

# Drugs used in anxiety and panic disorders

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## *Objectives*

*By the end of this lecture, the students will be able to:*

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- **Define different types of anxiety disorders**
- **Classify types of drugs used for treatment of anxiety**
- **Recognize the pharmacokinetics & pharmacodynamics of different classes of anti-anxiety drugs.**
- **Identify the specific clinical applications of each class of anti-anxiety drugs.**
- **Know side effects of different classes of anti-anxiety drugs.**



# Antianxiety drugs

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**Drugs that can relieve anxiety without interfering with mental or physical function.**

# What is anxiety ?

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**Physical and emotional distress which interferes with normal life.**





# Symptoms of anxiety

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- ❑ **Psychological or emotional symptoms.**
- ❑ **Physical or somatic symptoms.**



# **Emotional symptoms of anxiety**

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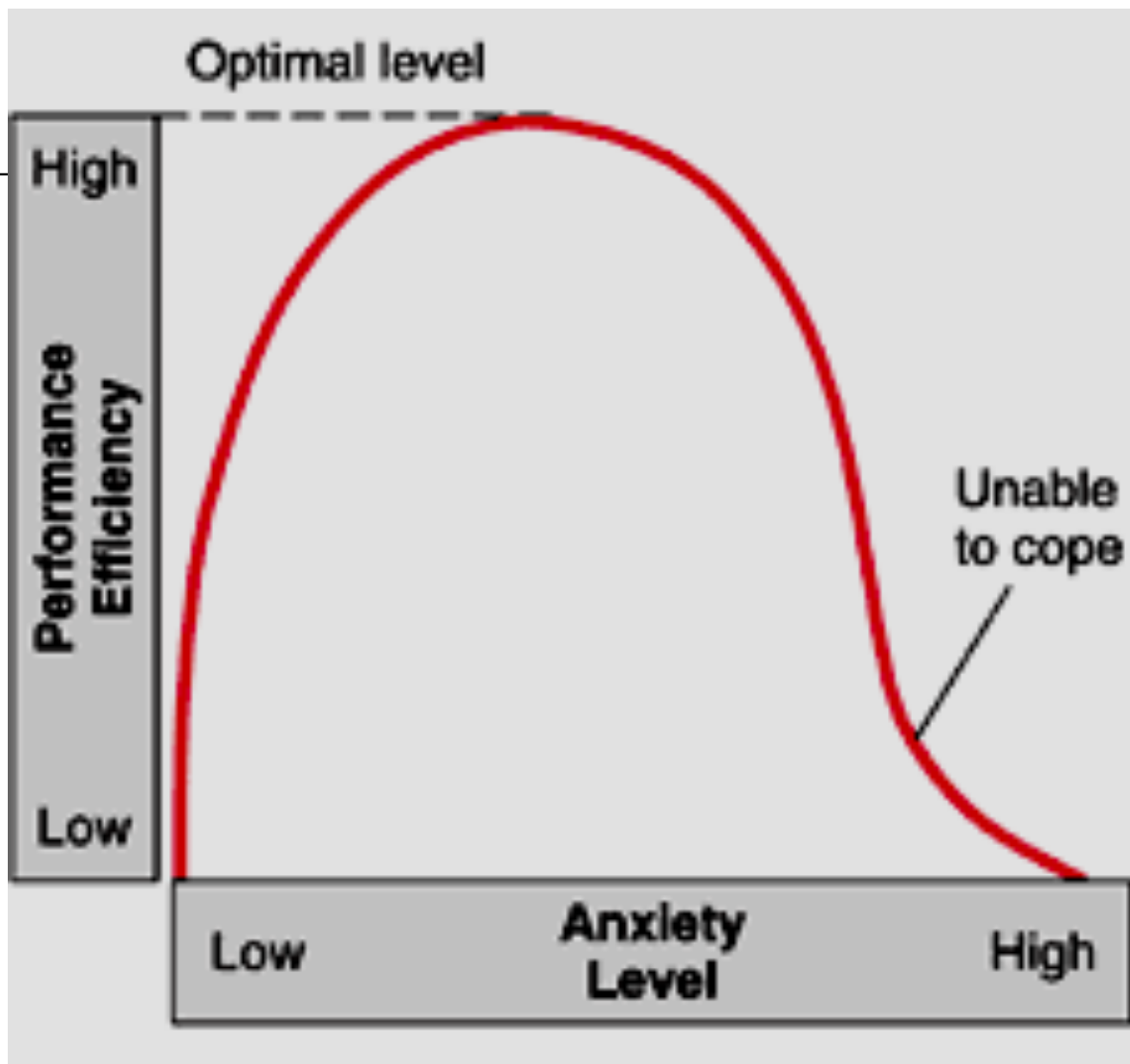
- Feeling tense**
- Trouble concentrating**
- Irrational and excessive fear and worry**
- Irritability**
- Restlessness**



