ANXIOLYTICS AND HYPNOTICS

Dr Ruwan Parakramawansha
MBBS, MD, MRCP(UK),MRCPE, DMT(UK)
(2013/04/02)

LEARNING OUTCOMES

By the end of the lecture, students will be able to…

- define i. an anxiolytic ii. a hypnotic
- list different classes of commonly used anxiolytic/hypnotic drugs with examples
- describe the mechanism of action, pharmacological effects, pharmacokinetics, adverse effects and important drug interactions of anxiolytics/hypnotics.
- explain the clinical significance of pharmacokinetics of benzodiazepines
- describe the problems encountered with the continued use of hypnotics and the measures that can be taken to minimize them.

OUTLINE....

A. Definitions

B. Types of anxiolytics/hypnotics

C. Benzodiazepines

- pharmacodynamics
- Pharmacokinetics
- ADRs

D. “Z” compounds & Buspirone

DEFINITIONS…

- **Anxiolytic** – a drug which reduces anxiety and causes calm and quietness in the patient
- **Sedative** – a drug that decreases activity and calms the recipient
- **Hypnotic** – a drug that produces drowsiness and facilitates the onset and maintenance of a state of sleep that resembles natural sleep

DEFINITIONS…

- **Anxiety→ Drowsiness→ Sleep→ Anaesthesia→ Coma→ Death**

- The difference between sedatives and hypnotic is usually the dose:
  - Lower dose – calming effect
  - Higher dose – cause sleep

- Some newer medicines have separated the effects e.g. Buspirone- an anxiolytic without sedation

ANXIETY

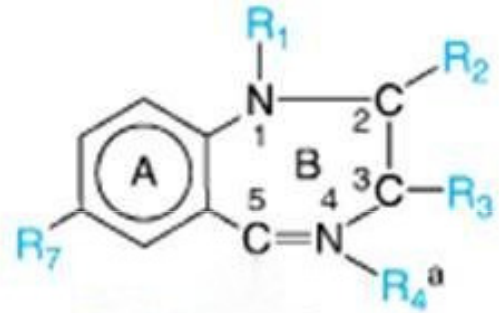
- Anxiety is a normal adaptive response

- anxiety is a disorder if:
  - chronic
  - disproportionate to the situation
  - occurs without an identifiable stimulus
  - interferes with a person's concentration and ability to do routine tasks

ANXIOLYTICS/SEDATIVES/HYPNOTICS

1. Benzodiazepines
2. “Z”componds e.g. Zolpidem
3. Barbiturates e.g. Phenobarbital
4. Chloral Hydrate
5. Buspirone
6. Melatonin Congeners e.g. Ramelteon

