King Saud University

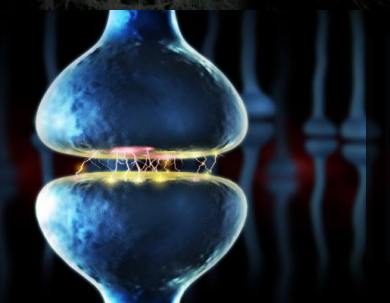
College of Medicine

2nd Year, 1st Block

PHARMACOLOGY 433

MED 433 Teams

L5: ANTIANXIETY

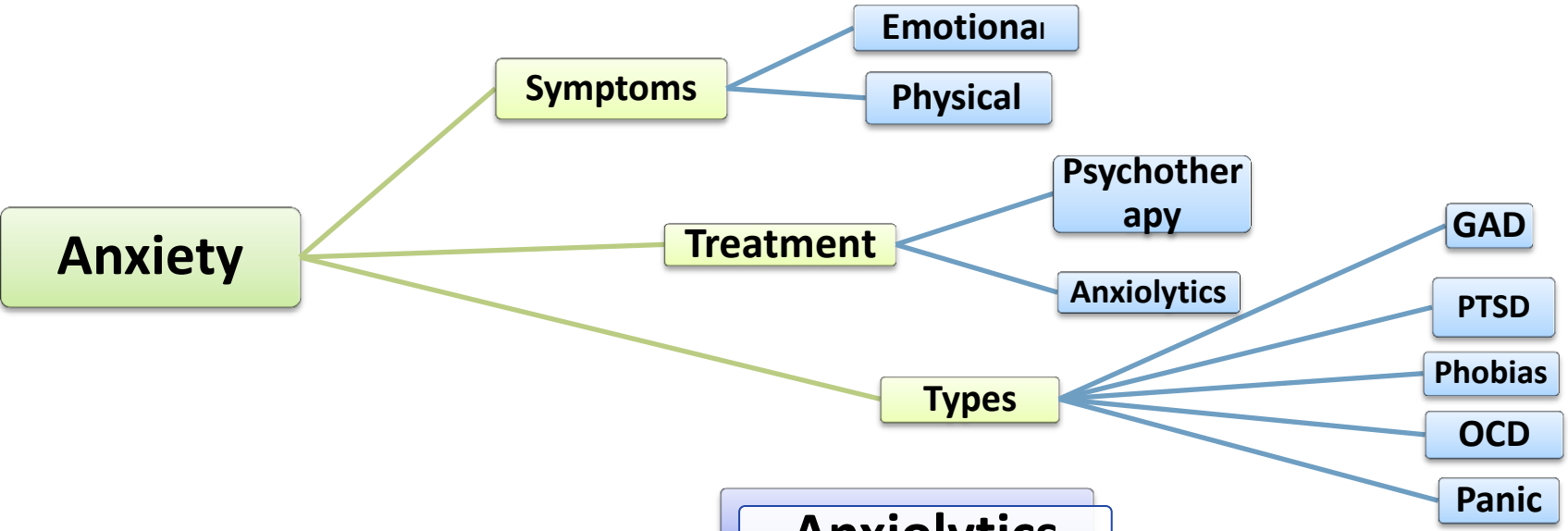


CNS Block

Objectives

- ✓ **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.**

Mind Map



Anxiolytics

- **BDZ**
  - binding to BZ receptors in the brain
  - enhance GABA action on brain
  - reduction of neural excitability
- **5HT reuptake inhibitors**
  - blocking uptake of 5-HT
- **$5HT_{1A}$ agonists**
  - agonist at brain $5HT_{1A}$ receptors
- **Antidepressants**
  - reducing uptake of 5HT & NA
- **Beta-blocker**
  - blocking peripheral sympathetic system
- **MAO inhibitors**
  - blocking the action of MAO enzymes

What is anxiety?