# Physical Symptoms of Anxiety

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- **Sweating**
- **Tachycardia**
- **Shortness of breath**
- **Stomach upset**
- **Frequent urination or diarrhea**
- **Sleep disturbances (**Insomnia**)**
- **Fatigue**







# Types of anxiety

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

# Generalized Anxiety Disorder (GAD)

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

# Obsessive-Compulsive Disorder (OCD)

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

**Washing their hands**



# Post-traumatic stress disorder (PTSD)

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



# Phobia

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**An intense, uncontrolled fear of a specific situation such as**

**open spaces      &      heights**



# Panic disorder

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**Sudden, intense and acute attacks of anxiety in certain situations. Panic attacks cannot be predicted.**



# Treatment of anxiety

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- **Psychotherapy**
- **Anxiolytics**





# Classification of anxiolytic drugs

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1. **Benzodiazepines ( BDZ ).**
2. **5HT reuptake inhibitors.**
3. **5HT<sub>1A</sub> agonists.**
4. **Antidepressants**
5. **Beta-adrenergic blockers**





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# **Benzodiazepines**

# Nomenclature of Benzodiazepines

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Have the suffix “zolam” or “zepam”

**Alprazolam**

**Estazolam**

**Triazolam**

**Lorazepam**

**Oxazepam**

**Temazepam**

**Diazepam**

**Flurazepam**

# Classifications of Benzodiazepines

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are classified according to duration of action into:

**Short acting (3-8 hours): “TO”**

**Triazolam- Oxazepam**

**Intermediate (10-20 hours): “ALET”**

**Alprazolam - Lorazepam**

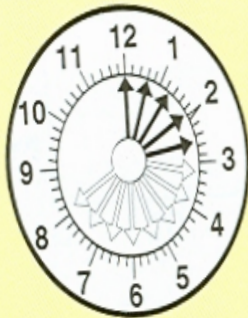
**Estazolam - Temazepam**

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

**Chlordiazepoxide -Diazepam - Flurazepam**

# Classifications of Benzodiazepines

## Short-acting



**3-8 Hours**

Oxazepam  
Triazolam

## Intermediate-acting



**10-20 Hours**

Alprazolam  
Estazolam  
Lorazepam  
Temazepam

## Long-acting



Clorazepate  
Chlordiazepoxide  
Diazepam  
Flurazepam  
Quazepam

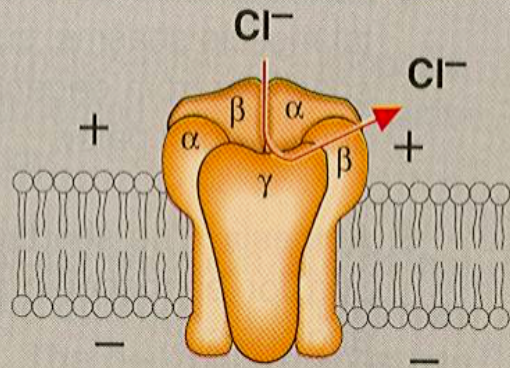
# Mechanism of Action

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**Benzodiazepines act by binding to BZ receptors in the brain → enhance GABA action on the brain → chloride channels opening → ↑ chloride influx to the cell → hyper-polarization → more difficult to depolarize → reduction of neural excitability.**

