Anxiolytics
Sedative/ Hypnotics

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Anxiety

- Fear for no adequate reason

Anti-anxiety drugs

1- Benzodiazepines

chemical substance act on **BNZ receptors** which present on **$GABA_A$ Receptor**

Alcohol
Opioid
Barbiturate
Meprobamate (1950)
BNZ (1960)
Buspirone

GABA inhibitory system

Neuronal systems consist of :

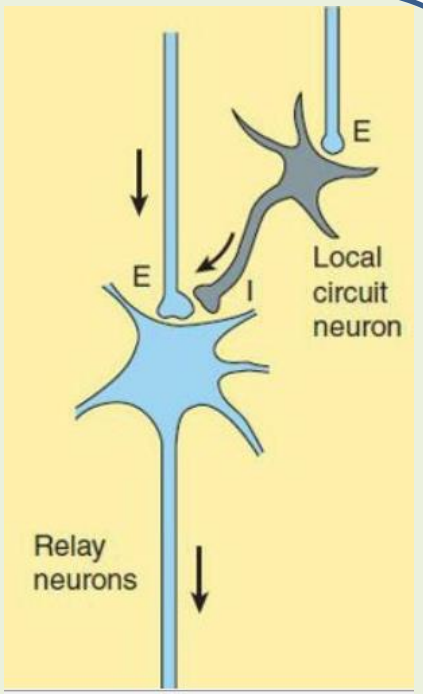
1- Hierarchical systems

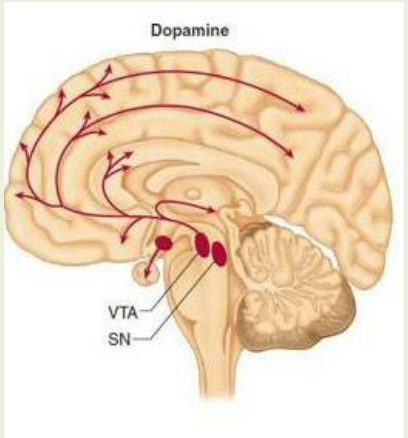
a. Projection (relay) neurons: ***excitatory,*** they release **Glutamate**

b. Local circuit neurons: smaller, synapse on projection neuron; they inhibitory, they release either GABA or glycine

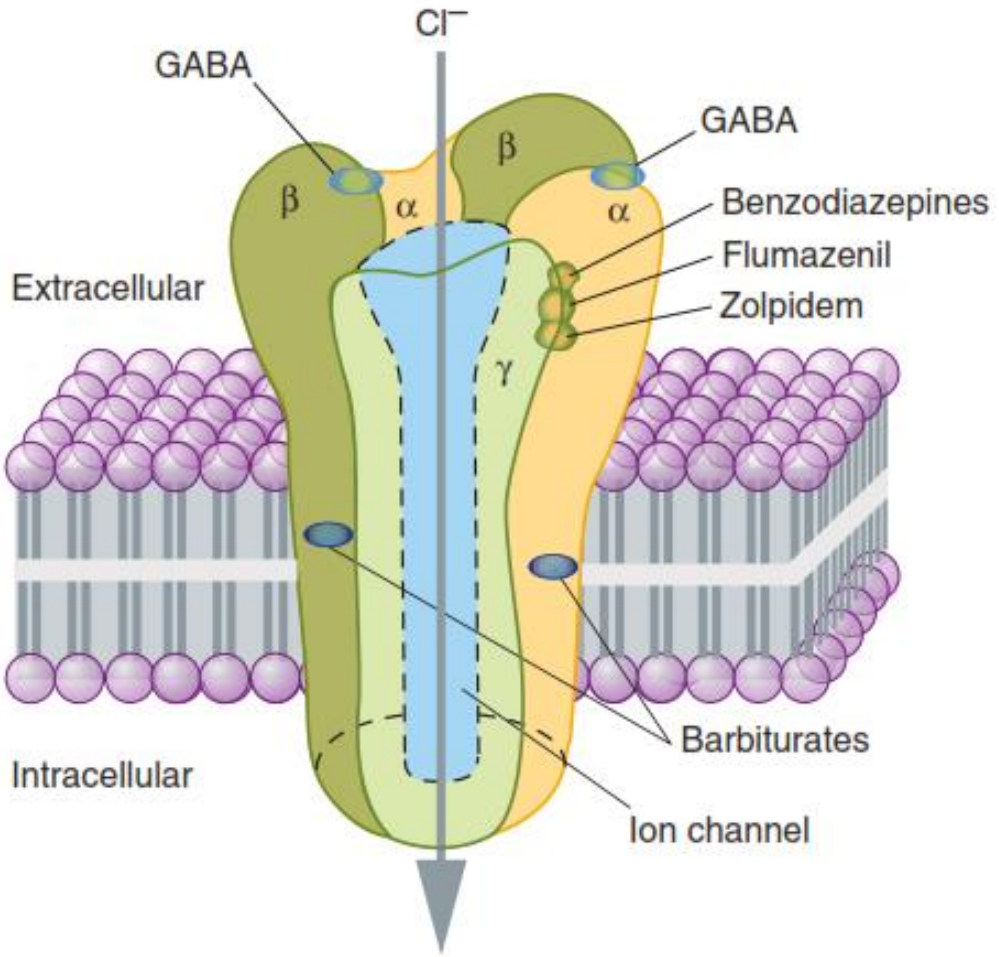
2- Diffuse neuronal systems

e.g DA , NE , Ach neurons

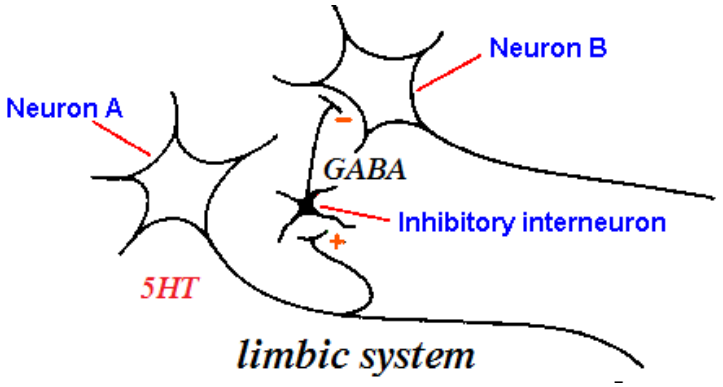




GABA Receptor



Benzodiazepine effects



- **Anxiolytic (at low dose)**

  mediated by **BNZ_2** Rc in Amygdala

show <u>no tolerance</u> with prolong use.

