LNCT GROUP OF COLLEGES

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Subject: Pharmacology-I (BP 404T)
Unit: IV
Topic: Anti Anxiety Agents

Anxiety

- I have a presentation
- I have a tough exam
- I have an important interview

Should I be anxious?

What is anxiety ?

Physical and emotional distress which interfere with normal life.

What are different symptoms of anxiety ?

- **Psychic or emotional state.**
- **Somatic or physical symptoms.**

Common Emotional Symptoms of anxiety

- irrational and excessive fear and worry
- Irritability
- Restlessness
- Trouble concentrating
- Feeling tense

Common Physical Symptoms of Anxiety

Sweating

Tachycardia

Stomach upset

Shortness of breath

Frequent urination or diarrhea

Sleep disturbances (Insomnia)

Fatigue

Types of anxiety

1. Generalized anxiety disorder
2. Post-traumatic stress disorder (PTSD).
3. Obsessive-compulsive disorder (OCD).
4. Panic disorder
5. Phobia

Generalized Anxiety Disorder (GAD)

- **Patients are usually and constantly worried about health, money, work with no apparent reasons.**

Obsessive-Compulsive Disorder (OCD)

An anxiety disorder in which people cannot prevent themselves from unwanted thoughts or behaviors that seem impossible to stop as

Washing their hands

Panic disorder

An disorder in which people have sudden and intense attacks of anxiety in certain situations.

Post-traumatic stress disorder (PTSD)

An anxiety disorder that affects people who have experienced a severe emotional trauma, such as rape or dramatic car accident, or even war.

Phobia

An intense, uncontrolled fear of a specific situation such as

open spaces & heights

Treatment of anxiety

- **Psychotherapy (cognitive behavioral therapy).**

- **Anxiolytics**

Anti anxiety drugs:-

Mild CNS depressants , aimed to control the symptoms of anxiety , produces a restful state of mind without interfering with normal mental or physical function classification.

CLASSIFICATION

1. *Benzodiazepines*	Diazepam Chlordiazepoxide Oxazepam Lorazepam, Alprazolam
2. *Azapirones*	Buspirone, Gepirone, Ispapirone
3. *Sedative antihistaminic*	Hydroxyzine
4. *β blocker*	Propranolol

Benzodiazepines

Classifications of Benzodiazepines

- **Short acting: (3-5 hours): triazolam**
- **Intermediate: (6-24 hours)**
  - **Alprazolam**
  - **Lorazepam**
  - **Oxazepam**
  - **Estazolam**
  - **Temazepam**