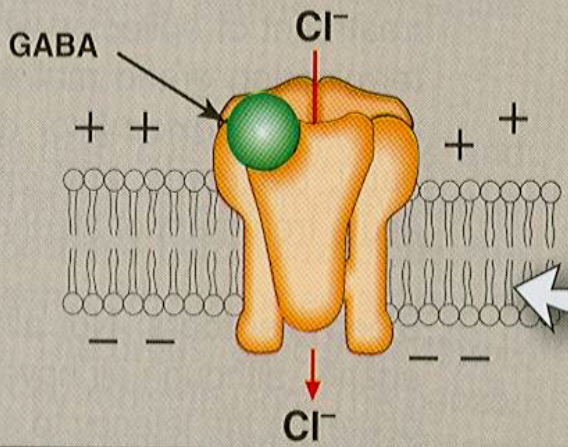
**GABA ( $\gamma$ -aminobutyric acid):  
is an inhibitory neurotransmitter**

**A** Receptor empty  
(no agonists)



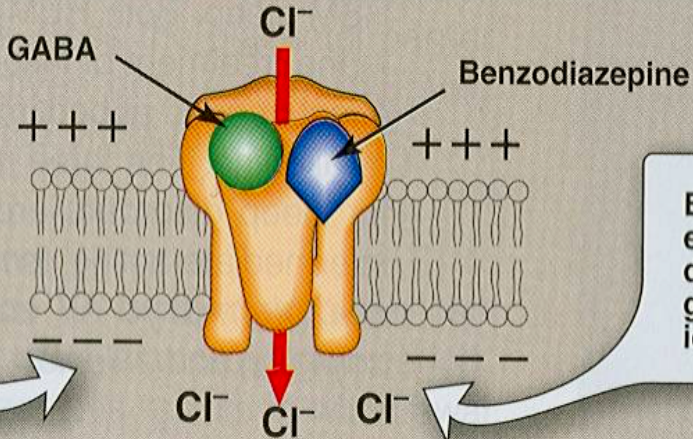
Empty receptor is inactive, and the coupled chloride channel is closed

**B** Receptor binding GABA



Binding of GABA causes the chloride ion channel to open, leading to hyperpolarization of the cell.

