SEDATIVE-HYPNOTIC DRUGS

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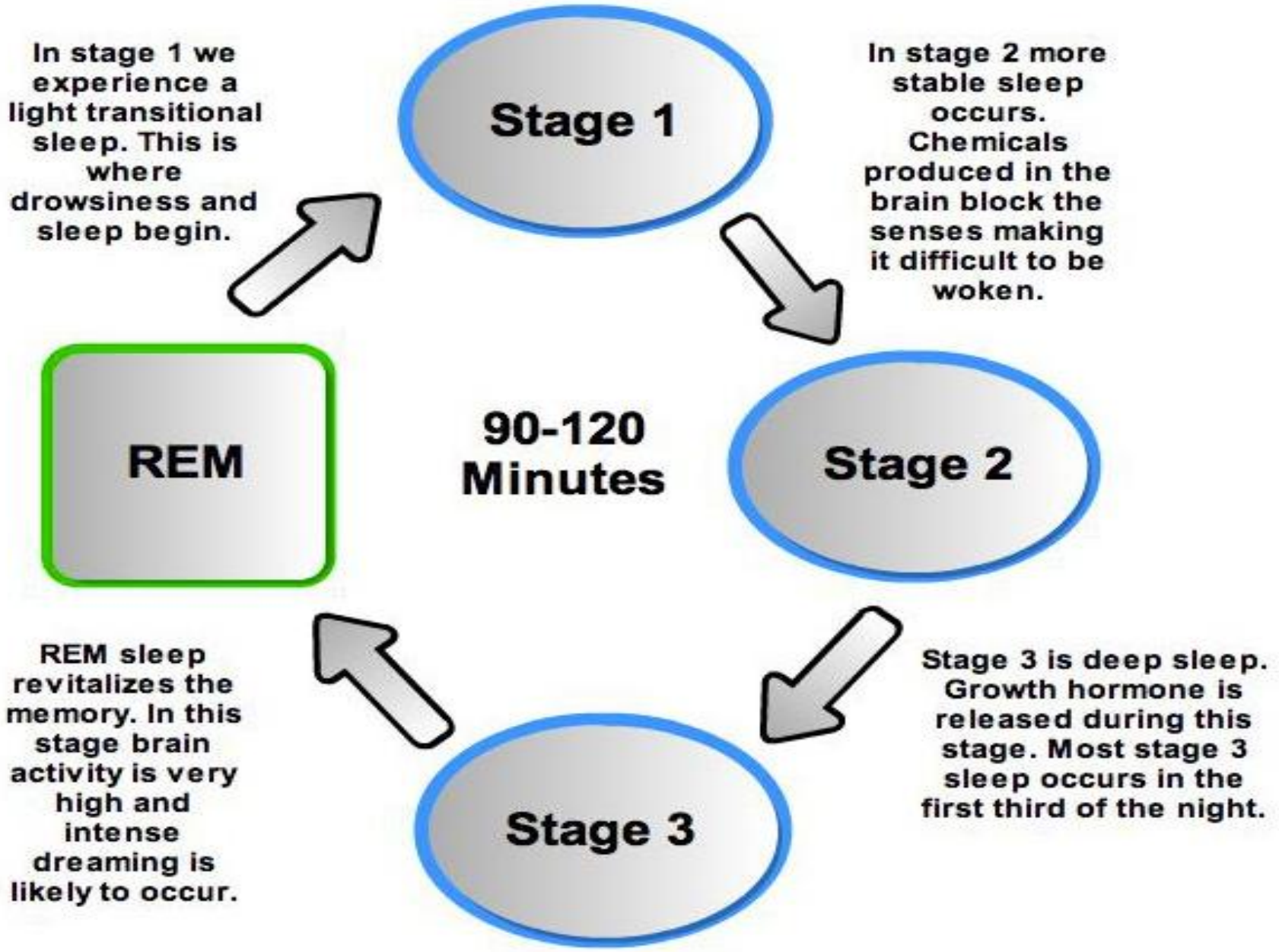
SEDATIVES – reduce anxiety and exert a calming effect

prescribed to cause sedation (for patients with anxiety)

HYPNOTICS - produces drowsiness and facilitates the onset and maintenance of a state of sleep.

or to encourage sleep (for patients with insomnia)


In stage 1 we experience a light transitional sleep. This is where drowsiness and sleep begin.
Stage 1
In stage 2 more stable sleep occurs. Chemicals produced in the brain block the senses making it difficult to be woken.
REM
90-120 Minutes
Stage 2
REM sleep revitalizes the memory. In this stage brain activity is very high and intense dreaming is likely to occur.
Stage 3
Stage 3 is deep sleep. Growth hormone is released during this stage. Most stage 3 sleep occurs in the first third of the night.

