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Margaret Gnegy  
Professor of Pharmacology

# Antianxiety Drugs: Benzodiazepines

Fall 2008



# The bottom line

- Benzodiazepines (BDZ) bind to GABA<sub>A</sub> receptors and enhance the action of GABA
- BDZs are useful for a wide variety of indications but have limited CNS depressant activity
- Principles important in onset and half-life of BDZs are lipophilicity, redistribution and metabolism
- Unwanted effects include a withdrawal syndrome and ‘hangover’
- The pharmacological and anatomical specificity of the GABA<sub>A</sub> receptor subunits has been exploited to develop drugs with sedative but not anxiolytic effects

# Antianxiety Drugs

- Benzodiazepines
- Buspirone
- Antidepressant medications
  - Selective serotonin reuptake inhibitors
  - Tricyclic antidepressants
  - Monoamine oxidase inhibitors

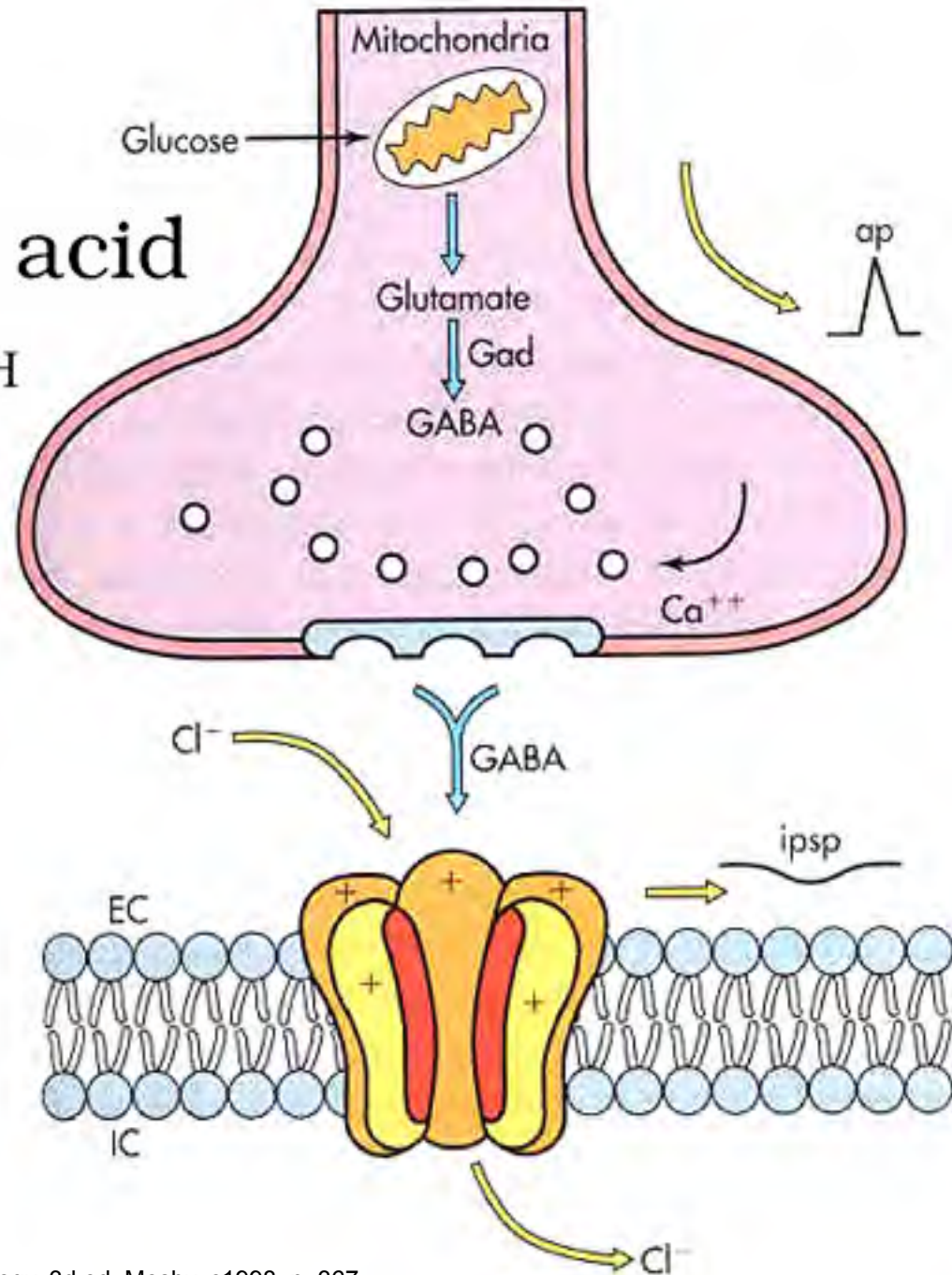
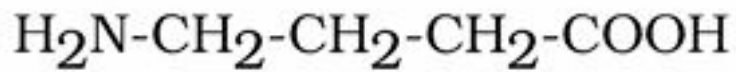
# Pharmacological actions of benzodiazepines

