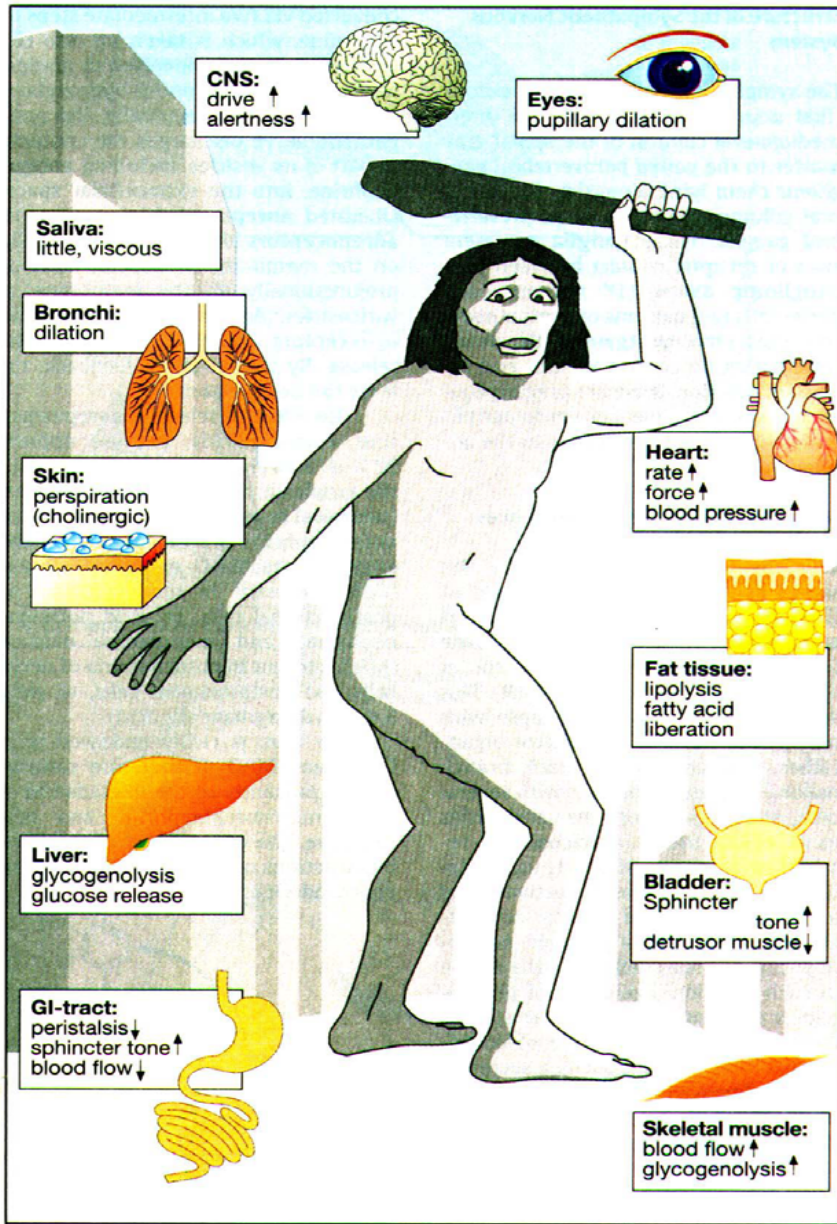


Anksiolitiki in uspavala

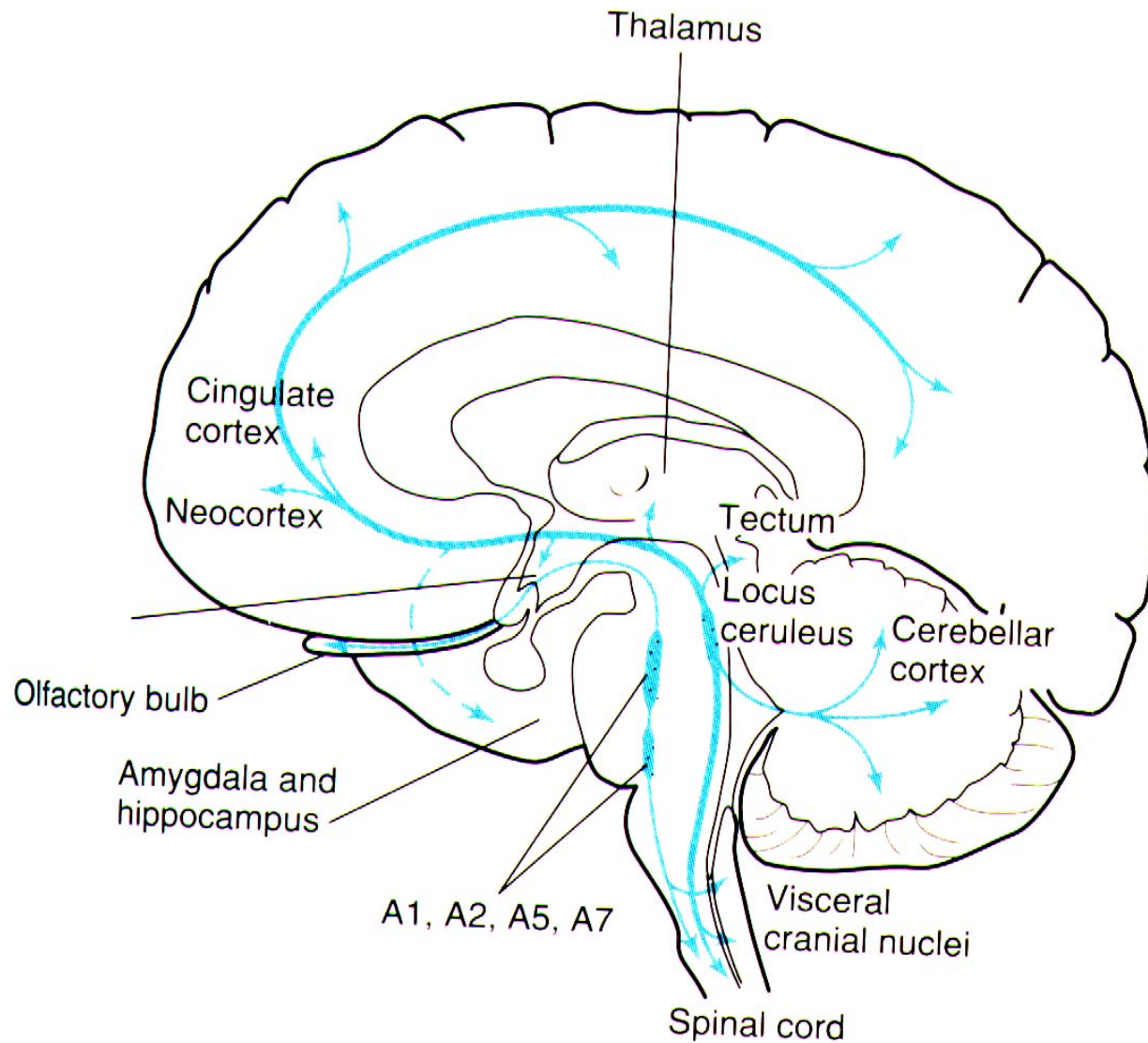
Prof. dr. Mojca Kržan



Inštitut za farmakologijo in eksperimentalno toksikologijo,
Medicinska fakulteta, Univerza v Ljubljani



Noradrenergične poti v osrednjem živčevju



Posledice strahu

Simpatična stimulacija



Strah

Dilatacija pupil

Tahikardija

Tremor

Potenje

Th: klonidin, beta bloker



Limbični lobus

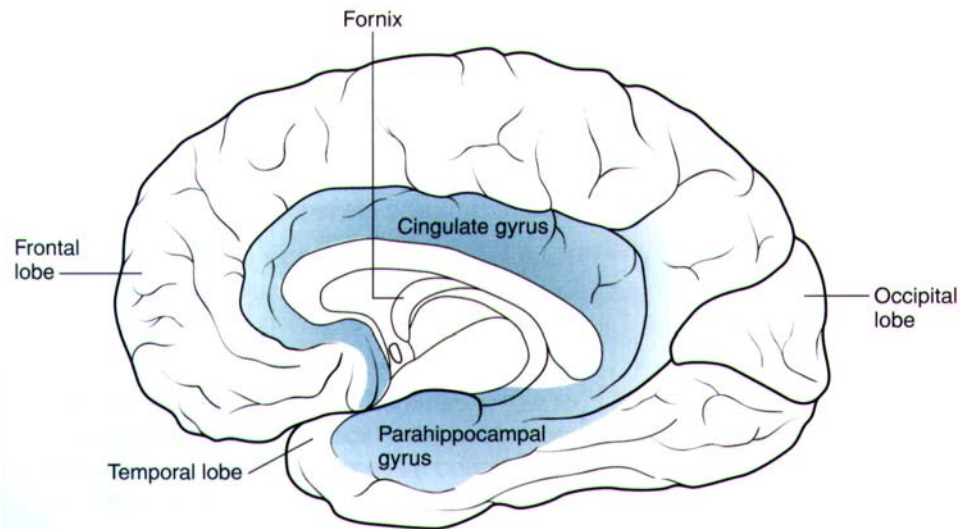


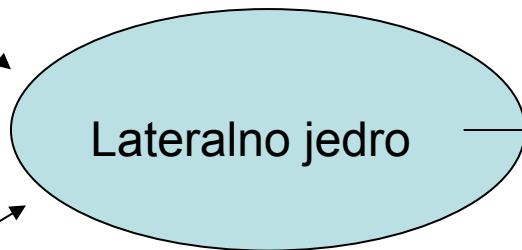
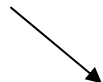
Figure 15-1. The limbic lobe. This ring of tissue (limbus) encircles the upper brain stem and consists of evolutionarily older forms of cortex. It comprises the cingulate and parahippocampal gyri as well as deeper structures such as the hippocampus and amygdala.



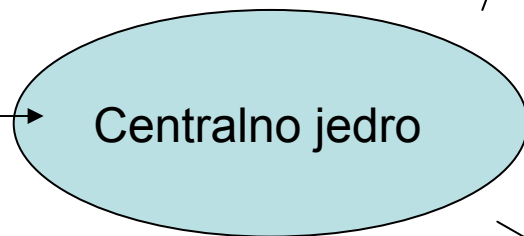
Strah

Amigdala

Talamus



Lateralno jedro



Centralno jedro



Sivina: obrambno vedenje, hipoalgezija

Lateralni hipokampus: avtonomni arousal

PVN: sproščanje kortizola

LC, raphe, VTA: spremenjena percepcija, ↑ vigilanca

Senzorična in asociacijska skorja



Živalski modeli anksioznosti

- Dvignjen labirint
- Hkratno doživljanje prijetnega in neprijetnega občutka (hrana + elektrošok)
- Novo okolje (neofobija)

