Drugs used in anxiety and panic disorders

Prof. Hanan Hagar

Pharmacology Unit

College of Medicine

Objectives

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

- **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

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

What is anxiety ?

Physical and emotional distress which interferes with normal life.

Symptoms of anxiety

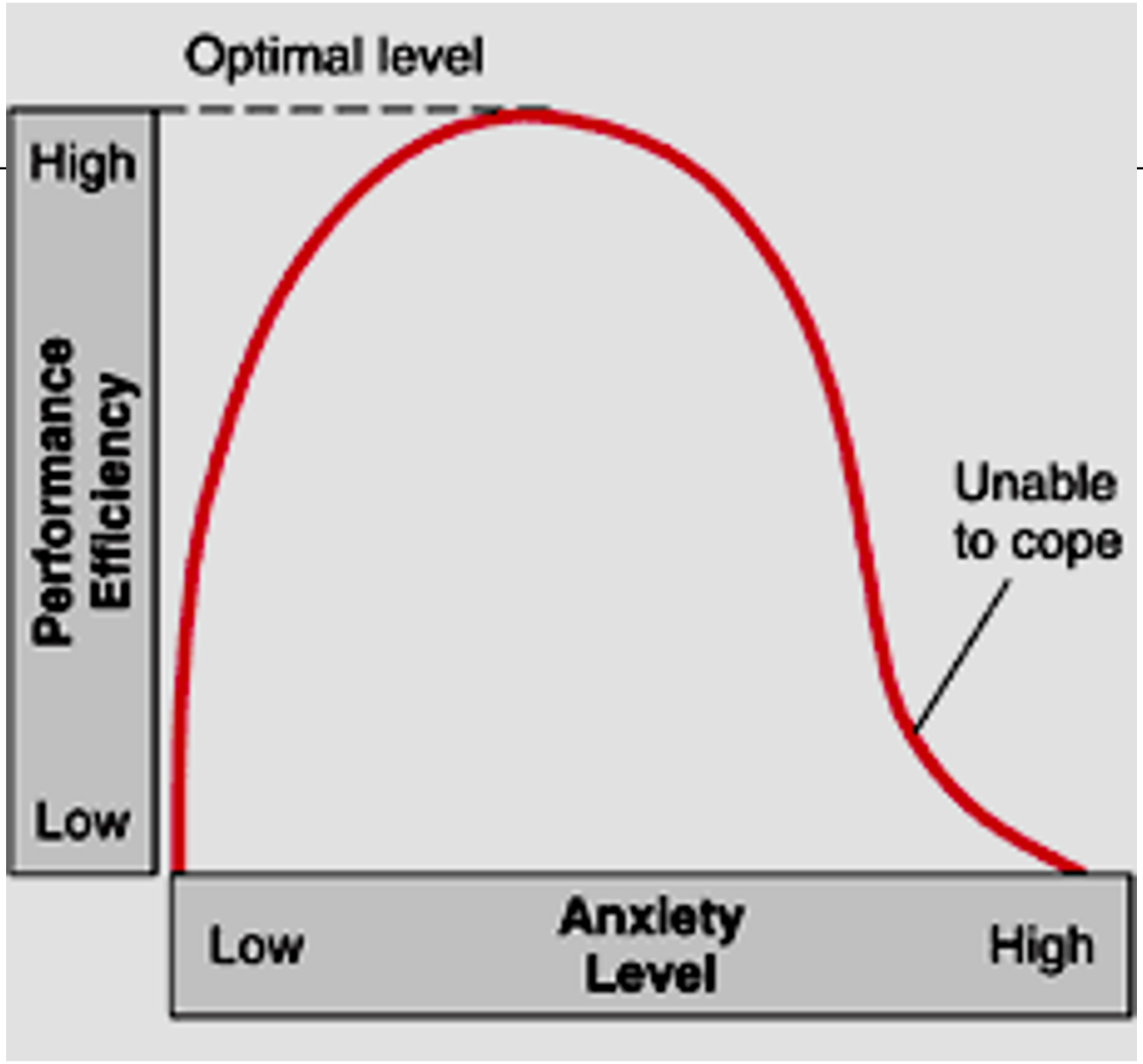
- **Psychological or emotional symptoms.**
- **Physical or somatic symptoms.**