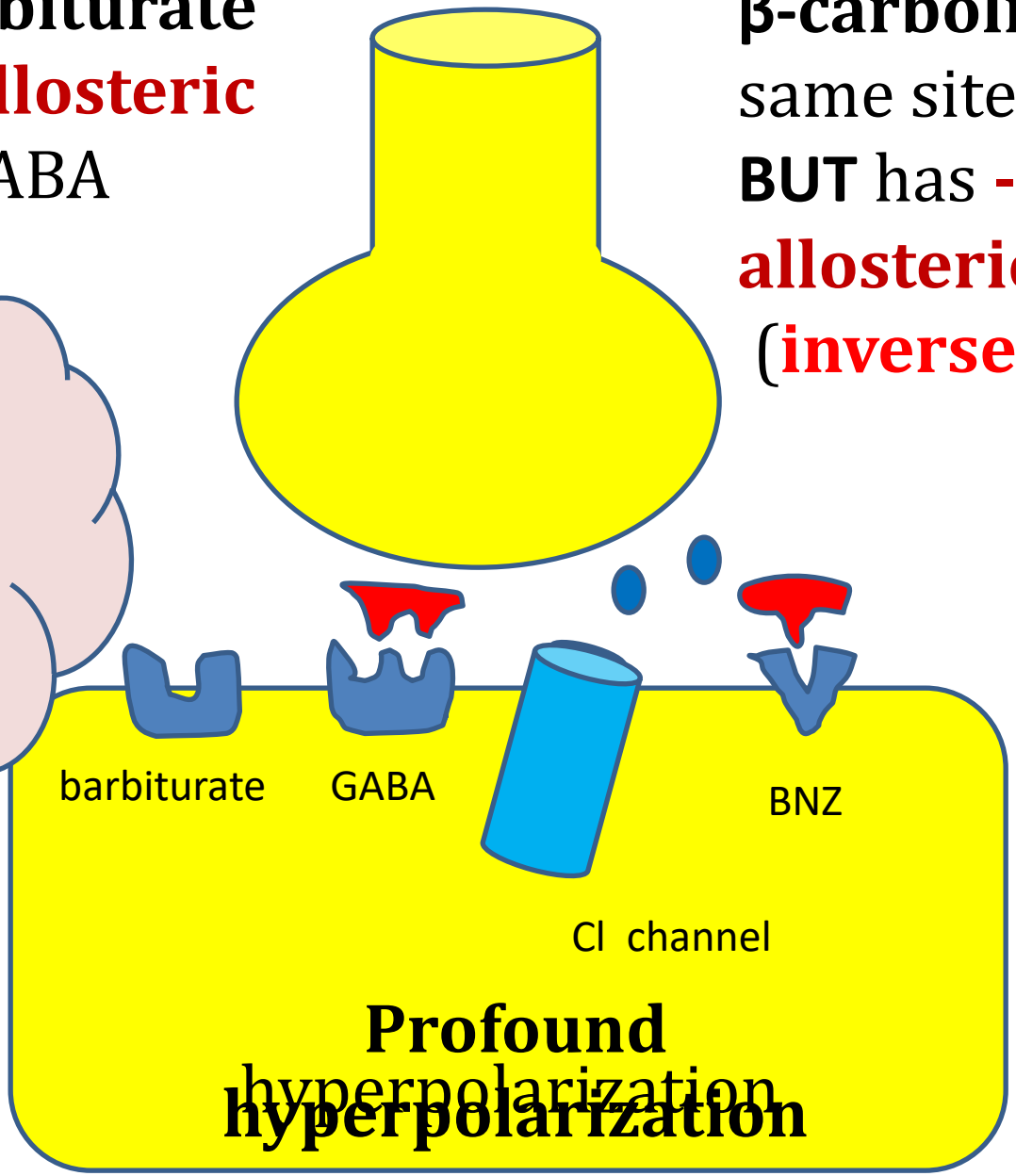
- **Sedation ; hypnosis ;anticonvulsant (at high dose)** mediated by **BNZ_1** Rc in cortex, thalamus , cerebellum **show <u>tolerance</u> with prolong use.**
- **Muscle relaxant (at high dose)**

  mediated by **BNZ_2** Rc in spinal cord

BNZ & barbiturate have **+ ve allosteric effect** on GABA receptor.

β-carboline act on same site of **BNZ BUT** has **-ve allosteric effect.** (**inverse agonist**)

Allosteric effect
second ligand binding to the macromolecule & altering its affinity towards the first



Benzodiazepines indications

- **Anxiety , long $t_{1/2}$ drugs**
- **Panic anxiety & phobia**
- **Insomnia, short $t_{1/2}$ drugs**
- **Muscle relaxant , infantile spasm** (a rare seizure disorder that occurs in young children, usually under one year of age).

