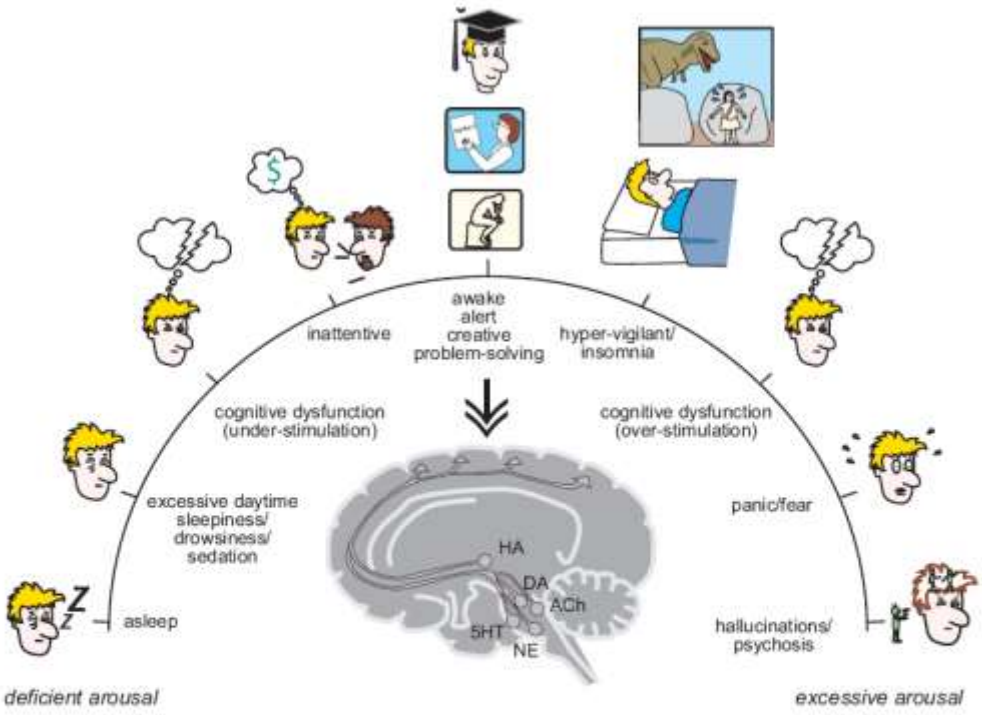
OBAT HIPNOTIK - SEDATIF

Fathiyah Safithri

Laboratorium Farmakologi FK-UMM

Arousal spectrum of sleep and wakefulness

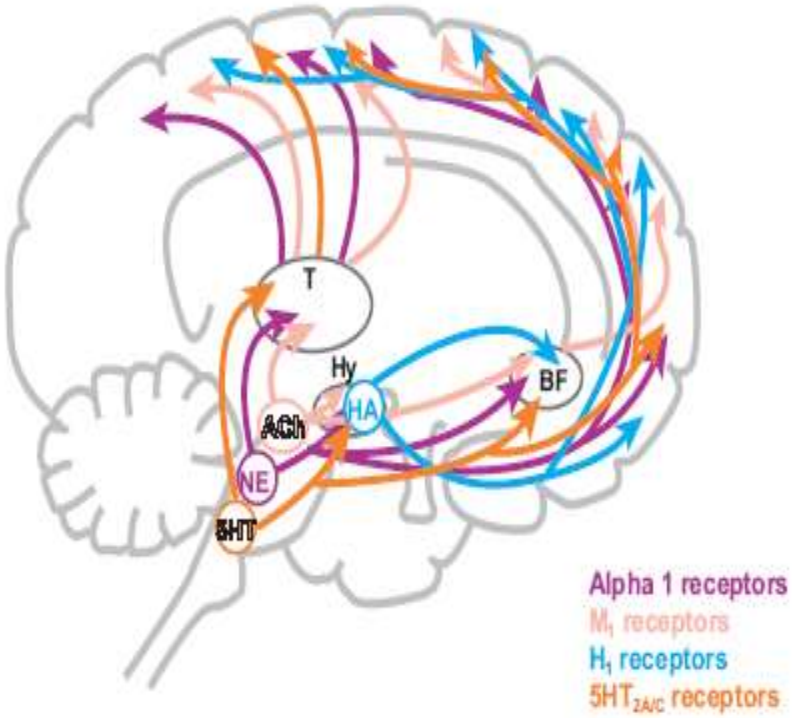


HA=histamine; DA=dopamine; ACh=acetylcholine; 5-HT=serotonin; NE=norepinephrine.

Stahl SM. *CNS Spectr.* Vol 13, No 12. 2008.

" Wake-promoting and sleep-promoting " neurotransmitters

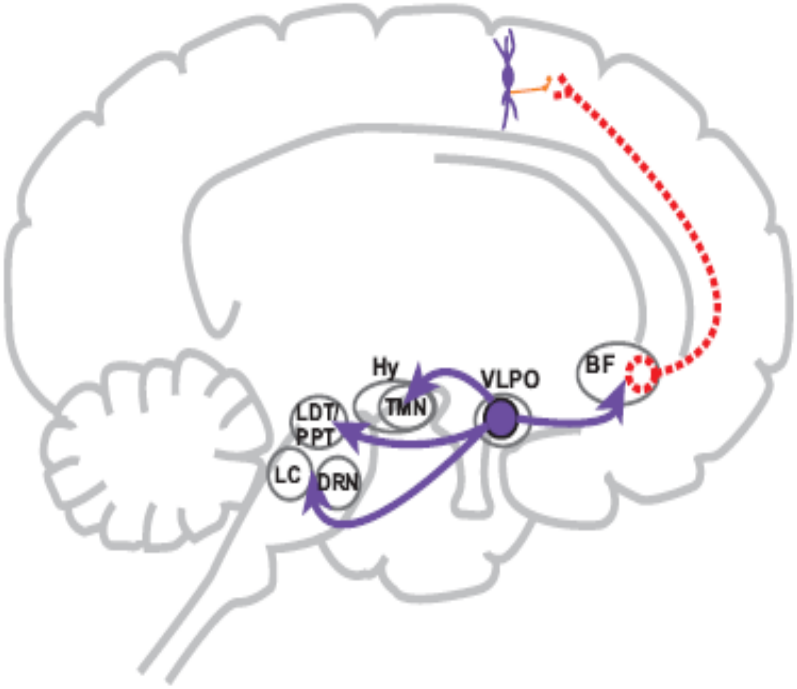
FIGURE 1.
Cortical Arousal



T=thalamus; Hy=hypothalamus; ACh=acetylcholine; HA=histamine; BF=basal forebrain; NE=norepinephrine; 5-HT=serotonin; M=muscarinic; H=histamine.

Stahl SM. *CNS Spectr.* Vol 13, No 12. 2008.