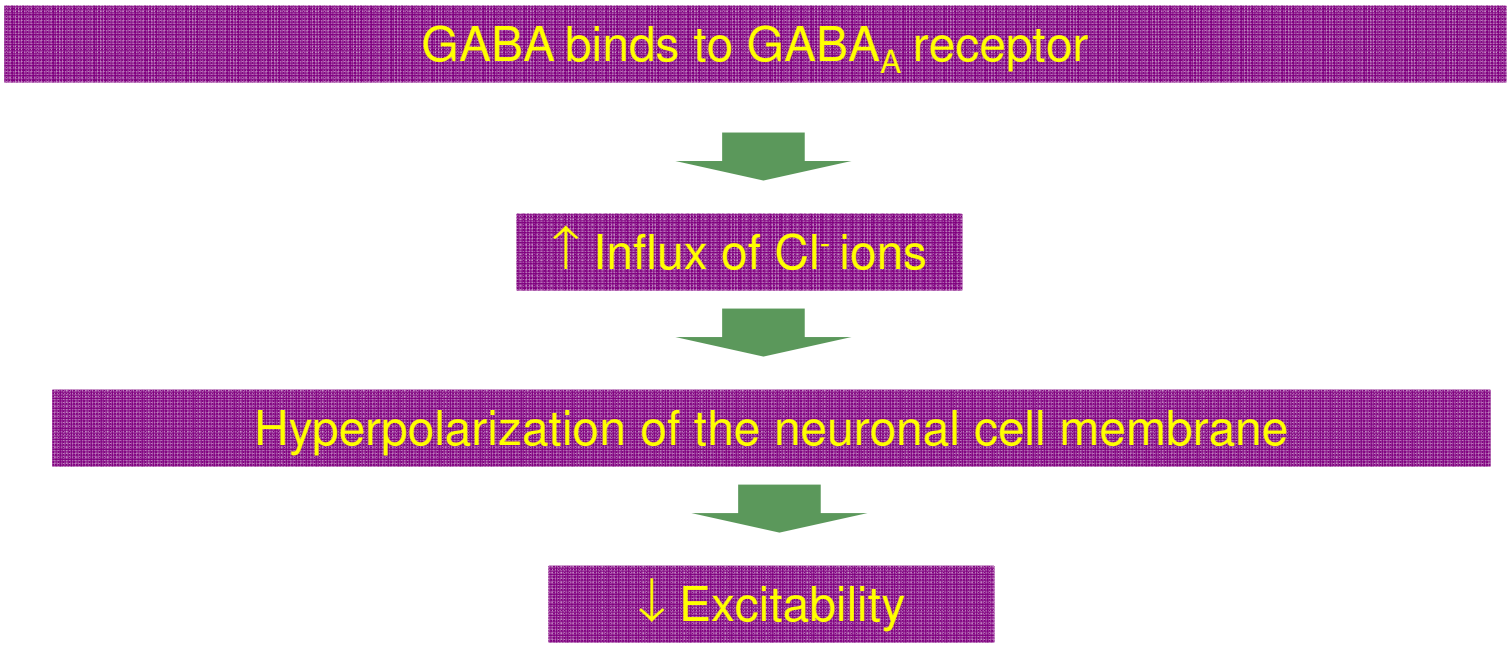
BENZODIAZEPINES

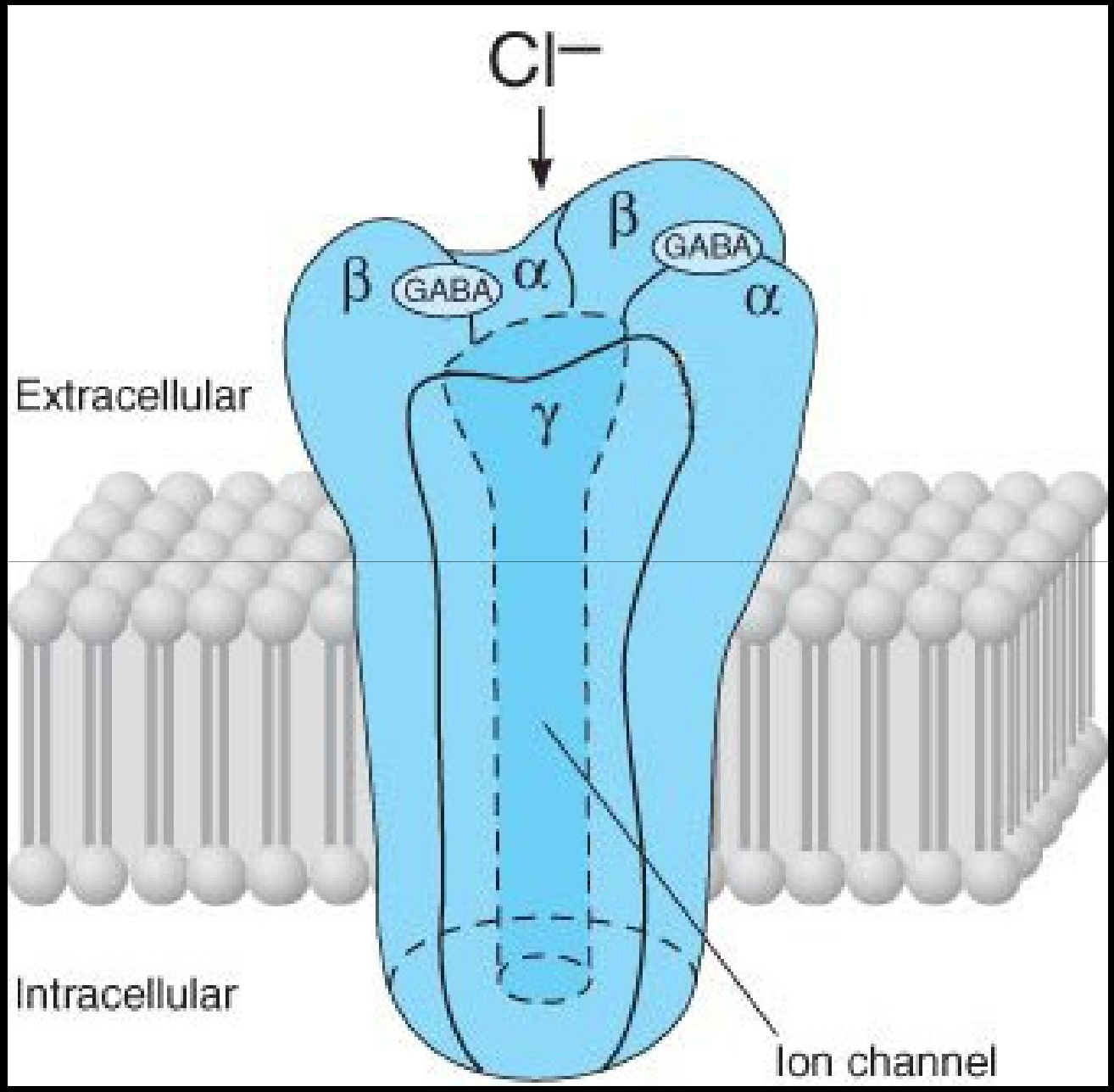


- The term *benzodiazepine* refers to the portion of the structure composed of a benzene ring (A) fused to a seven-membered diazepine ring (B).
- Approved for use ~ 50 years ago
  - Chlodiazepoxide - 1960
  - Diazepam - 1961

