



# Anti-anxiety drugs



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# ..תרופות נוגדות חרדה

- ❖ Benzodiazepines (BZDs)
- ❖ Buspirone
- ❖ Antihistamines
- ❖ Antidepressants
- ❖ Anti-epileptic drugs (AEDs)
- ❖ Atypical antipsychotics

# תרופות שלא משומשות יותר לחרדה

- Typical antipsychotics (e.g., thioridazine - מלריל)
- Barbiturates

# Benzodiazepines (BZDs)

## The Problem

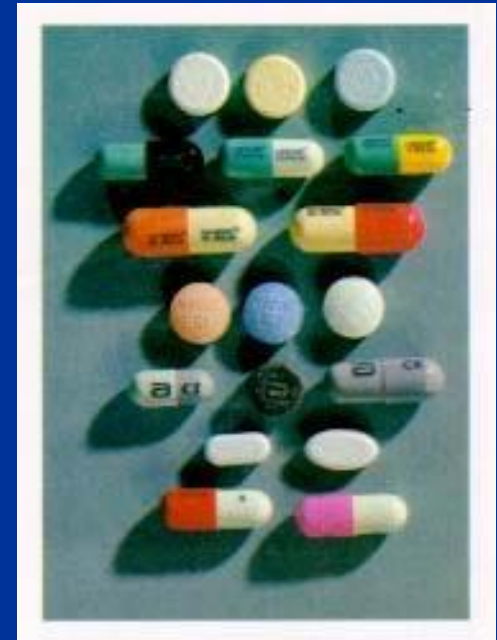
- About 2 per cent of the adult population of the US (around 4 million people) appear to have used prescribed benzodiazepine hypnotics or tranquillisers regularly for 5 to 10 years or more. Similar figures apply in the UK, over most of Europe and in some Asian countries.
- Surveys of general practices show that there are over 180 long-term prescribed users per general practice.
- Despite repeated recommendations to limit benzodiazepines to short-term use (2– 4 weeks), doctors in the UK and worldwide are still prescribing them for months or years.
- Dependence upon prescribed benzodiazepines is now recognised as a major clinical problem and the National Performance Assessment Framework for the NHS makes it a national priority to reduce this within each health board area.

# History of benzodiazepines

- 1912 phenobarbital
- 1961 chlordiazepoxide (Librium): 1st BDZ
- 1963 diazepam
- 1970 highest level of use
- 1980s reduced use because of social concerns

# BZD

- ❖ Alprazolam (Xanax)
- ❖ Clonazepam (clonex)
- ❖ Diazepam (Valium, Assival)
- ❖ Lorazepam (Lorivan)
- ❖ Oxazepam (Vaben)
- ❖ Clorazepate (Tranxal)
- ❖ Chlordiazepoxide (Librium)



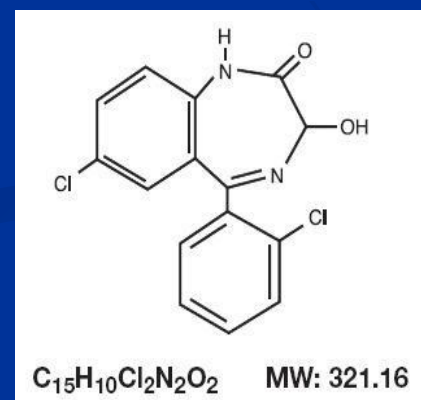
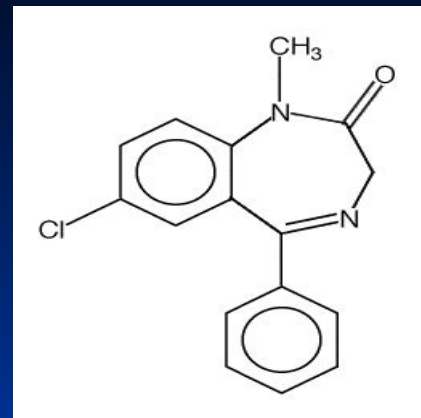
# History

- ❖ The first benzodiazepine (benzo) was synthesized by an Austrian scientist - Dr. Leo Sternbach in the mid 1950's while working at Hoffman-La Roche.
- ❖ The new compound's potential as a pharmaceutical was not initially recognized, however, Dr. Sternbach's persistent research eventually uncovered it's efficacy as a tranquilizer.
- ❖ In 1959, chlordiazepoxide (Librium) was introduced as the first of many benzos to come.
- ❖ Just four years later, in 1963, diazepam (Valium) came on the market.
- ❖ Clinicians quickly recognized the potential of benzos as a safer alternative to the barbiturate class of anxiolytics.

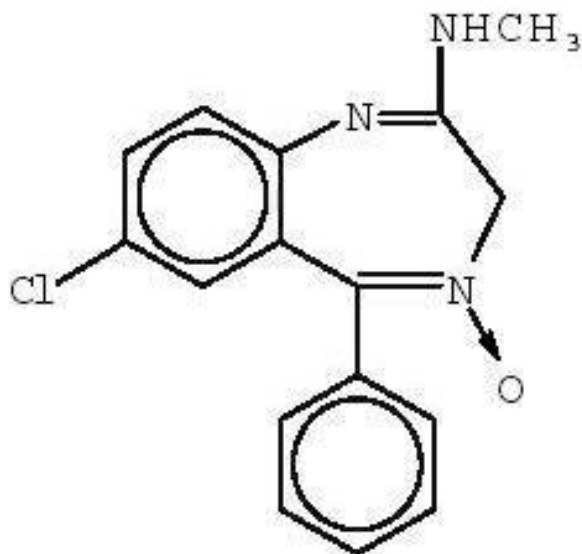


# Structure

- 2-Keto Benzos
  - Some administered as prodrug
  - All have active metabolites (commonly desmethyldiazepam)
  - Long half-lives (most in excess of 60 hours)
- 3-hydroxy Benzos