Benzodiazepines indications

- **Epilepsy**

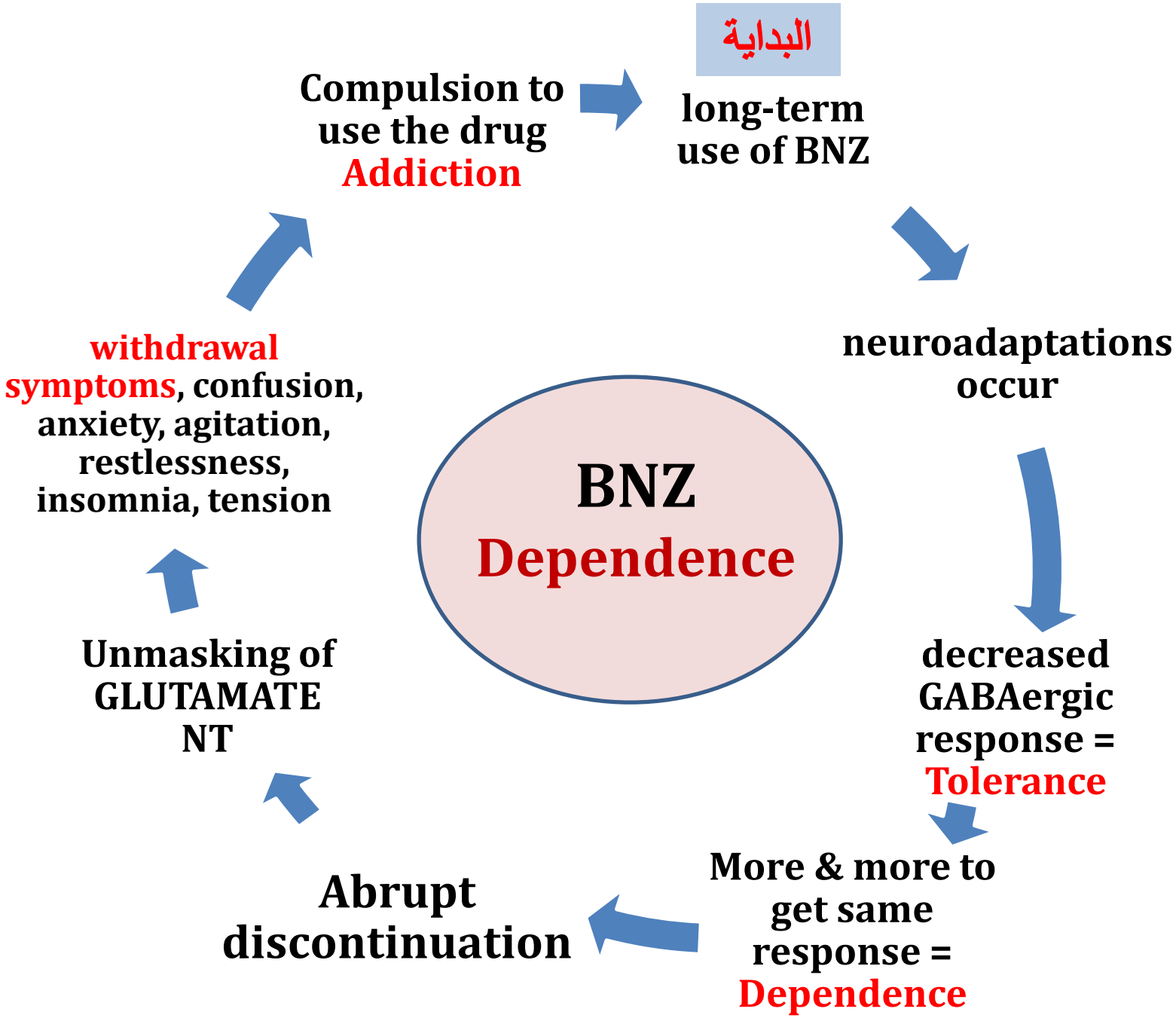
(status epilepticus : diazepam I.V; lorazepam I.M)
(maintanence : clonazepam)

- **Alcohol withdrawal**

- **Allay anxiety before surgery**

Benzodiazepines side effects

- ↓ psychomotor function
- Sleepiness (action or s/e)
- Amnesia (deficit in memory)
- Hangover (delayed drowsiness due to active metabolites).
- Paradoxical effect (agitation; insomnia; over activity in children).


البداية
long-term use of BNZ
neuroadaptations occur
decreased GABAergic response = Tolerance
More & more to get same response = Dependence
Abrupt discontinuation
Unmasking of GLUTAMATE NT
withdrawal symptoms, confusion, anxiety, agitation, restlessness, insomnia, tension
Compulsion to use the drug Addiction
BNZ Dependence

Drugs	$t_{1/2}$ hr	metab olites	Remarks
Alprazolam	16	Inactive	Antidepressant activity used in panic disorder
Chlordia-zepoxide	20	Active metab. 80 hr	Low lipid soluble = low permeation to brain (intermediate onset) & less sedative Active metabolite= long acting
Clonazepam	25	Inactive	Maintenance antiepileptic
Diazepam	43	Active metab. 80 hr	High lipid soluble = high permeation to brain =rapid onset then rapid offset (rapid delivery to brain and short acting in brain) but long acting due active metabolite

Drugs	$t_{1/2}$ hr	metab olites	Remarks
Diazepam Cont.			IV inj. Anticonvulsant then redistributed >> loss of anticonvulsant effect but retain anti-anxiety effect
Lorezepam	20	Inactive	Lower lipid solubility than Diazepam so it slower onset & offset than diazepam But more effective IM than diazepam (due to pharma. formula). Main difference from Chlordiazepoxide that Lorazepam is short acting because has no active metabolite

Drugs	$t_{1/2}$ hr	metab olites	Remarks
Midazolam	3	Inactive	High lipid soluble (rapid onset) Short $t_{1/2}$ = short acting For endoscopy
Nitrazepam	30	Inactive	Superseded due to long $t_{1/2}$ more sedative hypnotic abuse in Iraq
Triazolam	3	active metab.	Tolerance frequently develops within a few days For amnesia prior surgery

Benzodiazepine antagonist

- **Flumazenil**

BNZ antagonist (I.V inf. $t_{1/2}$1hr) used for sever sedated patient.