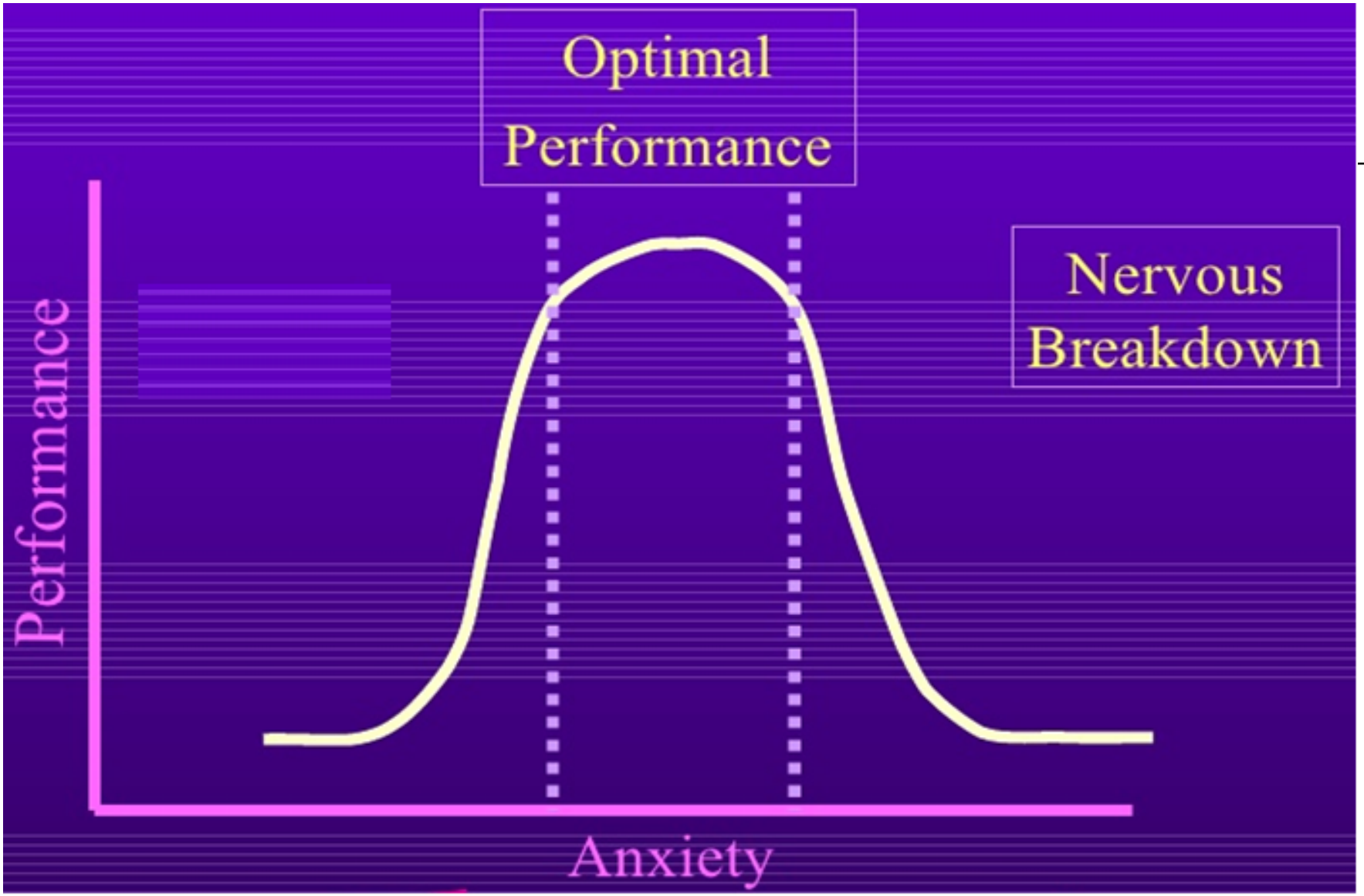
Emotional symptoms of anxiety

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

Physical Symptoms of Anxiety

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


Optimal level
High
Performance
Efficiency
Low
Unable
to cope
Low
Anxiety
Level
High


Optimal Performance
Nervous Breakdown
Performance
Anxiety

Types of anxiety

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)

- **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 behaviours that seem impossible to stop as