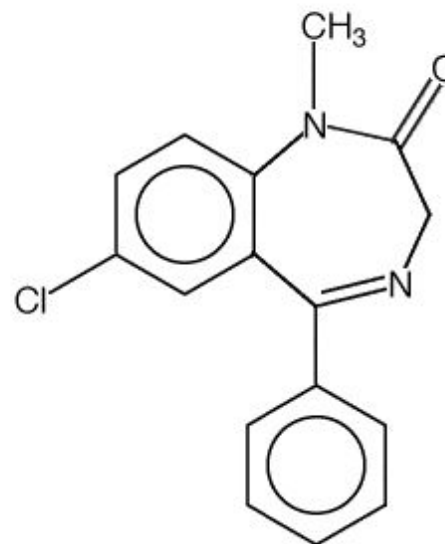


# 2-Keto Benzos



Chlordiazepoxide (Librium)

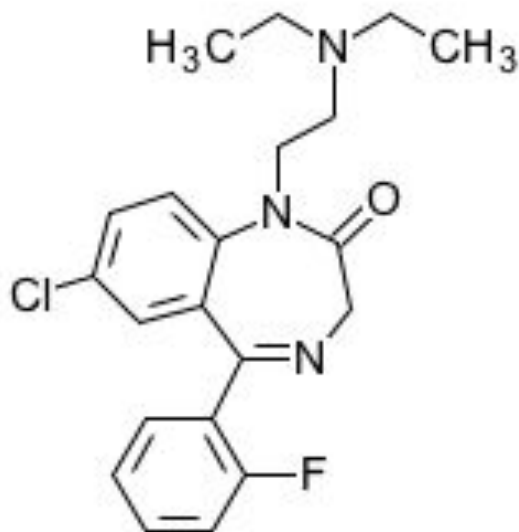
- First isolated benzo
- Oxidized to desmethyldiazepam in the liver
- Indicated for treatment of anxiety and insomnia



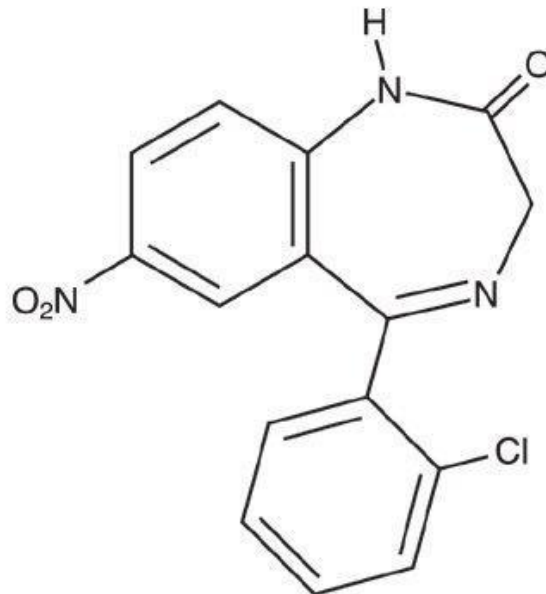
Diazepam (Valium)

- Most prolific and versatile benzo
- Indicated for treatment of anxiety, seizure, muscle tension, insomnia, and alcohol withdrawal

# 2-Keto Benzos



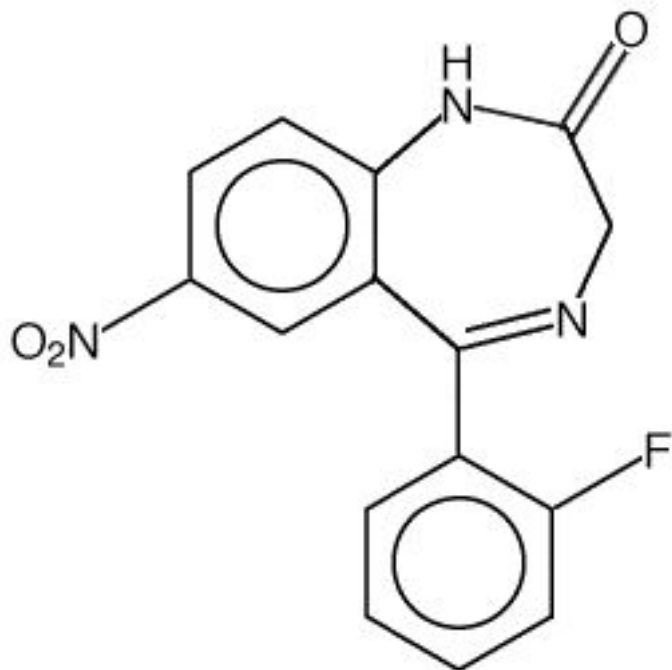
Flurazepam (Dalmane)



Clonazepam (Klonopin)

- Longest half-life of any benzo (~ 40-250 hours)
- Indicated primarily for treatment of insomnia, may also serve as an anxiolytic
- **High potency (~ 20 times stronger per milligram than diazepam)**
- Causes moderate anterograde amnesia
- Indicated for treatment of anxiety, also a highly effective anticonvulsant

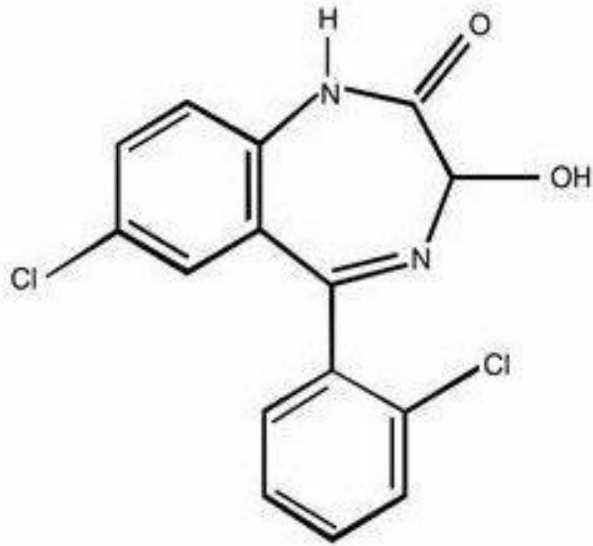
# 2-Keto Benzos



Flunitrazepam (Rohypnol)