Anti-anxiety drugs

2. Buspiron

- **Not** act on GABA receptor but its partial agonist of 5HT receptor

  compete with full agonist 5HT ➔ allay anxiety

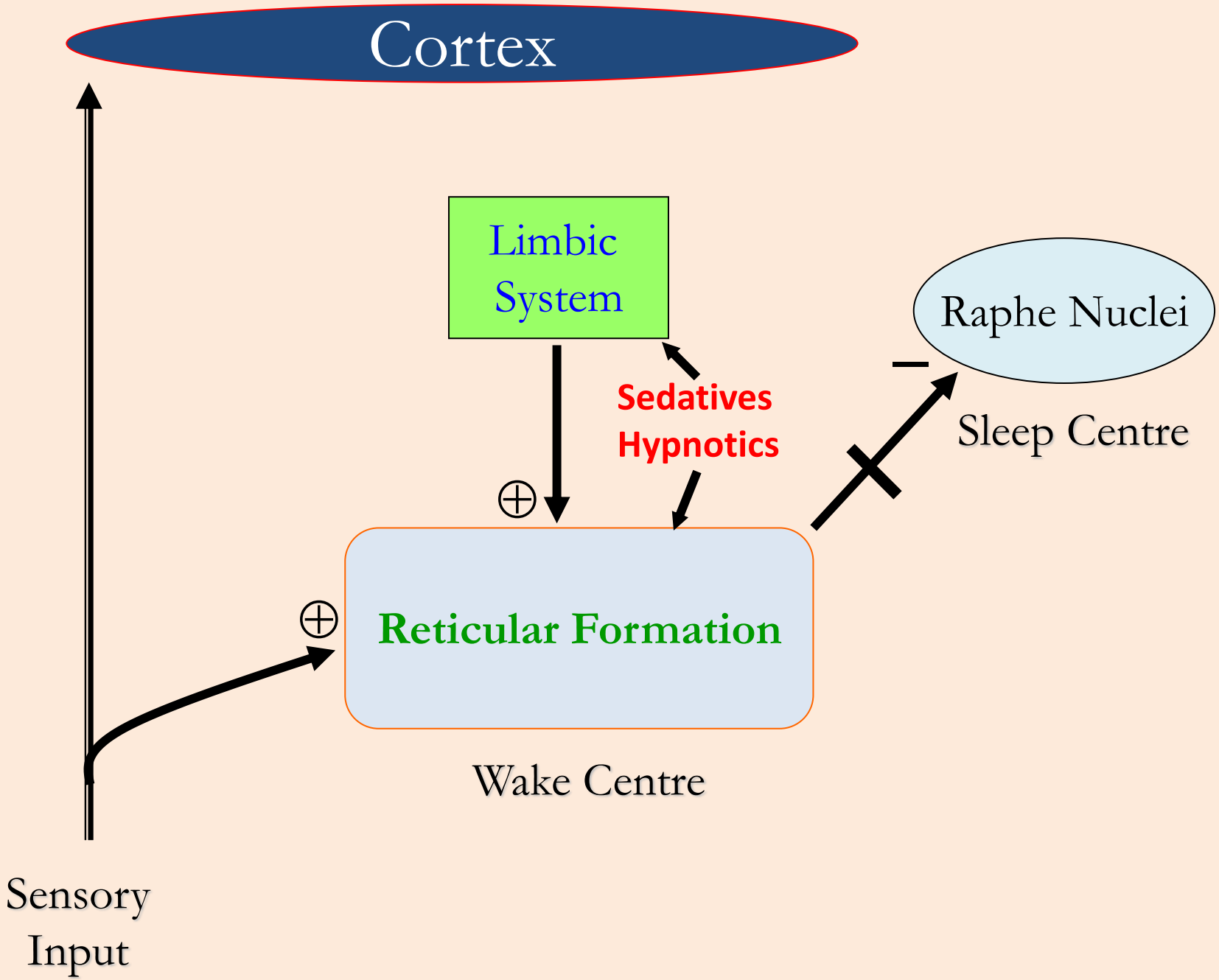
- useful for chronic treatment of Generalized Anxiety Disorder.
- **Not** effective for short-term or "as-needed" treatment of **acute anxiety states** due to its effect after 2 weeks