- Relief of anxiety
- Drowsiness and sedation
- Skeletal muscle relaxation
- Anticonvulsive activity
- Anterograde amnesia

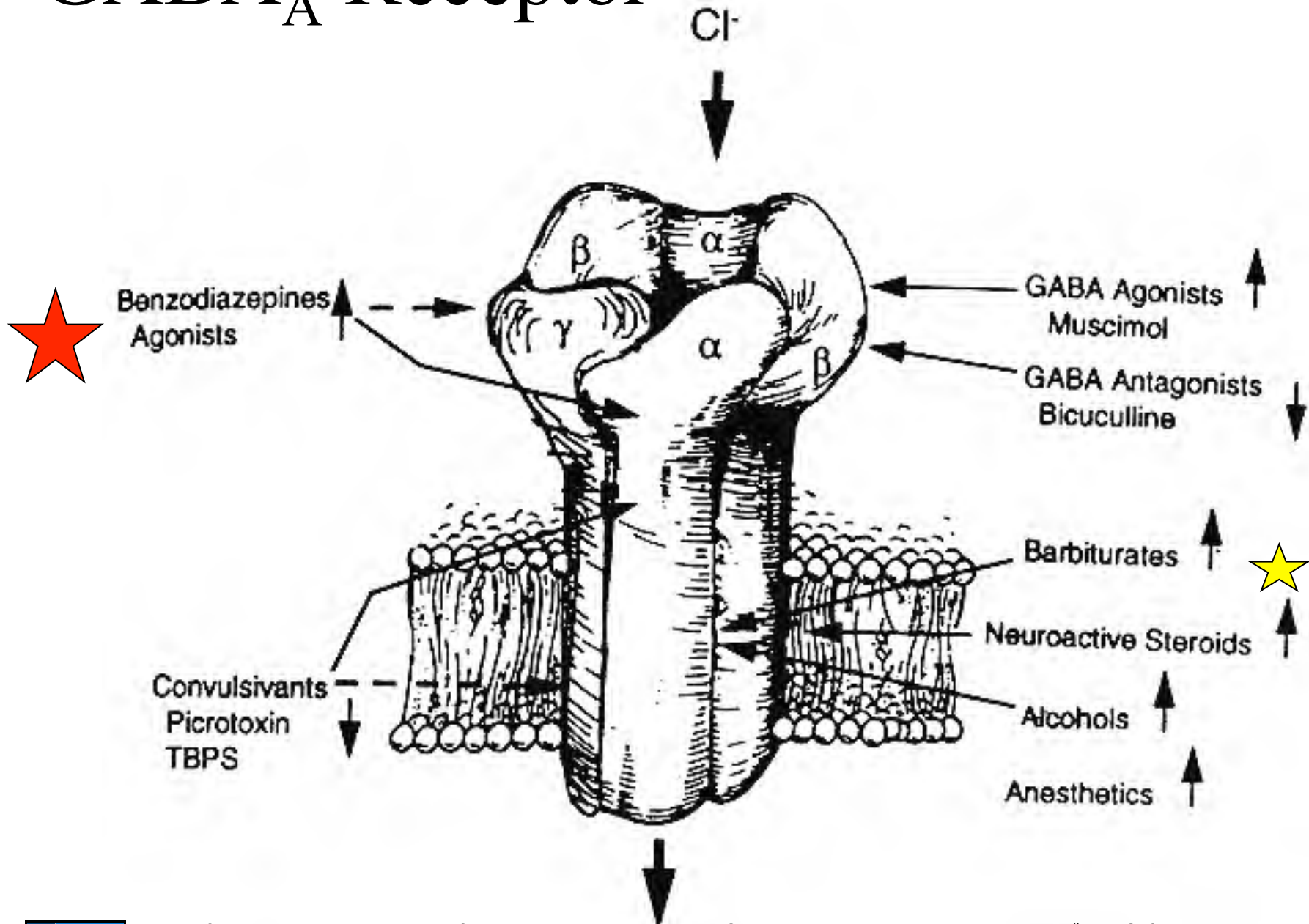
All due to actions in CNS at GABA<sub>A</sub> receptors<sub>6</sub>