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

Symptoms

Emotional symptoms of anxiety

(Psychological)

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

Physical symptoms of Anxiety

(Similar to over stimulation of sympathetic nerves system)

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

Types of anxiety

Types	Definition
Generalized anxiety disorder (GAD)	Patients are usually and constantly worried about health, money, work with no apparent reasons.
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.
Obsessive-compulsive disorder (OCD) (الوسواس القهري)	An anxiety disorder in which people cannot prevent themselves from unwanted thoughts or behaviours 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.
Phobias	An intense, uncontrolled fear of a specific situation such as open spaces & heights

Benzodiazepines

Mechanism of Action

Benzodiazepines act by:

binding to BZ receptors in the brain → enhance GABA action in the brain

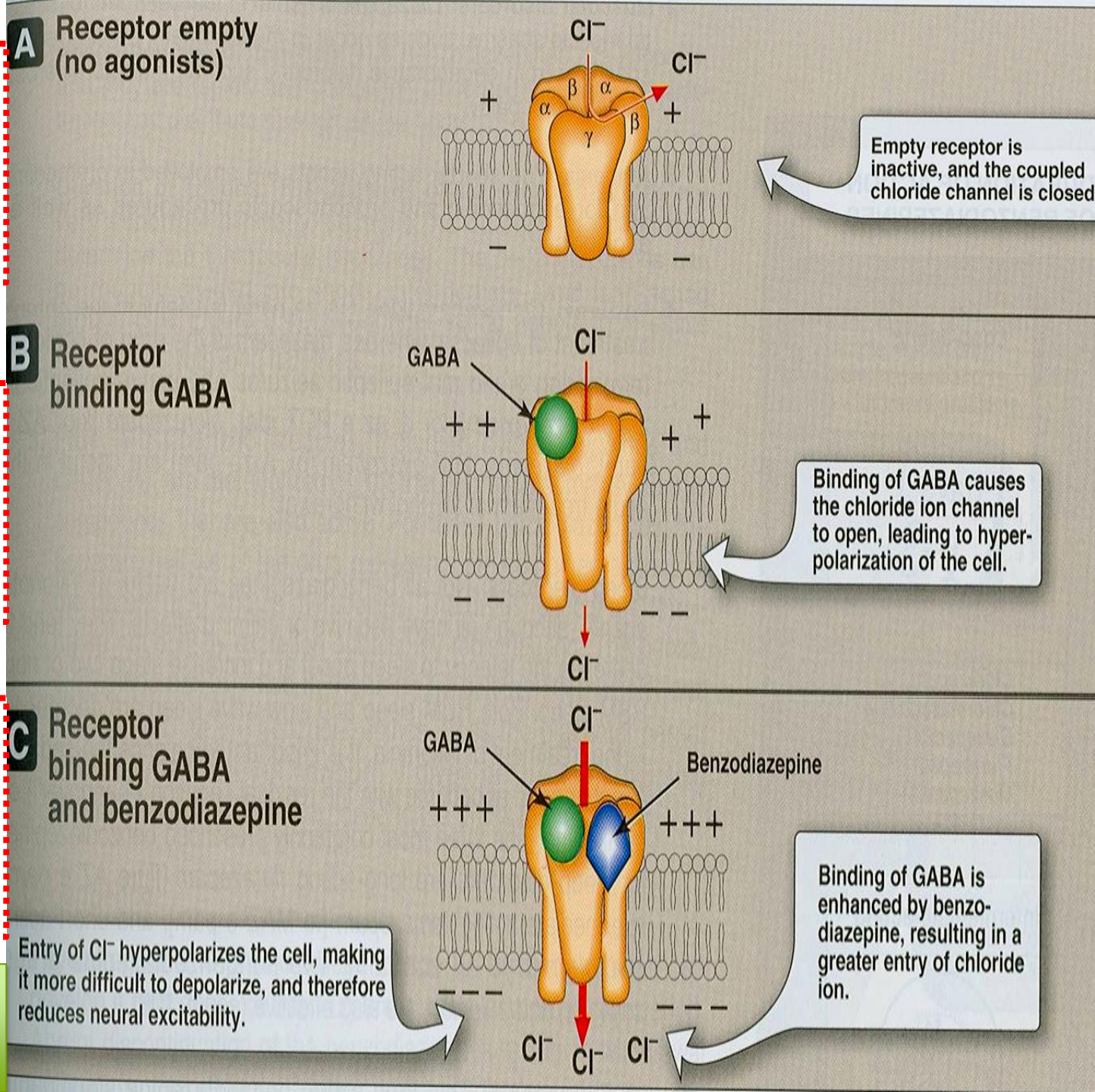
Benzodiazepines :CNS depressant by induce inhibitory neurotransmitter GABA