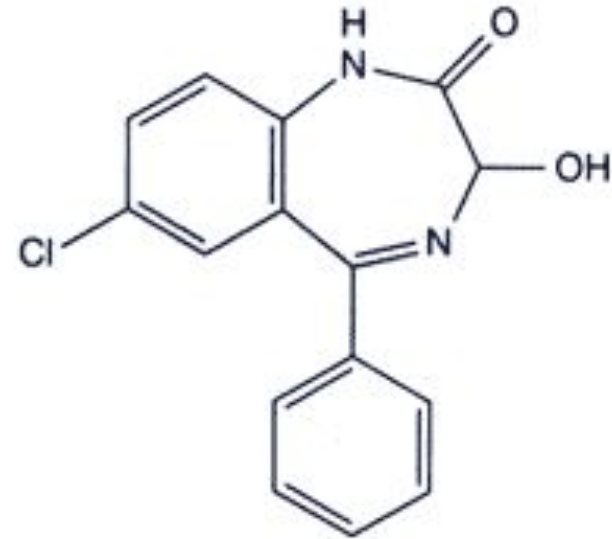
- The original date-rape drug, and the origin of the term “roofie”
- Pharmacologically very similar to clonazepam, but possesses much stronger amnesic properties.
- One of only two drugs in the U.S. for which a first possession charge is a mandatory felony. The other of the two is crack cocaine.

# 3-hydroxy Benzos



Lorazepam (Ativan)

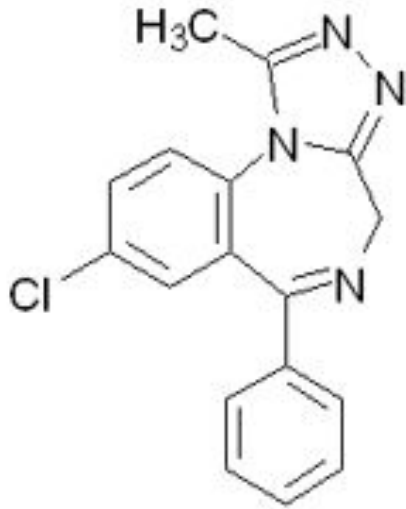
- Indicated for treatment of anxiety, seizure, insomnia, panic disorder, and alcohol withdrawal.
- Unique among benzos in its use as an adjunctive anti-emetic



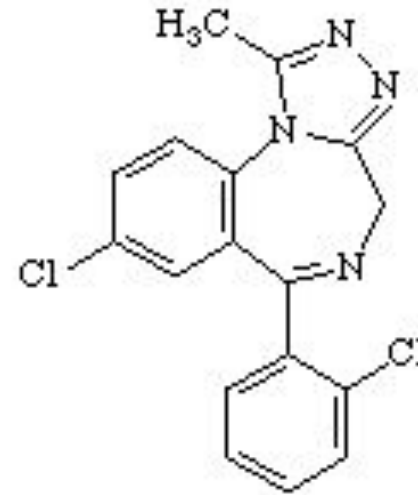
Oxazepam (Serax)

- Indicated for treatment of anxiety, insomnia, and alcohol withdrawal.
- Common metabolite of many 2-keto benzos following their oxidation to desmethyldiazepam

# Triazolo Benzos



Alprazolam (Xanax)



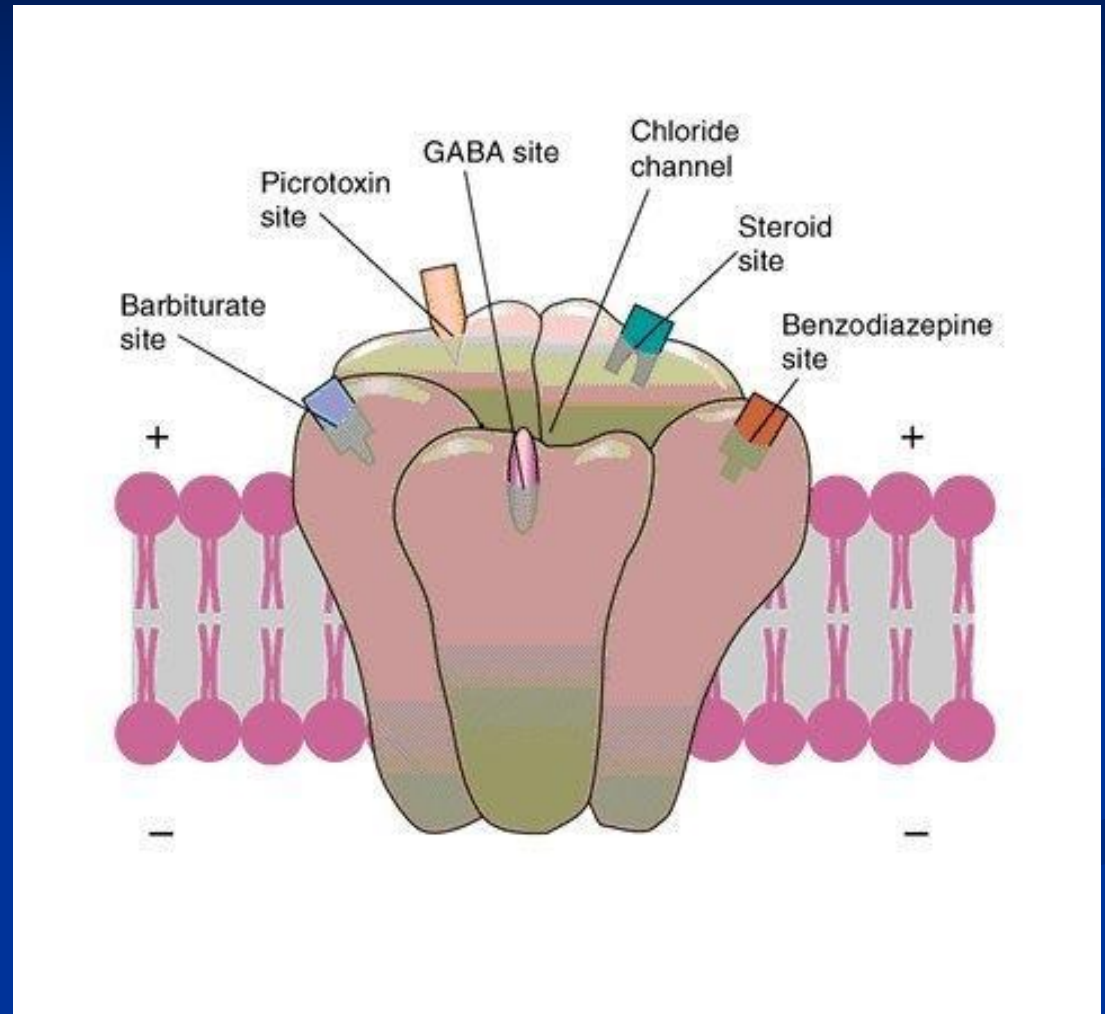
Triazolam (Halcion)