**C** Receptor binding GABA and benzodiazepine



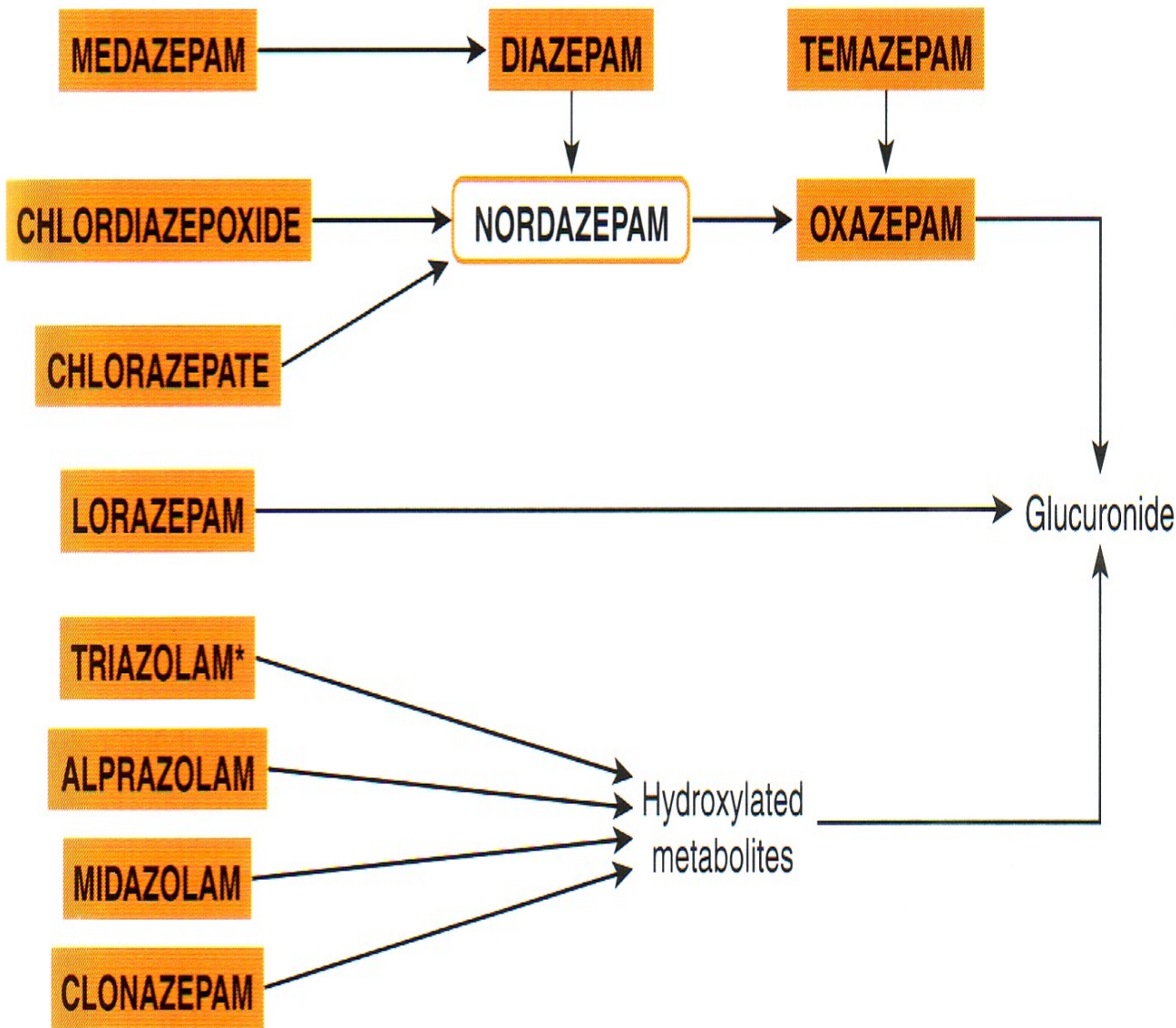
Binding of GABA is enhanced by benzodiazepine, resulting in a greater entry of chloride ion.

Entry of  $\text{Cl}^-$  hyperpolarizes the cell, making it more difficult to depolarize, and therefore reduces neural excitability.

# Pharmacokinetics

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- are lipid soluble
- well absorbed orally
- **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**) and excreted in urine.



**Fig. 36.4** The metabolism of benzodiazepines. The N-demethylated metabolite nordazepam is formed from a number of benzodiazepines and is important because it is biologically active and has a very long half-life. Compounds with pharmacological activity are shown in blue. Drugs available for clinical use are shown in shaded boxes.

\*Triazolam withdrawn in UK





# Pharmacological actions

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- ❑ **CNS depressants**
- ❑ **Anxiolytic action.**
- ❑ **Sedation**
- ❑ **Hypnotic action**
- ❑ **Anterograde amnesia**
- ❑ **Depression of cognitive and psychomotor function**
- ❑ **some have skeletal muscle relaxing effect**  
**(diazepam)**



# Pharmacological actions

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- ❑ **Some have anticonvulsant effect e.g. clonazepam, diazepam, lorazepam.**
- ❑ **Therapeutic doses have minimal depressant effects on**
  - ❑ **cardiovascular system**
  - ❑ **respiratory system**



# Therapeutic uses of benzodiazepines

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## **Anxiety disorders:**

Benzodiazepines are fast acting—typically bringing relief within thirty minutes to an hour.