# GABA

$\gamma$ -aminobutyric acid

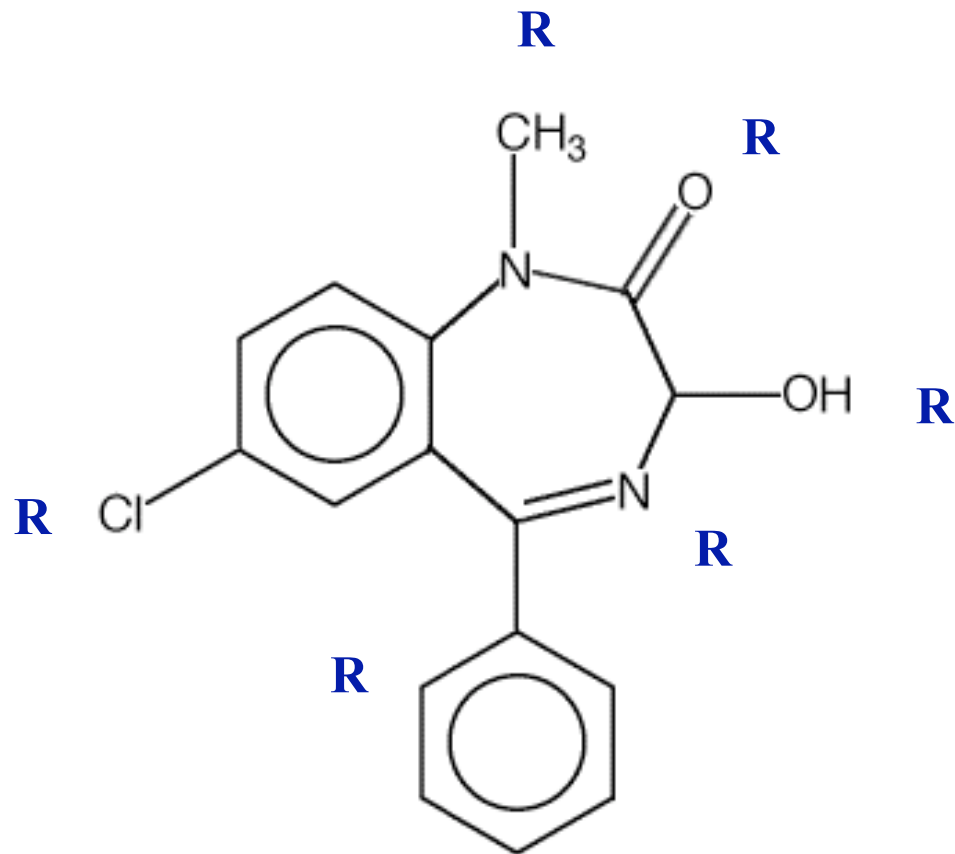


# GABA<sub>A</sub> Receptor



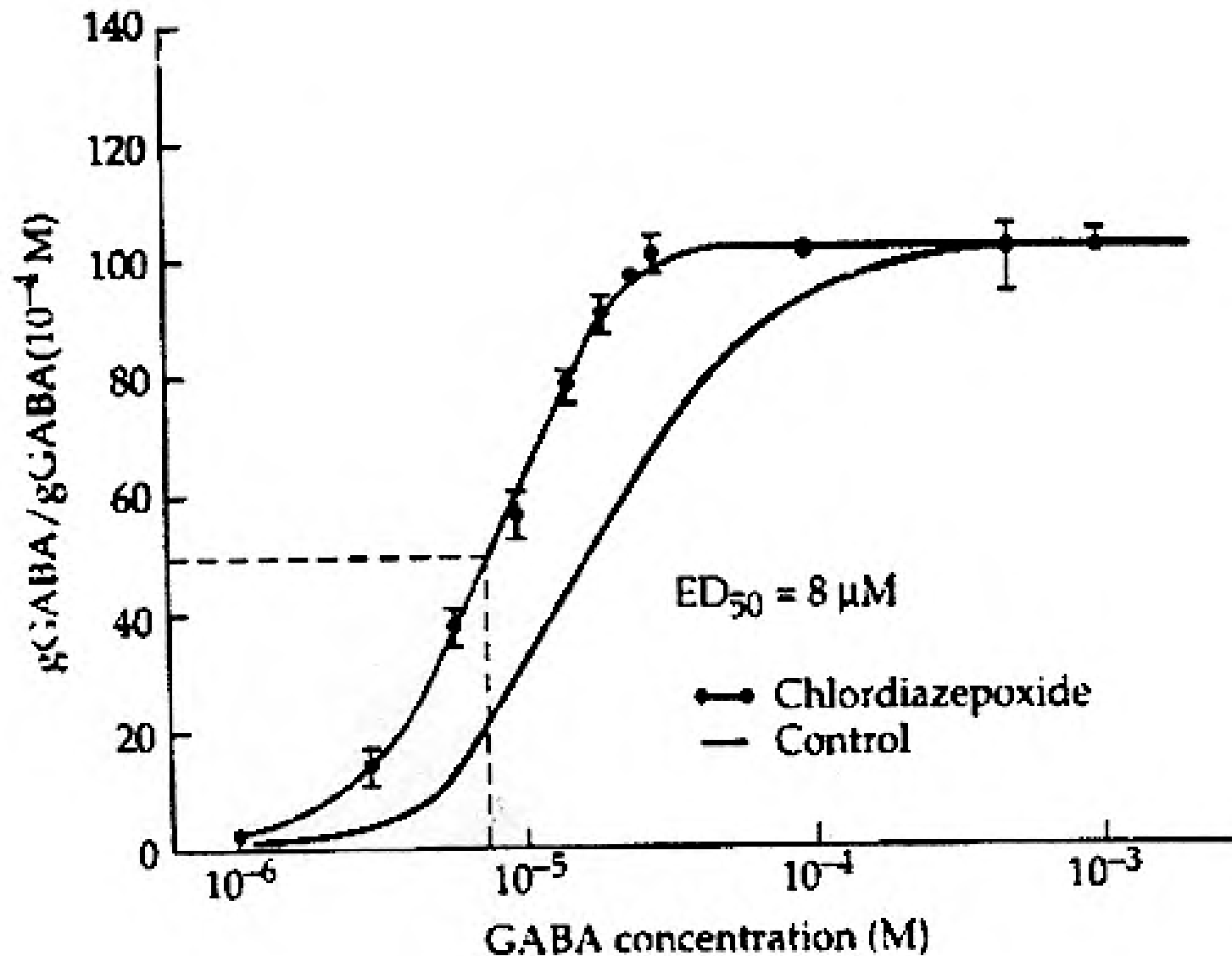


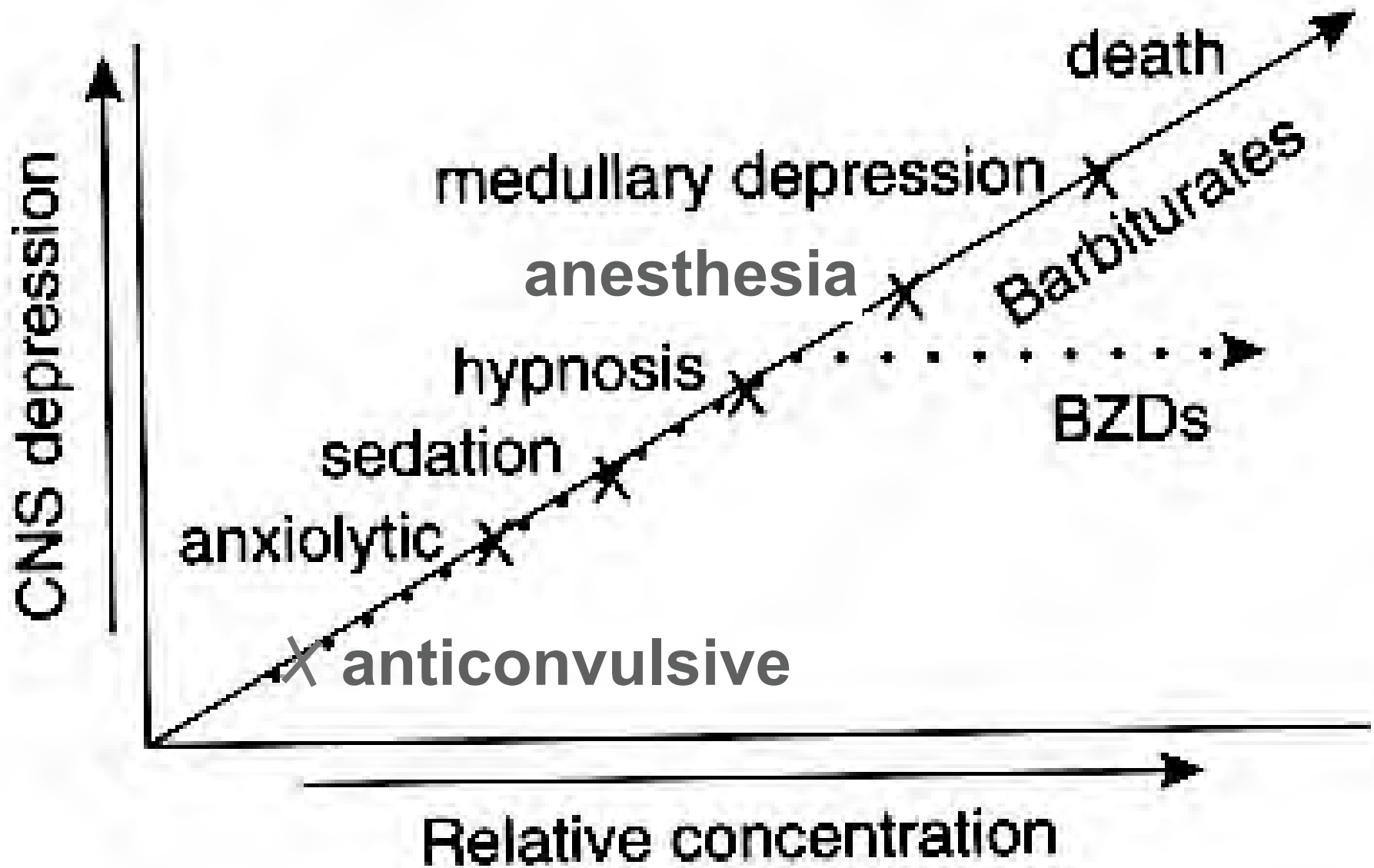
# Benzodiazepine structure



Temazepam

# BDZ-induced shift in GABA Dose Response Curve

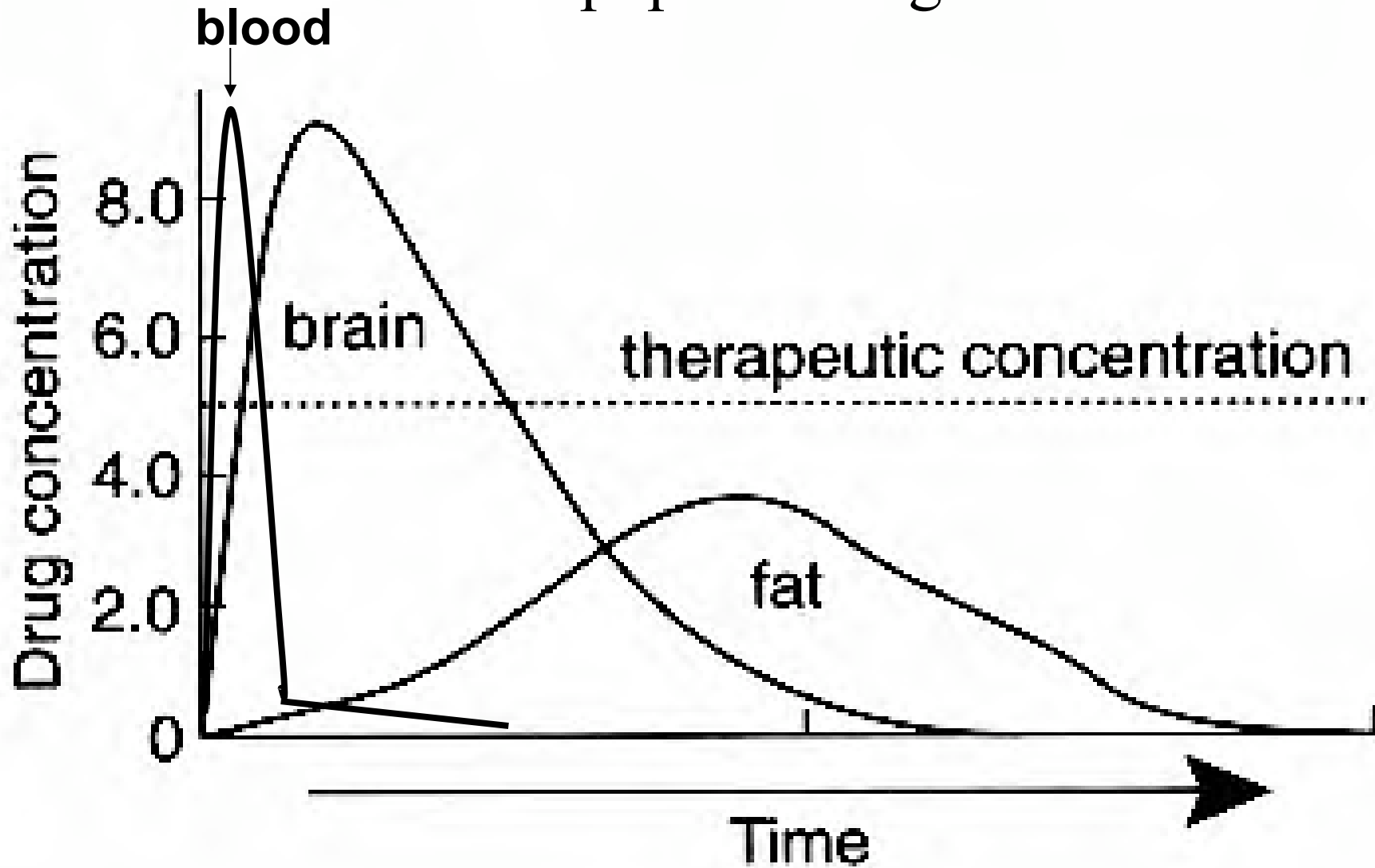




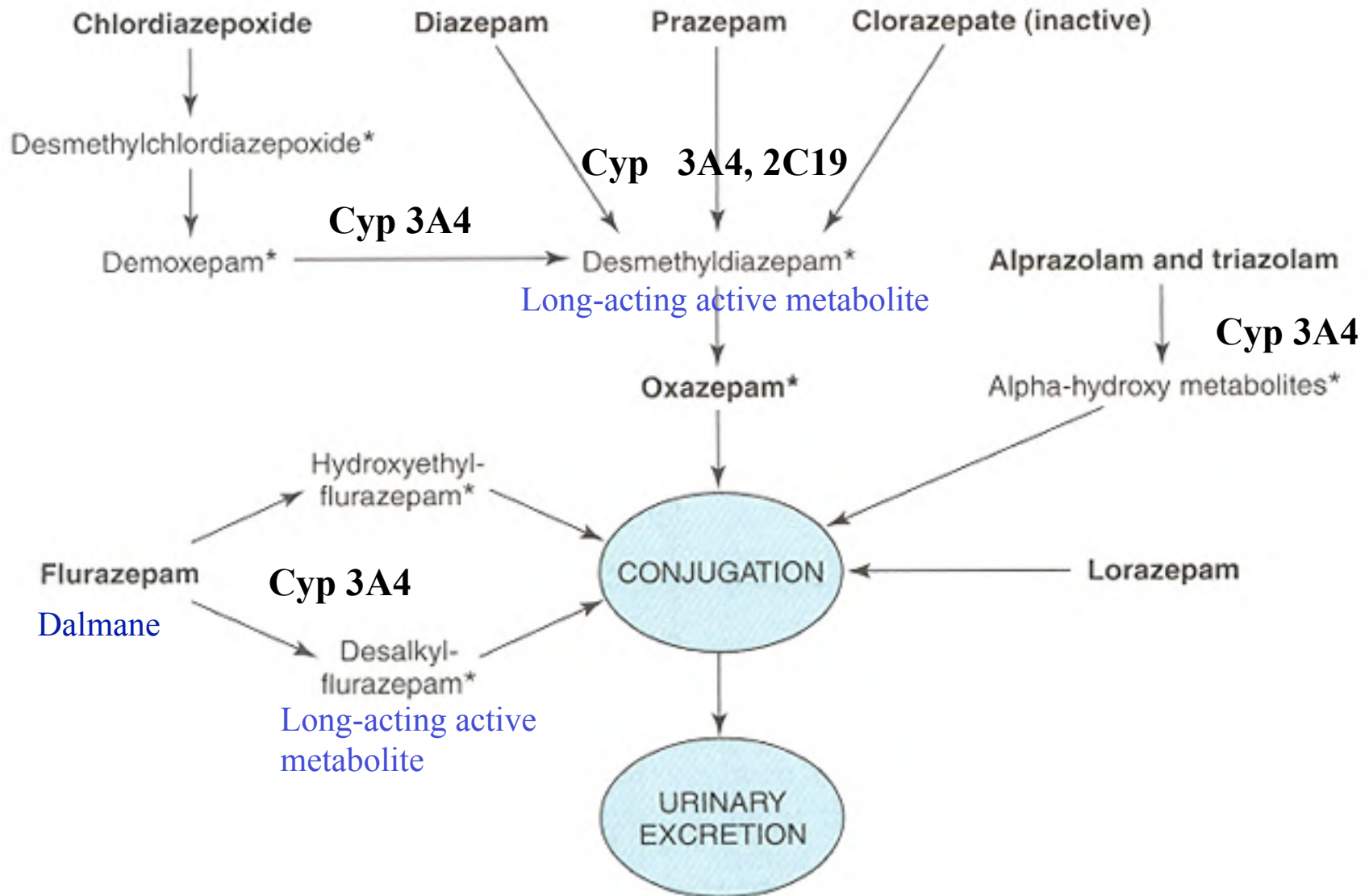
# Absorption, metabolism and excretion

- Relative rates of absorption, metabolism and excretion differ markedly
- Drugs are prescribed for their pharmacokinetics
- Greater lipid solubility leads to greater absorption and more rapid onset of action