Pregled anksiolitikov

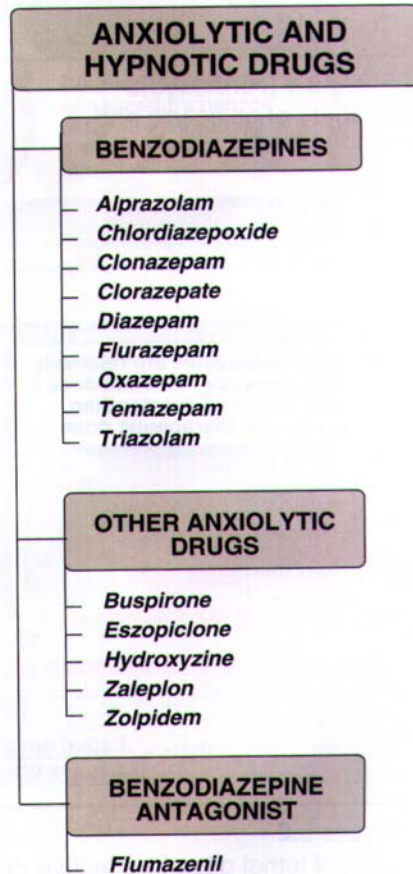


Figure 9.1
Summary of anxiolytic and hypnotic drugs.
(Figure continues on next page.)

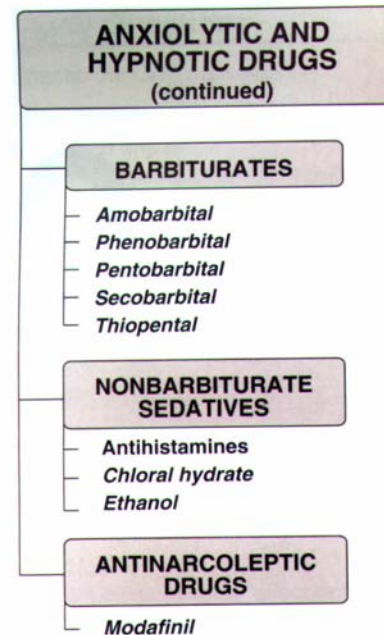
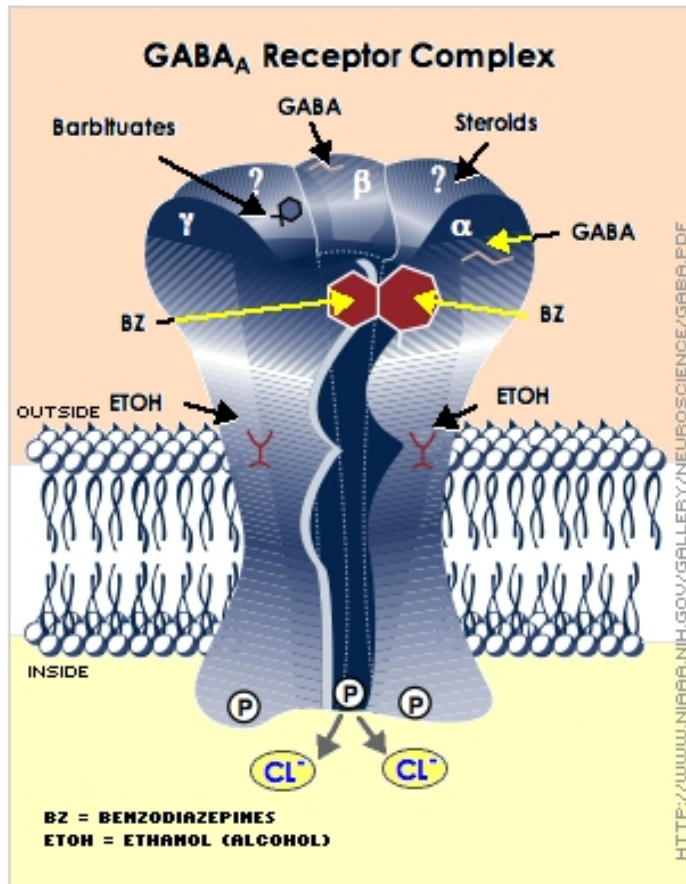


Figure 9.1 (continued)
Summary of anxiolytic and hypnotic drugs.



Receptor GABA A



Pentamer različnih podenot:
 $n\alpha n\beta n\gamma$ ($n = 1 - 3$)

$\alpha 1 - \alpha 6$

$\beta 1 - \beta 4$

$\gamma 1 - \gamma 2$

δ

(možnih

več kot 2000 kombinacij)

$\gamma 2$, $\beta 2$ več oblik kot posledica alternativnega zlepljanja intronov in eksonov razlike na mestu, kjer je mesto za fosforilacijo PKC