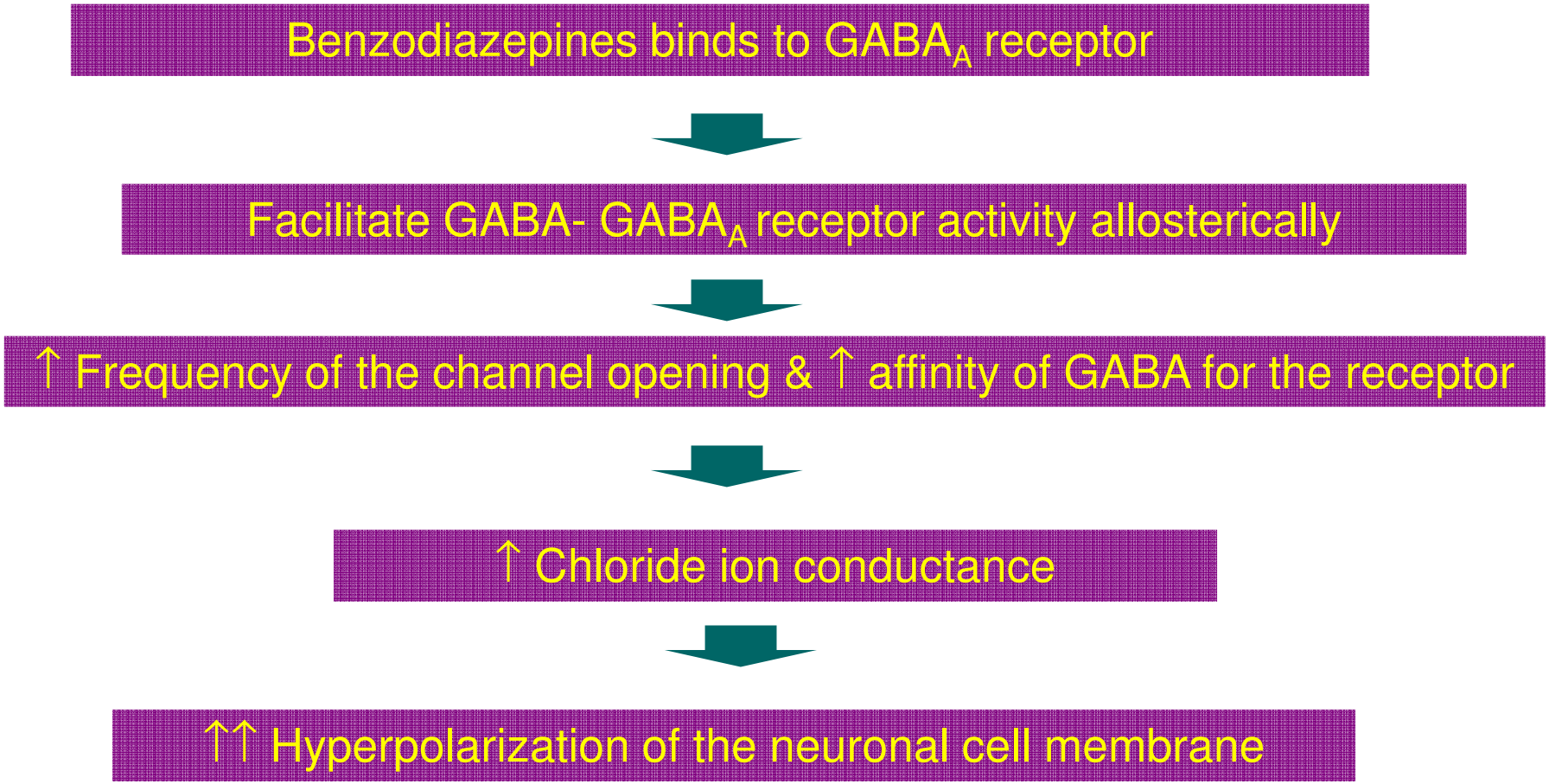
MODE OF ACTION

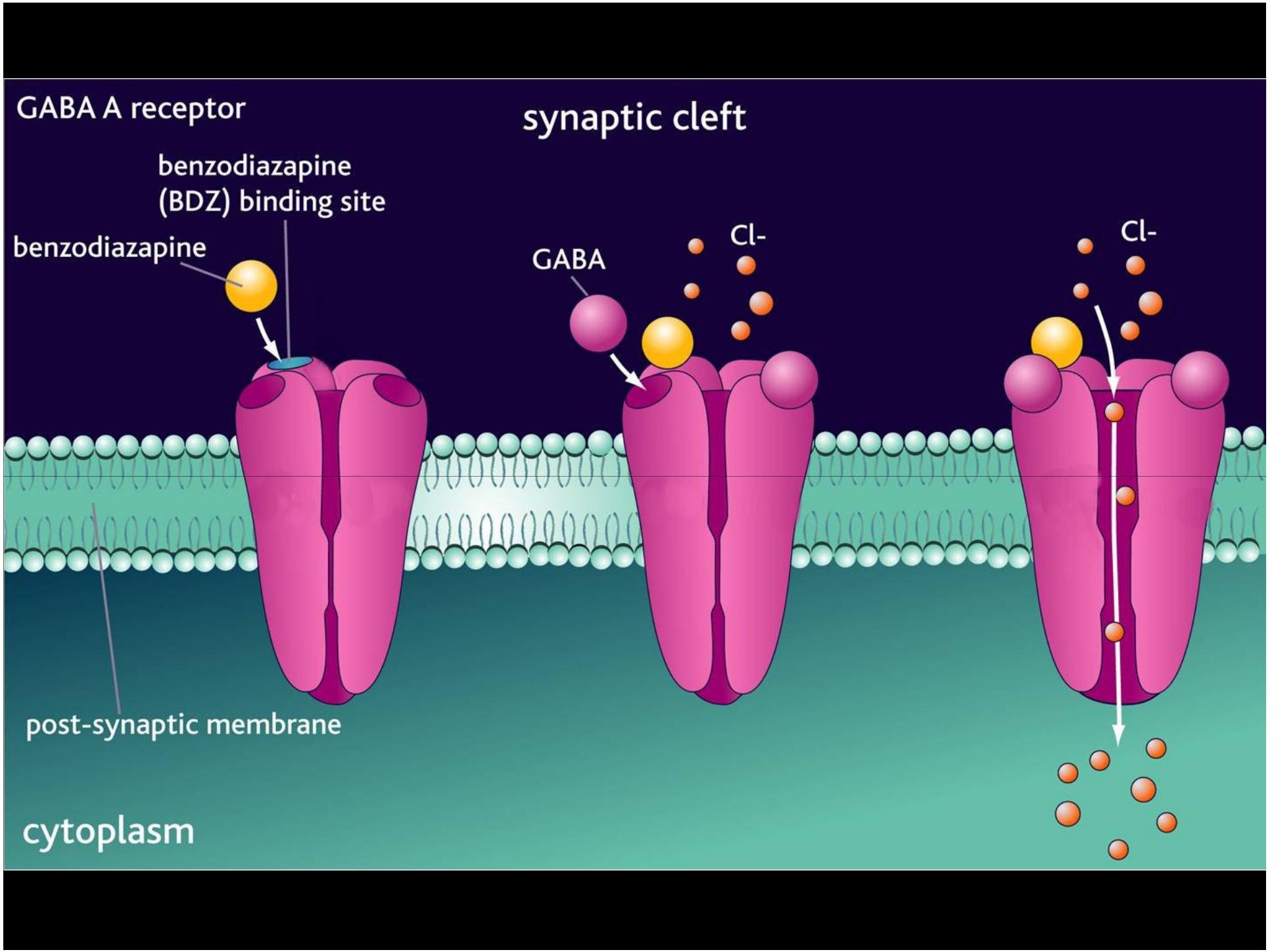
- γ – Aminobutyric acid (GABA) – the predominant inhibitory neurotransmitter in CNS.
- $GABA_A$ receptor is a ligand-gated ion channel




Cl−
β
GABA
α
β
GABA
α
γ
Extracellular
Intracellular
Ion channel

MODE OF ACTION




GABA A receptor
synaptic cleft
benzodiazapine
(BDZ) binding site
benzodiazapine
GABA
Cl-
Cl-
post-synaptic membrane
cytoplasm

PHARMACOLOGICAL EFFECTS

1. Reduction of anxiety and aggression
2. Induction of sleep
3. Anterograde amnesia
4. Anticonvulsant effect
5. Reduction of muscle tone and coordination
6. Effects on respiration
7. Effects on CVS

Reduction of anxiety and aggression

- All benzodiazepines show anxiolytic effects
- Can cause paradoxical hyperexcitability - *range from talkativeness and excitement, to aggressive and antisocial acts*

Induction of Sleep

- Reduce sleep latency, increase sleep time, reduce the number of awakenings after sleep onset, and improve overall sleep quality

- Alter sleep architecture
  - Reduce rapid eye movement (REM)sleep (∴increase REM sleep after withdrawal)

Anterograde Amnesia

- Minor surgical or invasive procedures can be performed without leaving unpleasant memories