Washing their hands

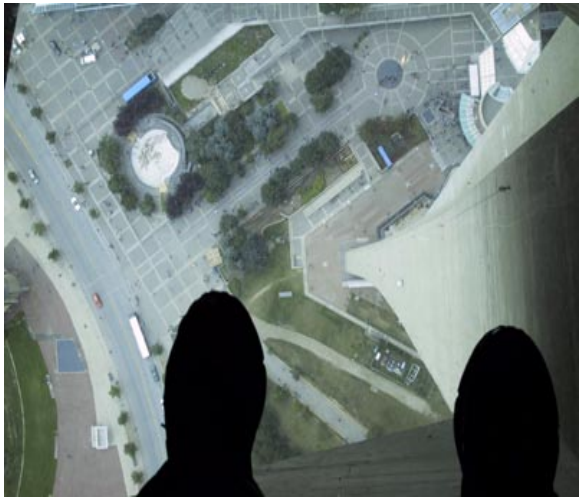
Post-traumatic stress disorder (PTSD)

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



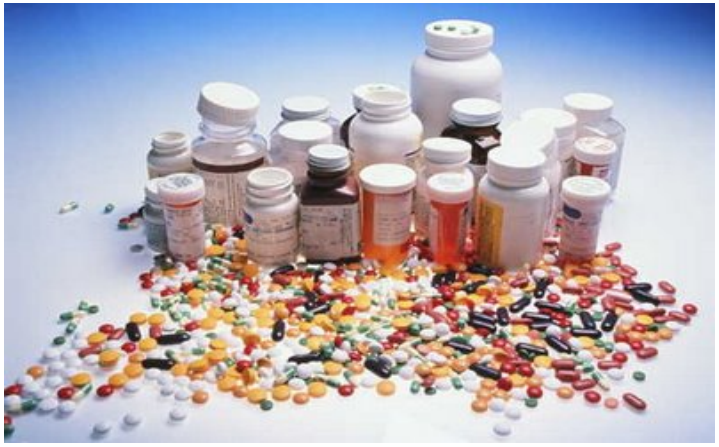
Panic disorder

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

Treatment of anxiety

- **Psychotherapy**

- **Anxiolytics**



Classification of anxiolytic drugs

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

Benzodiazepines

Nomenclature of Benzodiazepines

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"