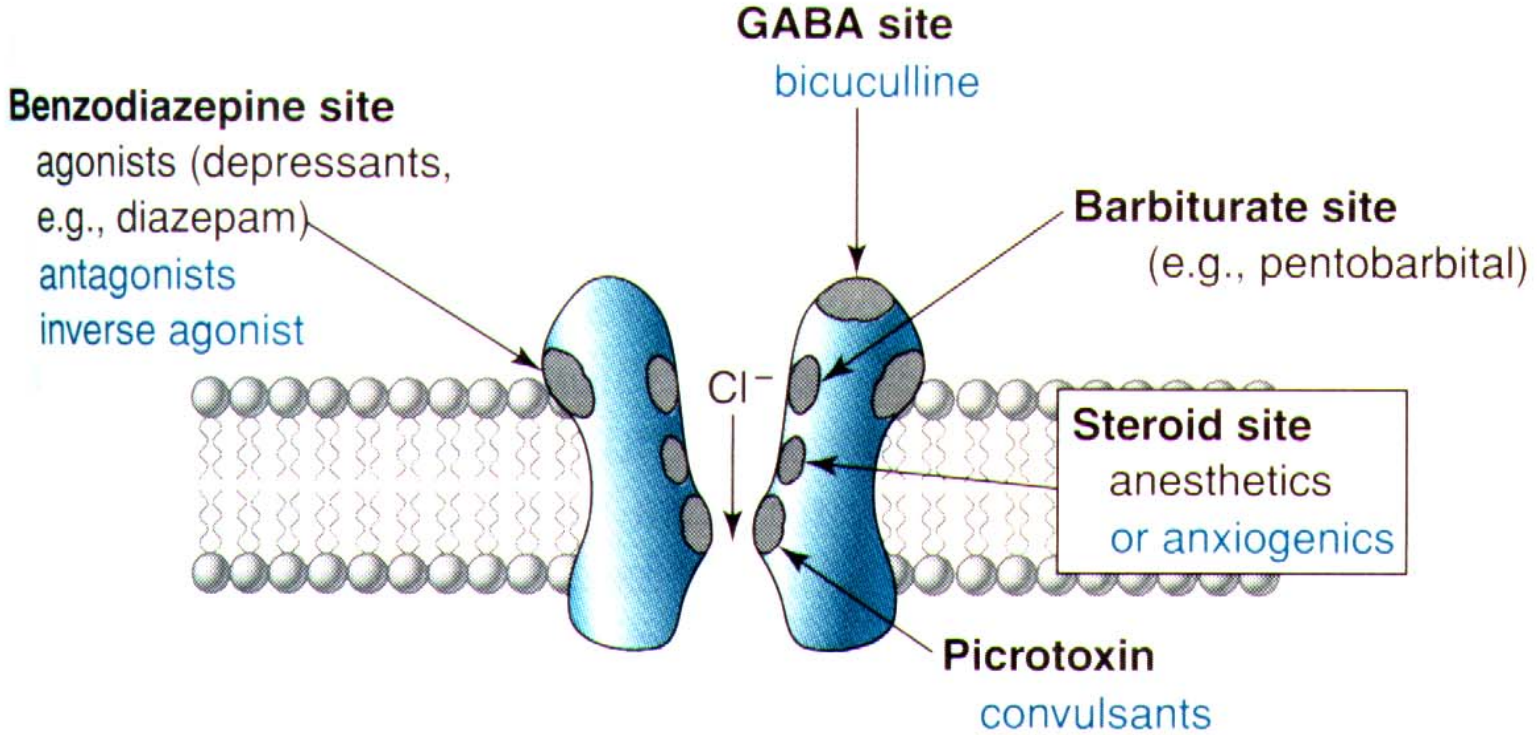


Table 15-2 Pharmacologically Significant Binding Sites on GABA_A Receptors

Site	Agonists	Antagonists	Inverse Agonists
GABA	GABA Muscimol	Bicuculline	
Benzodiazepine	Diazepam	Flumazenil	β-carbolines RO-15-4513
Barbiturate	Pentobarbital		
Convulsant ¹	Picrotoxin Pentylentetrazole		
Neuroactive steroid ² (site uncertain)	3α and 5α-THP	DHEA-S	

¹The categorization of picrotoxin and pentylentetrazole as agonists at this site may seem paradoxical because these agents antagonize GABA_A receptor function. The term *agonist* is used to indicate that the drugs bind to an allosteric site in the receptor complex that exerts an effect (albeit an inhibitory one) on the receptor.

² See Chapter 13 for a more in-depth discussion of neuroactive steroids.

3α and 5α-THP, tetrahydroprogesterone; DHEA-S, dehydroepiandrosterone sulfate.



GABA_A receptor

Vezavno mesto za BENZODIAZEPINE je na α -podenoti
- alosterično regulatorno vezavno mesto in ne receptor v ožjem pomenu