- First benzo approved by FDA for treatment of panic disorder.
- Also used as an adjunctive treatment for depression while adjusting to SSRIs.

- Very rapid onset
- Very short half-life
- Possesses amnesic properties similar to clonazepam
- Used almost exclusively as a pre-op anesthetic

# Mechanism of Action

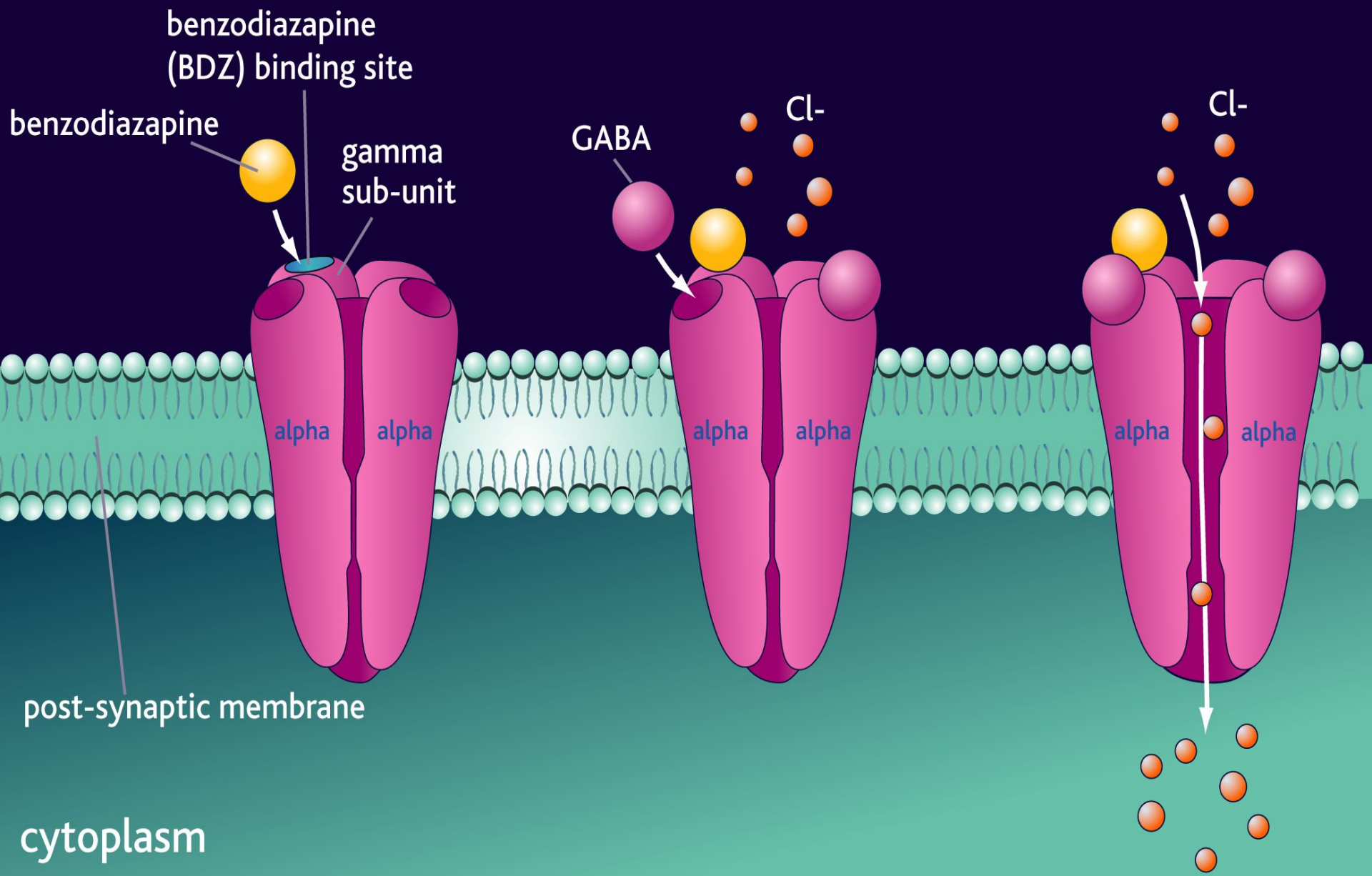
Benzodiazepines act as GABA ( $\gamma$ -aminobutyric acid) potentiators. They bind to BZ receptors on the GABA-BZ receptor complex, which allows them to allosterically modulate and enhance the activity of GABA. This results in increased hyperpolarization at target neurons, making them less responsive to excitatory stimuli.