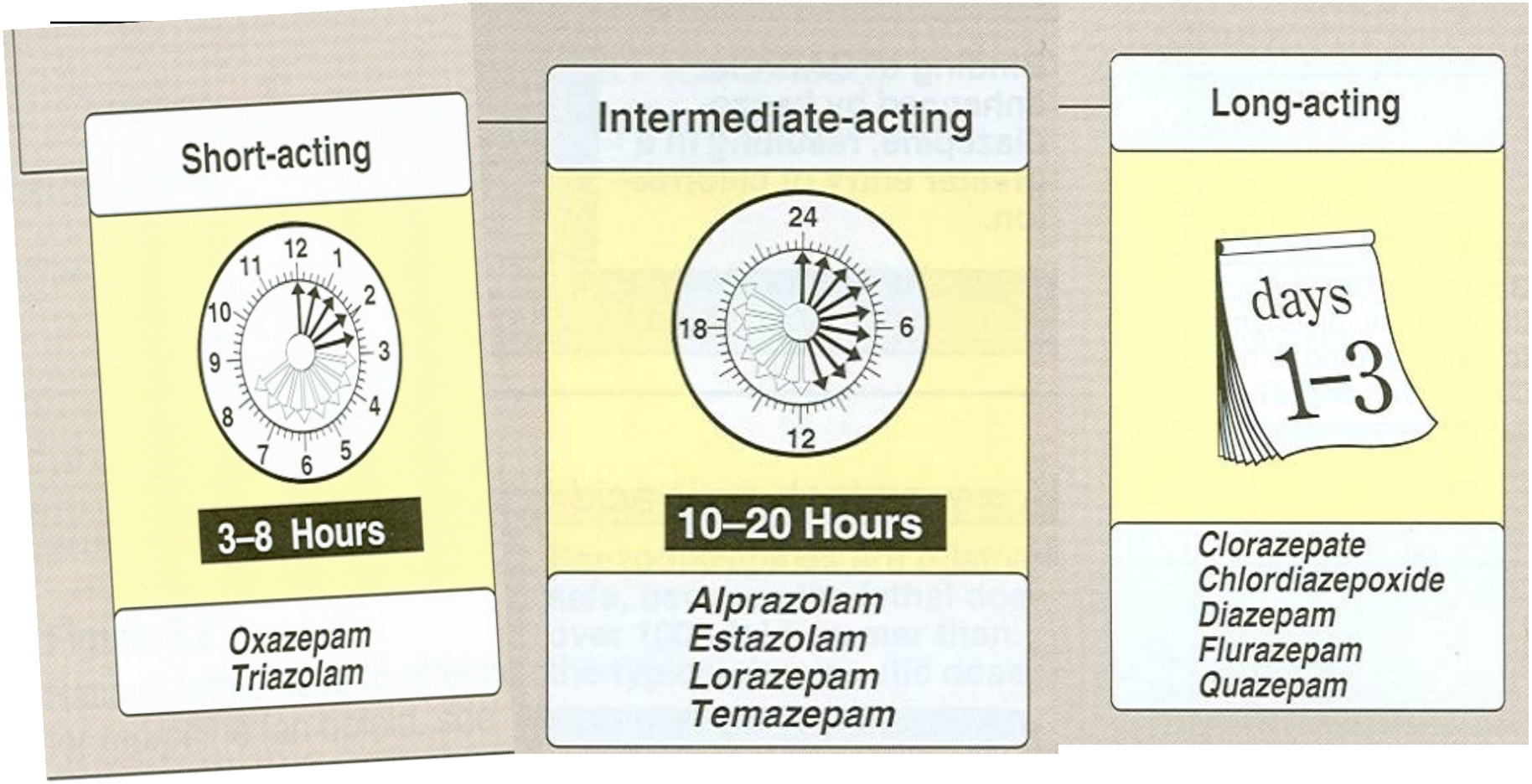
Alprazolam - Lorazepam

Estazolam - Temazepam

Long acting: (24-72 hours)