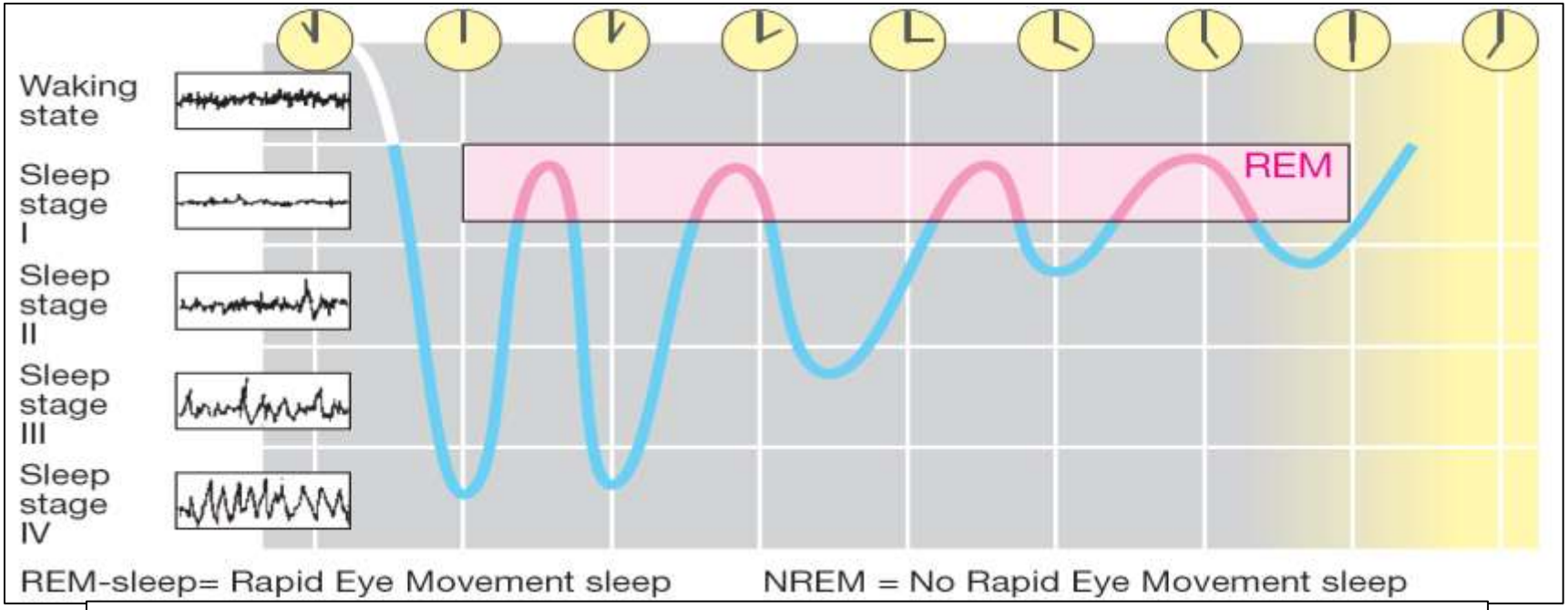
FIGURE 2.
Sleep-promoting GABA system

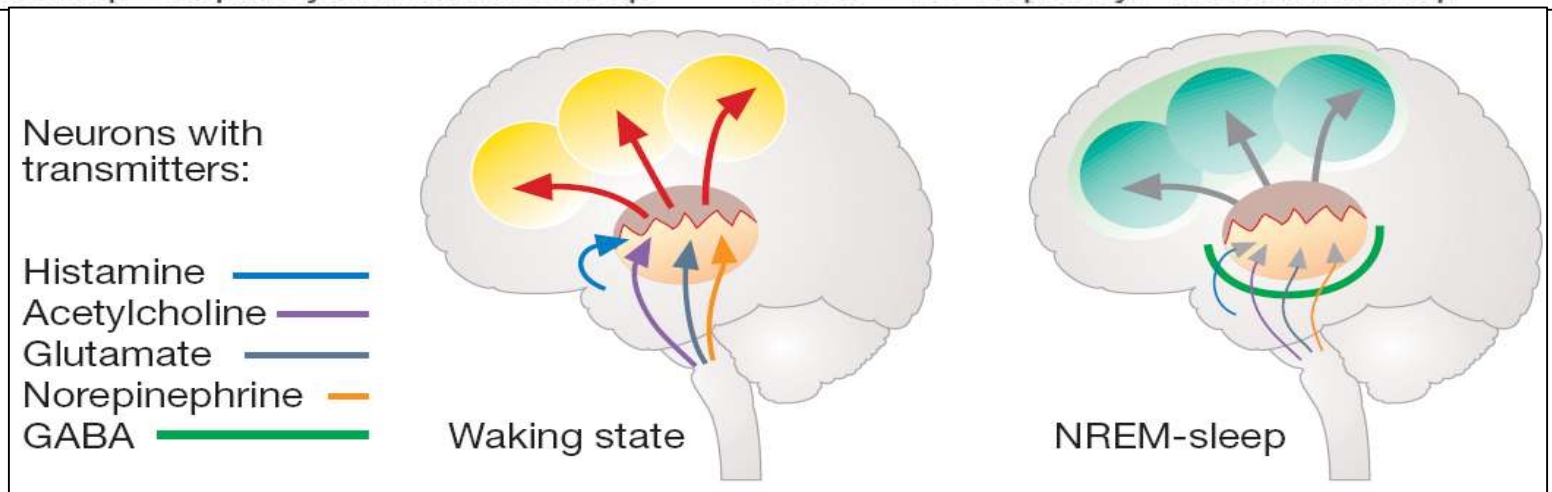


GABA=γ-aminobutyric acid; Hy=hypothalamus; BF=basal forebrain; LDT=laterodorsal tegmental; PPT=peduncolopontine tegmental; TMN=tuberomamillary nucleus; VLPO=ventrolateral preoptic nucleus; LC=locus coeruleus; DRN=dorsal raphe nucleus.

Stahl SM. *CNS Spectr.* Vol 13, No 12. 2008.

FASE-FASE TIDUR





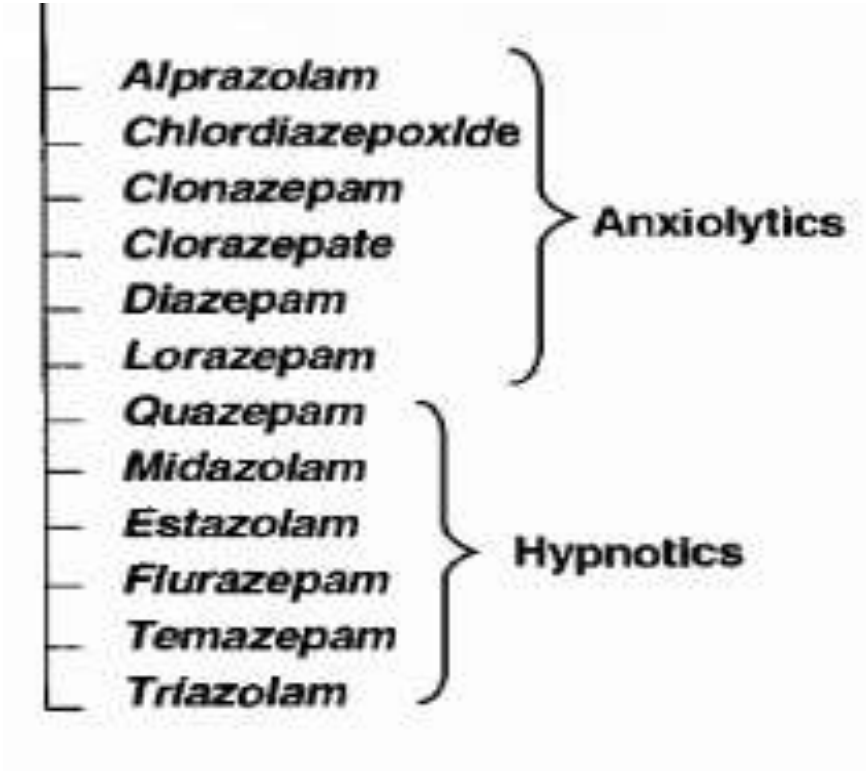
- **Insomnia**
  - Causes - noise, worries, stress, drugs, pain, uncomfortable temperature, disease, etc.
  - Types
    - onset insomnia - trouble falling asleep
    - maintenance insomnia - awaken frequently during the night
    - termination insomnia - wake up too early and cannot get back to sleep