Classifications of Benzodiazepines

- **Long acting: (24-72 hours)**

  Clonazepam

  Chlordiazepoxide

  Diazepam

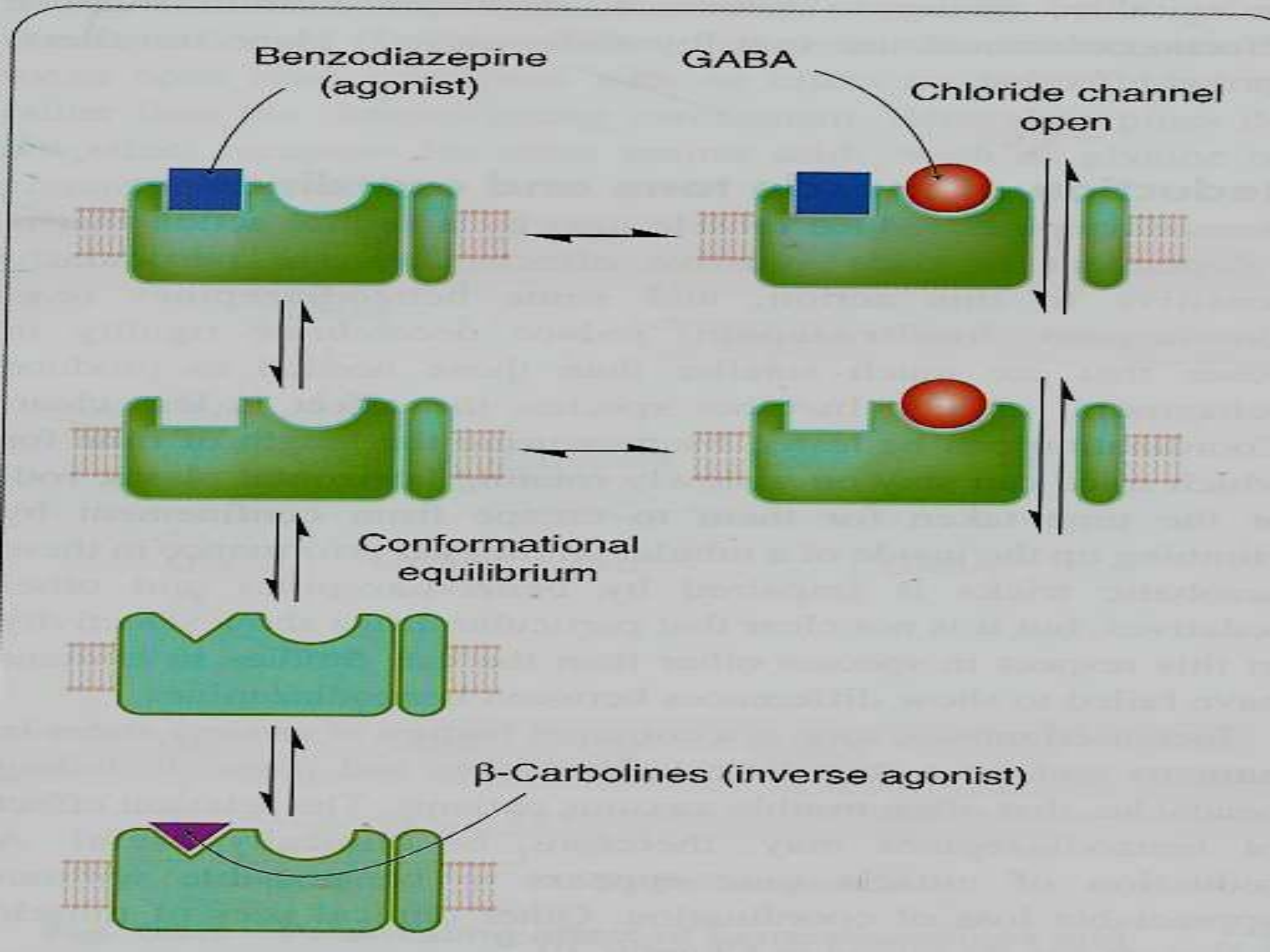
  Flurazepam

Mechanism of Action

Benzodiazepines act by binding to BZ receptors

in the brain → enhance GABA action on brain → chloride channels opening → ↑ chloride influx to the cell → hyper- polarization → inhibition of brain.

GABA (γ-aminobutyric acid):
is an inhibitory neurotransmitter


Benzodiazepine
(agonist)
GABA
Chloride channel
open
Conformational
equilibrium
β-Carbolines (inverse agonist)

PHARMACOKINETICS

- are lipid soluble
- well absorbed orally,
- can be given parenterally
- Chlordiazepoxide- Diazepam
- widely distributed.
- cross placental barrier (Fetal depression).
- excreted in milk (neonatal depression).

- **metabolized in the liver to active metabolites**

Redistribution from CNS to skeletal muscles,

adipose tissue.

Pharmacological Actions

- **Anxiolytic action.**
- **Depression of cognitive and psychomotor function**
- **Sedative & hypnotic actions**
- **Anterograde amnesia.**

Pharmacological Actions

- **Minimal depressant effects on**
  - **Cardiovascular system**
  - **Respiratory system**
- **Some have anticonvulsant effect:**
  - **clonazepam, diazepam.**

Therapeutic Uses

Anxiety disorders:

short term relief of severe anxiety
General anxiety disorder
Obsessive compulsive disorder
Panic attack with depression **Alprazolam (antidepressant effect)**

Sleep disorders (Insomnia).

- Triazolam, Lorazepam, Flurazepam

Therapeutic Uses

Treatment of epilepsy

Diazepam – Lorazepam

In anesthesia

- Preanesthetic medication (diazepam).
- Induction of anesthesia (Midazolam, IV)