**Short term relief of severe anxiety**

**General anxiety disorder**

**Obsessive compulsive disorder**

**Panic disorder with depression **Alprazolam**  
(antidepressant effect)**

## **Sleep disorders (Insomnia):**

**Triazolam, Lorazepam, Flurazepam**



# Therapeutic uses of benzodiazepines

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## Treatment of epilepsy

**Diazepam – Lorazepam**

## In anesthesia

- **Pre-anesthetic medication (diazepam).**
- **Induction of anesthesia (Midazolam, IV)**

**Alcohol withdrawal syndrome (diazepam)**



# Adverse Effects

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- **Cognitive impairment.**
- **Ataxia (motor incoordination)**
- **Impairment of driving ability**
- **Anterograde amnesia**
- **Hangover: (excess sedation, drowsiness, confusion)**
- **Tolerance**
- **Psychological & physical dependence with continuous use.**



# Adverse Effects

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- **Risk of withdrawal symptoms:**

**Rebound insomnia, anorexia, anxiety, agitation, tremors & convulsion).**

- **Respiratory & cardiovascular depression in large doses only (toxic effects).**

# Flumazenil

- is a selective benzodiazepine receptor antagonist.
- Given by injection.
- It has short plasma half life so repeated dosing is required.
- It is used in benzodiazepines overdose (antidote).
- It can precipitate withdrawal symptoms in benzodiazepines addicts.



# Drug interactions

Drugs	Examples
CNS depressants e.g. <b>alcohol &amp; antihistaminics</b>	↑ <b>effect of benzodiazepines</b> <b>(Additive effect)</b>
Cytochrome P450 inhibitors e.g. <b>cimetidine &amp; erythromycin</b>	↑ <b>t<sub>1/2</sub> of benzodiazepines</b>
CYT P450 inducers <b>phenytoin &amp; rifampicin</b>	↓ <b>t<sub>1/2</sub> of benzodiazepines</b>





# Precautions:

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- **Pregnant women or breast-feeding.**
- **Dose reduction is recommended in**
  - **Liver disease**
  - **Old people.**