HYPNOTIC AGENTS

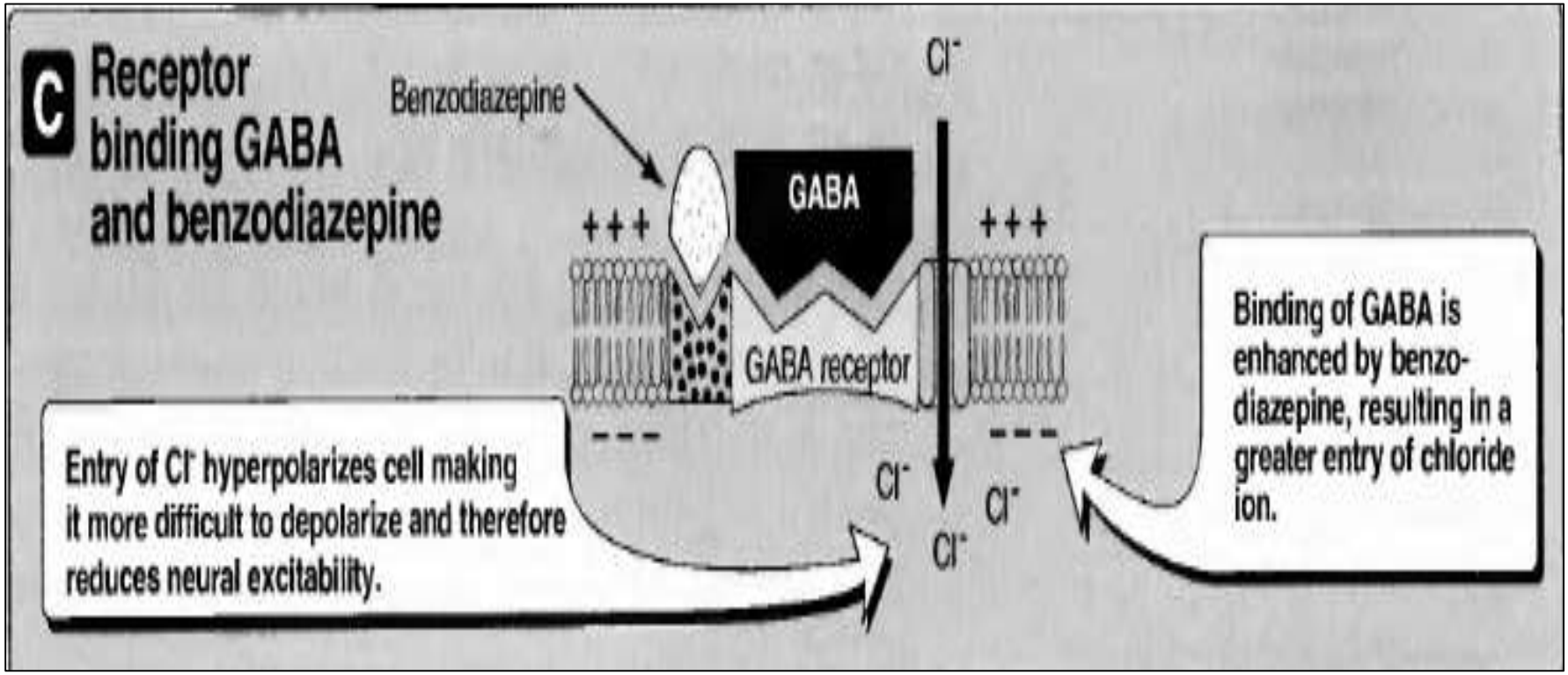
- **Hypnotic Agents That Act by Enhancing GABA**
- **Hypnotic Agents That Act by Blocking Wake-Promoting Neurotransmitter Systems**