Adverse Effects

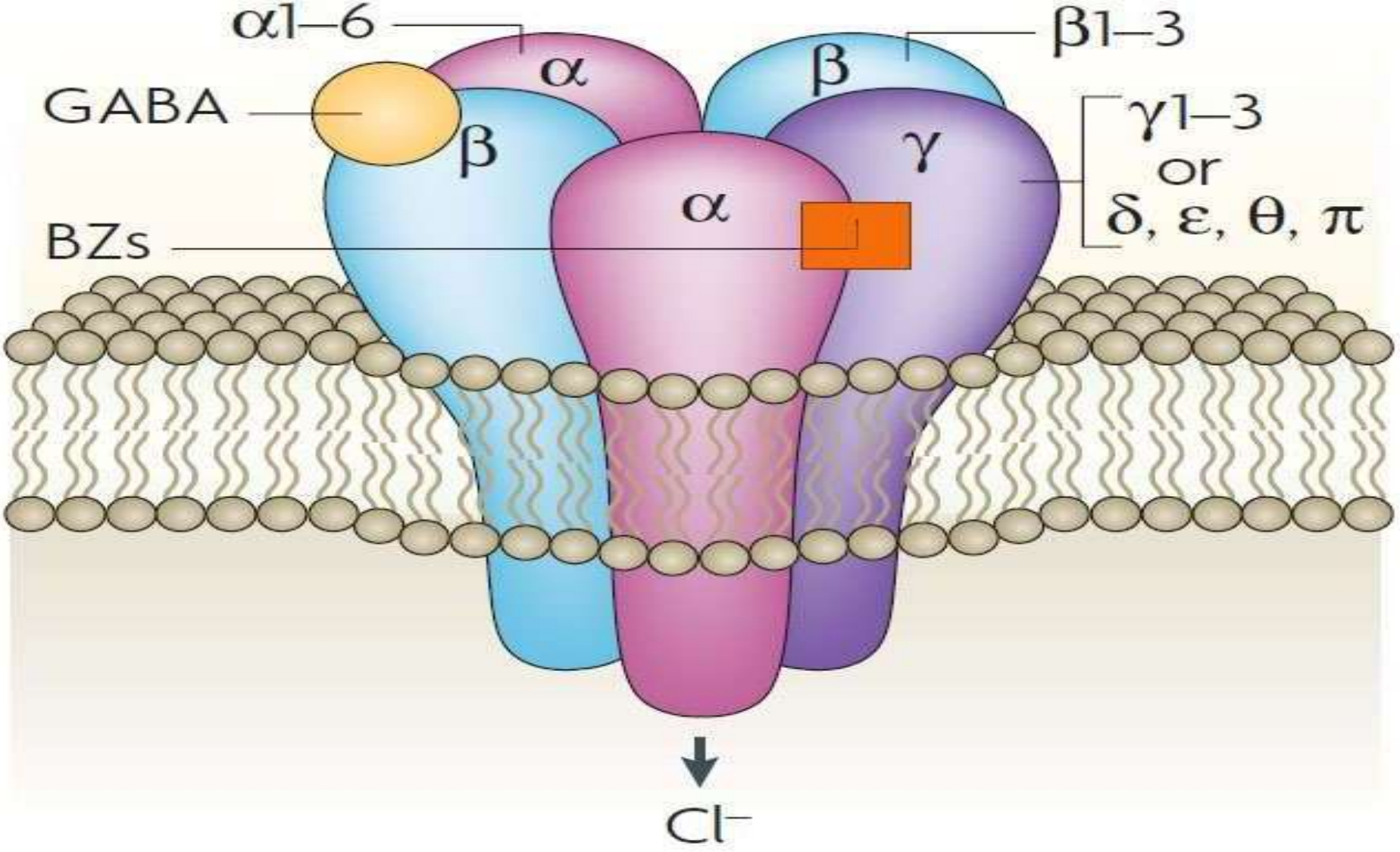
- Ataxia (motor incoordination)
- Cognitive impairment.
- Hangover: (drowsiness, confusion)
- Tolerance & dependence
- Risk of withdrawal symptoms

Rebound Insomnia, anorexia, anxiety, agitation, tremors and convulsion.