Vezavno mesto za zolpidem je na α -podenoti

Vezavno mesto za GABA je na β -podenoti

Vezavno mesto za BARBITURATE je v bližini kanala za Cl⁻



Podenote GABA_A receptorja

$\alpha 1$ – spanje

$\alpha 1$ – spomin

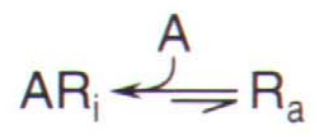
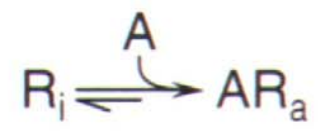
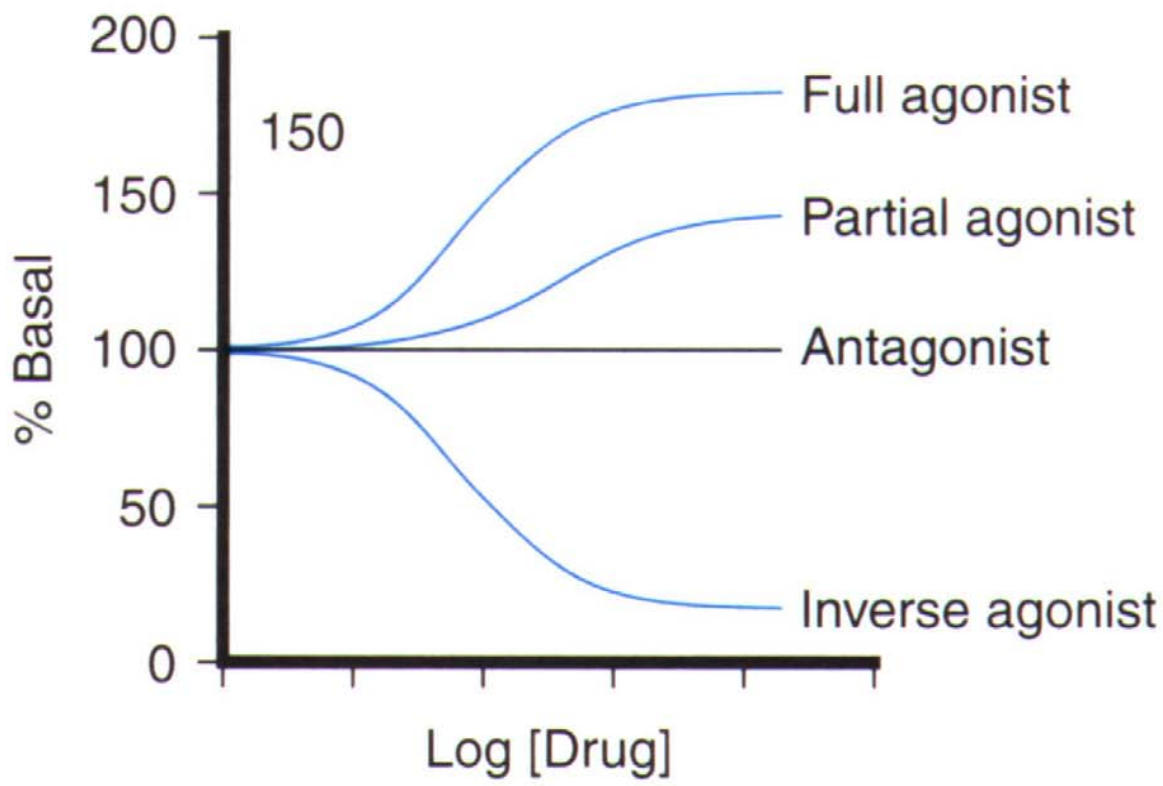
$\alpha 1$ – delno antikonvulzivno delovanje

$\alpha 2$ - anksioliza

$\alpha 2$ – mišična relaksacija (presinaptična inhibicija)

$\alpha 5$ – kognitivni učinki





Zdravila, ki se vežejo na BDZ mesto

Agonist: anksiolitik, sedativ, hipnotik, antikonvulziv, amnestik, odvisnost

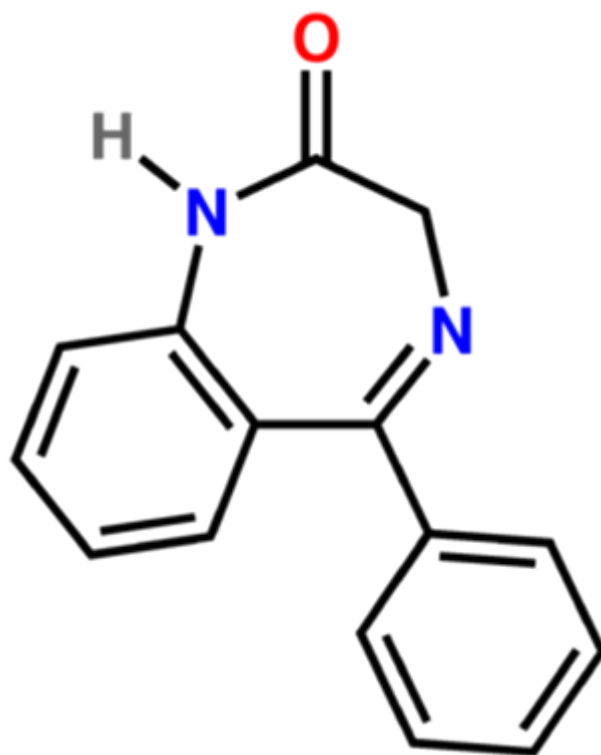
Delni agonist: anksiolitik

Antagonist (flumazenil): brez učinka

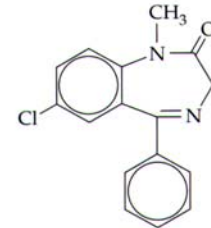
Delni inverzni agonist: promnestik, anksiogen

Inverzni agonist (β -karbolin): promnestik, anksiogen, prokonvulziv

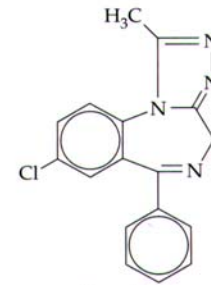




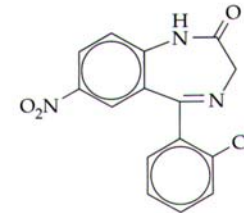
Primeri anksiolitikov



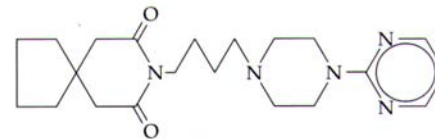
Diazepam



Alprazolam



Clonazepam



Buspirone



- [alprazolam](#) (Xanax, Helex)
- [bromazepam](#) (Lexaurin, Lekotam, Lexilium)
- [klordiazepoxide](#) (Librium)
- [klonazepam](#) (Klonopin)
- klobazam (Frisium)
- [diazepam](#) (Apaurin, Valium)
- [estazolam](#) (ProSom)
- [flunitrazepam](#) (Rohypnol)
- [flurazepam](#) (Fluzepam, Dalmane)
- [lorazepam](#) (Loram, Lorsilan, Ativan)
- [lormetazepam](#) (Loramet)
- medazepam (Ansilan)
- [meksazolam](#) (Sedoxil)
- [midazolam](#) (Dormicum)
- [nitrazepam](#) (Cerson, Mogadon)
- [oksazepam](#) (Adumbran, Praxiten, Serax)
- Prazepam (Demetrin)
- [temazepam](#) (Restoril)
- [triazolam](#) (Halcion)