Hypnotic Agents That Act by Enhancing GABA
- AGONIS GABA -

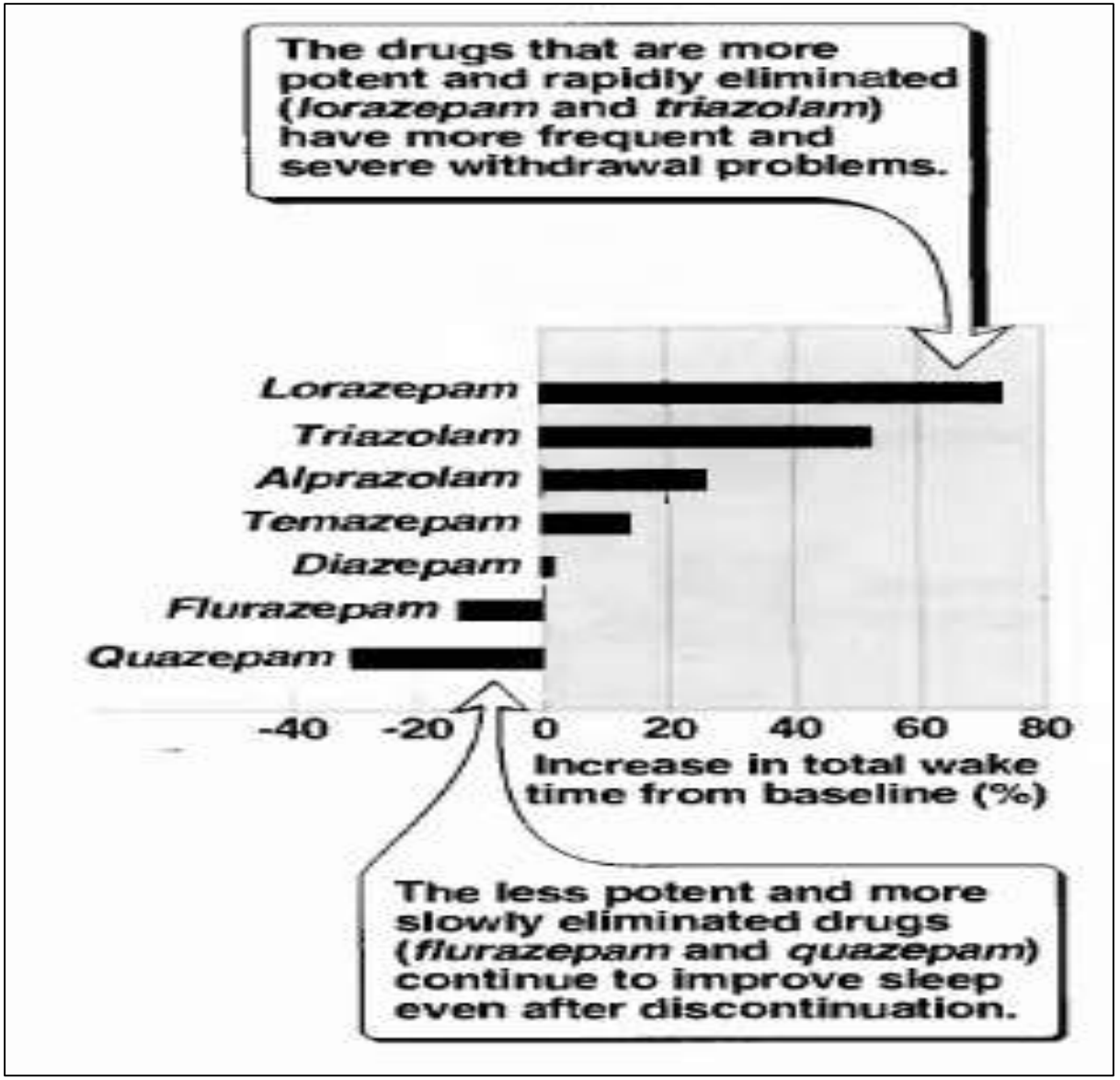
- Benzodiazepin



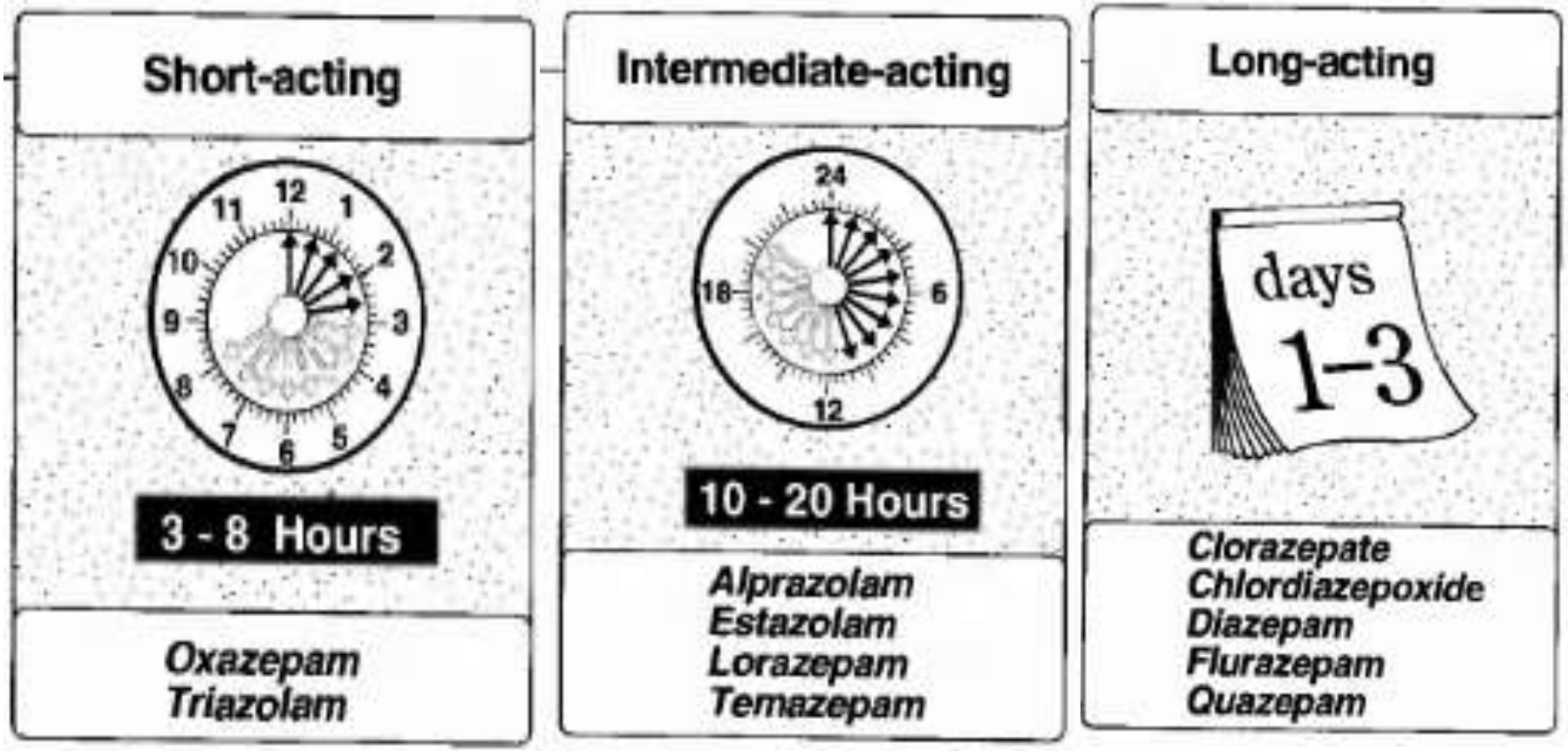
Benzodiazepin



Rebound insomnia



Benzodiazepin



RESUME

Sedative-Hypnotics-I (Treatment for Insomnia)

Benzodiazepines:

- *Rapid onset, short acting*
  - triazolam
- *Delayed onset, intermediate acting*
  - temazepam, estazolam
- *Rapid onset, long acting*
  - flurazepam
  - quazepam

→
- Act at benzodiazepine receptors and increase the inhibitory action of GABA
- High doses required
- Develop tolerance

Nonbenzodiazepines:

- *Rapid-onset, short acting*
  - Zaleplon
  - Zolpidem
  - Zopiclone

→
- Binds to omega-1 but not to omega-2 benzodizepine receptors
- Less cognitive, memory and motor side effects
- Shorter half life
- No dependence, tolerance or withdrawal symptoms

Sedative-Hypnotics II

Sedative antidepressants:

tricyclics (anticholinergic/antihistaminergic) → Good choice with AD properties

trazodone ($5HT_{2A}$ antagonist)
mirtazapine ($5HT_{2A}$ antagonist)
nefazodone ($5HT_{2A}$ antagonist)
→ Safe with other psychotropic drugs which disrupts sleep, such as SSRIs

Sedative antihistamines:

diphenylhydramine
doxylamine
hydroxyzine

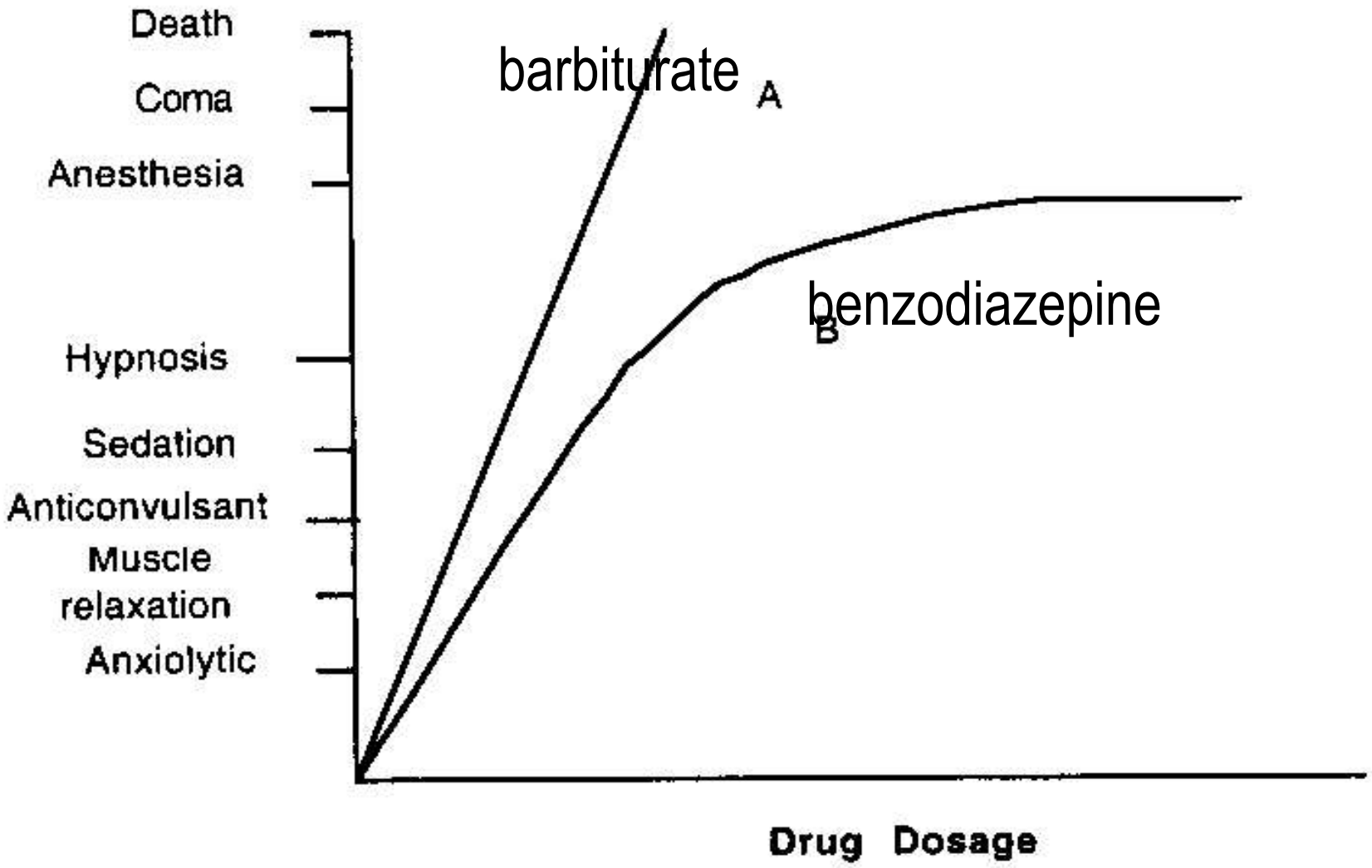
Other sedative:

chloral hydrate → Short-term use
Causes dependency
Tolerance

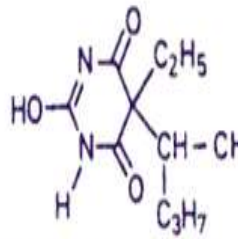
Natural products:

melatonin

A Crucial Difference

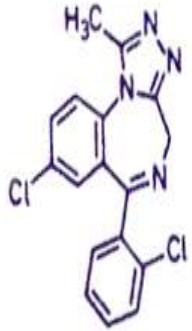


Barbiturates:

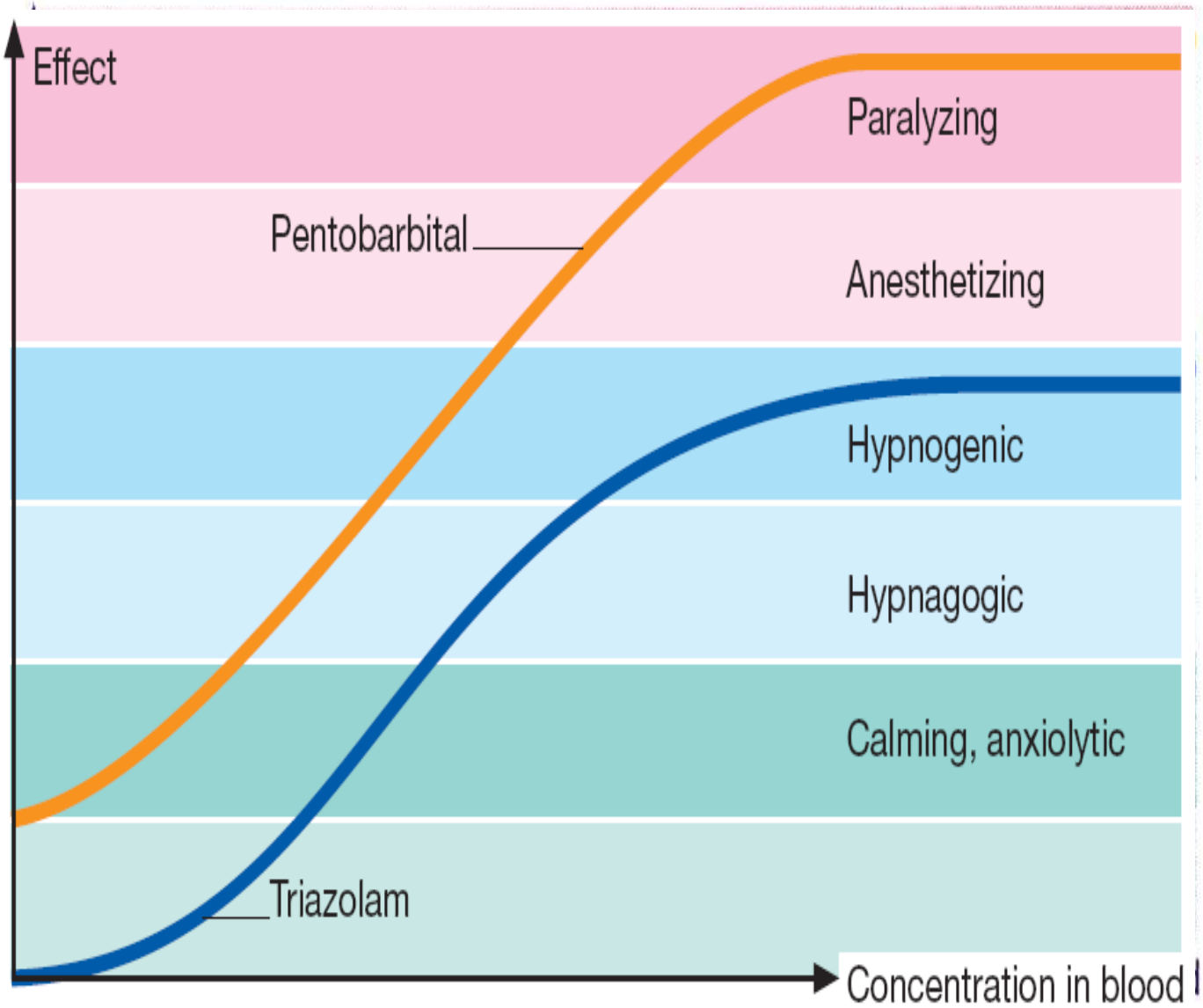


Pentobarbital

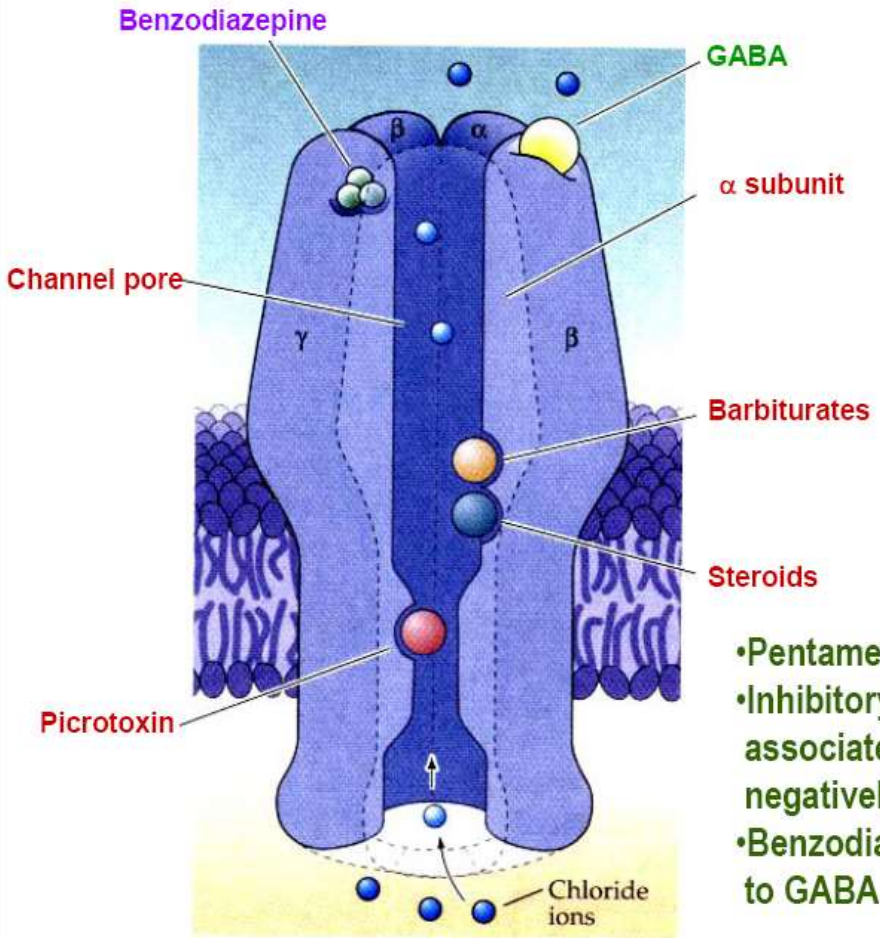
Benzo-
diazepines:



Triazolam

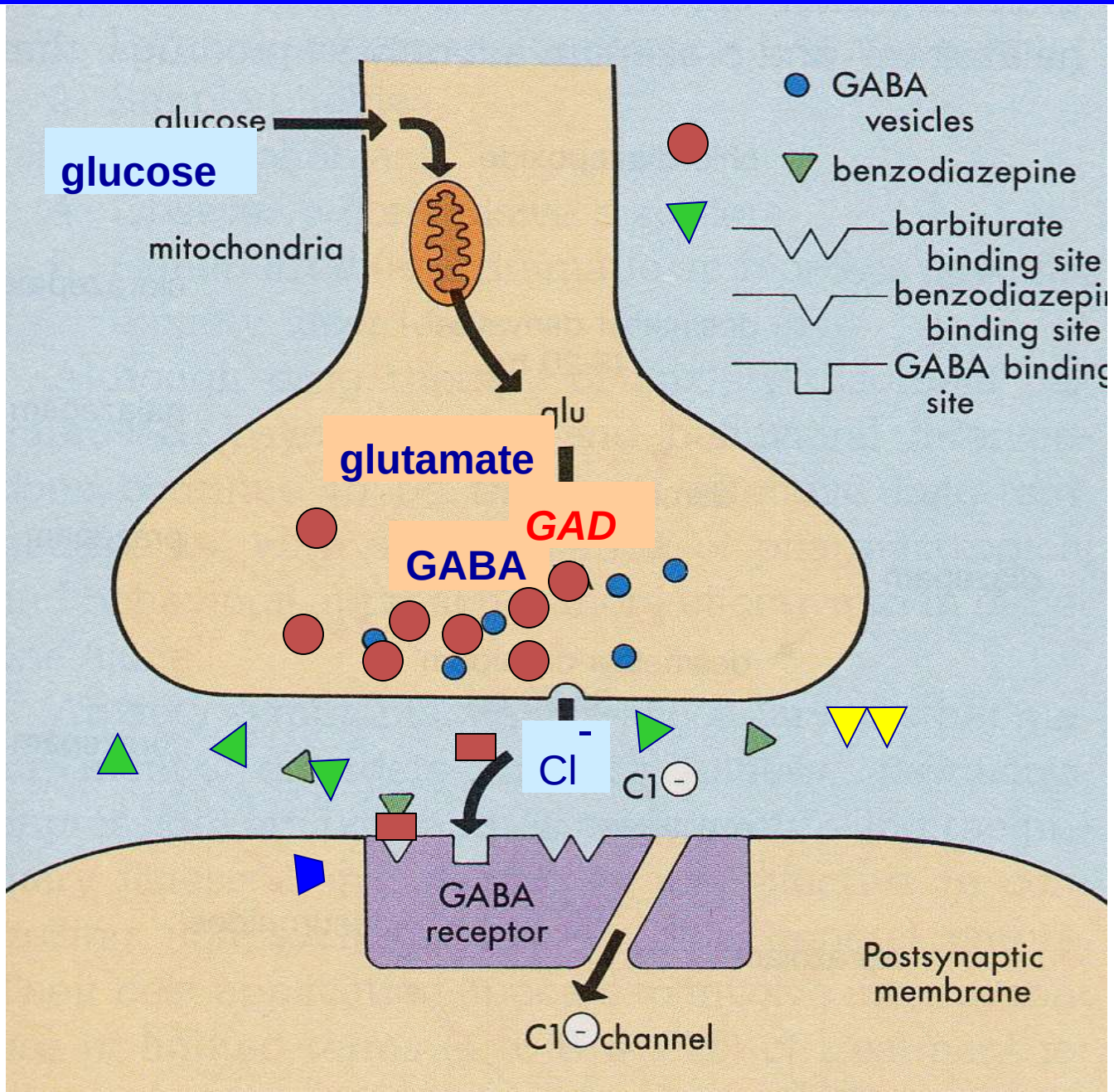


Ionotropic GABA Receptors



- Pentamers
- Inhibitory in action because the associated channels are permeable to negatively charged Cl^- ions
- Benzodiazepines are allosteric modulators to GABA neurotransmission

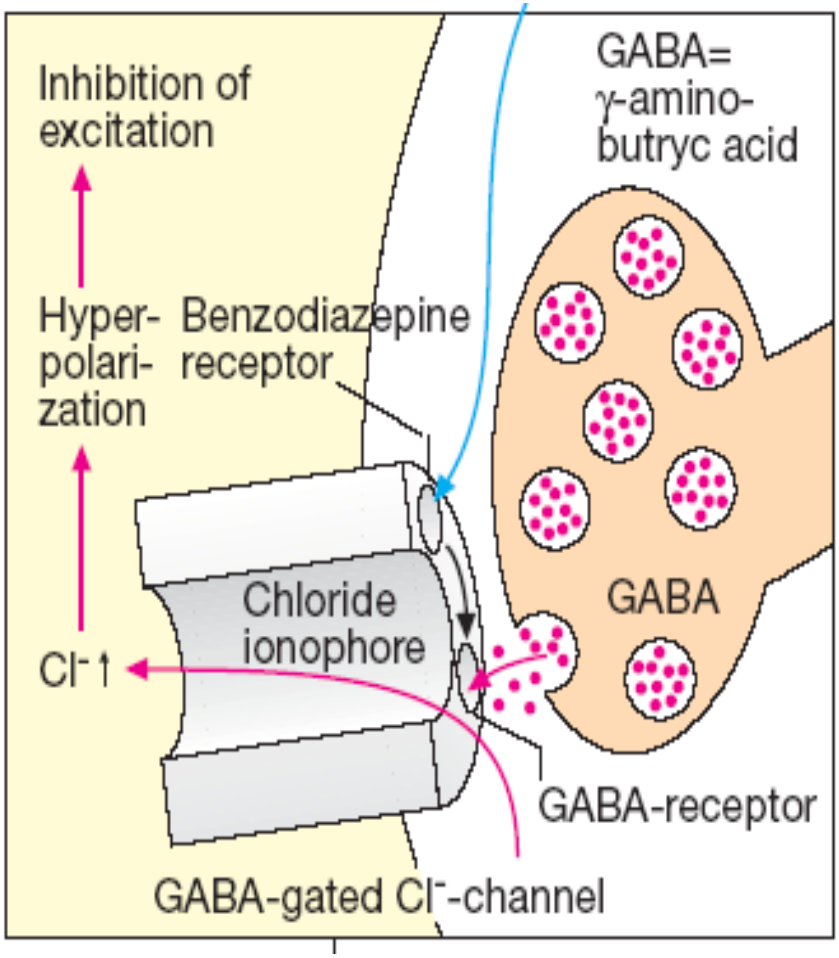
GABAergic SYNAPSE



Benzodiazepines

Mechanism:

Increase the frequency of opening of the GABA receptor, thereby increasing the effect of GABA-mediated hyperpolarization. Also increase GABA binding.



Benzodiazepine Effects

Therapeutic:

- Anxiolytic (diazepam, alprazolam)
- Hypnotic (triazolam)
- Muscle relaxant (diazepam, lorazepam)
- Anticonvulsant (diazepam, lorazepam, clonazepam)
- Sedation (midazolam)

Adverse:

- Cognitive impairment, decreased motor skills, daytime sedation
- Additive CNS depression (ethanol, antihistamines, opioids)
- Dependence
- Behavioral disinhibition (paradoxical)
- Anterograde amnesia
- Abrupt withdrawal panic attack, rebound anxiety
- Risk of fetal deformation (1st trimester)

Anxiolytic and Hypnotic Drugs

- 1. Sedasi: ↓ arousal, ↓ behaviour, ↓alertness, ↓ response to stimuli

- 2. Hypnotic:
  - Semua sedative/hypnotics pada dosis besar → menyebabkan tidur.
  - Normal sleep terdiri dari beberapa stage (berdasarkan 3 ukuran :electroencephalogram, electromyogram, electronystagmogram.
  - Ada 2 phases yang terjadi secara siklik tiap 90 min:
    1) Non-rapid eye movement (NREM). 70-75% dari total sleep.
       Ada 4 stages. Hampir semua tidur → stage 2.
    2) Rapid eye movement (REM). Fase mimpi (dreams).

Hypnotic

a) Menurunkan latency of sleep (waktu yang diperlukan untuk mulai tidur).

b) Meningkatkan lama tidur stage 2 NREM

c) Memperpendek fase REM sleep

d) Memperpendek fase slow-wave sleep (fase terjadinya somnambulism dan nightmares occur)

→ Efek tolerance terjadi setelah 1-2 minggu

→ Penghentian mendadak → meningkatkan fase REM sleep (rebound effects)

REM sleep (5-HT dan NE activity di RAS

3. Anesthesia:

- ✓ Dosis besar menghilangkan kesadaran, amnesia (anterogade amnesia), dan hilangnya reflex
  Beberapa BARBs (Thiopental) dan BZDs (Midazolam) ➔ menyebabkan anestesia

4. Antieplepsi:

Efek antiepilepsi sebaiknya dibawwah efek sedasi
Phenobarbital,Diazepam,Lorazepam → dipakai pada status epilepticus

5.Relaksasi otot bergaris (Muscle Relaxant):

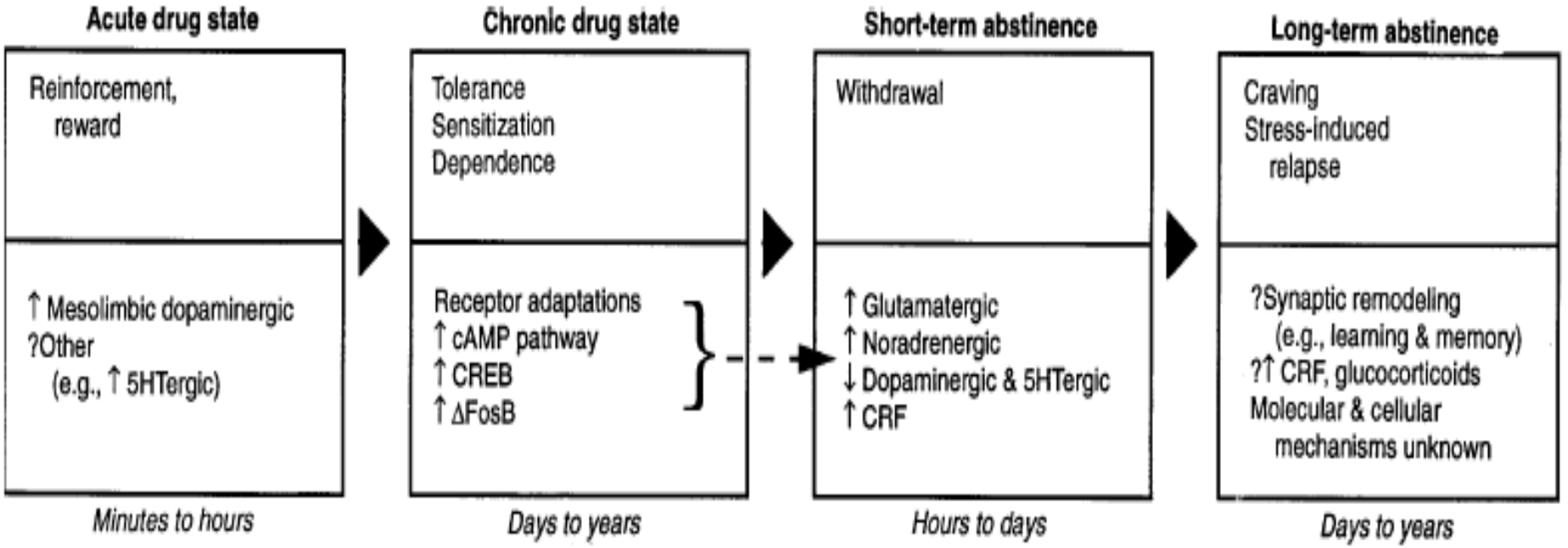
Semua sedative-Hypnotic dosis besar → relaksasi otot bergaris
Diazepam dosis sedasi → muscle relaxant