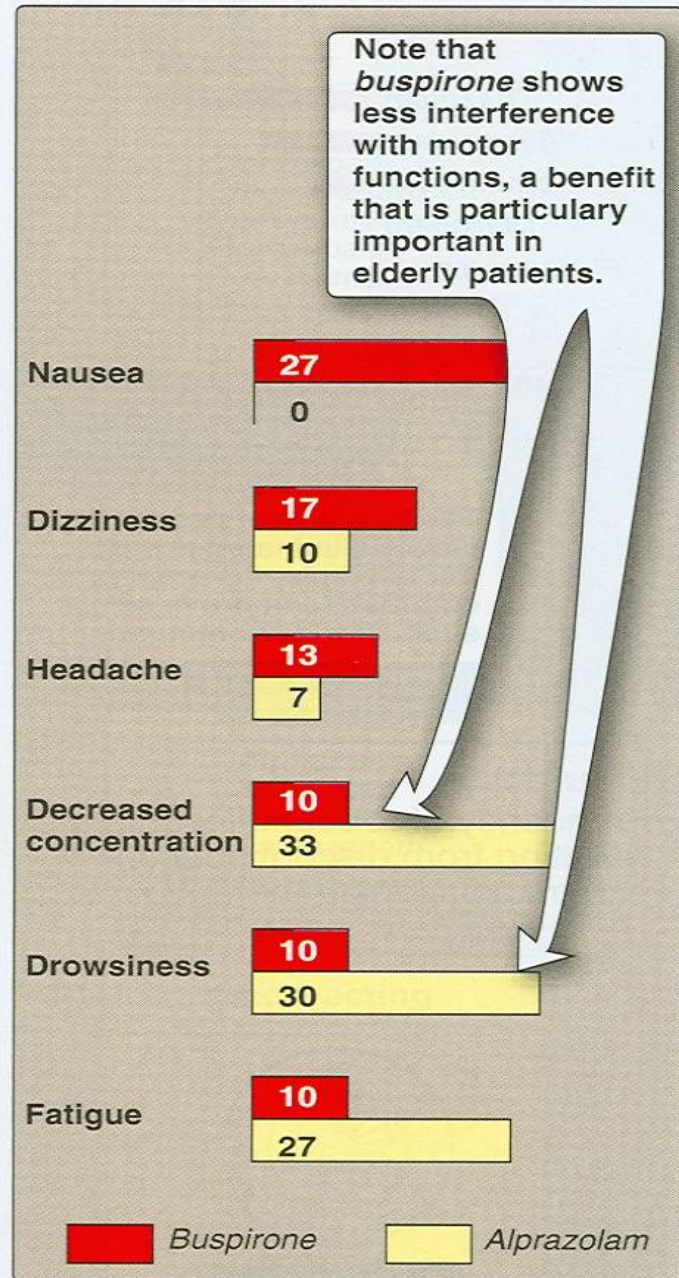
# 5HT<sub>1A</sub> agonists

## Buspirone

- acts as a partial agonist at brain 5HT<sub>1A</sub> receptors
- rapidly absorbed orally.
- Slow onset of action (**delayed effect**)
- T<sub>1/2</sub> : (2 – 4 h).
- Undergoes extensive hepatic metabolism, its clearance is reduced by liver dysfunction.

# Buspirone

- ❑ Only anxiolytic
- ❑ **No** hypnotic effect.
- ❑ **No** muscle relaxant effect.
- ❑ **No** anticonvulsant action.
- ❑ **No** alcohol additive effect.
- ❑ It doesn't impair memory and coordination.
- ❑ Does not affect driving skills.
- ❑ Minimal risk of dependence.
- ❑ No withdrawal symptoms.





# Uses of buspirone

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**As anxiolytic in generalized anxiety disorders.**



# Disadvantages of buspirone

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- ❑ **Slow onset of action (delayed effect)**
- ❑ **GIT upset, dizziness, drowsiness**
- ❑ **Not effective in severe anxiety/panic disorders**
- ❑ **Drug interactions with CYT P450 inducers and inhibitors**

# Drug interactions

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- **CYP450 3A4 Inhibitors (verapamil, diltiazem) → ↑ buspirone level.**
- **CYP450 3A4 Inducers (Rifampin) → ↓ buspirone level.**



# Precautions

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**Should be used with precaution in**

- **Pregnant women or breast-feeding.**
- **People over 65**
- **Dose reduction is recommended in liver disease and old people.**

# Selective serotonin reuptake inhibitors (SSRIs)

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## Fluoxetine

- acts by blocking uptake of 5-HT
- given orally.
- has long half life
- Considered the first line of treatment for most anxiety disorders (panic disorder, OCD, GAD, PTSD, phobia) because they are well tolerated, have low risk for dependency and abuse and low potential for overdose.





## **Side effects of SSRIs**

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- ❑ Delayed onset of action (weeks).**
- ❑ Nausea, diarrhea**
- ❑ Weight gain or loss**
- ❑ Sexual dysfunction**
- ❑ Dry mouth**
- ❑ Sleep disturbance or insomnia**
- ❑ Seizures**



# Tricyclic Antidepressants

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## **Doxepin- imipramine – desipramine**

- act by reducing uptake of 5HT & NA.**
- Used for anxiety especially associated with depression.**
- Effective for panic attacks.**
- Delayed onset of action (weeks).**

