PHARMACOLOGY TEAM

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- Team notes : red color
- summary : last 4 pages

Antianxiety drugs

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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

Frequent urination or diarrhea

Shortness of breath

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.

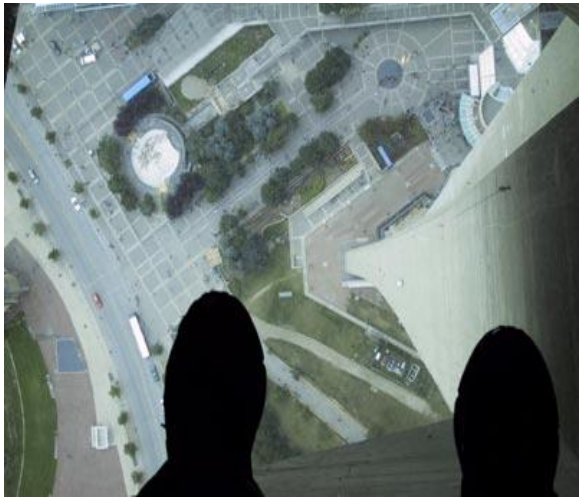
Post-traumatic stress disorder (PTSD)

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**

Classification of anxiolytic drugs:

1. **Benzodiazepines (BDZ).**
2. **$5HT_{1A}$ agonists.**
3. **5HT reuptake inhibitors.**
4. **Antidepressants**
5. **beta-adrenergic blockers**
6. **MAO inhibitors**

Benzodiazepines

Classifications of Benzodiazepines

- **Short acting: (3-5 hours): tria**zolam
- **Intermediate: (6-24 hours)**
  - **Alpra**zolam
  - **Lora**zepam
  - **Oxa**zepam
  - **Esta**zolam
  - **Tema**zepam

Classifications of Benzodiazepines

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

  Clonazepam

  Chlordiazepoxide

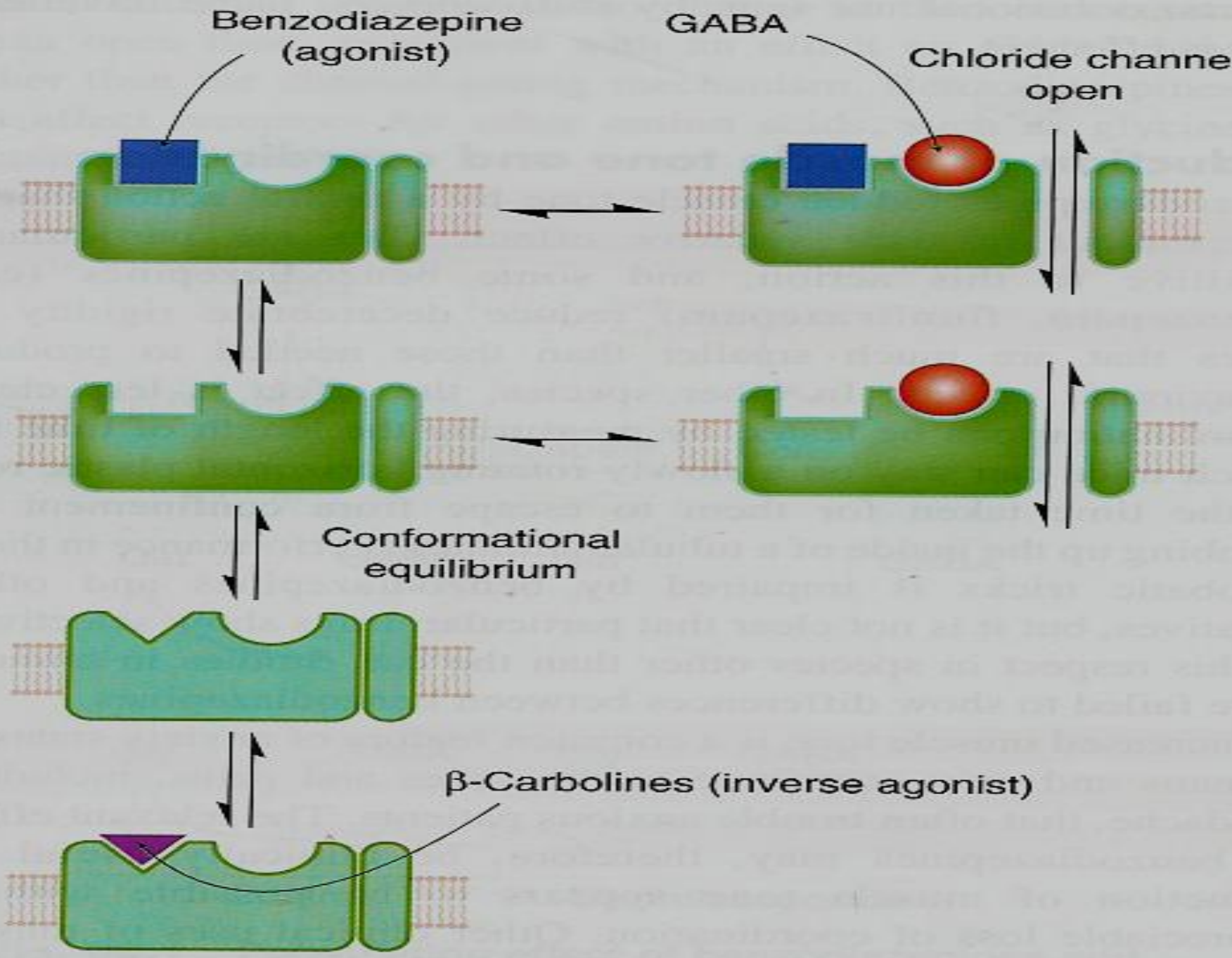
  Diazepam

  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 (IV only NOT IM)

