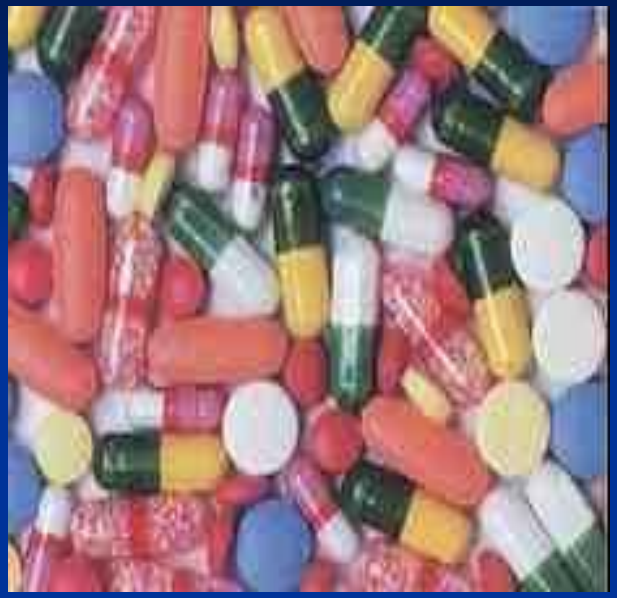
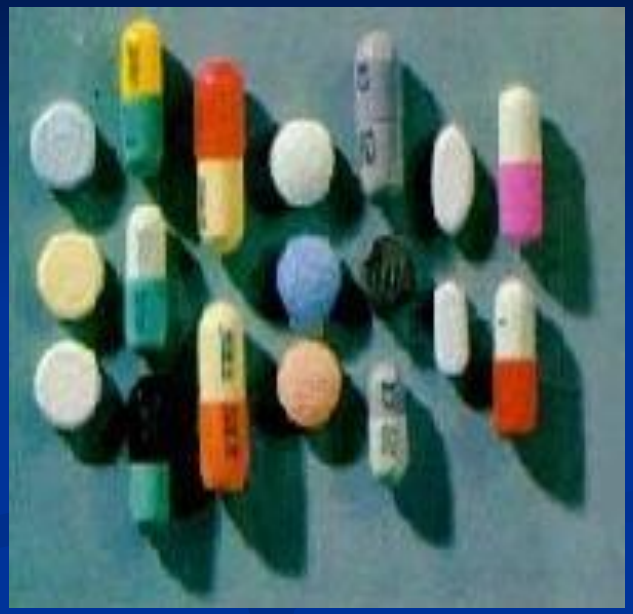
Anti-anxiety drugs





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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

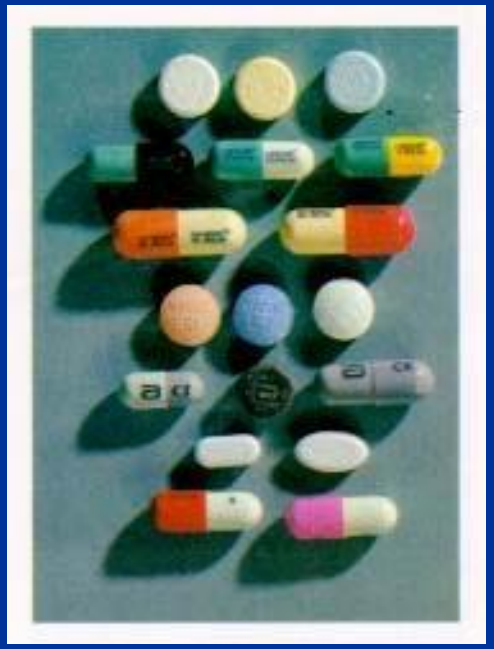
- About 2 per cent of the adult population of the US (around 4 million people) appear to have used prescribed benzodiazepine hypnotics or tranquillisers regularly for 5 to 10 years or more. Similar figures apply in the UK, over most of Europe and in some Asian countries.
- Surveys of general practices 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)

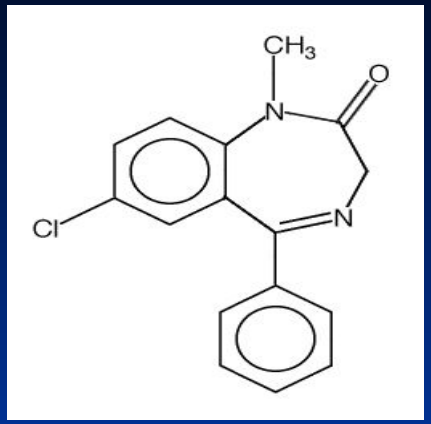


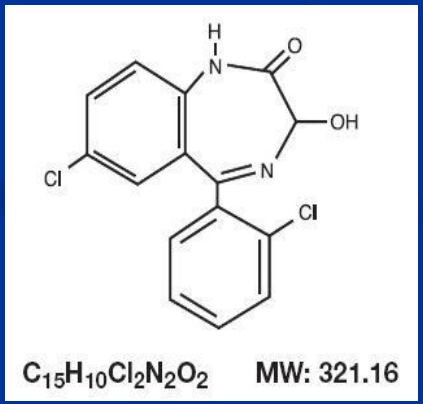
History

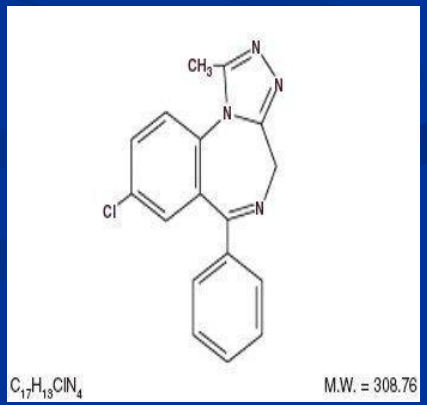
- The first benzodiazepine (benzo) was synthesized by an Austrian scientist - Dr. Leo Sternbach in the mid 1950's while working at Hoffman-La Roche.
- The new compound's potential as a pharmaceutical was not initially recognized, however, Dr. Sternbach's persistent research eventually uncovered it's 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