Closed Cl- channel. When there's no GABA

GABA opens Cl- channel

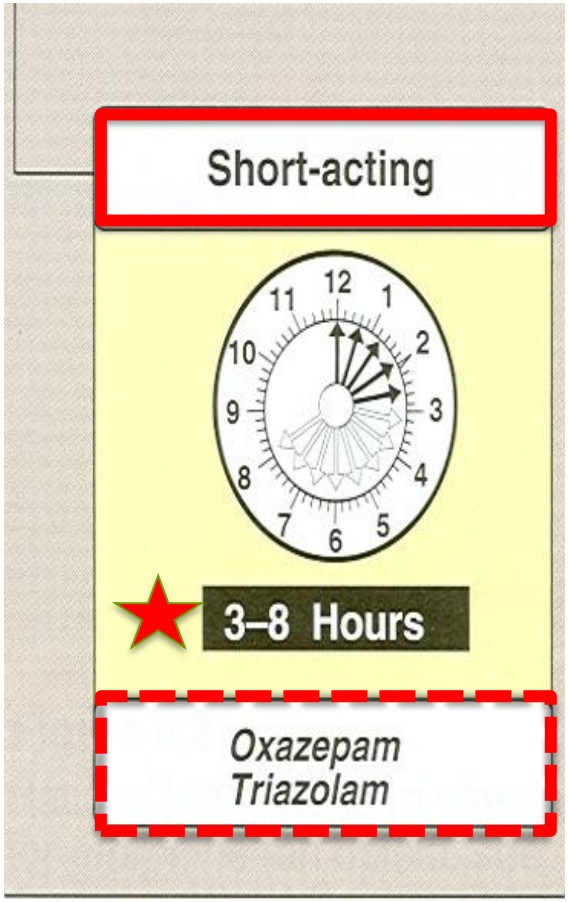
Benzodiazepine binding the enhance of GABA resulting in greater cl influx

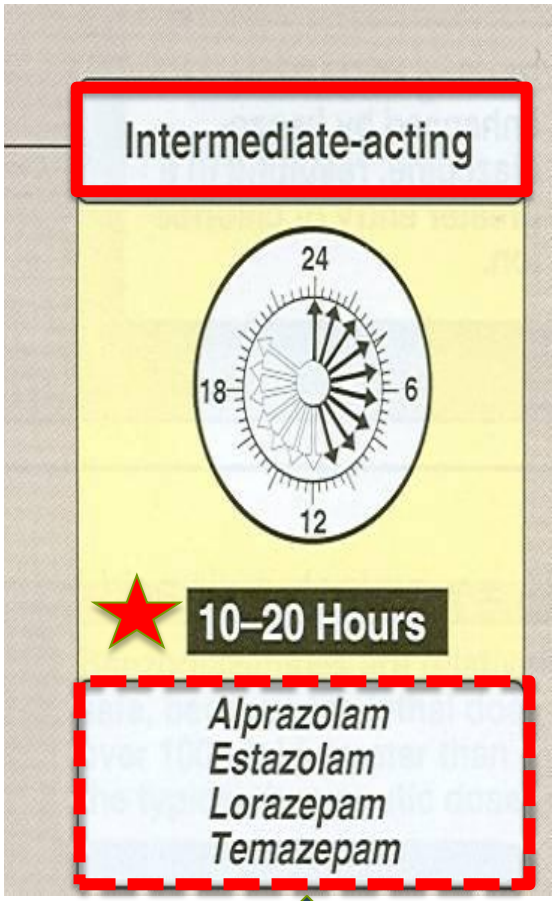
↑ chloride influx to the cell → hyper-polarization



Classifications of Benzodiazepines

(according to duration of action)





"ALET"

Benzodiazepines

Pharmacological actions:

- CNS depressant
- Anxiolytic action

•Sedation and Hypnotic action

•Depression of cognitive and psychomotor function

•have skeletal muscle relaxing effect (diazepam)

•Anterograde amnesia

•Some have anticonvulsant effect e.g. clonazepam, diazepam, lorazepam.

•Therapeutic doses have minimal depressant effects on

- ✓ cardiovascular system
- ✓ respiratory system

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.

NORDAZEPAM has along half life

Because it converted to another active form (active metabolite)

LORAZEPAN doesn't have active metabolite so it has short duration of action.