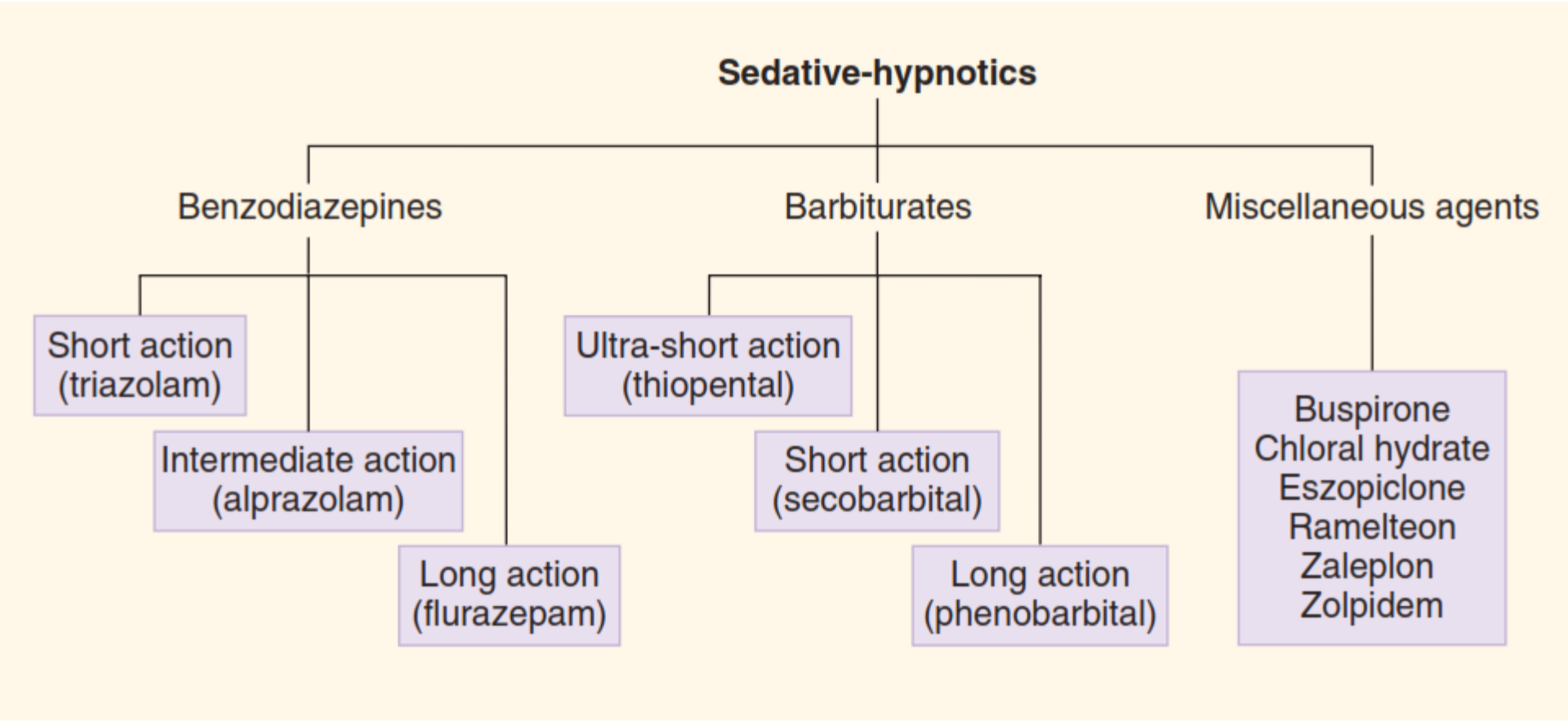
SEDATIVES AND HYPNOTICS

Act on sleep control centers, the important factor is inhibition produced by excitatory inputs that come from two major sources:

1. **Afferent input from sensory nerves (e.g. tactile, visual, auditory)**
2. **Impulses from the limbic system (e.g. emotions)**

Both of which stimulate the reticular formation system (wake centre) that in turn inhibit raphe nuclei (sleep centre)


Cortex
Limbic System
Raphe Nuclei
Sedatives
Hypnotics
Sleep Centre
Reticular Formation
Wake Centre
Sensory Input


Sedative-hypnotics
Benzodiazepines
Barbiturates
Miscellaneous agents
Short action (triazolam)
Intermediate action (alprazolam)
Long action (flurazepam)
Ultra-short action (thiopental)
Short action (secobarbital)
Long action (phenobarbital)
Buspirone
Chloral hydrate
Eszopiclone
Ramelteon
Zaleplon
Zolpidem