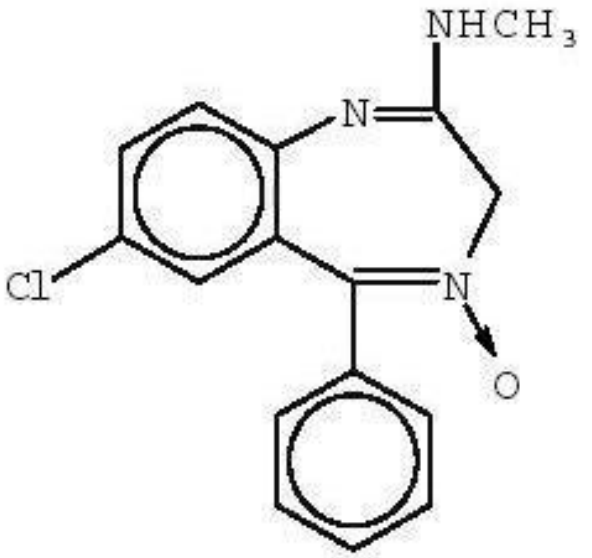
- 2-Keto Benzos
  - Some administered as prodrug
  - All have active metabolites (commonly desmethyldiazepam)
  - Long half-lives (most in excess of 60 hours)
- 3-hydroxy Benzos





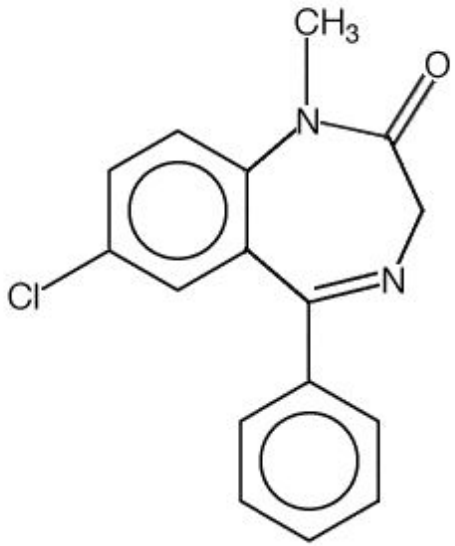


2-Keto Benzos



Chlordiazepoxide (Librium)

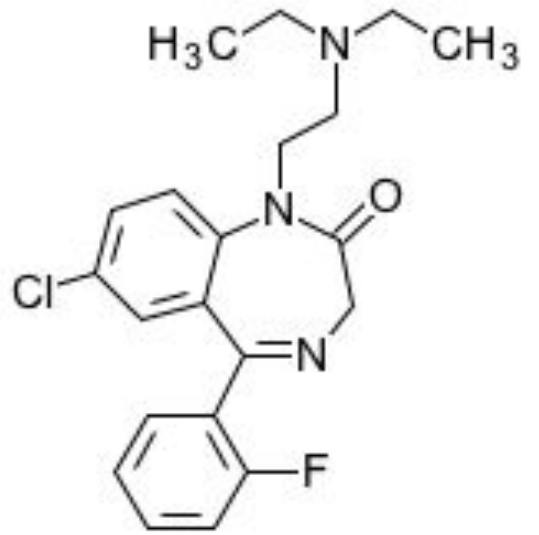
- First isolated benzo
- Oxidized to desmethyldiazepam in the liver
- Indicated for treatment of anxiety and insomnia



Diazepam (Valium)

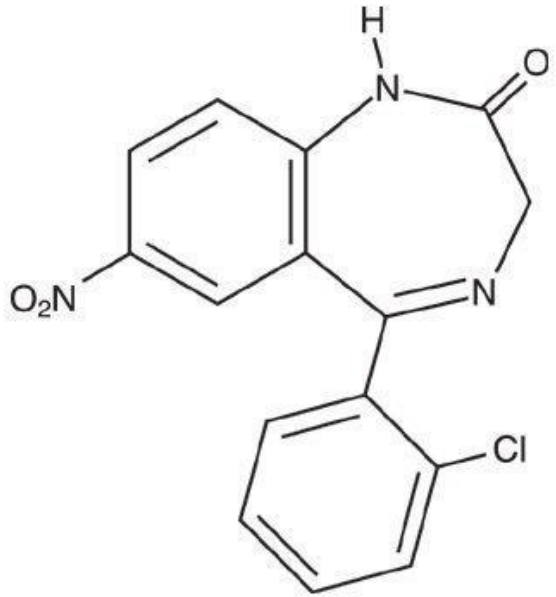
- Most prolific and versatile benzo
- Indicated for treatment of anxiety, seizure, muscle tension, insomnia, and alcohol withdrawal

2-Keto Benzos



Flurazepam (Dalmane)

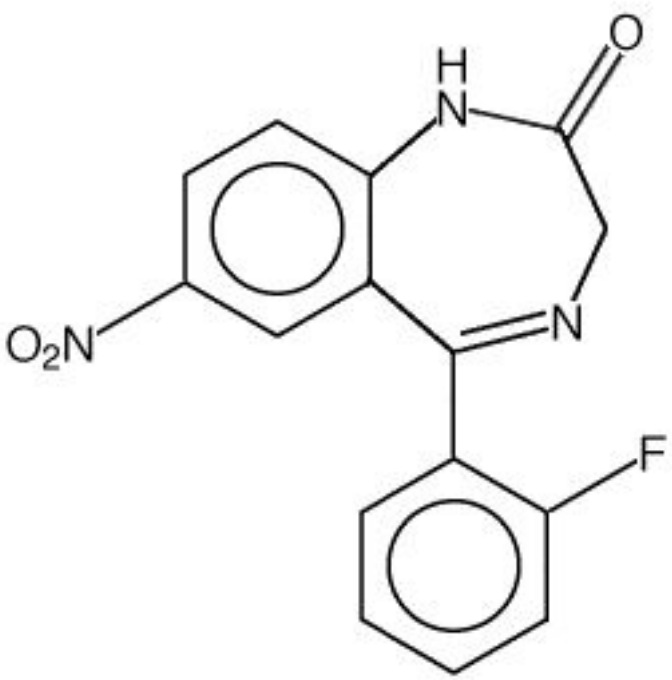
- Longest half-life of any benzo (~ 40-250 hours)
- Indicated primarily for treatment of insomnia, may also serve as an anxiolytic