CHEMICAL CLASSIFICATION

- **Benzodiazepines:** diazepam, nitrazepam, oxazepam, estazolam, triazolam, flunitrazepam , etc. (with same nucleus and different substituents)
- **Barbiturates:** pentobarbital, phenobarbital, thiopental, etc.
- **Others:** buspirone, chloral hydrate, meprobamate, etc.
- Antipsychotic, antidepressant drugs and certain antihistaminic agents

A. *Benzodiazepines*

1. *ADME*

(1) Oral absorption

(2) Lipid solubility-dependent distribution (across BBB), placental penetrability (effect on fetus)

(3) Hepatic metabolism ---active metabolites

(4) Urinary excretion

A. *Benzodiazepines*

1. *ADME*

(5) Classification according to duration of action

Short-acting: laorazepam, oxazepam, triazolam, etc

Medium and long-acting: diazepam, nitrazepam, chlordiazepoxide, flurazepam etc

A. *Benzodiazepines*

2. *Pharmacological effects and clinical uses*

(1) Reduction of anxiety: at small doses, used as anxiolytics (not work on schizophrenia)

(2) Sedative-hypnotic effects

-- at relatively higher doses

-- no anesthetic effect

-- no enzyme induction

-- no remarkable effect on REM, decrease slow wave sleep

-- used for insomnia and preanesthetic medication (as adjuvant to anesthetics)

A. *Benzodiazepines*

(3) Antiepileptic and anticonvulsant effects

epilepsy, status epilepticus (*i.v.*), convulsion

(4) Centrally acting muscle relaxant effect

-- relaxing the spasticity of skeletal muscle, probably by increasing presynaptic inhibition in the spinal cord.

-- used for the treatment of skeletal muscle spasms caused by central or peripheral diseases.