Chlordiazepoxide -Diazepam - Flurazepam

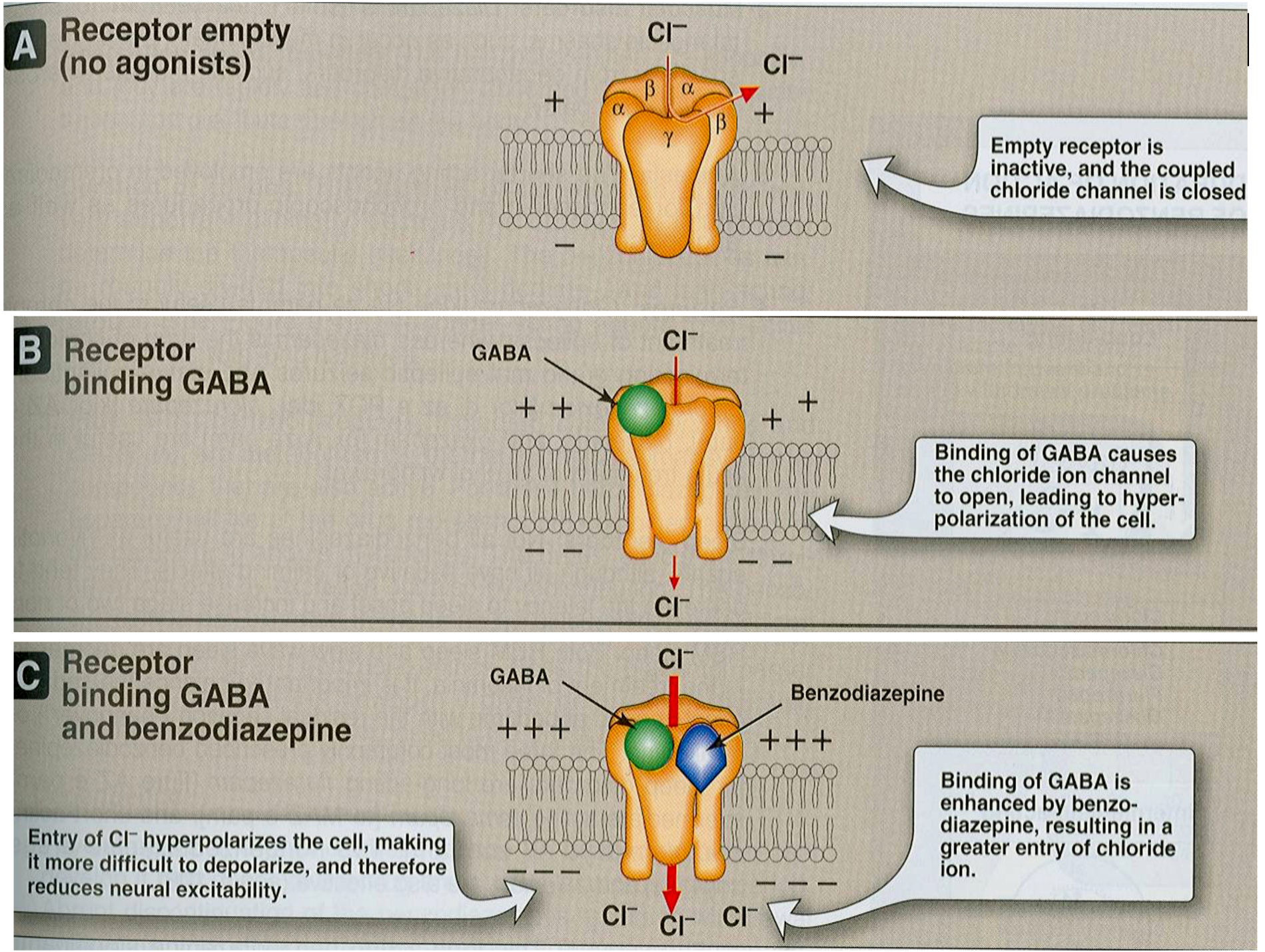
Classifications of Benzodiazepines



Mechanism of Action

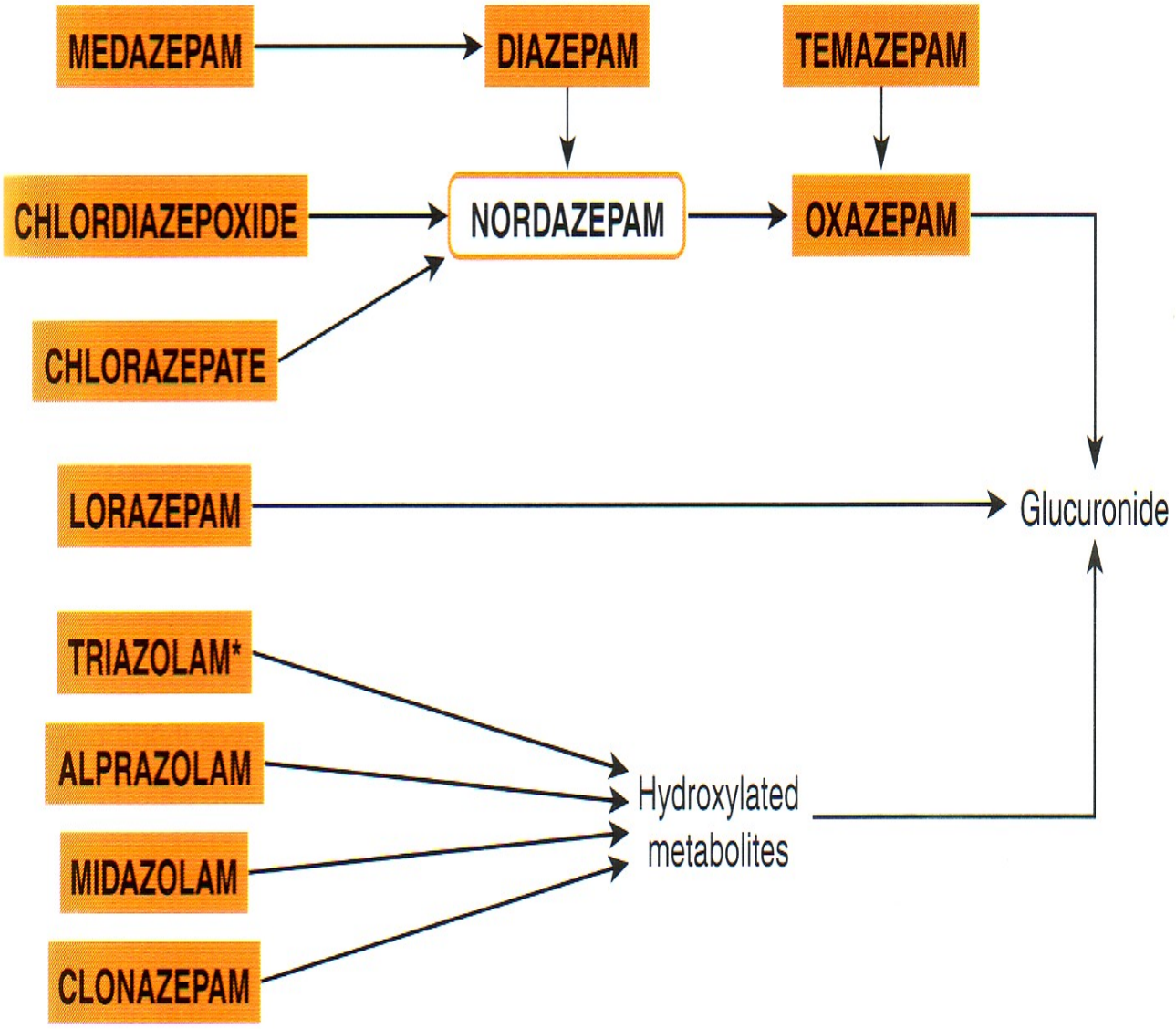
Benzodiazepines act by binding to BZ receptors in the brain → enhance GABA action on the brain → chloride channels opening → ↑ chloride influx to the cell → hyper- polarization → more difficult to depolarize → reduction of neural excitability.