Clonazepam (Klonopin)

- High potentcy (~ 20 times stronger per miliigram than diazepam)
- Causes moderate anterograde amnesia
- Indicated for treatment of anxiety, also a highly effective anticonvulsant

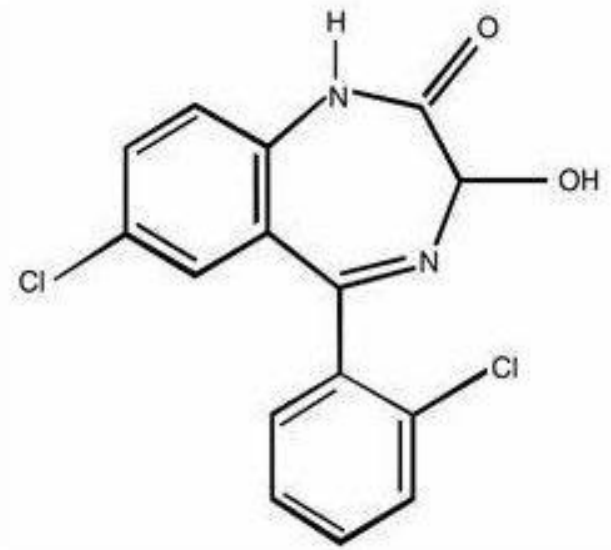
2-Keto Benzos



Flunitrazepam (Rohypnol)

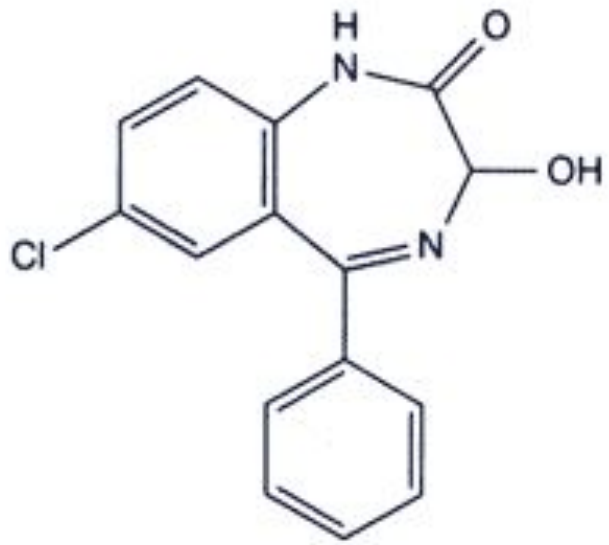
- The original date-rape drug, and the origin of the term “roofie”
- Pharmacologically very similar to clonazepam, but possesses much stronger amnesic properties.
- One of only two drugs in the U.S. for which a first possession charge is a mandatory felony. The other of the two is crack cocaine.

3-hydroxy Benzos



Lorazepam (Ativan)

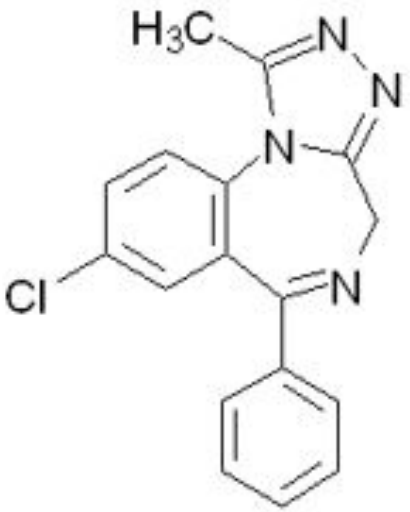
- Indicated for treatment of anxiety, seizure, insomnia, panic disorder, and alcohol withdrawal.
- Unique among benzos in it's use as an adjunctive anti-emetic



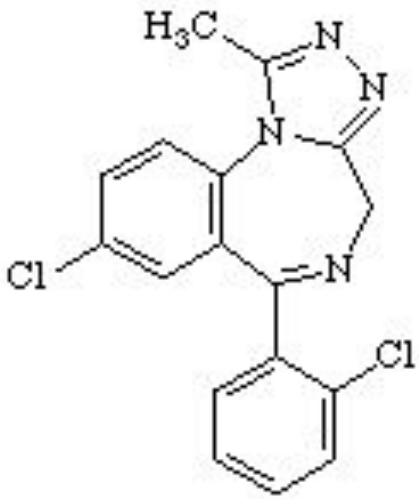
Oxazepam (Serax)

- 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)