A. *Benzodiazepines*

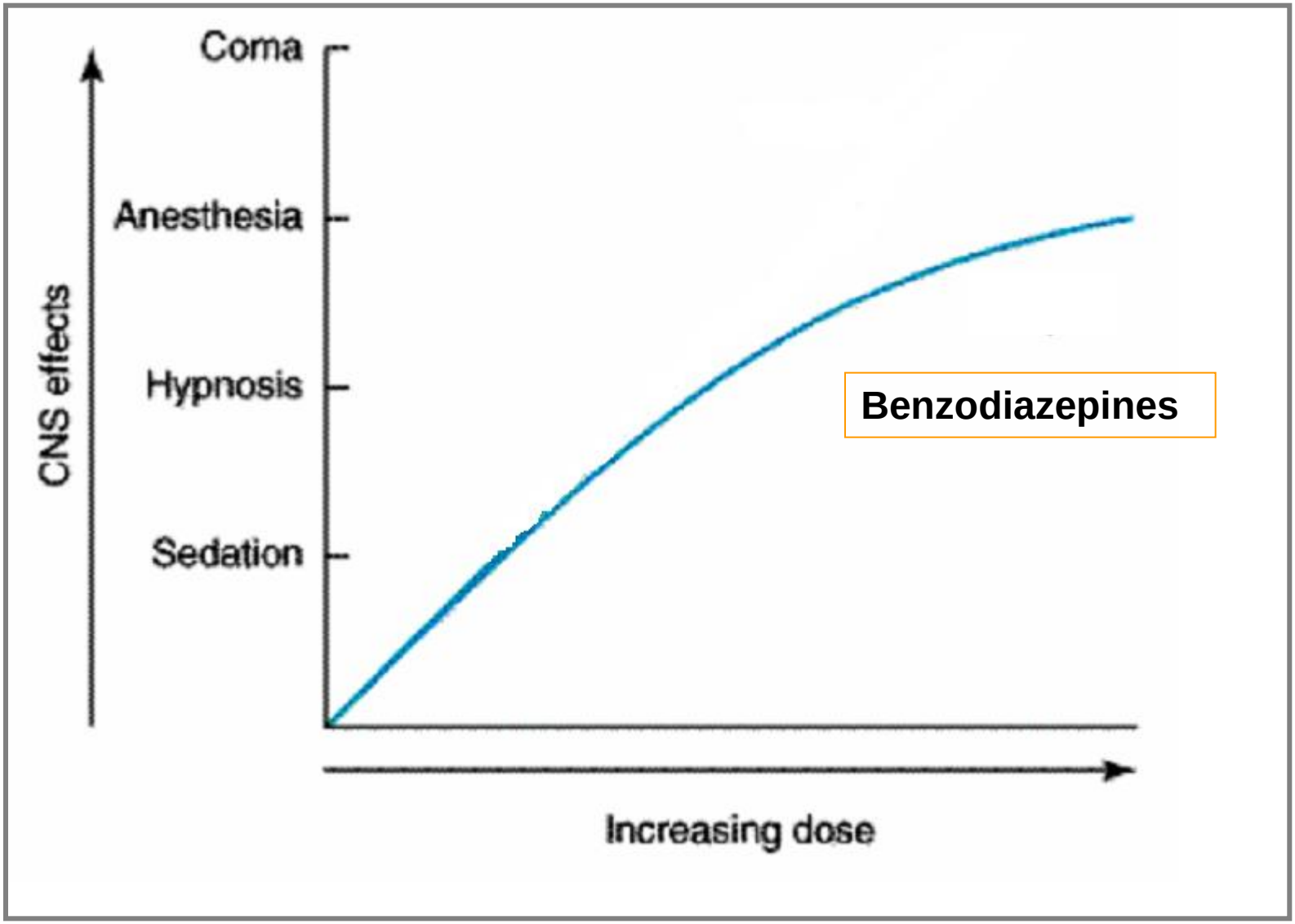
(5) Others

--dose-dependent anterograde amnesic effects (*i.v.*）

- for unpleasant examination or therapy (cardioversion, endoscope, etc)

--respiratory and CVS effects (central inhibition)

-- alleviate the withdraw syndromes



Graded dose-dependent depressive effect of sedative-hypnotics on central nervous system function