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


A
Receptor empty (no agonists)
Cl⁻
Cl⁻
β
α
α
β
γ
Empty receptor is inactive, and the coupled chloride channel is closed
B
Receptor binding GABA
GABA
Cl⁻
Binding of GABA causes the chloride ion channel to open, leading to hyper-polarization of the cell.
Cl⁻
C
Receptor binding GABA and benzodiazepine
GABA
Cl⁻
Benzodiazepine
Entry of Cl⁻ hyperpolarizes the cell, making it more difficult to depolarize, and therefore reduces neural excitability.
Binding of GABA is enhanced by benzo-diazepine, resulting in a greater entry of chloride ion.
Cl⁻
Cl⁻
Cl⁻

Pharmacokinetics

- 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.



*Triazolam withdrawn in UK

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.

Pharmacological actions

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

Pharmacological actions

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

Therapeutic uses of benzodiazepines

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

Treatment of epilepsy

Diazepam – Lorazepam

In anesthesia

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

Alcohol withdrawal syndrome (diazepam)

Adverse Effects

- 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

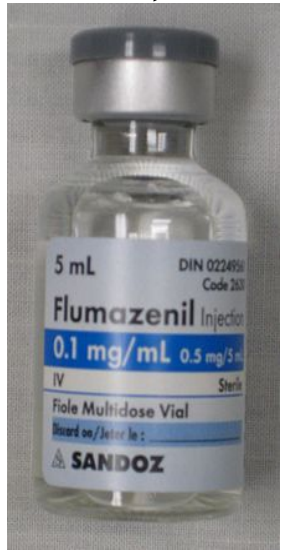
- **Risk of withdrawal symptoms:**

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. alcohol & antihistaminics	↑ effect of benzodiazepines (Additive effect)
Cytochrome P450 inhibitors e.g. cimetidine & erythromycin	↑ $t_{½}$ of benzodiazepines
CYT P450 inducers phenytoin & rifampicin	↓ $t_{1/2}$ of benzodiazepines

Precautions:

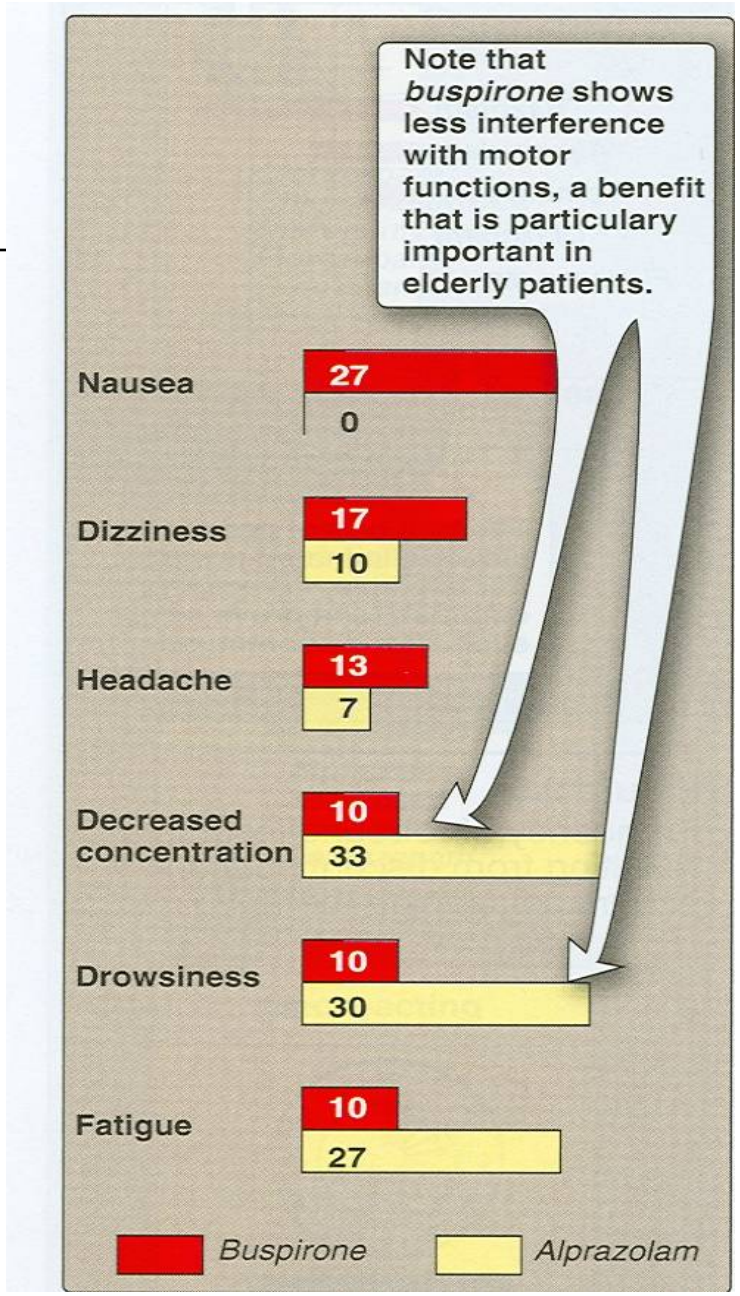
- Pregnant women or breast-feeding.
- Dose reduction is recommended in
  - Liver disease
  - Old people.

$5HT_{1A}$ agonists
Buspirone

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

As anxiolytic in generalized anxiety disorders.

Disadvantages of buspirone

- 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

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

- **CYP450 3A4 Inducers (Rifampin) → ↓ buspirone level.**

Precautions

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)

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

- **Delayed onset of action (weeks). Increase in anxiety symptoms, insomnia or headache in the first days or weeks of treatment**
  may↓ compliance
- **Nausea, diarrhea**
- **Weight gain**
- **Sexual dysfunction**
- **Dry mouth**
- **Sleep disturbance or insomnia**
- **Seizures**

Tricyclic Antidepressants

Doxepin- imipramine – desipramine

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

Side effects of tricyclic antidepressants

- **Atropine like actions (muscarinic blocking actions)**

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

- **α-blocking activity (Postural hypotension).**
- **Sexual dysfunction.**
- **Weight gain.**

Monoamine oxidase inhibitors (MAOIs)