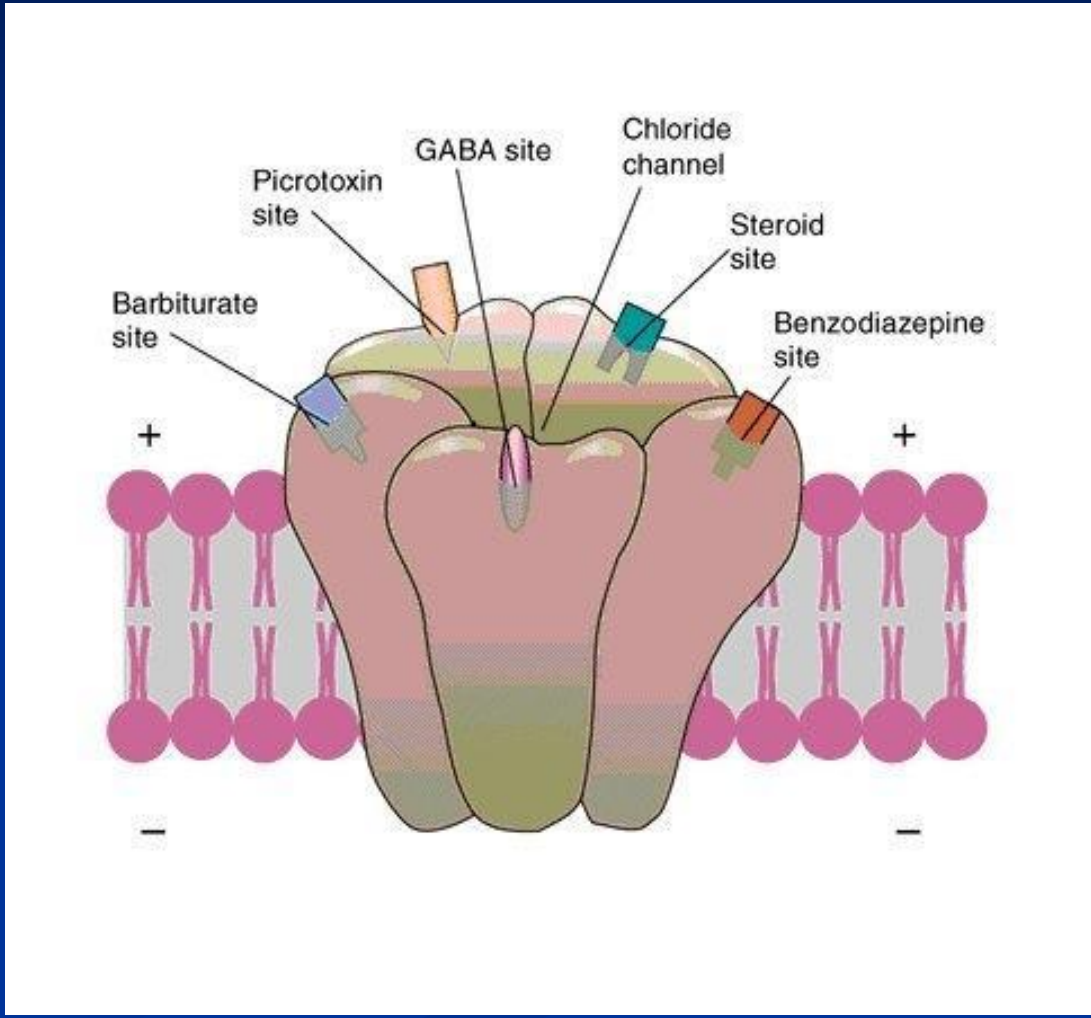
Triazolam (Halcion)

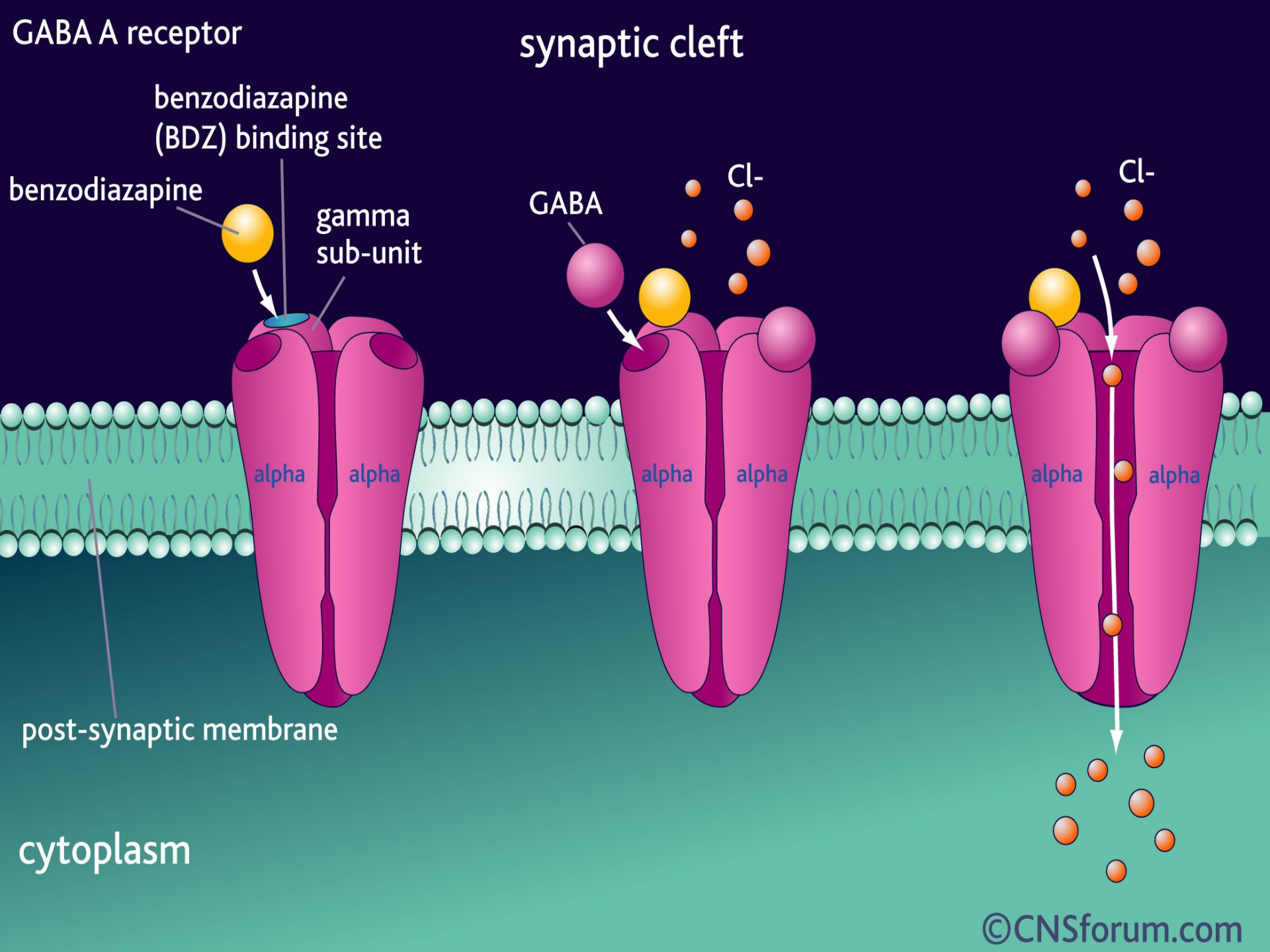
- First benzo approved by FDA for treatment of panic disorder.
- Also used as an adjunctive treatment for depression while adjusting to SSRIs.