A. *Benzodiazepines*

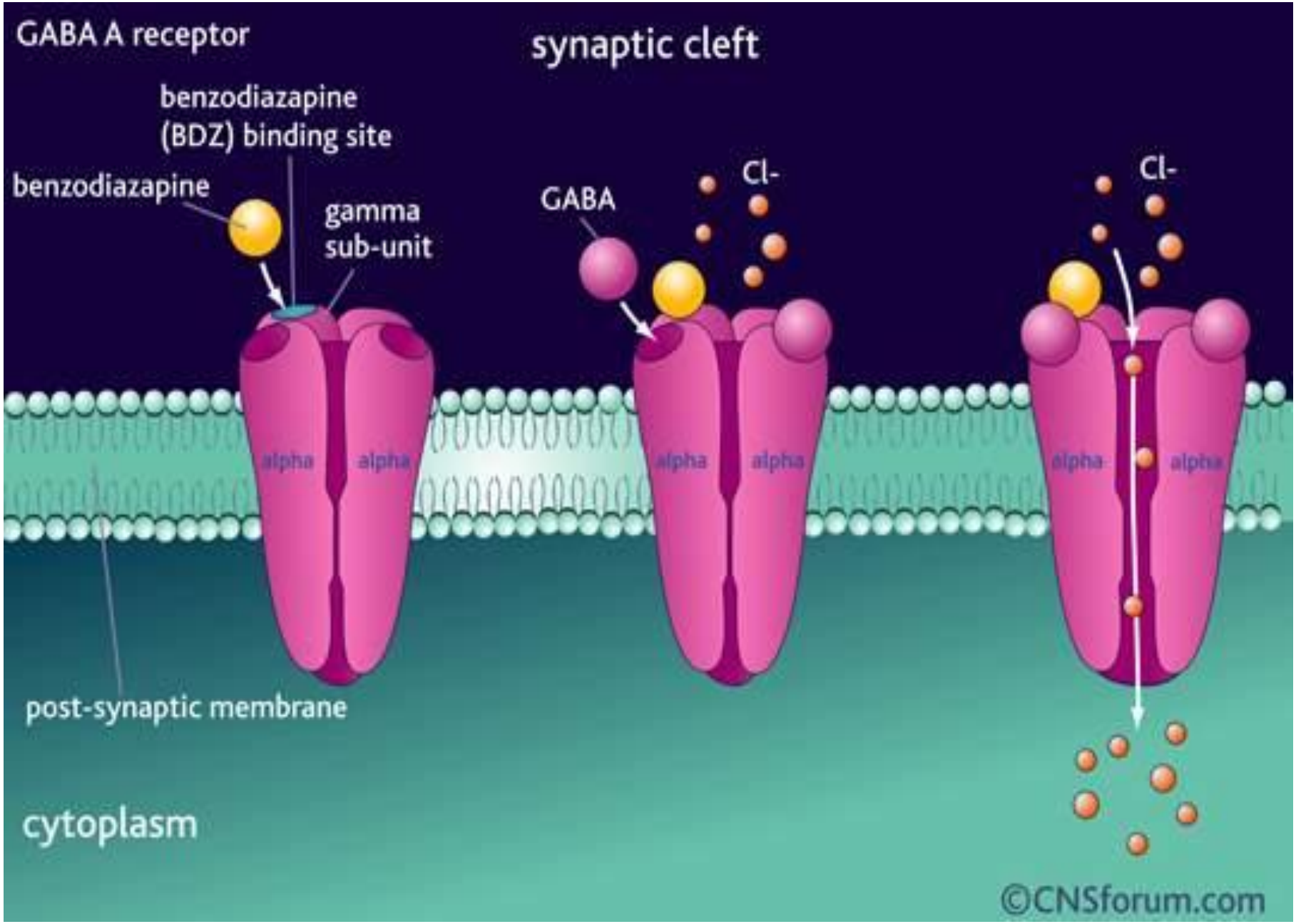
3. *Mechanisms of actions*

(1) Sites of action: mainly acts on limbic system (anxielytic) and midbrain reticular formation (hypnotic).

(2) Interaction with $GABA_A$ receptor

-----increase the frequency of GABA-induced channel-opening events

----- GABA dependent efficacy


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
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A. *Benzodiazepines*

4. *Adverse effects*

(1) Central depression

Most common: drowsiness and confusion

ataxia; cognitive impairment (hangover effect)

Antagonized by BZ receptor antagonist flumazenil

Additive with other CNS depressant drugs

(2) Tolerance: lethal dose is not altered

(3) Dependence: compulsive misuse

Withdrawal syndrome (shorter acting agents): restlessness, anxiety, weakness, orthostatic hypotension and generalized seizures

A. *Benzodiazepines*

(3) Others

Respiratory and CVS reactions

Teratogenic effects (Pregnancy Category D or X)