Barbiturates

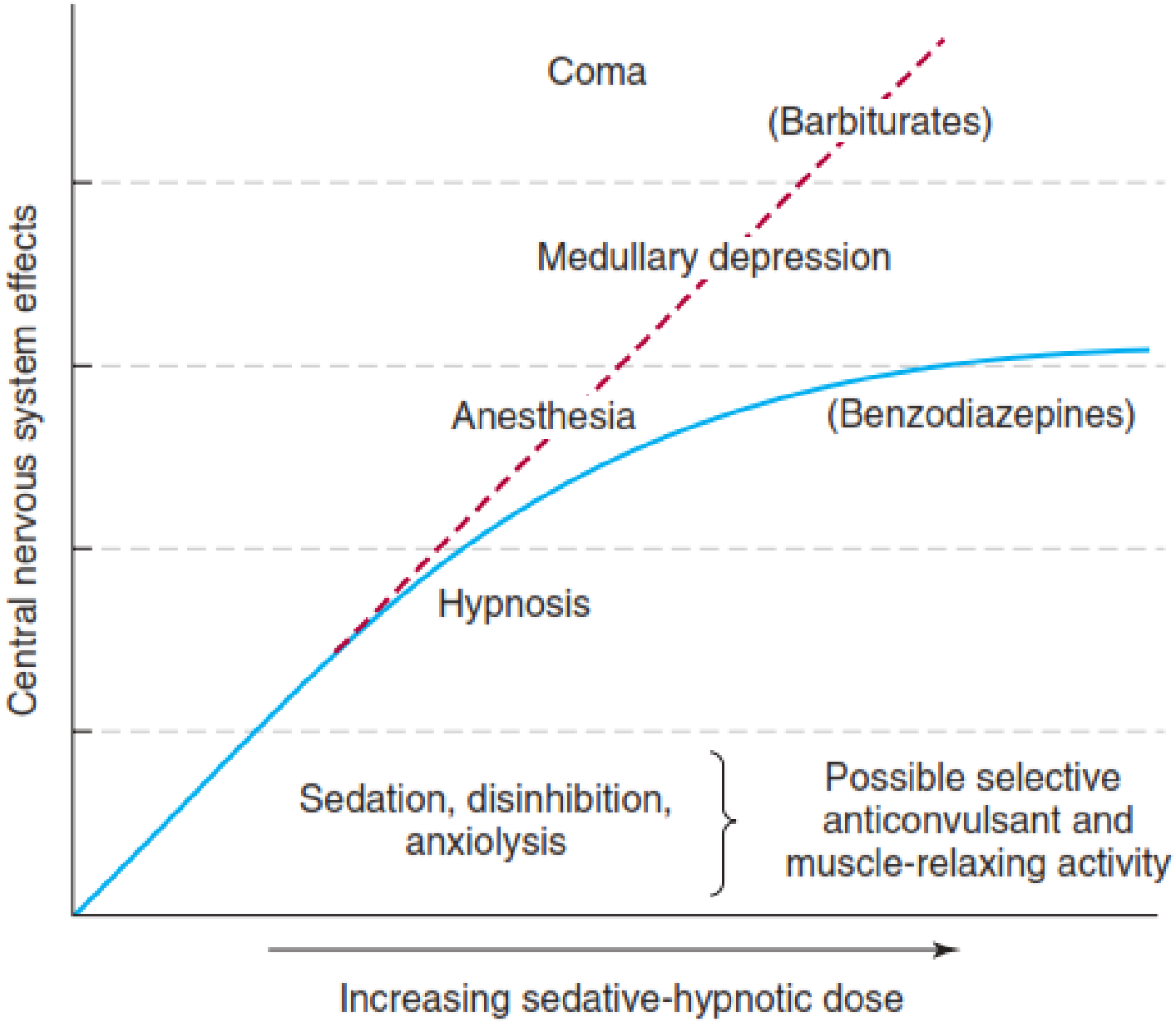
Barbiturates

(1903)

Today mostly used as **antiepileptic drugs** (Phenobarbital) and for induction of **general anaesthesia** (Thiopental).

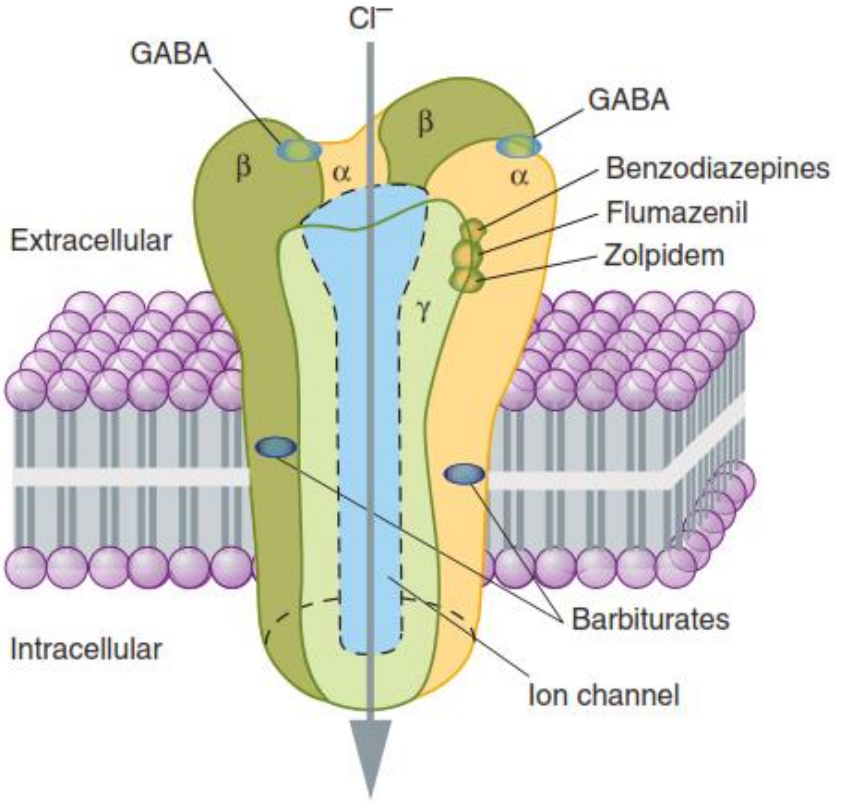
Too toxic to be used as sedative or hypnotic. Due to:

- Narrow therapeutic index due to **steep dose response curve.**
- Associated with very severe withdrawal symptoms.


Coma
(Barbiturates)
Medullary depression
Anesthesia
(Benzodiazepines)
Hypnosis
Sedation, disinhibition, anxiolysis
Possible selective anticonvulsant and muscle-relaxing activity
Central nervous system effects
Increasing sedative-hypnotic dose

Mechanism of action

- binding site on the $GABA_A$ receptor ➔ potentiate GABA action on chloride entry into the neuron.