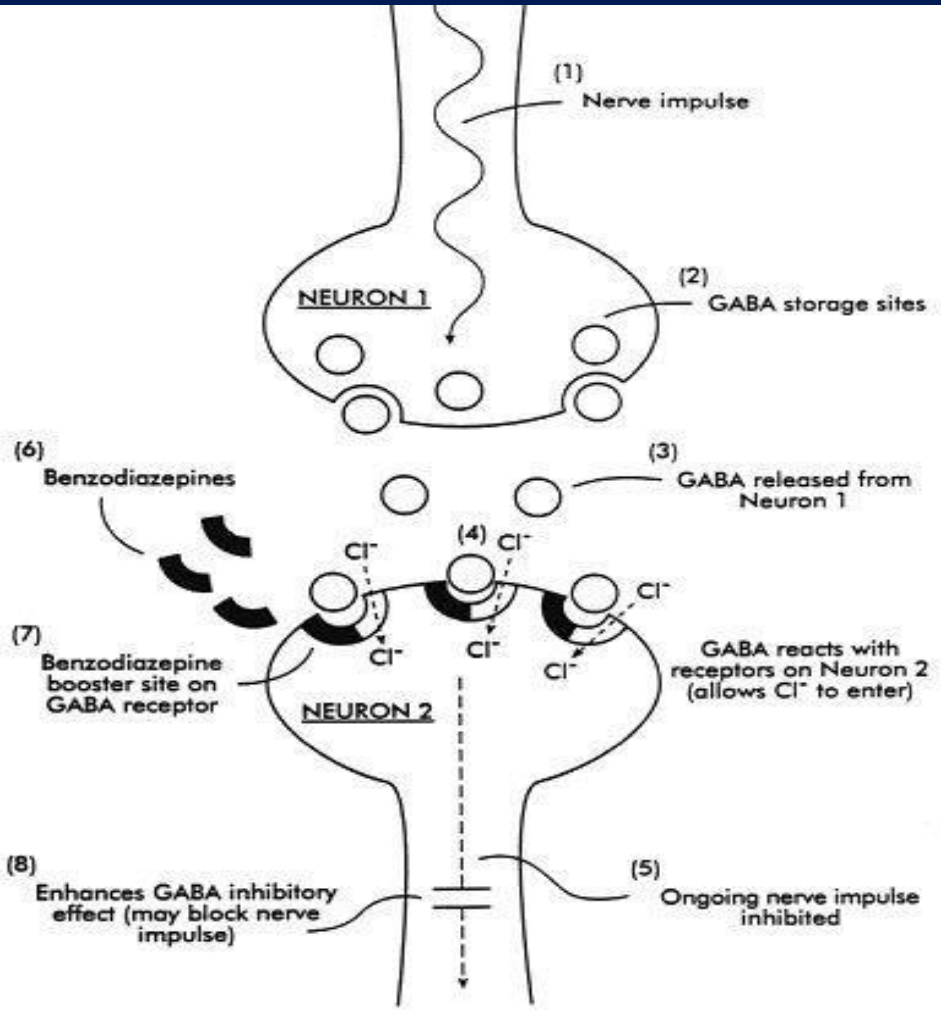
- Very rapid onset
- Very short half-life
- Possesses amnesic properties similar to clonazepam
- Used almost exclusively as a pre-op anesthetic

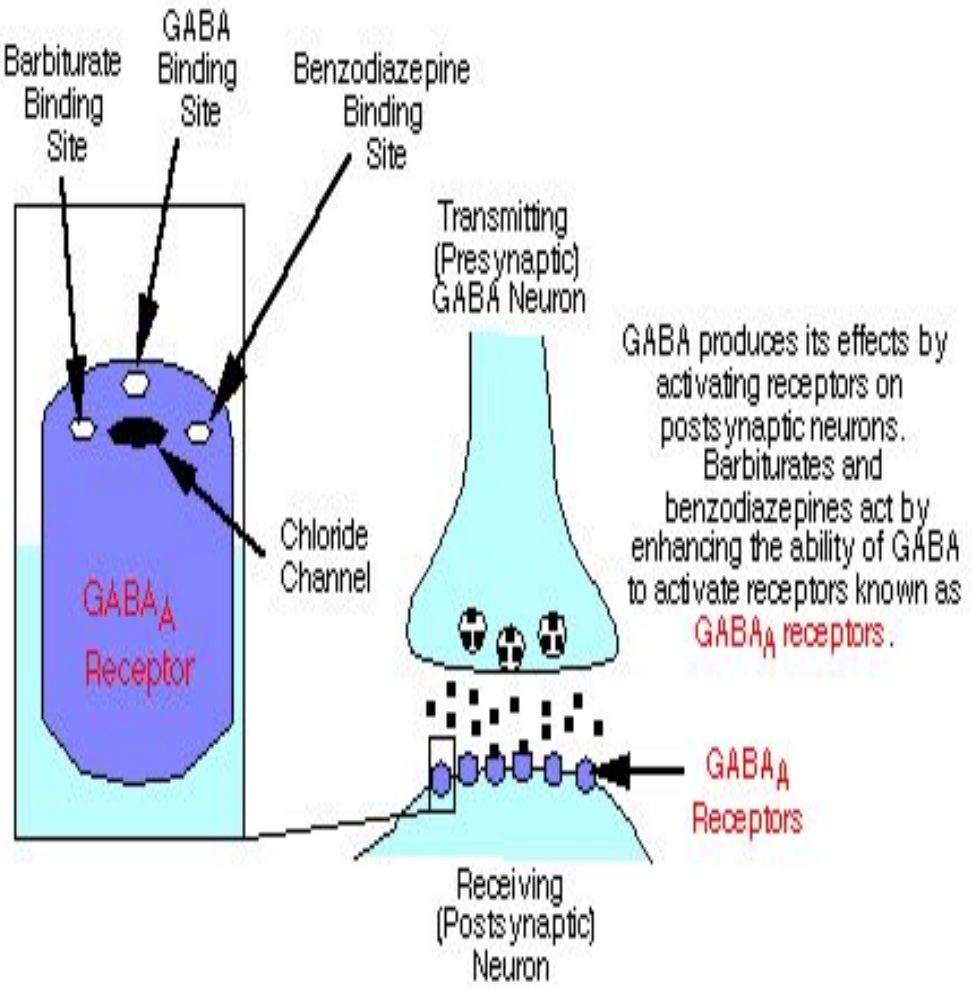
Mechanism of Action

Benzodiazepines act as GABA (γ-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
benzodiazapine
(BDZ) binding site
benzodiazapine
gamma
sub-unit
GABA
Cl-
Cl-
alpha
alpha
alpha
alpha
alpha
alpha
post-synaptic membrane
cytoplasm
©CNSforum.com


