and the nonbenzodiazepines.

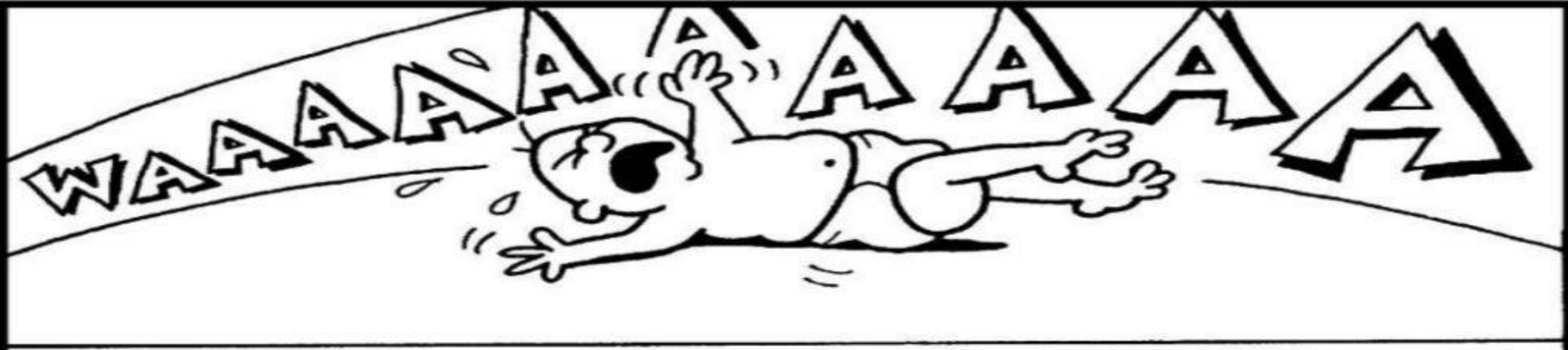
Other Hypnotic Agents

- **Antidepressants**
  - *Doxepin* an older tricyclic agent with SNRI mechanisms of antidepressant and anxiolytic action, was recently approved at low doses for the management of insomnia.
  - Other antidepressants, such as *trazodone*, *mirtazapine* and other older tricyclic antidepressants with strong antihistamine properties are used off-label for the treatment of insomnia

Recent Advances

- 5-HT_{2A} receptor antagonists:
  - 5-Hydroxytryptamine (5-HT)2A antagonists are promising therapeutic agents for the treatment of sleep maintenance insomnias
  - unlike hypnotics, they have limited effects on sleep initiation.
  - 5-HT2A antagonists: eplivanserin, volinanserin
- Orexin receptor antagonist
  - Orexin is believed to be responsible for maintaining wakefulness
  - Suvorexant, Elmorexant

THANK YOU



MARK PARISI

offthemark.com

SNOOZE BELLY BUTTONS: THE SORT OF GENETIC ENGINEERING WE COULD **REALLY** USE.