BARBITURATES USES

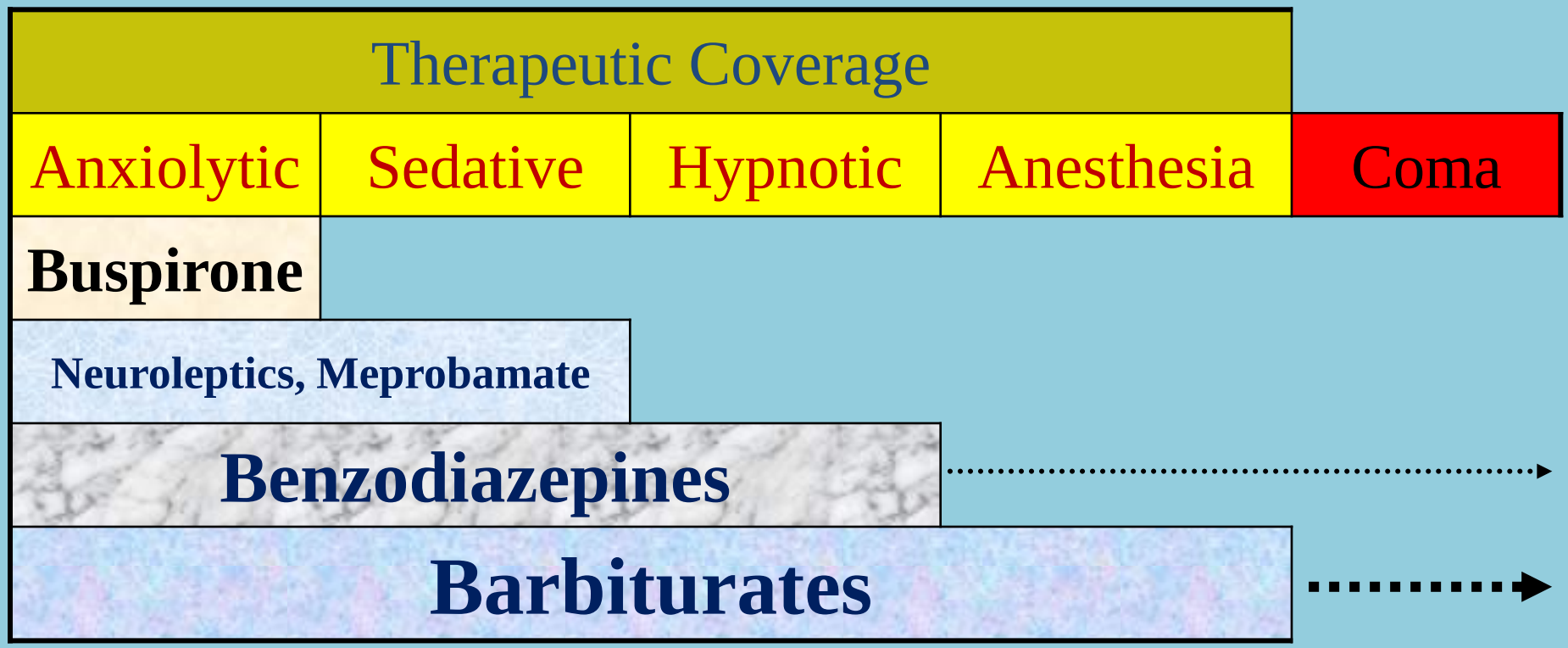
Sub-group	Prototype	Lipid solubility	Action		Typical Indication
			Onset minutes	Duration hours	
Ultra-short acting	thiopental (Pentothal®)	High	0.5	0.2	Induction of anesthesia; convulsion
Short acting	secobarbital (Seconal®)	Moderate	10-15	3-4	Insomnia
Long acting	phenobarbital (Luminal®)	Low	60	10-12	Epilepsy

Barbiturates side effect

1. Sedation
2. Impaired cognition
3. Enzyme induction
4. Low therapeutic index
5. Addiction risk

Barbiturates poisoning

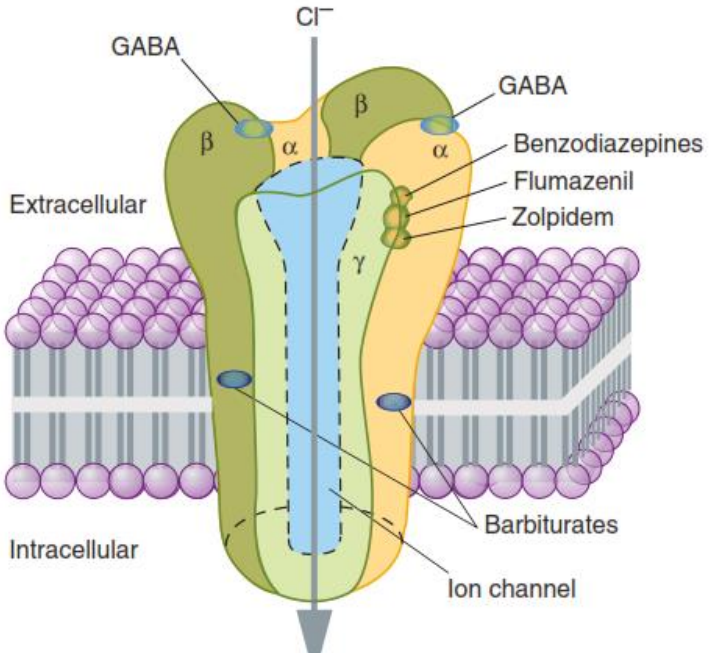
- If poisoning occurs, **no specific antidote is available,** *treated by gastric* lavage, symptomatic treatment and with **forced alkaline diuresis. Hemodialysis can** also be done.


Therapeutic Coverage
Anxiolytic
Sedative
Hypnotic
Anesthesia
Coma
Buspirone
Neuroleptics, Meprobamate
Benzodiazepines
Barbiturates

Non-Benzodiazepine Hypnotics

Zopiclone ; Zolpidem; Zaleplon

- Act on BNZ1 site & blocked by flumazenil .
- Used in **insomnia**
- Have <u>low tendency</u> for tolerance; withdrawal symptoms
  - They lack antianxiety, muscle relaxant and anticonvulsant actions.



Miscellaneous Hypnotics

- **Chloral hydrate** (active metabolite is trichloroethanol) indicated for nocturnal sedation, preoperative sedative that allays anxiety and induces sleep without depressing respiration or cough reflex .
- **Meprobamate** (a metabolite of carisoprodol, a skeletal muscle relaxant) have CNS depressant properties but are rarely used in clinical practice.