Table 15–3 Commonly Used Benzodiazepines

Agonists

Alprazolam	Flurazepam	Prazepam
Chlordiazepoxide	Halazepam	Quazepam
Clonazepam	Lorazepam	Temazepam
Clorazepate	Midazolam	Triazolam
Diazepam	Nitrazepam	Zolpidem ¹
Estazolam	Oxazepam	

Antagonist

Flumazeni

¹The nonbenzodiazepine, zolpidem, is an imidazopyridine that acts on the same site of the GABA_A receptor as do benzodiazepines.



Učinki benzodiazepinov

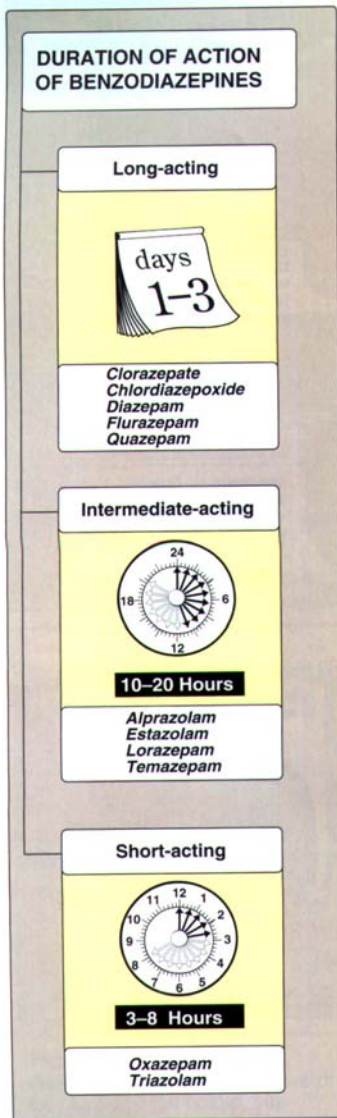
- **anksiolitik**
- **sedativ**
- **Hipnotik (kratkodelujoči)**
- **Antikonvulziv**
- **Amnestik – anterogradna amnezija (kratko delujoči, z visoko afiniteto)**
- **odvisnost**



Neželeni učinki benzodiazepinov

- vpliv na dihanje (bolniki s KOPB, obstruktivno apnejo med spanjem, smrčanje)
- KVS: minimalen vpliv (midazolam - ↓ PU, ↓ pretok krvi po možganih; diazepam ↓ delo levega ventrikla, ↓ CO, vazodilatacija koronark)
- GIT: zaščita pred ulkusi, ki jih povzroča stres (↓ nočna sekrecija HCl)





Protiepileptična zdravila

Anksiolitik, pri detoksifikaciji, napadi panike, manj sedativni

Hipnotiki

Figure 9.4
Comparison of the durations of action of the benzodiazepines.



Farmakokinetika

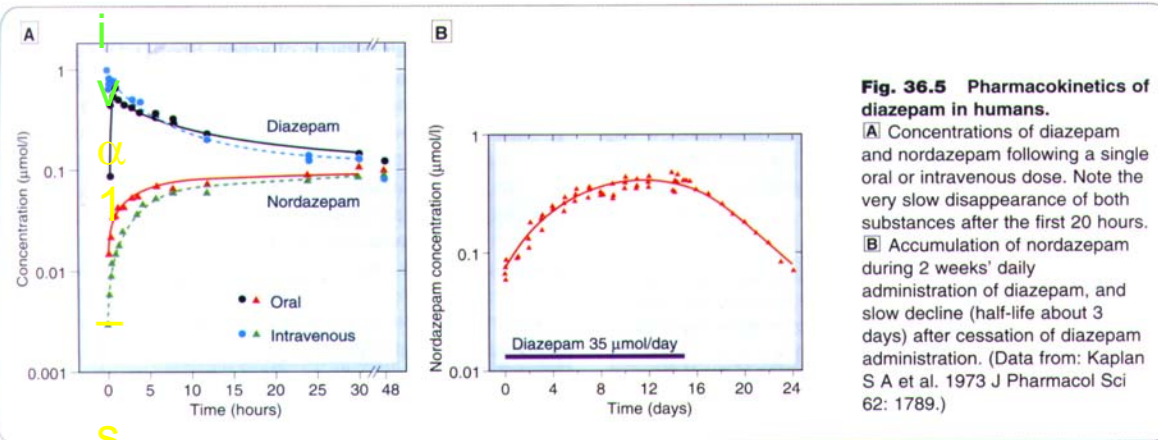
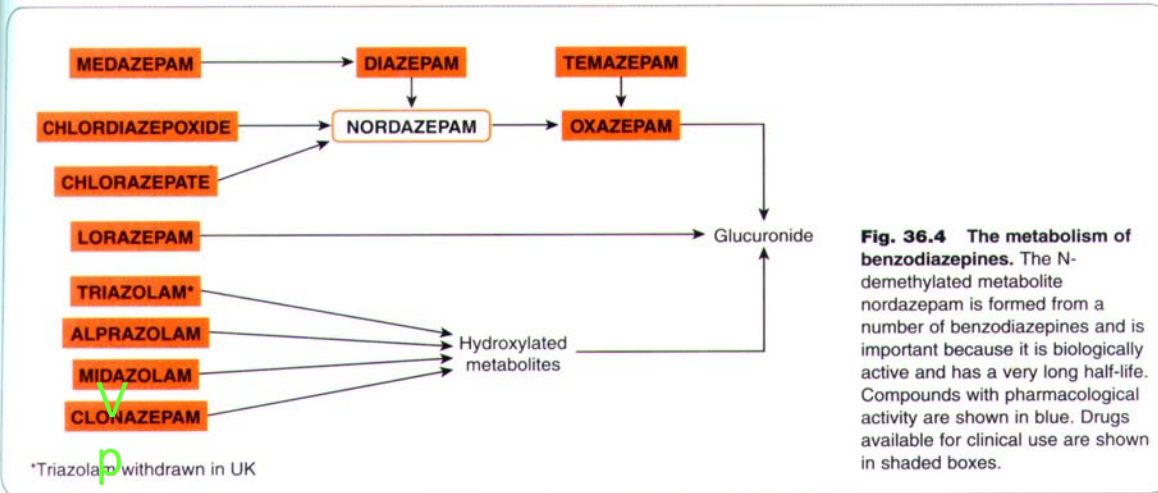
- Sistem dveh ali treh (zelo lipofilni) kompartmentov