- Elimination half-life determined by metabolism

Representative of **Diazepam**, a highly lipophilic drug



# Metabolism of benzodiazepines



## Pharmacokinetic characteristics of some benzodiazepines

<b>Agonist</b>	<b>Trade name</b>	<b>Time to [peak plasma] (hr)</b>	<b>Elim. Half-life (hr)</b>	<b>Comments</b>
<b>Diazepam</b>	Valium	0.5-2.0	30-60	Very lipid soluble, anxiety, status, preanesthetic, muscle relaxant
<b>Lorazepam</b>	Ativan	1-6	10-18	More H <sub>2</sub> O soluble, anxiety
Temazepam	Restoril	2-3	8-15	Slower oral absorption, insomnia
Triazolam	Halcion	1-2	1.5-4	Rapidly inactivated, insomnia, disturbances
Midazolam	Versed	I.V., I.M.	2-5	Rapidly inactiv., pre-anesthetic, amnesia

# Half-life advantages to benzodiazepines

- Therapeutic uses of a benzodiazepine depend on half life
- BDZs used as anticonvulsants have a long half life; rapid entry into brain needed for status epilepticus (diazepam or lorazepam)
- Want a short elimination half-life for hypnotics, ex. temazepam
- Anti-anxiety agents should have longer half life, ex. lorazepam



# Drug interactions with benzodiazepines

- Benzodiazepines are safe, but are CNS depressants
- Have potentiative effects with other CNS depressants: antipsychotics, opioids, alcohol, antihistamines, MAO inhibitors, tricyclic antidepressants, anticonvulsants
- Inhibitors or activators of CYP3A4:
  - inhibitors: erythromycin, ritonavir, grapefruit juice
  - activator: carbamazepine, phenobarbital

# Side effects of benzodiazepines

- Lightheadedness, increased reaction time
- Hangovers: drowsiness and confusion, especially with drugs with long  $t_{1/2}$
- Rebound withdrawal effects: rebound anxiety or wakefulness, especially with drugs with short  $t_{1/2}$  or abrupt discontinuation of the drug
- Ataxia and nystagmus
- Anterograde amnesia
- Paradoxical excitement: uninhibited behavior, hostility rage, hypomanic behavior