- **widely distributed.**
- **cross placental barrier (Fetal depression).**
- **excreted in milk (neonatal depression).**

- **metabolized in the liver to active metabolites (long duration of action- cumulative effect).**

active metabolites → chance of drug to accumulate inside our body because the initial drug is active also the metabolized form is active "" ولهذا السبب يطول في الجسم

- **Redistribution from CNS to skeletal muscles, adipose tissue) (termination of action).**

Redistribution (relocation) from brain to deposite in other fat tissue so:
1- they are far away from their site of action .
2- they aren't longer active pharmaclogical – don't produce any effect

Pharmacological Actions

- **Anxiolytic action.**
- **Depression of cognitive "ability to learn and concentrate" and psychomotor function**
- **Sedative & hypnotic (causes sleep) actions**

  "when we ↑ the dose"
- **Anterograde amnesia**

. memory loss relates to events occurring after taking the drug **"""نسيان الاحداث القريبة بعد تناول الدواء"**

Pharmacological Actions

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

Therapeutic Uses of Benzodiazepines

Anxiety disorders:

General anxiety disorder

Obsessive compulsive disorder

Panic attack with depression :

the drug of choice in this case is

Alprazolam (antidepressant effect)

Not for short term relief of mild anxiety

Sleep disorders (Insomnia).

- **Triazolam, Lorazepam, Flurazepam**

Therapeutic Uses

Treatment of epilepsy:

Diazepam – Lorazepam- clonazepam

"drugs which have anticonvulsant effect "

In anesthesia

- **Preanesthetic medication (diazepam).**

Before we give anesthetic we give diazepam for 2 reason:

1- sedative effect (Reduction of anxiety, stress, irritability)

2-anterograde amnesia

- **Induction of anesthesia (Midazolam, IV)**

Adverse Effects

- **Ataxia (motor incoordination)**
- **Cognitive impairment."**
- **Hangover"** The continuing influence of the drug for a long time after taking

Characterize by :(drowsiness, confusion)

- **Tolerance"**↓ the response to therapeutic dose**" & dependence** = إدمان
- **Risk of withdrawal symptoms → :**

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

Adverse Effects

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

Drug interactions

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

Dose should be reduced in

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

Precautions

- **Not for pregnant women or breast-feeding.**
- **Not for people over 65.**
- **Used for limited time (2 weeks)** ! to avoid dependence and withdrawal symptoms

$5HT_{1A}$ agonists
Buspirone

- acts as partial agonist at brain $5HT_{1A}$ receptors
- rapidly absorbed orally.
- Slow onset of action (delayed effect)
- T½ : (2 – 4 h).

Buspirone

- Only anxiolytic
- No hypnotic effect.
- No muscle relaxant action.
- No anticonvulsant activity.
- 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 generalized anxiety disorders (mild anxiety).

- 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**

Tricyclic Antidepressants

Doxepin- imipramine

- act by reducing uptake of 5HT & NA "nor adrenalin".

→↑ serotonin concentration in the brain

- Used for anxiety especially associated with depression.
- Effective for panic attacks.!!!
- Delayed onset of action (weeks).

Adverse effects

- Atropine like actions *(dry mouth, constipation, blurred vision).*
- Postural hypotension *(α-blocking activity).*
- Sexual dysfunction, weight gain.

Selective serotonin reuptake inhibitors (SSRIs)

Fluoxetine (1st class to treat depressant and selective for anxiety)

- acts by blocking uptake of 5HT →↑ serotonin concentration in the brain
- Orally
- Delayed onset of action (weeks).
- Used for depression- panic disorder –

OCD 'Obsessive compulsive disorder'-

Generalized anxiety disorders - phobia.

Side Effects:

- GIT disorders (nausea, diarrhea), weight gain, sexual dysfunction.

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)

Conclusion of anxiolytics

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

Imp. Points of **benzodiazepines** !!!

*** Cimetidine + Erythromycin + Alcohol + Antihistamines increase**

$t_{½}$ of benzodiazepines

lead to cardiac and respiratory depresssion

*** Chlordiazepoxide- Diazepam parenteral form of benzodiazepines**

*** Panic attack with depression → Alprazolam**

*** Preanesthetic ⟶ diazepam**

*** Induction of anesthesia → Midazolam**

*** epilepsy: Diazepam – Lorazepam- clonazepam**

Short acting (3-5 h)	Intermediate acting (ALTOE)	long acting (all zepam CDF + Ch)
Triazolam	Alprazolam Lorazepam Temazepam Oxazepam Estazolam	Clonazepam Diazepam Flurazepam Chlordiazepoxide