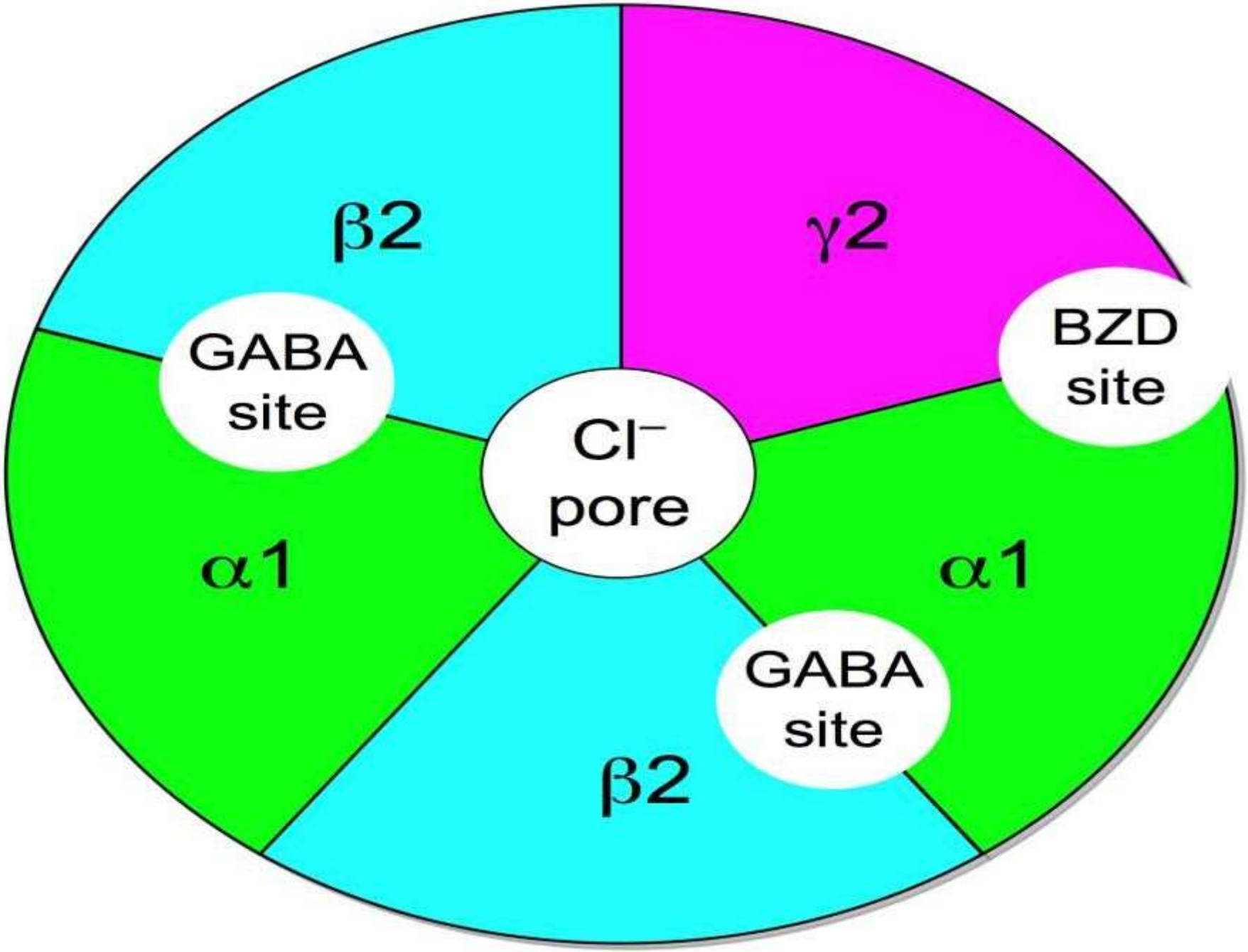
Adverse Effects

- **Toxic effects: respiratory & cardiovascular depression in large doses.**

$GABA_A$ receptor



Jacob et al., Nature Reviews Neuroscience, 2008


β2
γ2
GABA site
BZD site
Cl⁻ pore
α1
α1
GABA site
β2

Benzodiazepine derivatives and oral doses

Name	Bed time hypnotic single dose mg Δ	Total ** daily anxiolytic dose mg
I ***Effective half-life more than 24 hrs :**		
Chlordiazepoxide (Librium)	—	30-100
Diazepam *** (Valium, Calmpose)	5 - 15	10 - 30
Flurazepam (Dalmane)	15 - 30	15 - 30
Chlorazepate (Tranxene)	3.75 - 15	7.5 - 22.5

II **Effective half-life 5-24 hrs :**		
Nitrazepam (Nitravate, Hypnotex)	5 - 10	5 - 10
Lorazepam (Larpose)	0.5 - 2	1 - 4
Oxazepam (Serapax)	15 - 30	45 - 60
Temazepam	15 - 30	10 - 30

III Effective half-life less than 5 hrs :

Alprazolam (Alprax)	-	0.75-1.50
Triazolam (Halcion)	0.25	-

Flumazenil:-

Rapidly reverse effects of BZD , can cause withdrawal syndrome in patients getting BZD . Orally effective. Also given IV

Uses:-

1. **BZD poisoning**

2.Reversal of BZD induced anesthesia

Adverse effects –

agitation, discomfort,anxiety,coldness & withdrawal seizures.