# Contraindications to benzodiazepine use

- Benzodiazepines may decrease muscular tone in upper airway
  - Avoid in COPD and obstructive sleep apnea
- Alcoholics and older patients with liver problems
  - Older patients can use a benzodiazepine not metabolized by a P450

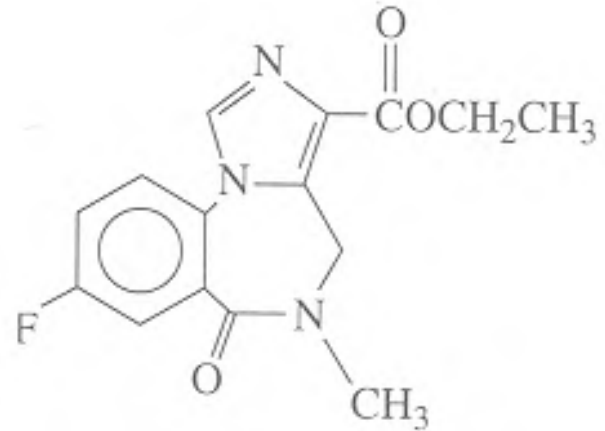
# Tolerance, abuse, dependence

- Some risk for dependence and abuse but much less than for other drugs like barbiturates
- Abuse may be more prevalent in people that also abuse other substances
- May be no abstinence syndrome following gradual withdrawal of drug
- May be physical dependence after long-term use

# Therapeutic uses for benzodiazepines

- Anxiety (lorazepam)
- Sleep disorders (lorazepam, triazolam, flurazepam, temazepam)
- Seizures (clonazepam, diazepam, lorazepam)
- Skeletal muscle spasms (diazepam)
- Alcohol withdrawal (diazepam, lorazepam)
- Preanesthetic medication (midazolam - good for injecting; diazepam, then lorazepam)