distribucija: - prekrvavitev (možgani)
- nalaganje (mišice, maščevje)

izločanje:



Vpliv metabolizma na čas delovanja benzodiazepinov



s
p
e

Toleranca in odvisnost - BDZ

- Farmakodinamčino pogojena toleranca
- Abstinenčni sindrom ob prenehanju – odvisen od $t_{1/2}$
- Rebound effect - insomnia



Primerjava neželenih učinkov alprazolama in buspirona

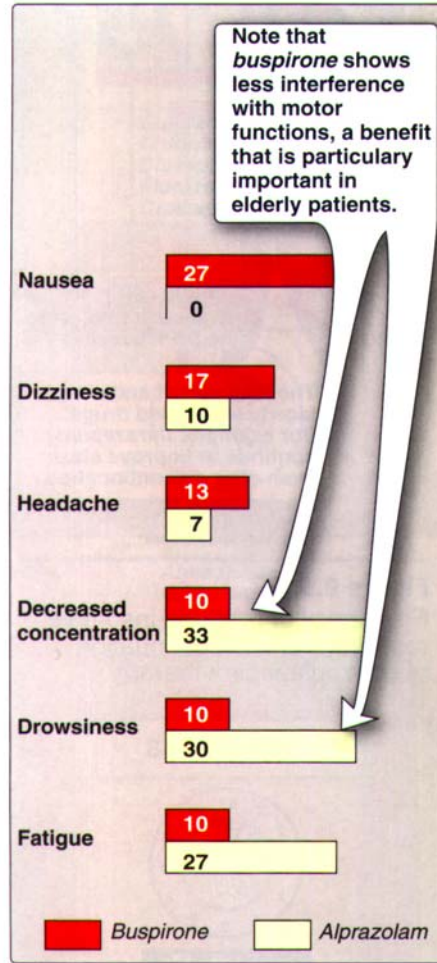


Figure 9.6

Comparison of common adverse effects of *buspirone* and *alprazolam*. Results are expressed as the percentage of patients showing each symptom.



Zolpidem, zaleplon

- kemično nista benzodiazepina
- $T_{1/2}$ 2h, 1h
- Vežeta se na $\alpha 1$ podenoto
- Th: nespečnost 7-10 dni



Buspiron

- delni agonist receptorjev 5-HT_{1A},
- 5-HT_{1A} so avtoreceptorji/presinaptični receptorji
- odložen odgovor
- povzroči “up-regulacijo” receptorjev
- Neučinkovit pri paničnih napadih



Varnost anksiolitikov v primerjavi z drugimi zdravili

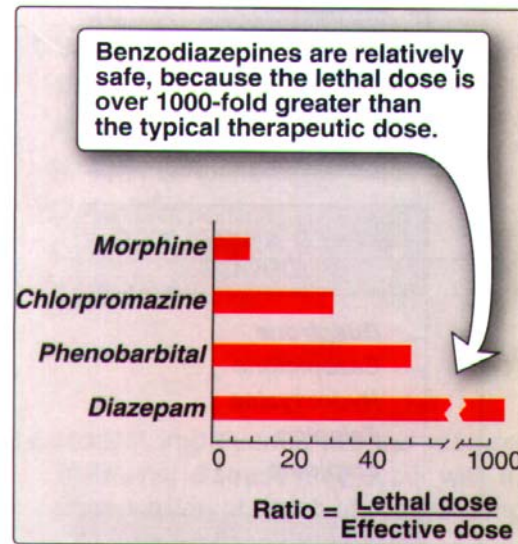


Figure 9.2

Ratio of lethal dose to effective dose for *morphine* (an opioid, see Chapter 14), *chlorpromazine* (a neuroleptic, see Chapter 13), and the anxiolytic, hypnotic drugs, *phenobarbital* and *diazepam*.