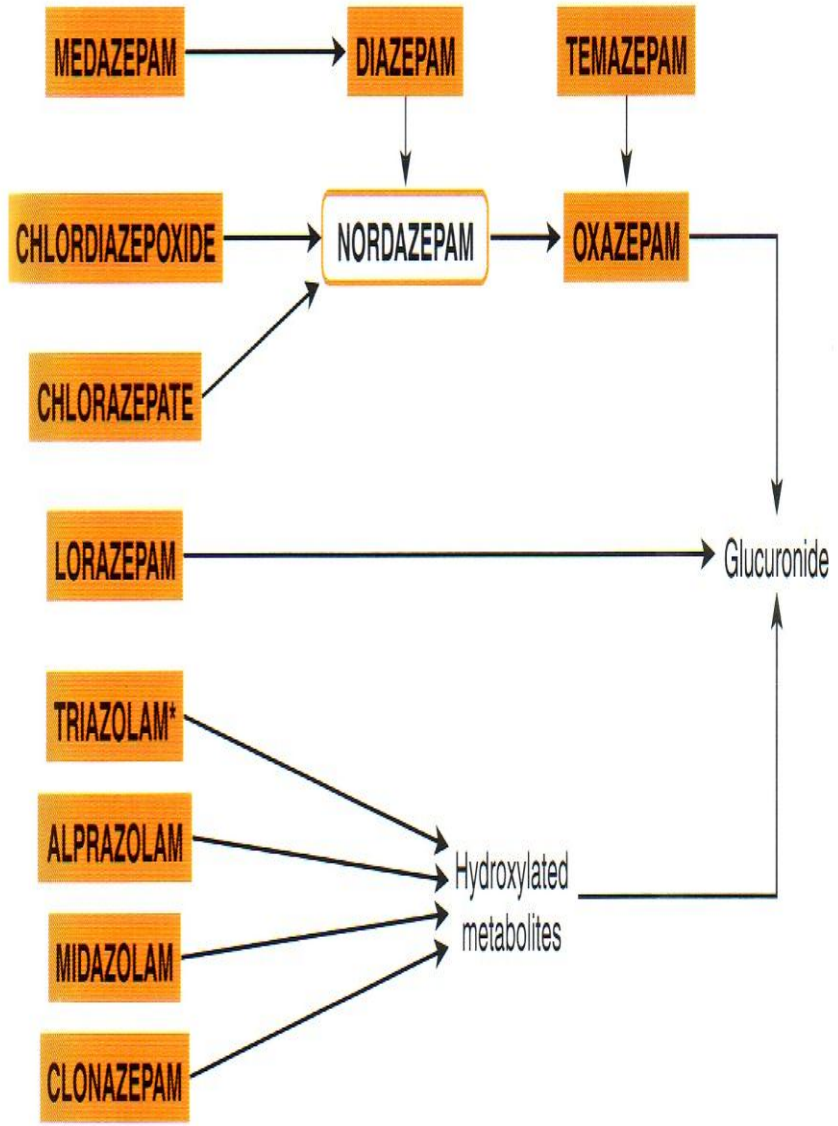
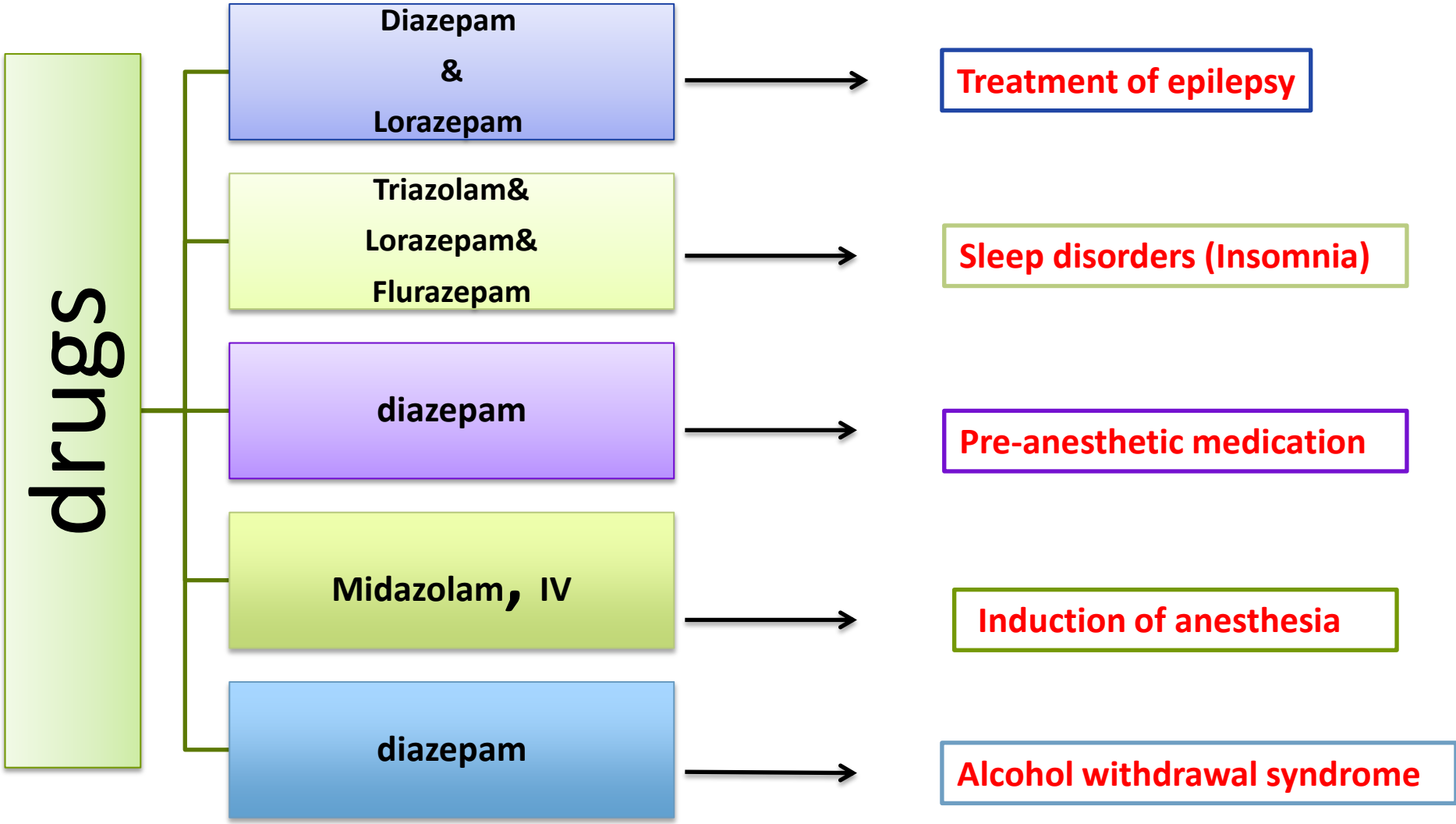