(4) Contraindications

Myasthenia gravis

Infants < 6 months

Pregnant and lactation mothers

Elderly with heart/lung/liver/kidney dysfunction

Workers requiring mental alertness and fine motor coordination

B. *Barbiturates*

1. *ADME*

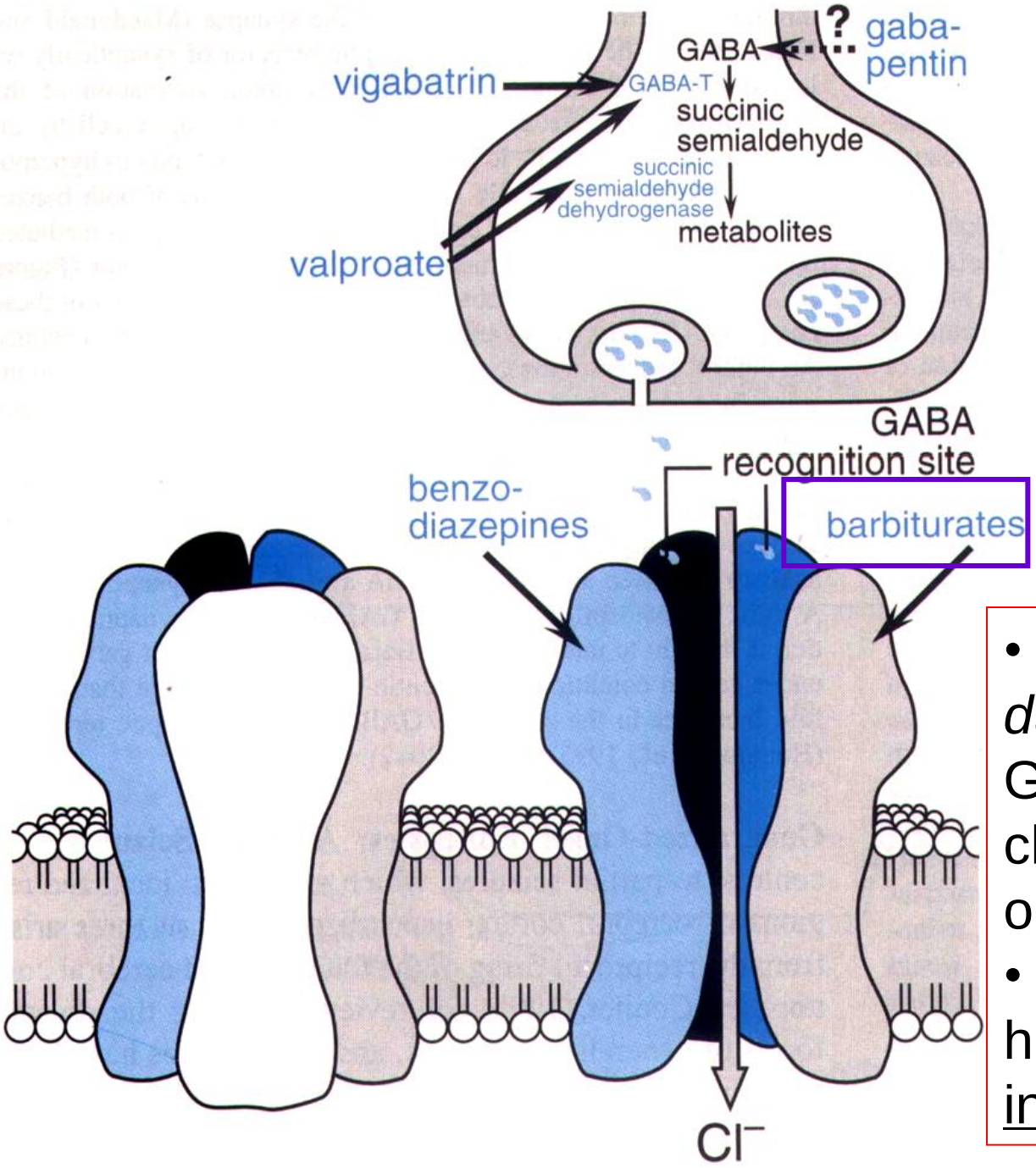
- hepatic enzyme inducer
- alkalizing urine (sodium bicarbonate): excretion ↑

2. *Pharmacological effects and clinical uses*

(1) Sedative-hypnotic effects - REM decrease

(2) Antiepileptic and anticonvulsant effects

(3) Preanesthetic medication



- increase the *duration* of the GABA-gated chloride ion channel openings
- GABA-mimetic at high dose – <u>GABA independent efficacy</u>