Drug interactions

	Examples
CNS depressants	Alcohol & Antihistaminics ↑ effect of benzodiazepines
Cytochrome P450 (CYT P450) inhibitors	Cimetidine & Erythromycin ↑ $t_{½}$ of benzodiazepines
CYT P450 inducers	Phenytoin & Rifampicin ↓ $t_{1/2}$ of benzodiazepines

Dose should be reduced in

- **Liver disease**
- **Old people.**

Precaution

Should not used in

- **pregnant women or breast-feeding.**
- **People over 65.**

$5HT_{1A}$ agonists
Buspirone

- acts as agonist at brain $5HT_{1A}$ receptors
- rapidly absorbed orally.
- Slow onset of action (delayed effect)
- T½ : (2 – 4 h).
- liver dysfunction → ↓ its clearance.
- Drug Interactions with CYT P450 inducers and inhibitors.

Buspirone

- Only anxiolytic
- No hypnotic effect.
- Not muscle relaxant.
- Not anticonvulsant.
- No potentiation of other CNS depressants.
- Minimal psychomotor and cognitive dysfunctions.
- Does not affect driving skills.
- Minimal risk of dependence.
- No withdrawal signs.

Uses of buspirone

- **As anxiolytic in mild anxiety & generalized anxiety disorders.**
- **Not effective in severe anxiety/panic disorder.**

Beta Blockers

- **Propranolol – atenolol**

act by blocking peripheral sympathetic system.

- **Reduce somatic symptoms of anxiety.**
- **Decrease BP & slow HR.**
- **Used in social phobia.**
- **are less effective for other forms of anxiety**

- Hydroxyzine – An H1 antihistaminic with sedative, antiemetic, antimuscarinic and spasmolytic properties.
- Hydroxyzine used in reactive anxiety or that associated with marked autonomic symptoms.
- It is useful in pruritus and urticaria.

- General anxiety disorder (GAD) -

- The current therapy of GAD include a combination of BDZ, SSRI and cognitive behavioral therapy. Some patients will need maintenance drug therapy almost life long.

- 1. short course of BZD – lowest dose & on as needed basis. Not > 4-6 wks. Short acting fast but day time anxiety and difficult to withdraw. Long acting sedation problem, slow withdrawal easier.
- 2. Buspirone – adv non sedating,but slow , effective in head injury & dementia pts.
- SSRIs & SNRIs – effective in anti depressant dose.
- Anti convulsants – gabapentine,tiagabine etc.

- R/ stress disorder – PTSD
- Short term BZD(clozapine 1-4mg) + psychotherapy in acute cases
- Chronic and recurrent cases –
- TCA – Imipramine, Amitryptiline
- MAOI – independent of antidepressant action
- SSRIs –
- Trazodone
- Carbamazepine – 400-800mg/d,
- Prazosin – 2-10mg at bed time.↓night mare.
- Propranolol and Morphine given during acute stage ,preventive for recurrence.

- Obsessive Compulsive Disorder –
- 50- 60% pts show improvement with only pharmacotherapy.
- Clomipramine – (50-150mg/d)
- Fluoxetine(5-60mg/d)
- Fluvoxamine(25-300mg/d)
- Sertraline(50-150mg/d)
- CBT (cognitive behaviour therapy)
- Deep brain stimulation

Conclusion of anxiolytics

CLASSES OF ANXIOLYTICS	USES
Benzodiazepines	Generalized anxiety disorders, OCD, phobia, panic attack
SSRIs (Fluoxetine)	Generalized anxiety disorders, OCD, phobia, panic attack
Tricyclic antidepressants (doxepin, imipramine)	anxiety with depression. panic attacks
5HT1A agonists (Buspirone)	Mild anxiety Not effective in panic attack
Beta blockers (propranolol, atenolol)	Phobia (social Phobia)
MAO inhibitors Phenelzine	Panic attack, phobia

Conclusion of anxiolytics

CLASSES OF ANXIOLYTICS	Adverse effects
Benzodiazepines	Ataxia, confusion, dependence, tolerance, withdrawal symptoms,
SSRIs (Fluoxetine)	weight gain, sexual dysfunction Dry mouth
Tricyclic antidepressants (doxepin, imipramine)	weight gain, sexual dysfunction, atropine like actions
5HT1A agonists (Buspirone)	Minimal adverse effects
Beta blockers (propranolol, atenolol)	Hypotension