6.Medullary Depressant:

Dosis besar menekan neuron di medulla→ repiratory arrest, hypotensi,cardiovascular collaps→fatal

7. Tolerance dan Drug Dependence:

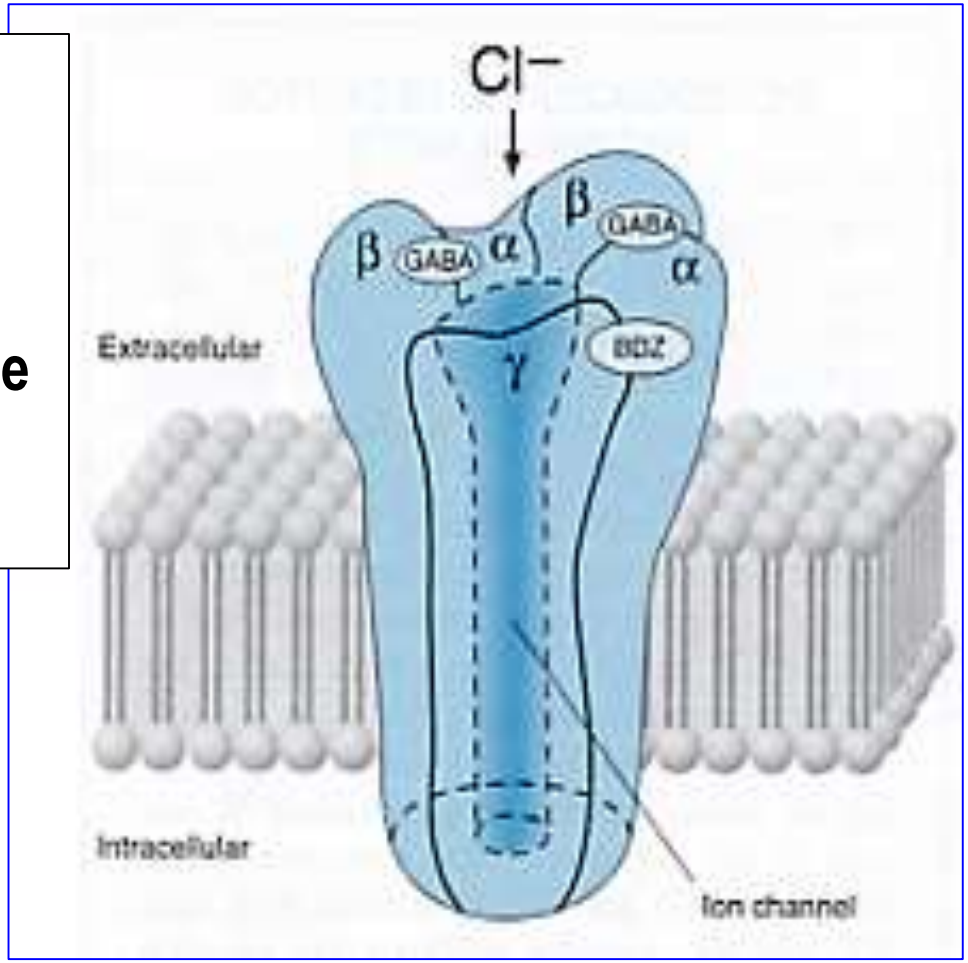
- ✓ Menyebabkan terjadinya :
  tolerance, psychological dependence, physical dependence
- ✓ Penghentian mendadak menyebabkan
  abstinencia syndrome (anxiety, hyperreflexia, seizure)
  Sering pada golongan short-acting (Pentobarbital, Secobarbital)
  Buspirone tidak menyebabkan ketergantungan obat


Acute drug state
Reinforcement, reward
↑ Mesolimbic dopaminergic
?Other
(e.g., ↑ 5HTergic)
Minutes to hours
Chronic drug state
Tolerance
Sensitization
Dependence
Receptor adaptations
↑ cAMP pathway
↑ CREB
↑ ΔFosB
Days to years
Short-term abstinence
Withdrawal
↑ Glutamatergic
↑ Noradrenergic
↓ Dopaminergic & 5HTergic
↑ CRF
Hours to days
Long-term abstinence
Craving
Stress-induced relapse
?Synaptic remodeling (e.g., learning & memory)
?↑ CRF, glucocorticoids
Molecular & cellular mechanisms unknown
Days to years

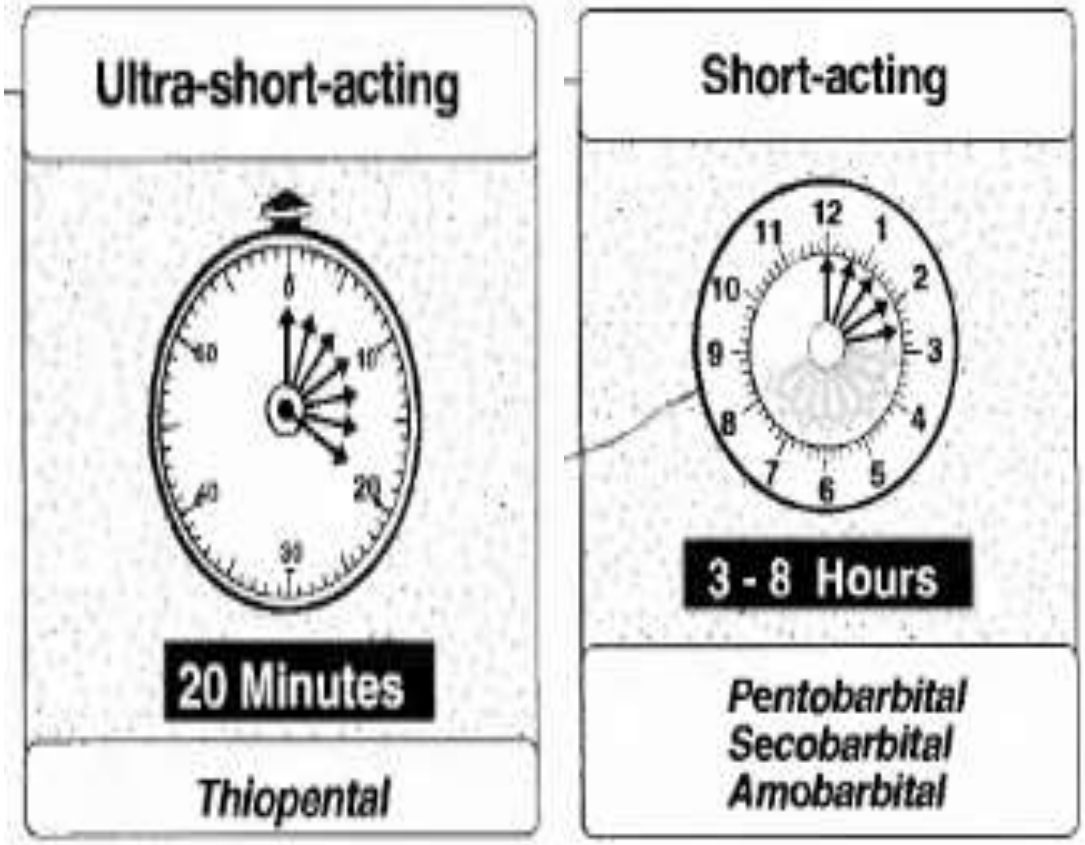
Barbiturates

Mechanism:

Prolongs the open time of the GABA receptor (a chloride channel), thereby increasing the effect of GABA-mediated hyperpolarization.