# Side effects of tricyclic antidepressants

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□ **Atropine like actions**

**(dry mouth-blurred vision, tachycardia, urinary retention).**

□  **$\alpha$ -blocking activity (Postural hypotension).**

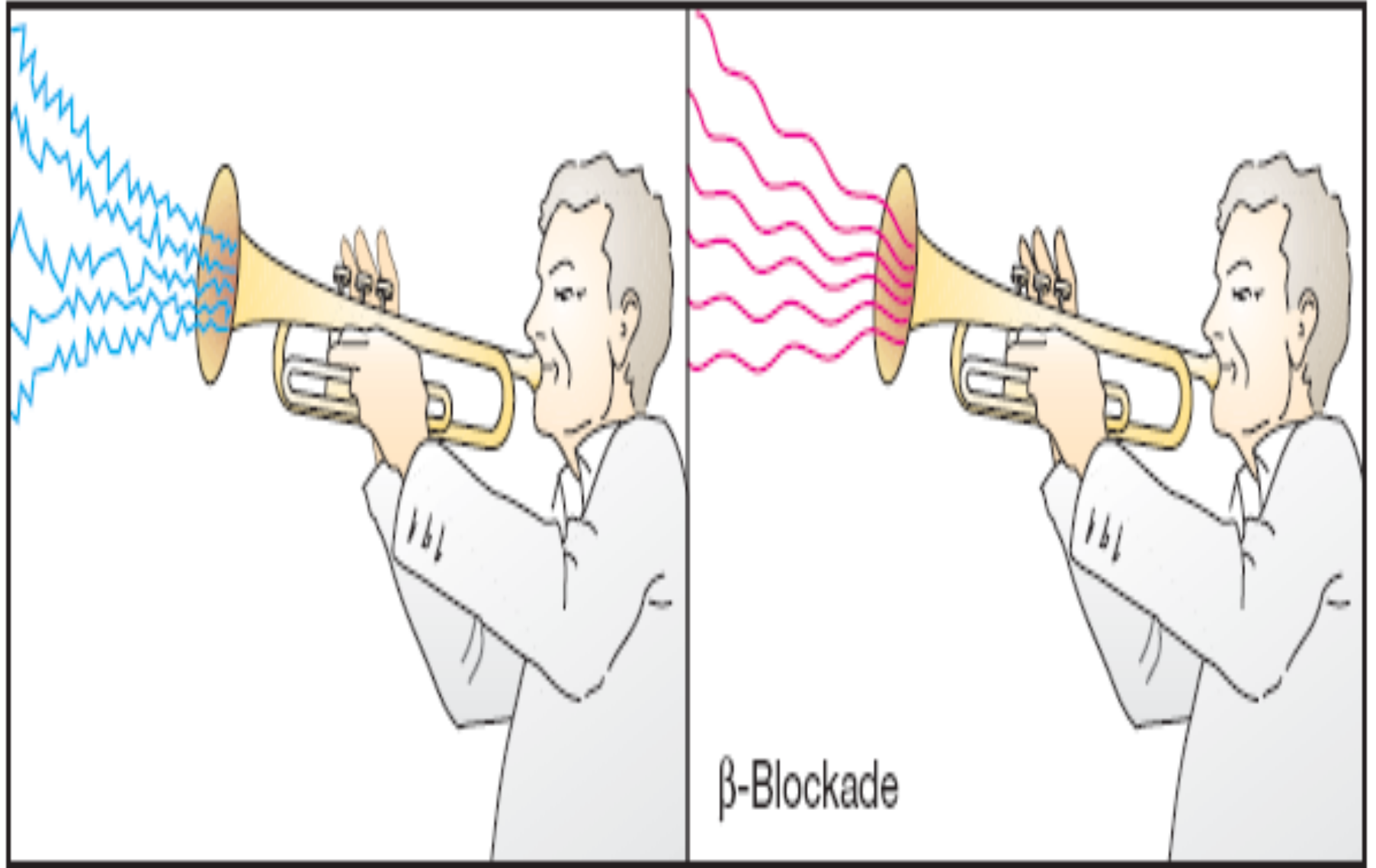
□ **Sexual dysfunction.**

□ **Weight gain.**

# Beta Blockers

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- ❑ **Drugs as Propranolol – atenolol**
- ❑ **act by blocking peripheral sympathetic system.**
- ❑ **Reduce somatic symptoms of anxiety.**
- ❑ **Decrease BP & slow heart rate.**
- ❑ **Used in performance or social anxiety.**
- ❑ **are less effective for other forms of anxiety**
- ❑ **should be used with caution in asthma, cardiac failure, peripheral vascular disorders**



C. "Anxiolytic" effect of  $\beta$ -sympatholytics

# Conclusion of anxiolytics

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

# Conclusion of anxiolytics

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