Anticonvulsant Effect

- All the benzodiazepines have shown anticonvulsant activity in animal tests
- Clonazepam used as an antiepileptic and diazepam in acute seizures

Effect on Muscle Tone

- Benzodiazepines reduce muscle tone by a central action on $GABA_A$ receptors primarily in the spinal cord

Effect on CVS

- In preanesthetic doses, all benzodiazepines decrease blood pressure and increase heart rate
- Midazolam – via reduced peripheral resistance
- Diazepam – via negative inotropic effect

Effect on Respiration

- Can decrease hypoxic respiratory drive and cause respiratory acidosis
- Can only affect respiration in children and individuals with impaired hepatic function, such as alcoholics
- Usually need respiratory support in toxicity if taken with another CNS depressant e.g. alcohol

TOLERANCE

- Tolerance (i.e. a gradual escalation of dose needed to produce the required effect) occurs with all benzodiazepines
- Tolerance occurs to hypnotic effect after 1-2 days of use
- Also seen with muscle relaxant and anticonvulsant effects

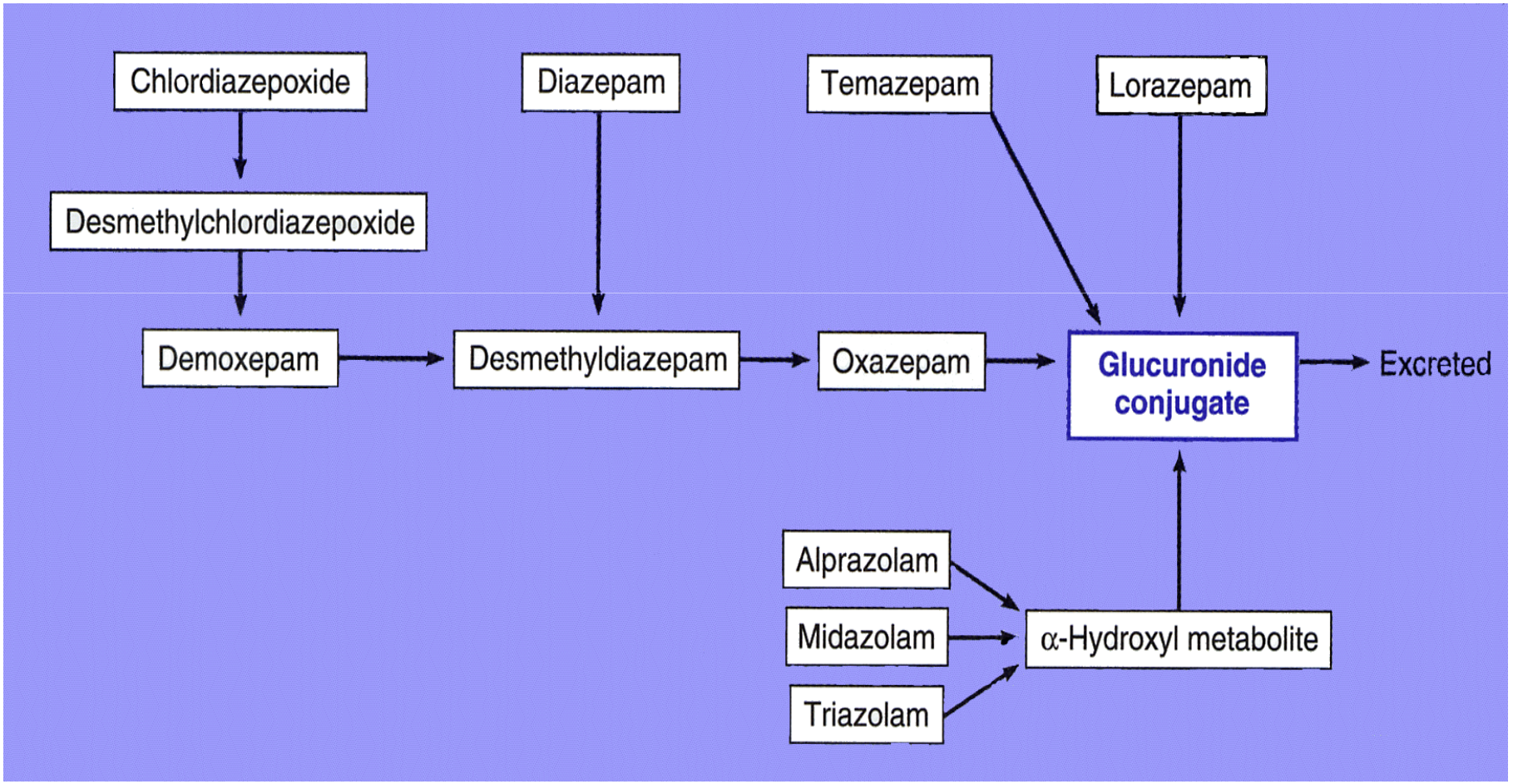
PHARMACOKINETICS

- Well absorbed after oral administration
- Bind strongly to plasma proteins
- Metabolized extensively by hepatic CYPs
- Metabolised and eventually excreted as glucuronide conjugates in the urine, several converted to active metabolites

PHARMACOKINETICS

- Vary greatly in duration of action
- Short-acting compounds – better hypnotics with reduced hangover effect on wakening
- Long-acting compounds -better anxiolytics and anticonvulsant drugs

BIOTRANSFORMATION



Drug	Peak Blood Level (Hours)	Elimination Half-Life[1] (Hours)	Comments
Alprazolam	1-2	12-15	Rapid Oral Absorption
Chlordiazepoxide	2-4	15-40	Active metabolites; erratic bioavailability from IM injection