(1)
Nerve impulse
NEURON 1
(2)
GABA storage sites
(6)
Benzodiazepines
(3)
GABA released from Neuron 1
(4)
Cl⁻
(7)
Benzodiazepine booster site on GABA receptor
NEURON 2
GABA reacts with receptors on Neuron 2 (allows Cl⁻ to enter)
(8)
Enhances GABA inhibitory effect (may block nerve impulse)
(5)
Ongoing nerve impulse inhibited


Barbiturate Binding Site
GABA Binding Site
Benzodiazepine Binding Site
Transmitting (Presynaptic) GABA Neuron
Chloride Channel
GABA$_A$ Receptor
GABA produces its effects by activating receptors on postsynaptic neurons. Barbiturates and benzodiazepines act by enhancing the ability of GABA to activate receptors known as GABA$_A$ receptors.
GABA$_A$ Receptors
Receiving (Postsynaptic) Neuron

The four types of receptors

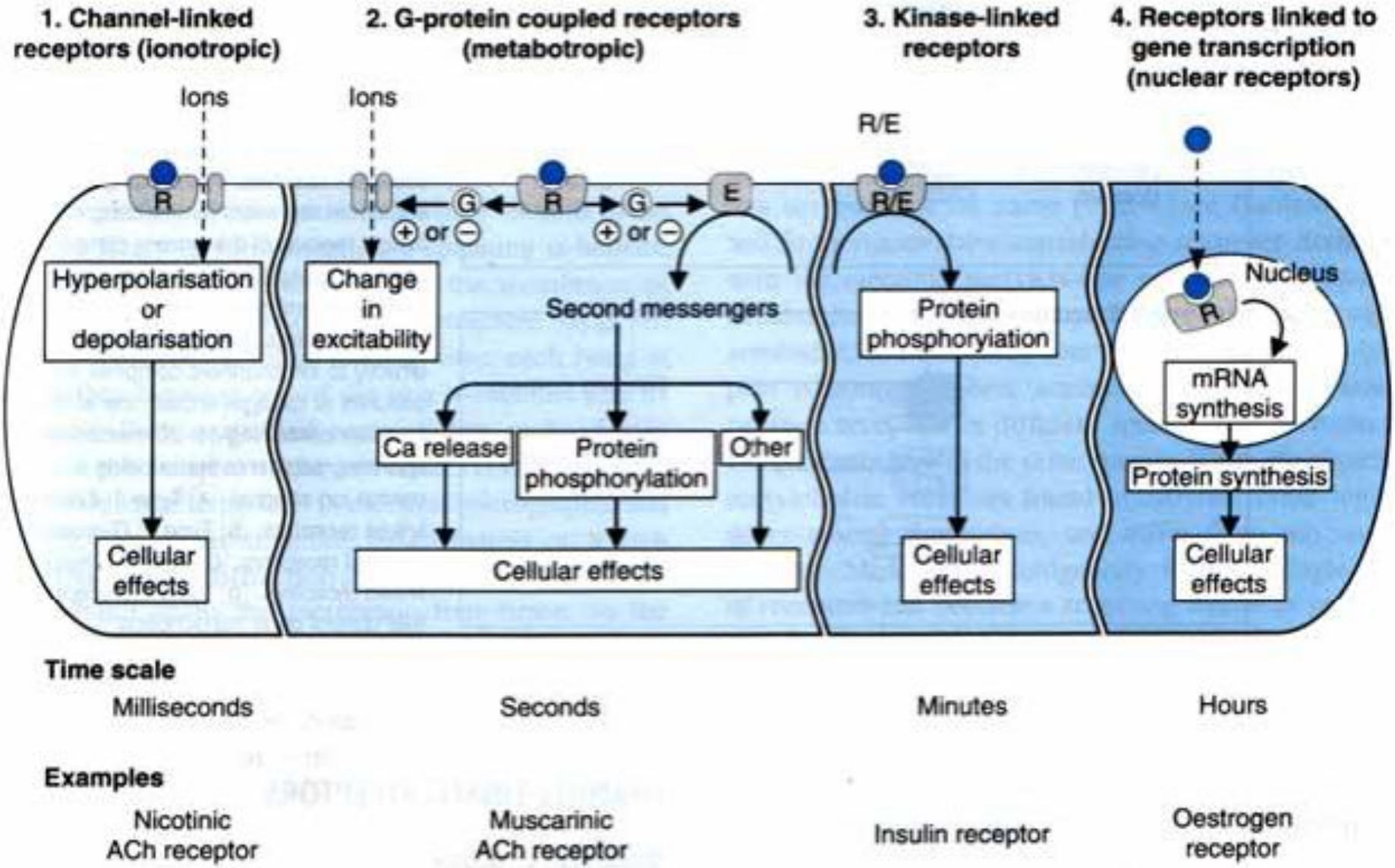
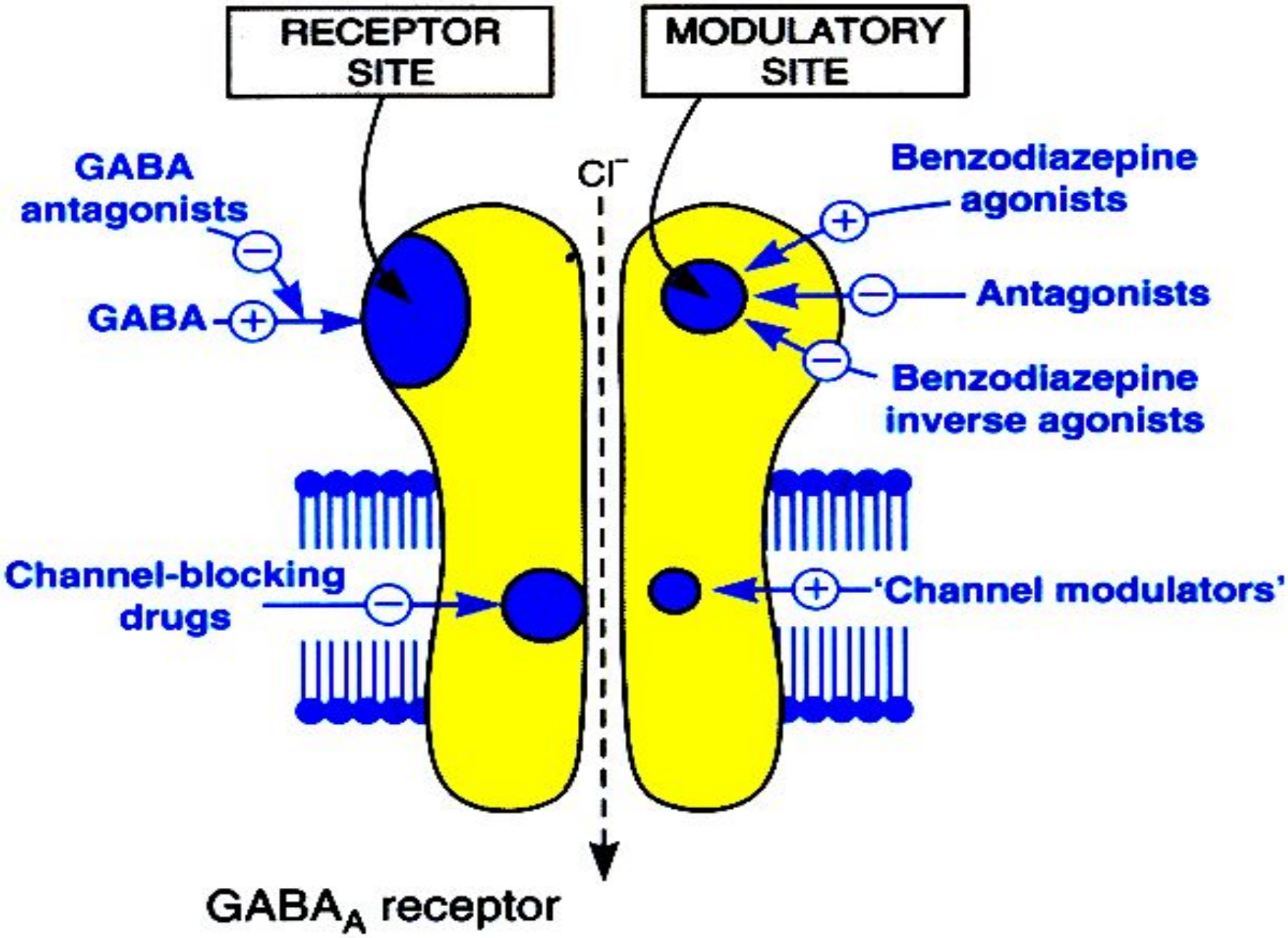
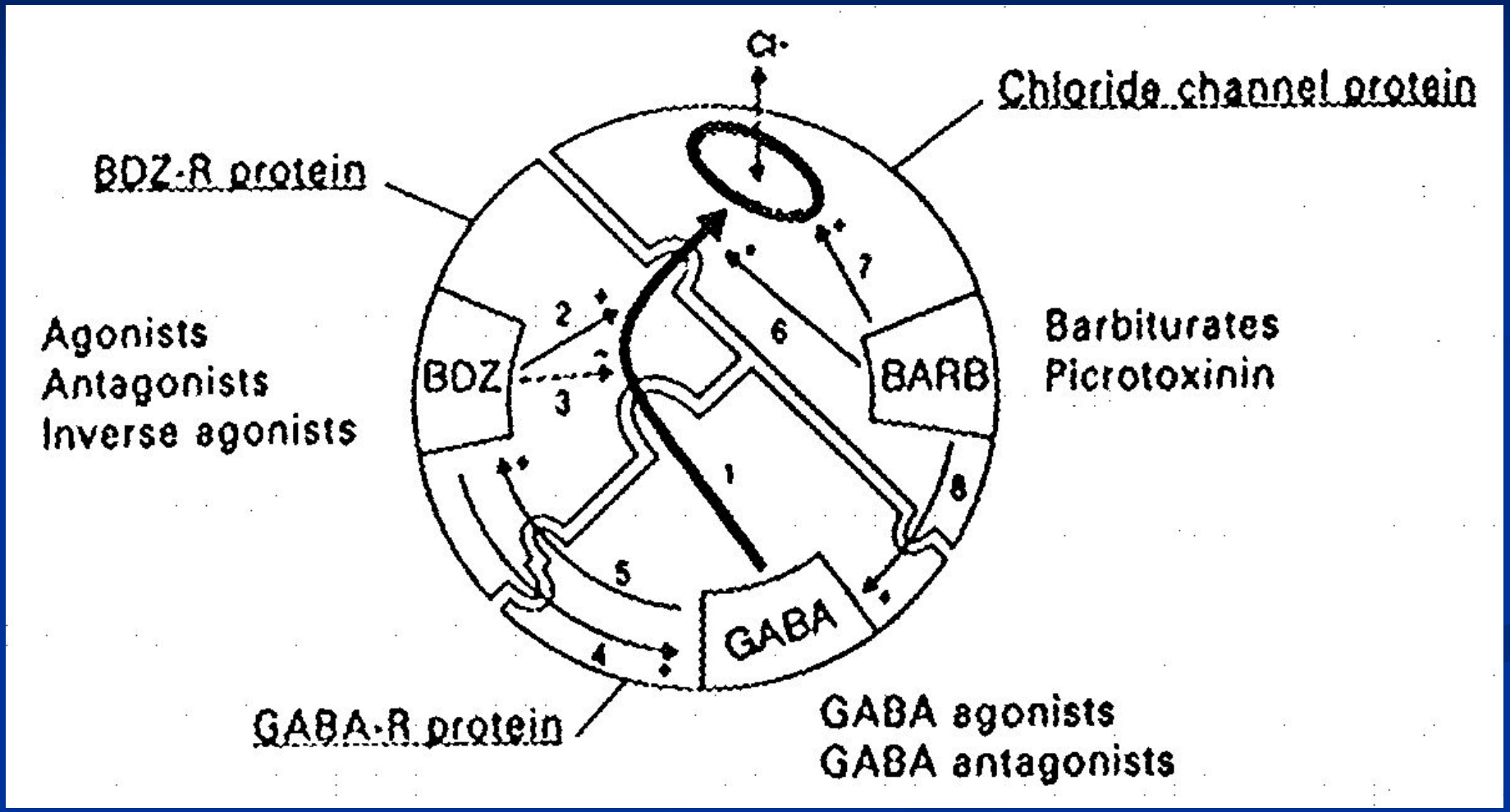