B. *Barbiturates*

3. *Adverse effects*

(1) Central depression: after (hangover) effect

(2) Tolerance and dependence: long-term uses, REM rebound

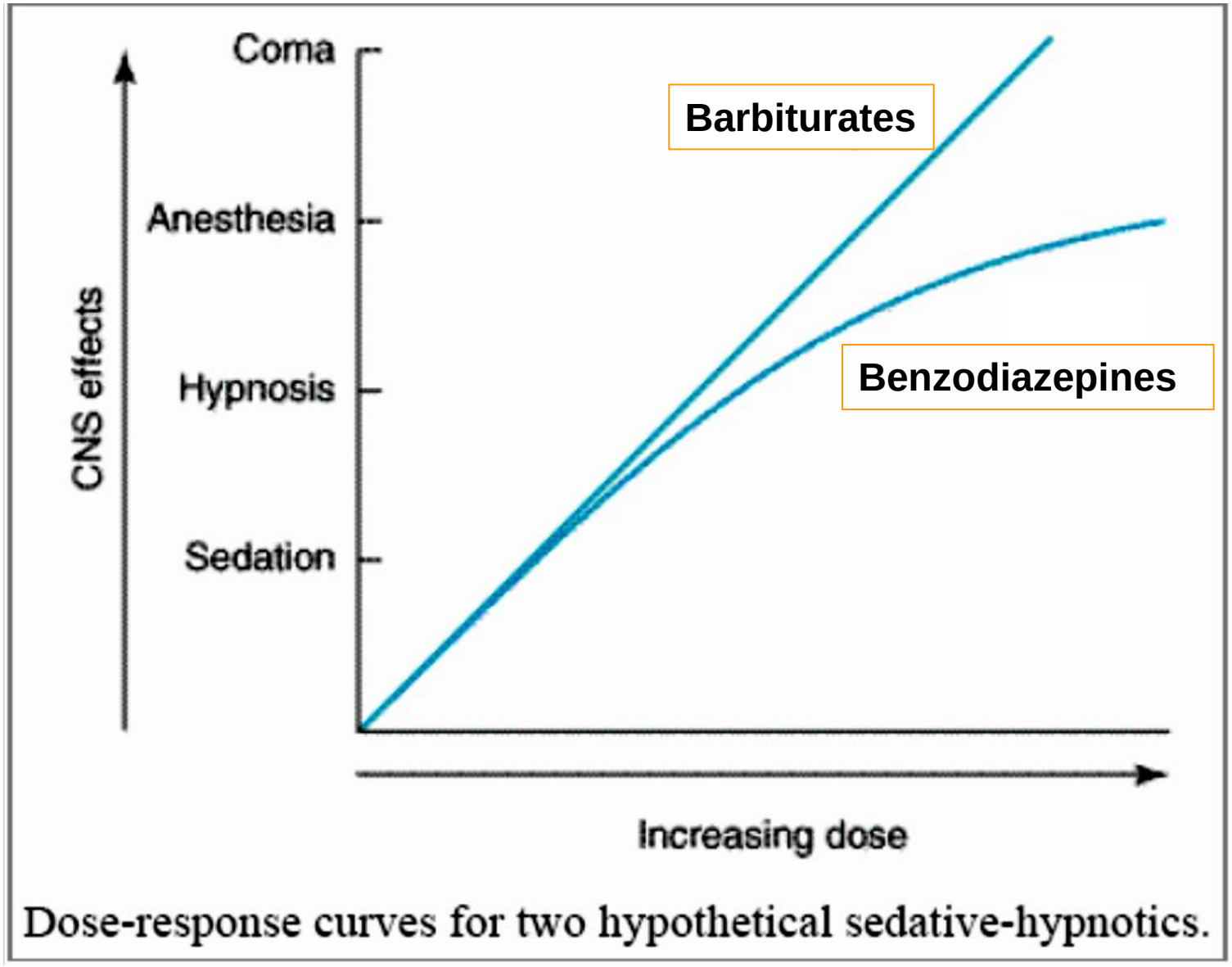
(3) Porphyria (enhances porphyrin synthesis): anemia, photosensitive skin injury

(4) Acute poisoning

---supporting therapies: oxygen inhalation, unblocked respiratory tract (tracheotomy), central stimulants

---alkalizing urine

---hemodialysis



Dose-response curves for two hypothetical sedative-hypnotics.

Graded dose-dependent depressive effect of sedative-hypnotics on central nervous system function

C. *Other sedative-hypnotic drugs*

- **Chloral hydrate**

  Sedative-hypnotic effects

  Anticonvulsant effect: children (anal administration)

- Meprobamate: sedative, hypnotive, anxiolytic
- Buspirone: anxiolytic, minimal abuse liability

C. *Other sedative-hypnotic drugs*

- Antipsychotics
- Antidepressant drugs
- Antihistaminic agents
- Ethanol
- Melatonin (pineal hormone)

Summary of clinical uses of sedative-hypnotics

For relief of anxiety
For insomnia
For sedation and amnesia before medical and surgical procedures
For treatment of epilepsy and seizure states
As a component of balanced anesthesia (intravenous administration)
For control of ethanol or other sedative-hypnotic withdrawal states
For muscle relaxation in specific neuromuscular disorders
As diagnostic aids or for treatment in psychiatry