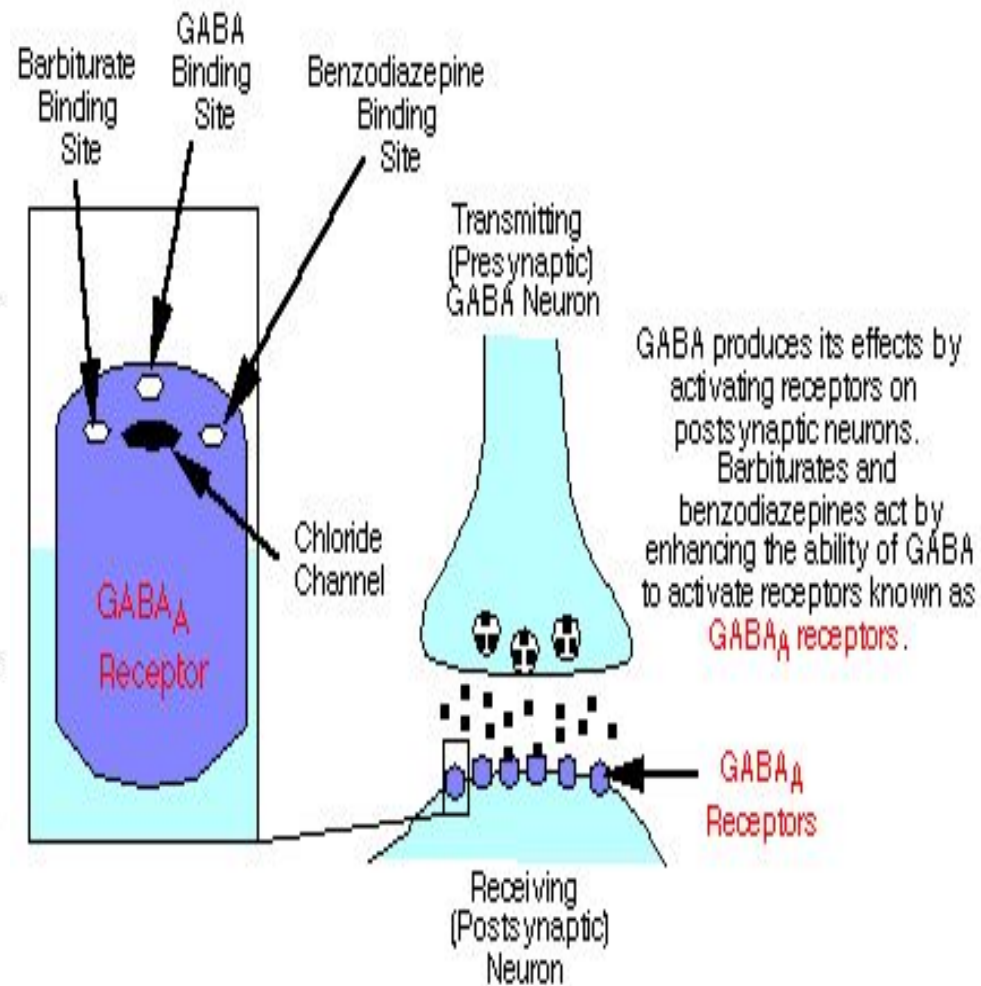
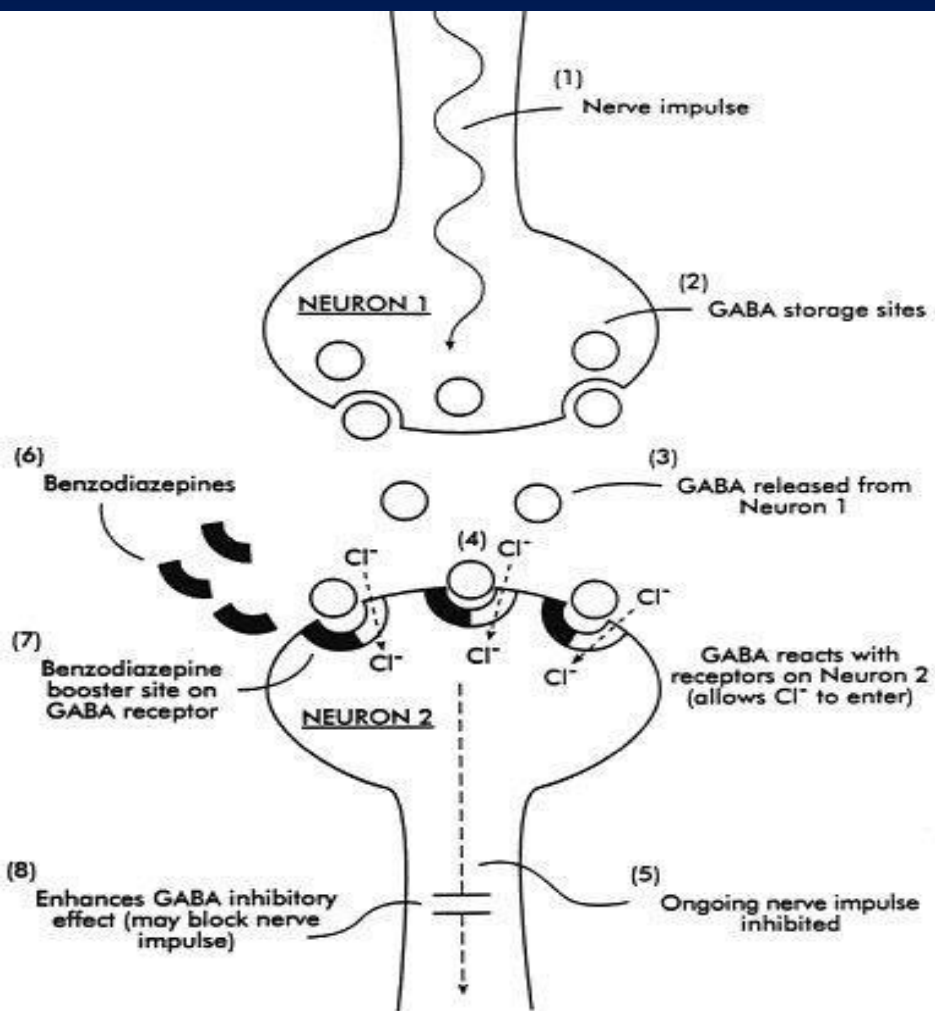