Fig. 2.2 Types of receptor–effector linkage. (R = receptor; G = G-protein; E = enzyme)


RECEPTOR SITE
MODULATORY SITE
GABA antagonists
GABA
Cl⁻
Benzodiazepine agonists
Antagonists
Benzodiazepine inverse agonists
Channel-blocking drugs
'Channel modulators'
GABA$_A$ receptor

Modulatory interactions at $GABA_A$ 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

Effects on sleep architecture	Effects on EEG during sleep
↓ 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 $GABA_A$ receptor

Potentiation of GABA-induced Cl^- conductance

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

Benzodiazepines

Binding sites

- ^{3}H-diazepam binding: **saturable, reversible, specific**
- sites unevenly distributed; parallel to $GABA_A$ 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 ½ min repaid after ½ min (max 3 mg)

Inverse agonists (negative modulators)

β-carbolines

Future therapeutic trends of benzodiazepine binding site (BDZ R) ligands

Drugs for a given binding site subtype:

BDZ R1 agonist	sedative, amnesic, (anticonvulsant)
BDZ R2 agonist	anxiolytic, muscle relaxant
BDZ R partial agonist	↓ dependence
BDZ R inverse agonist	↓ ethanol intake
abnormal BDZ R	specific disorder

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

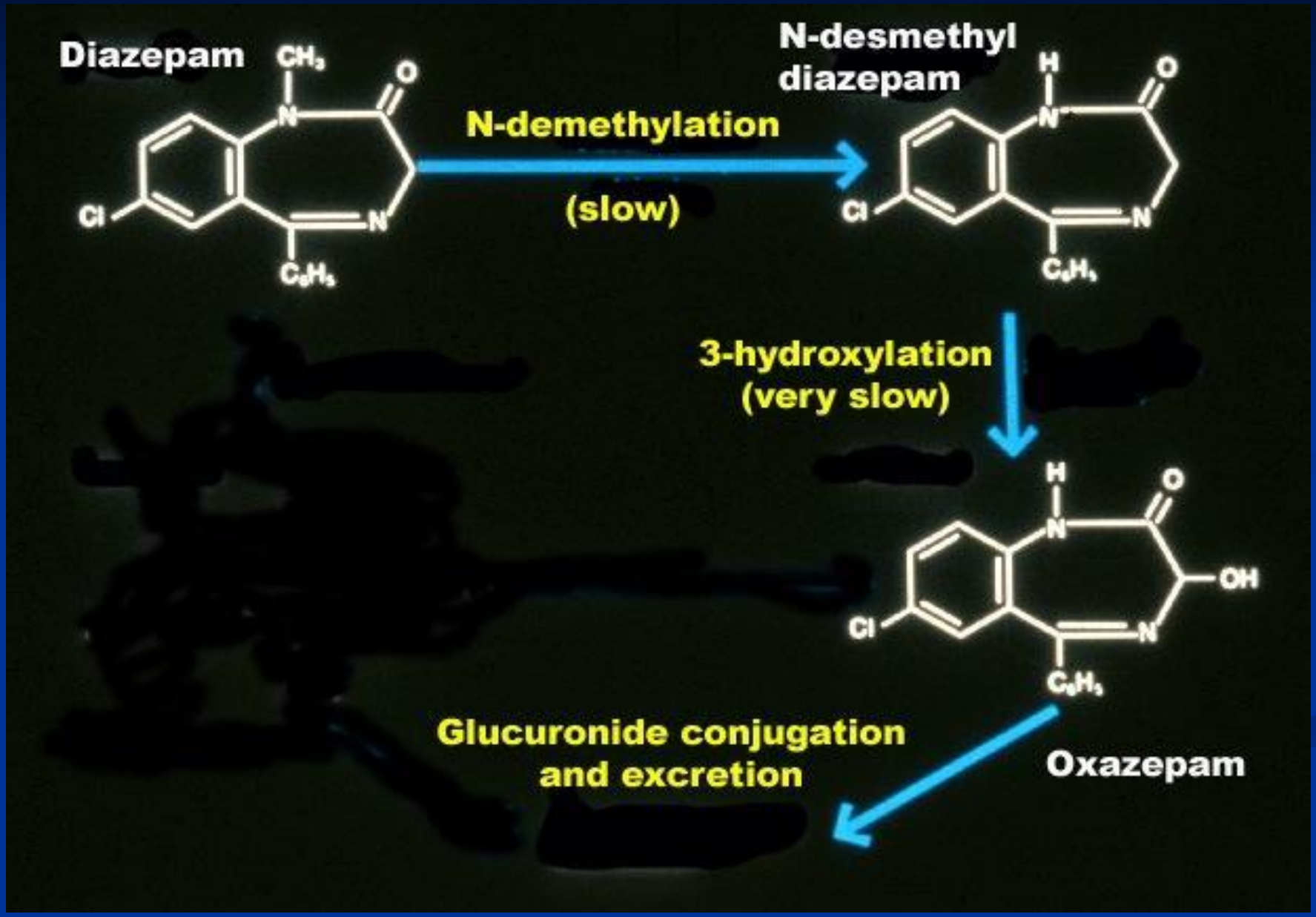
Diazepam Mean half-life 35-50 h (desmethyldiazepam) metabolites have long half-life

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