Diazepam	1-2	20-80	Active metabolites; erratic bioavailability from IM injection
Lorazepam	1-6	10-20	No active metabolites
Temazepam	2-3	10-40	Slow oral absorption; no active metabolites
Triazolam	1	2-3	Rapid onset; short duration of action
Oxazepam	2-4	10-20	No active metabolites

[1] *Includes half-lives of major metabolites*

ADVERSE EFFECTS

- Sedation → Hangover effect
- Ataxia(impaired coordination) - *affect ability to drive or operate machinery*
- Anterograde amnesia
- Confusion
- Muscle weakness

DEPENDANCE

- Psychological and physical
- Psychological dependence refers to drug craving that can lead to drug-seeking behaviour
- Physical dependence occurs when the drug is stopped and symptoms of withdrawal occur

WITHDRAWAL SYMPTOMS

- Typically mimic symptoms of anxiety disorders
  - Anxiety
  - Insomnia, Anorexia
  - Muscle twitching, Tremor, perspiration
  - Unsteadiness
  - Hypersensitivity to light and noise
  - Convulsions
  - Delirium tremens

"Z " COMPOUNDS

e.g. zolpidem, zopiclone

- Structurally unrelated to benzodiazepines
- Act as agonists on the benzodiazepine site of the $GABA_A$ receptor
- Little effect on the stages of sleep
- Tolerance and physical dependence – rare

BUSPIRONE

- An anxiolytic medicine
- **EFFICACY:**

  similar to that of benzodiazepines in anxiolytic effect
- **MODE OF ACTION:**

  Act as a partial agonist for serotonin 5-HT_{1A} receptors in the brain

BUSPIRONE

- **ADVANTAGES:**
  - No physical dependence/ withdrawal
  - No abuse potential
  - Less sedation and psychomotor impairment
  - Lack of interaction with alcohol
- **DISADVANTAGES:**
  - Slow onset of action (1-2 weeks)
  - Short $t_{1/2}$ (~2.5h) $\rightarrow$ b.d./ t.d.s. administration