# GABA A receptor

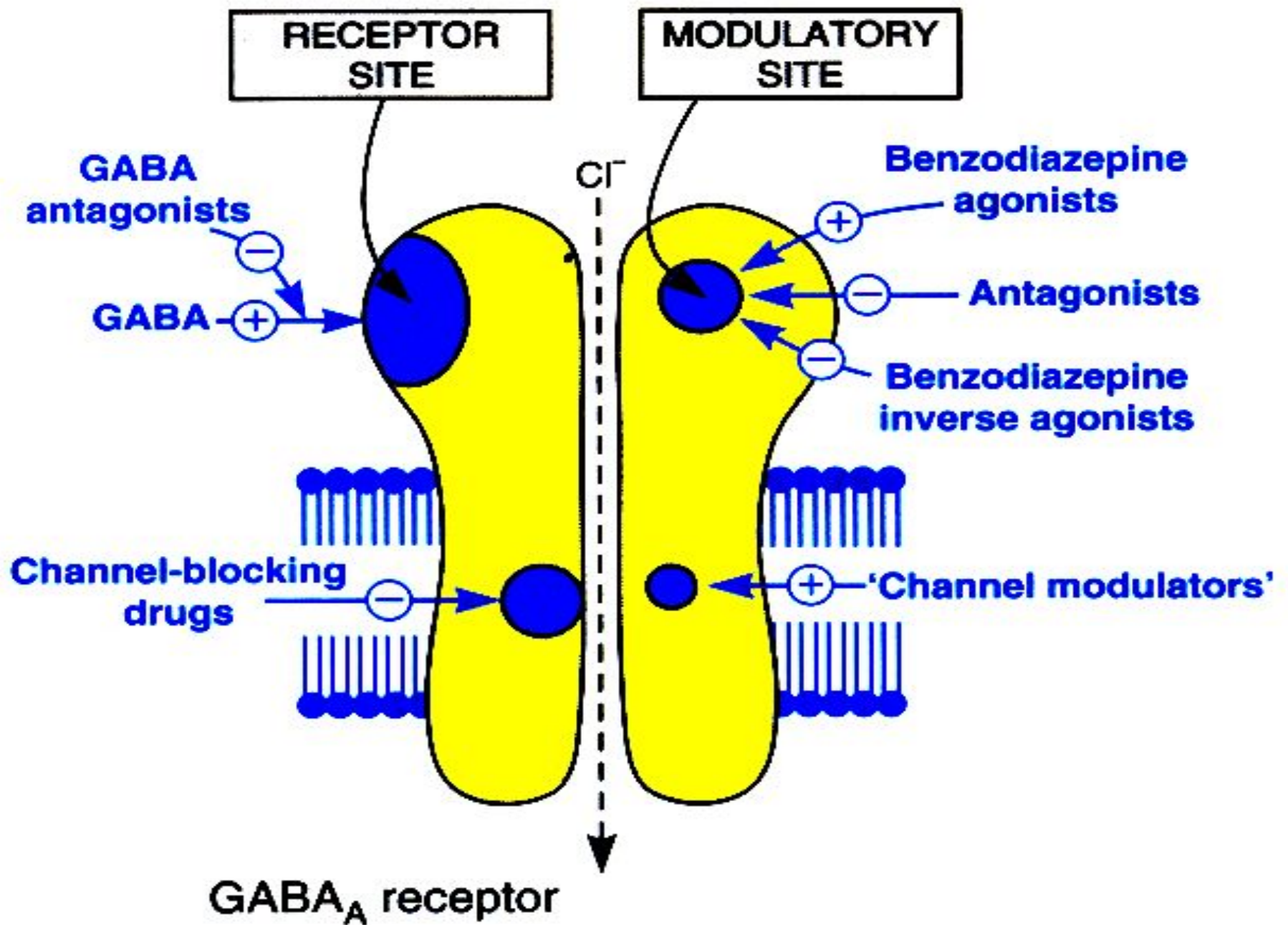
# synaptic cleft





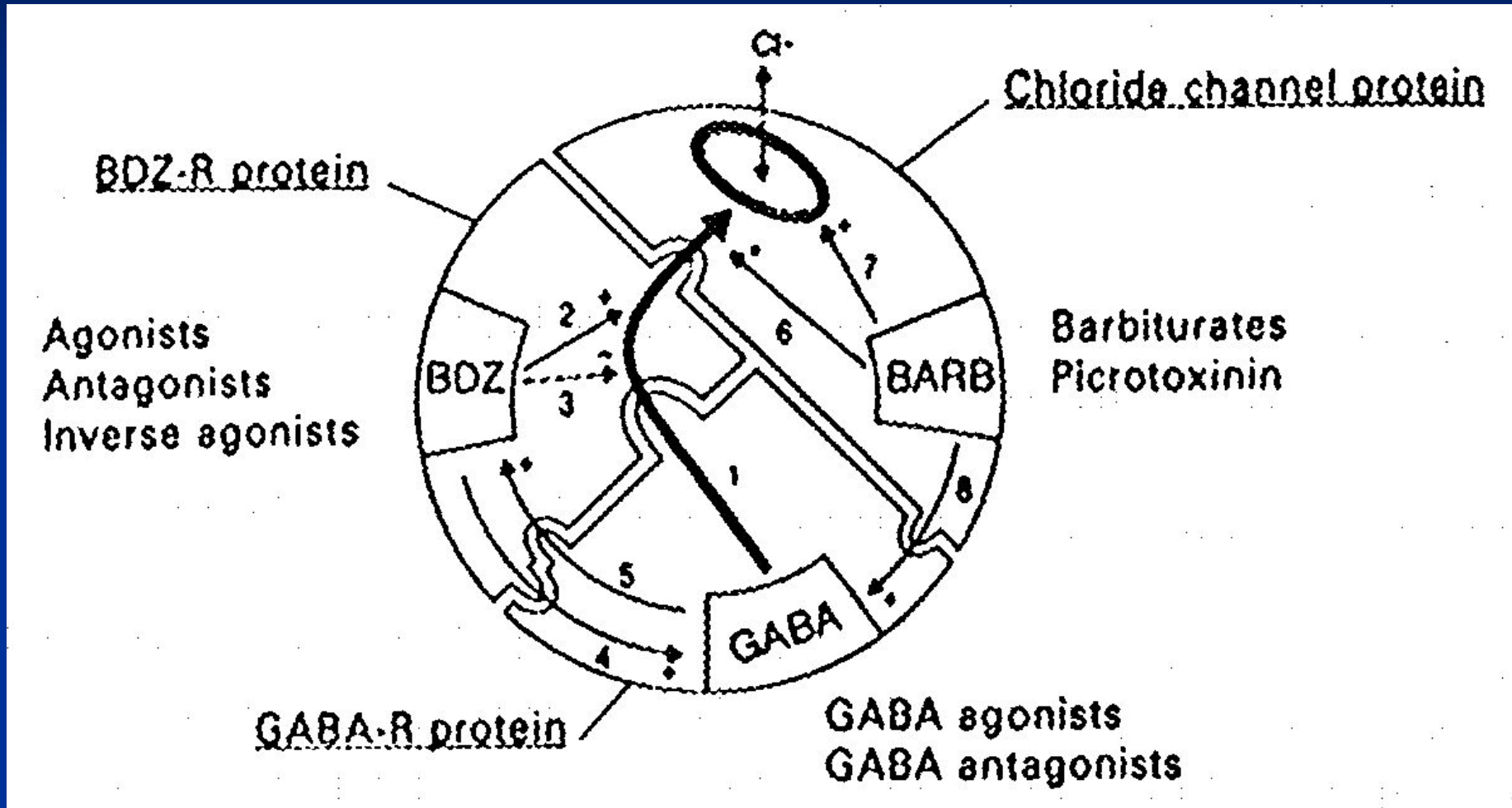








# Modulatory interactions at GABA<sub>A</sub> receptor



# Benzodiazepines

## Mechanism of action

Increase GABA-mediated inhibition:

- spinal cord
- cuneate nucleus
- cerebellum
- brain stem
- hippocampus
- neocortex

# Clinical Applications

- Anxiolytic
  - GAD, PTSD, OCD, etc.
  - Panic Disorder
  - Specific Phobias
- Anticonvulsant
  - Status epilepticus
  - Myoclonic epilepsy
- Muscle relaxant
- Sleep aid
- Pre-operative anesthesia
- Alcohol withdrawal

# Benzodiazepines

CNS - Antianxiety, sedative

- Hypnotic
- Amnesic
- Anticonvulsant
- Muscle relaxant

# Benzodiazepines

## Antianxiety - sedative effects

- relief of anxiety and tension
- emotional calming
- drowsiness (tolerance)
- motor incoordination (tolerance)



# Benzodiazepines

## Hypnotic effects

- ↓ latency of sleep onset
- ↓ awakenings
- ↑ stage 2 NREM sleep
- ↓ stage 3 & 4 NREM sleep
- ↓ REM sleep
- ↑ **total sleep time**

**Table 1 – Benzodiazepine effects on sleep architecture and on the electroencephalogram**

<b>Effects on sleep architecture</b>	<b>Effects on EEG during sleep</b>
↓ Sleep latency	↓ Delta power (delta activity)
↑ Total sleep time	↑ High frequencies (above 12 Hz) on the EEG
↓ Time awake after sleep onset	↑ Sigma power ("BZD spindles")