- **MELATONIN** is a hormone of pineal gland that synchronizes the circadian rhythm. It is used to reduce **symptoms of jet lag** (disruption of the internal body clock). Lowering of seizure threshold and psychiatric changes are the possible adverse effects.
- **Ramelteon** is agonist of MT1 and MT2 receptors of melatonin in suprachiasmatic nucleus. It is approved for long term use in treatment of **sleep onset insomnia**. It do not possess addictive property but causes hyperprolactinemia, dizziness, and fatigue as adverse effects.


Thank You

- **adverse effects and contraindications**
- • Due to the long duration of action, **hangover is common. Barbiturates can cause**
- distortion of sleep architecture by *decreasing the duration of REM and stage 3 and 4*
- *sleep and increasing the duration of stage 2 sleep.*
- • **Learning and memory impairment can occur.**
- • **Idiosyncratic reaction resulting in excitement can occur in some patients.**
- • These are **absolutely contraindicated in acute intermittent porphyria (because**
- porphyrin synthesis is increased due to induction of d-ALA synthase; rate limiting
- enzyme in porphyrin synthesis, by barbiturates).
- At high doses, acute poisoning may occur (manifests as coma, depressed respiration,
- hypotension, cardiovascular collapse and *barbiturate blisters).*

2. Benzodiazepines

- these drugs act by **GABA facilitatory action.**

Hypnotic:	Diazepam, flurazepam, nitrazepam, flunitrazepam, temazepam, triazolam, quazepam and midazolam
Anti-convulsants:	Diazepam, clonazepam, clobazam, lorazepam
Anti-anxiety:	Diazepam, oxazepam, lorazepam, alprazolam, chlordiazepoxide
Muscle Relaxant:	Diazepam

- BZDs have **flat dose response curves (these have high therapeutic index and** require high dose to produce coma).
- • These cause **less hangover and less distortion of sleep architecture. Duration of** REM sleep is shortened but increase in the number of REM cycles compensate for that. **Nitrazepam actually increases REM sleep.**
- • These are **less prone to drug interactions (because they do not induce microsomal** enzymes).
- • Abuse liability is less.
- • BZD poisoning can be treated with **specific antidote, flumazenil.**
- • Diazepam can produce analgesia whereas *barbiturates may even cause hyperalgesia.*

- **pharmacokinetics**
- *All BZDs are almost completely absorbed except clorazepate (converted to nordiazepam by*
- gastric juice which is absorbed). Most of the BZDs are metabolized in the liver to *produce*
- *active products (thus long duration of action). Active metabolites may result in cumulative effects.*
- After metabolism these are conjugated and are excreted via kidney. **Estazolam, lorazepam,**
- **oxazepam, temazepam and triazolam are directly conjugated without metabolism to**
- active products. These drugs are thus **short acting and do not accumulate on repeated**
- administration. Further these drugs can be **safely administered in liver failure and in**
- **elderly because these are conjugated directly without undergoing metabolism in the liver.**
- Compounds with *shorter half life are favored in patients with sleep onset insomnia whereas*
- *longer acting BZDs are favored in patients with day time anxiety.*

Benzodiazepine antagoniSt

- **Flumazenil is the substance that acts as a competitive antagonist at BZD receptor. It *blocks the***
- *depressant action of benzodiazepines, zolpidem and zaleplon as well as the convulsant action of inverse agonists (like β carboline).*
- It is administered i.v. **for the treatment of BZD poisoning(specificantidote)and can also** be used to reverse BZD anaesthesia.
- Its **duration of action is *approximately 30-40 minutes and* half life is 1 *hour.***

3. newer Hypnotic drugs

- **a. zopiclone**
- It stimulates GABA receptors by binding to a site different than benzodiazepines. It prolongs stage 3 and 4 sleep and does not affect REM sleep. Chances of **rebound insomnia and hangover are less than benzodiazepines and barbiturates. It is used for the treatment of** insomnia

- **B. zolpidem**
- It binds selectively to w
- A
- **subtype of benzodiazepine receptors and increases GABA mediated**
- neuronal inhibition. It possesses pronounced hypnotic and amnesic effects but **lacks**
- It has **little**
- **effect on sleep architecture**

- and
- **does**
- **not produce hangover and**
- **rebound insomnia.**
- Abuse potential of
- zolpidem is very
- low.
- It is also **indicated**
- **for the short term treatment of insomnia.**

- **4. other Hypnotics**
- **Chloral hydrate (active metabolite is trichloroethanol), glutethimide and meprobamate (a**
- metabolite of carisoprodol, a skeletal muscle relaxant) have CNS depressant properties but
- are rarely used in clinical practice.
- **Trazodone is an antidepressant that can be used for insomnia at low doses. Priapism is a rare**
- side effect of this agent.
- **MELATONIN is a hormone of pineal gland that synchronizes the circadian rhythm. It**
- increases the sleep during night but has no effect on latency or duration of sleep. It is **used**
- **to reduce symptoms of jet lag. It can also synchronize the sleep wakefulness cycle in shift**
- **workers and is also used in elderly hypnotic dependent insomniacs. Lowering of seizure**
- **threshold and psychiatric changes are the possible adverse effects.**
- Ramelteon is agonist of MT

- and MT
- receptors of melatonin
- in suprachiasmatic nucleus. It
- is approved for long term use
- in treatment of sleep onset
- insomnia.
- 2

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- Tolerance—a decrease in responsiveness—occurs when sedative-
- hypnotics are used chronically or in high dosage. Cross-tolerance
- may occur among different chemical subgroups. Psychological
- dependence occurs frequently with most sedative-hypnotics and
- is manifested by the compulsive use of these drugs to reduce
- anxiety. Physiologic dependence constitutes an altered state
- that leads to an abstinence syndrome (withdrawal state) when
- the drug is discontinued. Withdrawal signs, which may include
- anxiety, tremors, hyperreflexia, and seizures, occur more commonly
- with shorter-acting drugs.