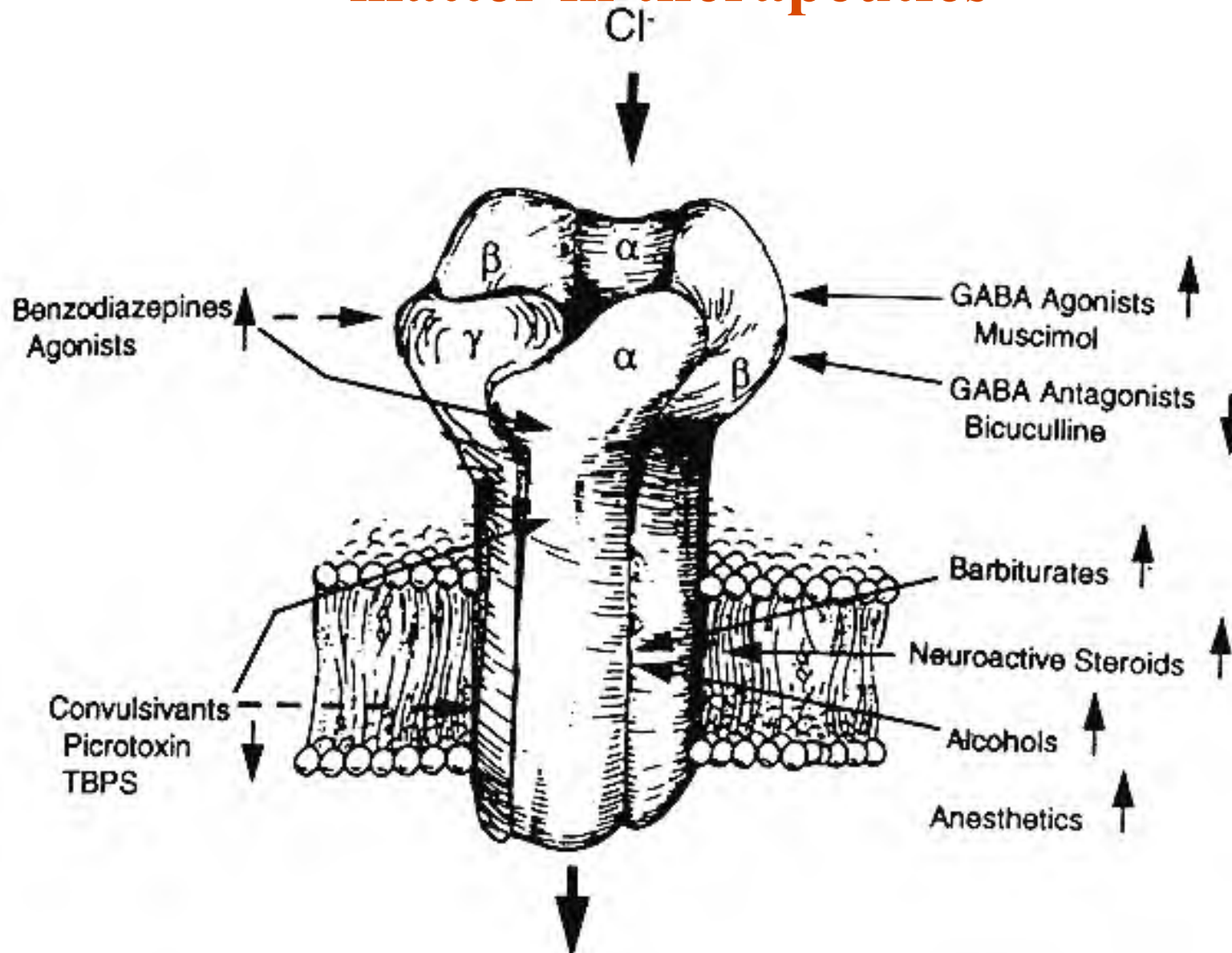
# Flumazenil



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- Benzodiazepine receptor antagonist
- Reverses the effects of benzodiazepines
- Hastening recovery from benzodiazepine sedation or anesthesia after diagnostic procedures or minor surgery
- Only available for IV administration

# GABA<sub>A</sub> receptor subtypes and their location matter in therapeutics



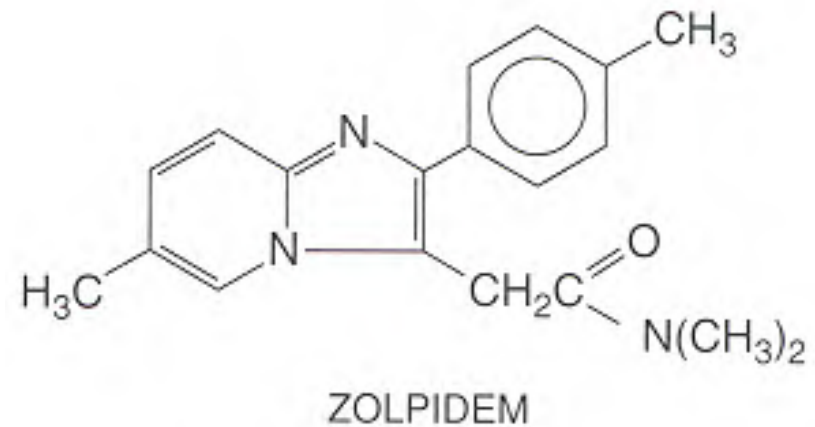
# Role and location of GABA<sub>A</sub> receptor subtypes

Subtype	Location	Function
α1	Widespread, cerebral cortex	Sedation, amnesia, seizure protection
α2	Limbic region, striatum, cortex	Anxiolytic
α5	Hippocampus	Associative learning & memory
β2, β3	Widespread	Consciousness (required for iv anesthetic action) <sub>24</sub>



# GABA<sub>A</sub> receptor subtype selective drugs

- Zolpidem (Ambien):  $\alpha$ 1-selective, hypnotic
  - Imidazopyridine, nonbenzodiazepine
  - Shortens sleep latency, prolongs sleep time
  - Readily absorbed from GI tract, completely metabolized in liver
  - Plasma half-life = 2 hrs
  - Wakeful behavior and amnesia
  - New zolpidem extended release



 Source Undetermined

Other subtype-selective drugs:

Zaleplon (Sonata):  $\alpha$ 1-selective, hypnotic,  $t_{1/2} = 1$  hr

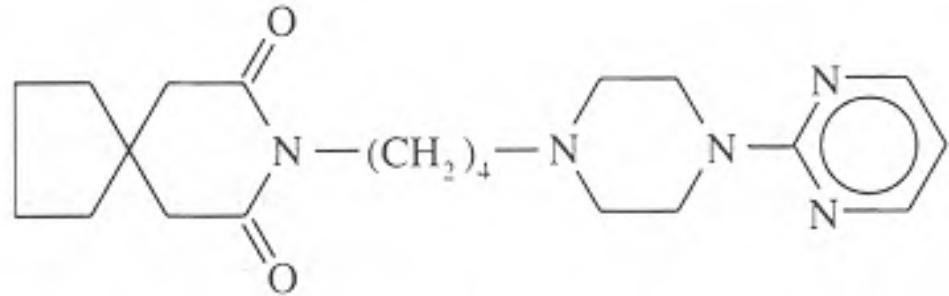
Eszopiclone (Lunesta):  $\alpha$ 1-selective, hypnotic,  $t_{1/2} = 6$  hr  
Not limited to short term use

Used primarily to shorten onset to sleep

# Safety and Adverse effects

- Risk of abuse and tolerance low when used as directed
- Few withdrawal reactions, although some have been reported
- No tolerance to therapeutic effect

# Buspirone (Buspar)



 Source Undetermined

- Used to treat generalized anxiety with limited severity
- Partial agonist at 5-HT<sub>1A</sub> receptors
- Lacks CNS depressant properties
- Minimal sedation
- Slow onset of action

# Chloral hydrate



- Rapidly converted to ethanol in liver
- Irritating to GI tract
- Useful for sedation in children or elderly undergoing uncomfortable procedures

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