↑ Latency for REM sleep	
↑ Stage 2 NREM sleep	
↓ Slow-wave sleep	
May not change the total percentage of REM sleep	
↓ REM density	

*EEG: electroencephalogram*

*Adapted from Poyares et al, 2005, Bases da Medicina e Biologia do Sono, Editora Manole, in press*

# Benzodiazepines

## Anticonvulsant effects

- interrupt status epilepticus or any existing seizures – diazepam (i.v.)
- prevent infantile myoclonus, absence seizures – clonazepam (orally)  
*tolerance → escape from seizure control*

# Benzodiazepines

## Muscle relaxant effects

*! No effect on NMJ (neuromuscular junction); a CNS effect!*

Diazepam:

- i.v. - tetanus
- stiff-man syndrome
- endoscopy, orthopedic manipulations

orally - not well documented

# Benzodiazepines

Effects on respiration and cardiovascular system

-usually insignificant

*Preexisting respiratory failure can be aggravated by any hypnotic -  
sedative drug*

# Enhancement of GABAergic inhibition

- GABA agonistic action
- enhancement of GABA release
  - enhancement of synthesis
  - depression of metabolism
- depression of GABA uptake
- allosteric enhancement of action at  $\text{GABA}_A$  receptor

# Potentialiation of GABA-induced Cl<sup>-</sup> conductance

- conductance of open channels
- **BARBITURATES**
  - *life-time of channel openings*
- **BENZODIAZEPINES**
  - *frequency of channel openings*