Barbiturates



Barbiturate Effects

Therapeutic:

- Anticonvulsant (phenobarbital)
- Anesthesia (thiopental)
- Sedative-hypnotic (pentobarbital)

Adverse (narrow margin of safety):

- Respiratory depression
- Abuse potential and dependence
- P-450 enzyme induction → drug interactions
- Interferes with REM sleep

Obat obat lain

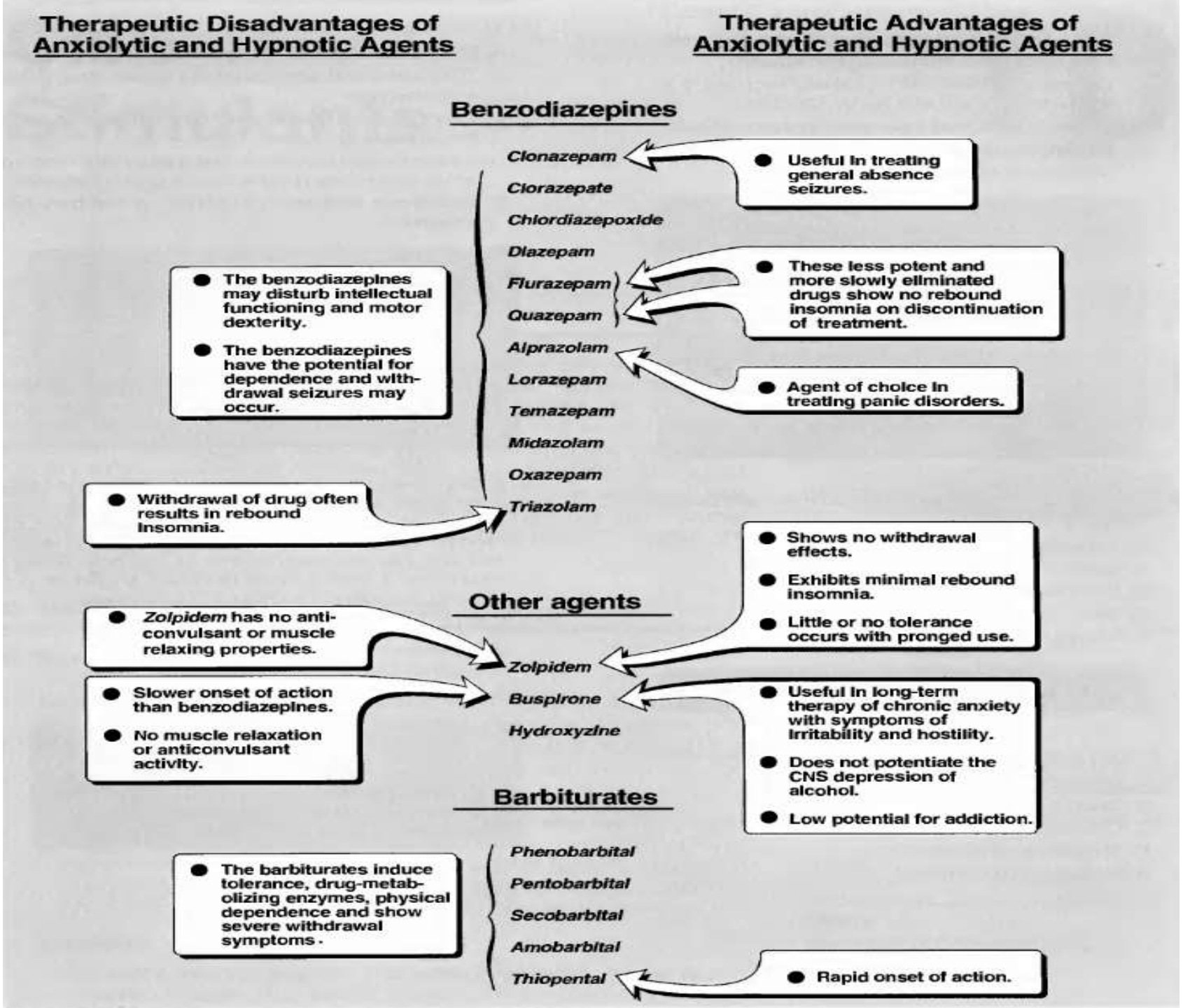
- Zolpidem
- Chloral hydrate
- Hydroxyzine
- Meprobamate (mirip BARBS)

Zolpidem

- Merupakan turunan Imidazopyridine (bukan BZDs).
- Pengobatan untuk insomnia →profil mirip Triazolam
- Efek : muscle relaxant dan anticonvulsant sangat lemah, hang over (-), addiksi (-), rebound insomnia (-)
- Metabolisme di liver→inactive metabolites (t ½ :3-5 j).
- Onset cepat, waktu paruh pendek
- Dosis harus dikurangi pada penderita dgn hepatic dysfunction,,usia lanjut, dan penderita yang menggunakan cimetidine.

- Kombinasi dengan TCA,Antipsychotic,Antihistamine→depresi SSP meningkat
- Mekanisme kerja :
  - Agonist selektif thd BZ_1 receptors.
  - Menyebabkan Facilitates GABA-mediated neuronal inhibition.
  - Efek diantagonist oleh Flumazenil

Table 22–3. Dosages of Drugs Used Commonly for Sedation and Hypnosis.			
Sedation		**Hypnosis**	
Drug	**Dosage**	**Drug**	**Dosage (at Bedtime)**
Alprazolam (Xanax)	0.25–0.5 mg 2–3 times daily	Chloral hydrate	500–1000 mg
Buspirone (BuSpar)	5–10 mg 2–3 times daily	Estazolam (ProSom)	0.5–2 mg
Chlordiazepoxide (Librium)	10–20 mg 2–3 times daily	Eszopiclone (Lunesta)	1–3 mg
Clorazepate (Tranxene)	5–7.5 mg twice daily	Lorazepam (Ativan)	2–4 mg
Diazepam (Valium)	5 mg twice daily	Quazepam (Doral)	7.5–15 mg
Halazepam (Paxipam)	20–40 mg 3–4 times daily	Secobarbital	100–200 mg
Lorazepam (Ativan)	1–2 mg once or twice daily	Temazepam (Restoril)	7.5–30 mg
Oxazepam	15–30 mg 3–4 times daily	Triazolam (Halcion)	0.125–0.5 mg
Phenobarbital	15–30 mg 2–3 times daily	Zaleplon (Sonata)	5–20 mg
		Zolpidem (Ambien)	5–10 mg


Therapeutic Disadvantages of Anxiolytic and Hypnotic Agents
Therapeutic Advantages of Anxiolytic and Hypnotic Agents
Benzodiazepines
Clonazepam
Clorazepate
Chlordiazepoxide
Diazepam
Flurazepam
Quazepam
Alprazolam
Lorazepam
Temazepam
Midazolam
Oxazepam
Triazolam
Useful in treating general absence seizures.
These less potent and more slowly eliminated drugs show no rebound insomnia on discontinuation of treatment.
Agent of choice in treating panic disorders.
The benzodiazepines may disturb intellectual functioning and motor dexterity.
The benzodiazepines have the potential for dependence and withdrawal seizures may occur.
Withdrawal of drug often results in rebound insomnia.
Other agents
Zolpidem
Buspirone
Hydroxyzine
Shows no withdrawal effects.
Exhibits minimal rebound insomnia.
Little or no tolerance occurs with pronged use.
Zolpidem has no anticonvulsant or muscle relaxing properties.
Slower onset of action than benzodiazepines.
No muscle relaxation or anticonvulsant activity.
Useful in long-term therapy of chronic anxiety with symptoms of irritability and hostility.
Does not potentiate the CNS depression of alcohol.
Low potential for addiction.
Barbiturates
Phenobarbital
Pentobarbital
Secobarbital
Amobarbital
Thiopental
Rapid onset of action.
The barbiturates induce tolerance, drug-metabolizing enzymes, physical dependence and show severe withdrawal symptoms.