Phenelzine

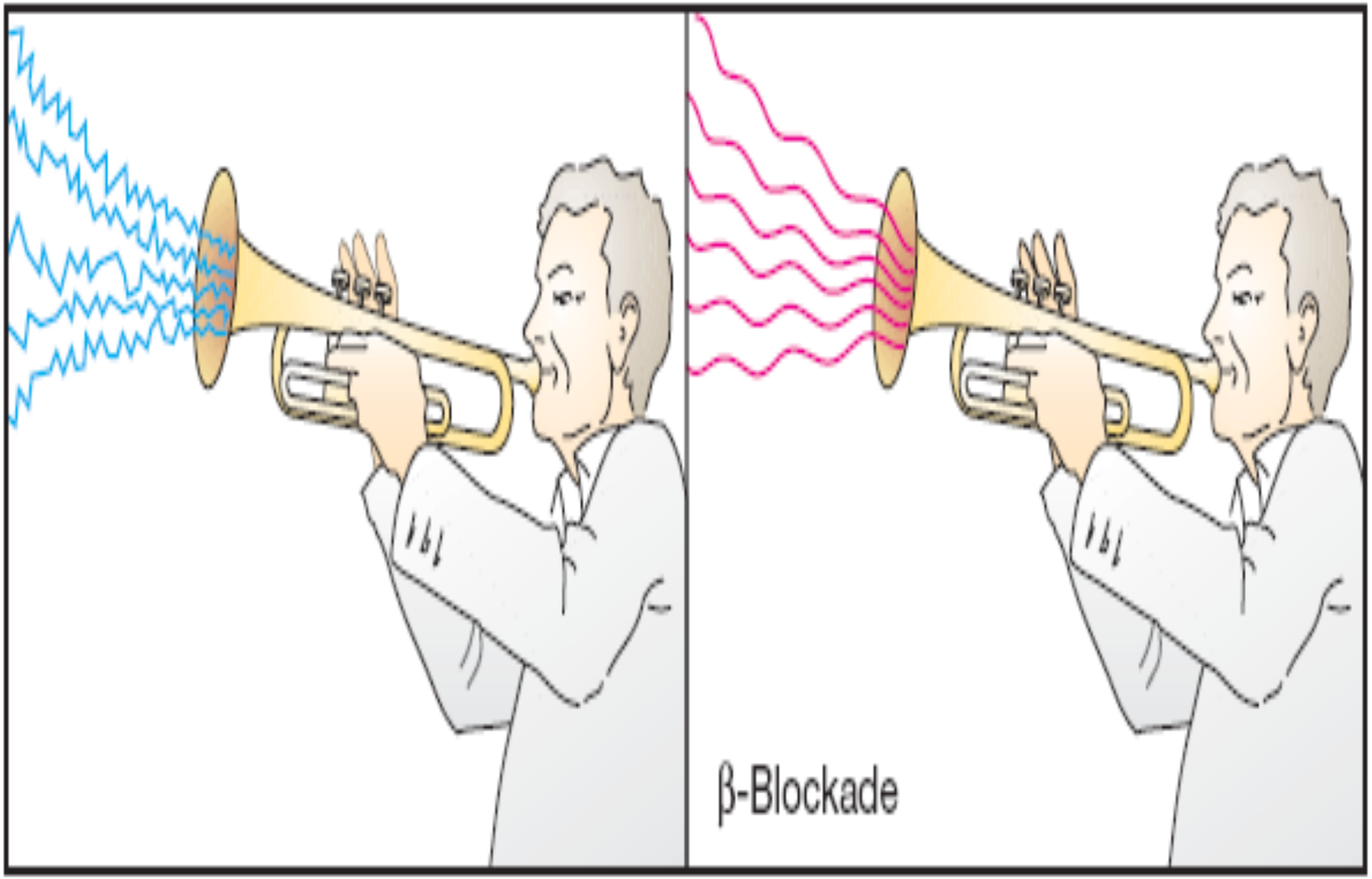
- act by blocking the action of MAO enzymes.
- Used for panic attacks and phobia.
- Require dietary restriction
- Avoid wine, beer, fermented foods as old cheese that contain tyramine (hypertensive crisis).

Side effects: Dry mouth, constipation, diarrhea, restlessness, dizziness.

Reserved for patients who have not responded to, or proved intolerant of, other treatments.

Beta Blockers

- **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 β-sympatholytics

Pregabalin

- Modulates calcium channels in CNS, ↓Ca++ influx & modulates release of neurotransmitters.
- Onset occurs in the first days of treatment
- Excreted unchanged in the urine.
- Effective in treatment & prevention of relapse of GAD (1st line as SSRIS).
- Used in epilepsy & neuropathic pain
- **ADRs:** dizziness and somnolence
- Withdrawal symptoms may occur but less severe than benzodiazepines

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)	Sexual dysfunction atropine like actions
Tricyclic antidepressants (doxepin, imipramine)	weight gain, sexual dysfunction, atropine like actions, arrythmia
5HT1A agonists (Buspirone)	Minimal adverse effects
Beta blockers (propranolol, atenolol)	Hypotension