# Benzodiazepines

## Binding sites

- $^3\text{H}$ -diazepam binding: **saturable, reversible, specific**
- sites unevenly distributed; parallel to  $\text{GABA}_A$  receptors

cortex      high

striatum

cerebellum

spinal cord    low



- affinity of various BDZ derivatives for the receptor correlates with biological and therapeutic potency



# Benzodiazepine binding site ligands

Agonists (positive modulators)

benzodiazepines

Antagonists (null modulators)

flumazenil

for BZD overdose - ( 0.5 mg  $\frac{1}{2}$  min repeated  
after  $\frac{1}{2}$  min (max 3 mg)

Inverse agonists (negative modulators)

$\beta$ -carbolines



# Benzodiazepine pharmacokinetics

## Absorption

rapid: diazepam, triazolam, flurazepam

intermediate: lorazepam

slow: oxazepam

## Plasma protein binding high

## Distribution

non-equilibrium: blood flow, lipid solubility

equilibrium: lipid solubility

# Benzodiazepine pharmacokinetics

## Metabolism

Oxidative reactions: active metabolites, long half-life, **influenced by age**, disease and other drugs - diazepam

**Conjugation:** loss of activity, far less influenced by age, disease and other drugs - lorazepam, oxazepam, active metabolites

# Benzodiazepines: pharmacokinetics

## Drug      Important differences

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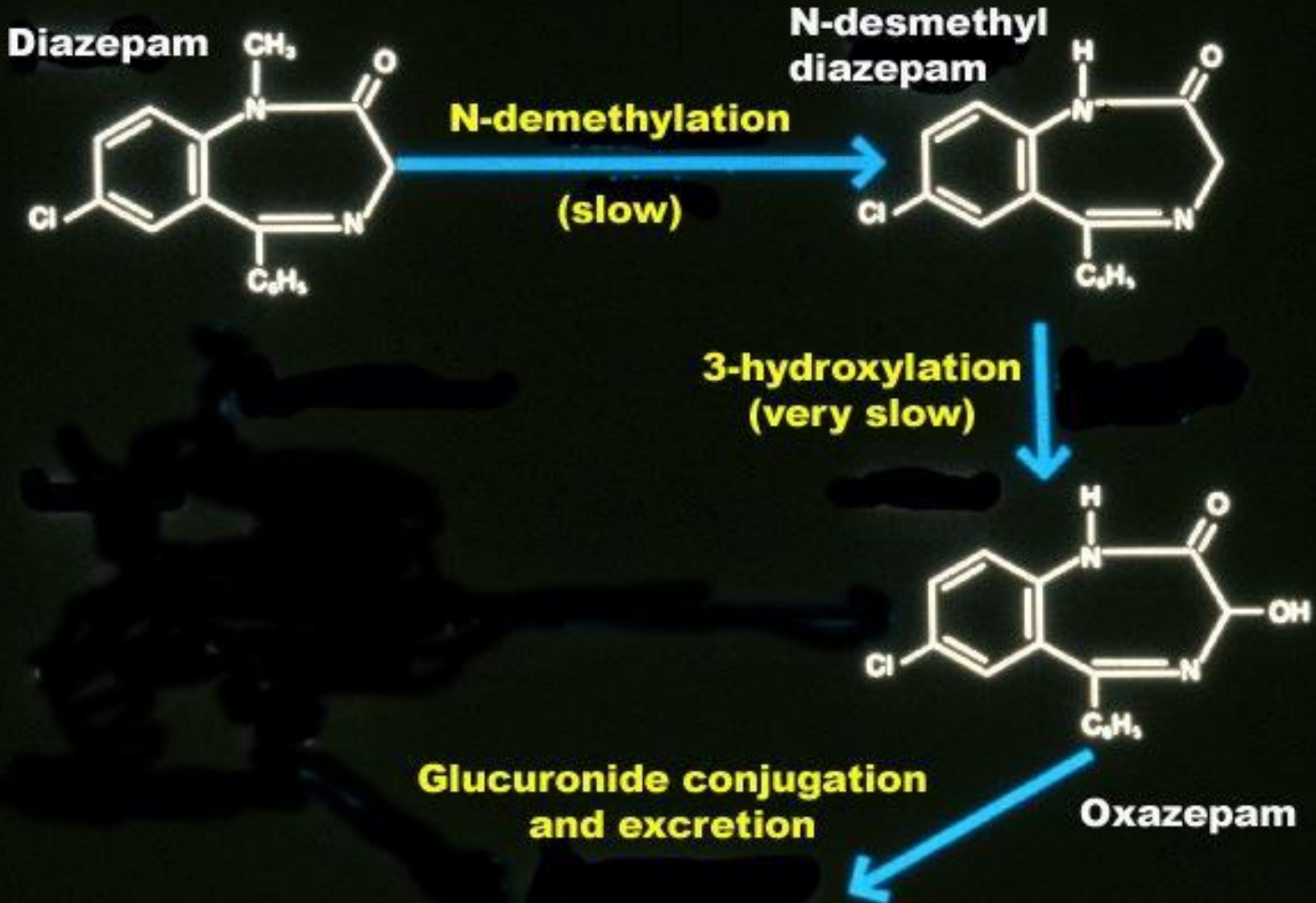
**Diazepam** Mean half-life 35-50 h (desmethyldiazepam)  
metabolites have long half-life

**Lorazepam** Mean half-life 12-20 h, rapid oral absorption,  
disposition not altered appreciably by liver  
disease, aging or inhibitors of drug metabolism

**Oxazepam** Mean half-life 6-10 h, slower absorption than  
lorazepam, disposition not altered appreciably  
by liver disease, aging or inhibitors of drug  
metabolism

**Triazolam** Mean half life 2-3 h, rapid absorption,  
disposition not altered appreciably by liver  
disease, aging or drugs

# Benzodiazepine metabolism



# Benzodiazepine metabolism