Barbiturati

- Vezava na mesto v bližini Cl⁻ kanala
- Podaljšajo odprtje Cl⁻ kanala
- V visokih odmerkih učinkujejo neodvisno od GABA
- Blokada Na⁺ kanalov
- Blokada receptorjev za glutamat
- Depresija dihanja



Razdelitev barbituratov

- Ultrakratkodelujoči – tiopenton – uvod v anestezijo
- Kratkodelujoči – pentobarbiton, sekobarbiton, amobarbiton – sedacija in hipnoza, niso anksiolitiki
- Dolgodelujoči – fenobarbiton - epilepsija



Učinki barbituratov

- Depresija CŽS: sedacija → hipnoza → anestezija → koma → smrt
- Ne vplivajo na bolečino
- Depresija dihanja



Farmakokinetika barbituratov

- ADME
- Inaktivacija z distribucijo
- Indukcija encimov



Toleranca in odvisnost – barbiturati

- Farmakodinamsko in farmakokinetično pogojena toleranca
- Abstinenčni sindrom ob prenehanju



Kloral hidrat

- Prozdravilo
- Pretvorba v trikloroetanol
- 30 min, učinek traja do 6h



Antihistaminiki

- Difenhidramin, doksilamin
- OTC
- Dolg učinek



Indikacije

- Panične reakcije
- GAD – generalized anxiety disorder
- PTSD
- Preproste fobije
- Socialne fobije



Kontraindikacije

- KOPB



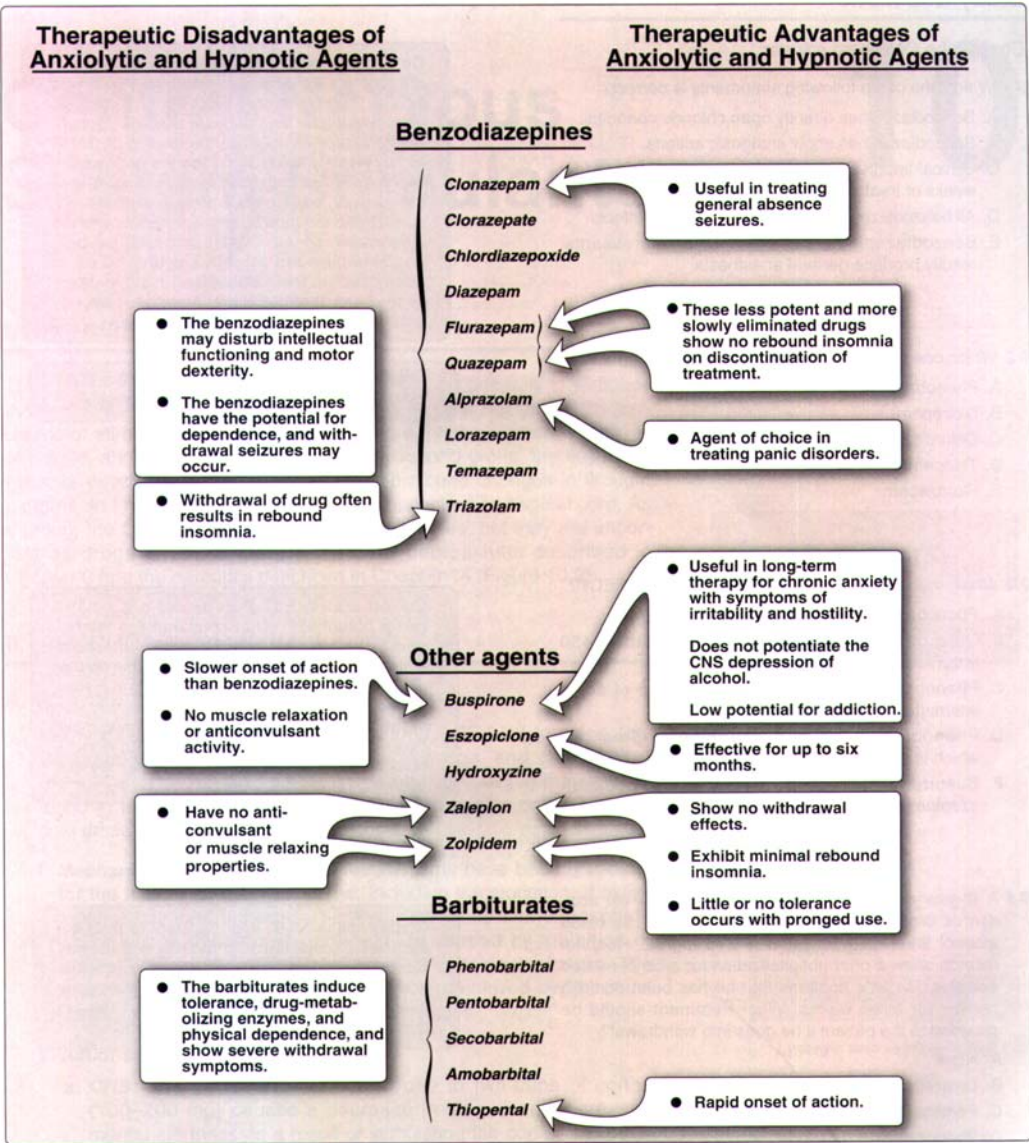


Figure 9.10
Therapeutic disadvantages and advantages of some anxiolytic and hypnotic agents. CNS = central nervous system.