Fig. 36.4 The metabolism of benzodiazepines. The N-demethylated metabolite nordazepam is formed from a number of benzodiazepines and is important because it is biologically active and has a very long half-life. Compounds with pharmacological activity are shown in blue. Drugs available for clinical use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

Therapeutic uses



***Puls* it use for all type of Anxiety disorders:** short term relief of severe anxiety +General anxiety disorder + Obsessive compulsive disorder + Panic disorder with depression

Alprazolam **(antidepressant effect)**

Benzodiazepines

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

CNS depressant "increase the effect of BDZ"

CYT P450 inhibitors "increase the half life of BDZ"

CYT P450 inducers "decrease the half life of BDZ"

Benzodiazepines

Side Effects:

- Cognitive impairment.
- Ataxia (motor in coordination)
- Impairment of driving ability
- Anterograde amnesia
- Hangover: (excess sedation, drowsiness, confusion)
- Tolerance
- Psychological & physical dependence with continuous use.
- Risk of withdrawal symptoms:
- Rebound insomnia, anorexia, anxiety, agitation, tremors & convulsion).
- Respiratory & cardiovascular depression in large doses only (toxic effects).

Precautions:

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

Serotonin 1A agonists & Selective serotonin reuptake inhibitors (SSRIs)

$5HT_{1A}$ agonists (Serotonin $_{1A}$ agonists)

Buspirone

Act on :	It has partial effect on the serotonin recepters
Absorption :	rapidly absorbed orally
Action & half life :	Low onset of action (delayed effect) T½ : (2 – 4 h)

Uses :

it use only for mild generalized anxiety disorders (only anxiolytic) so it has :

1. No hypnotic effect
2. No muscle relaxant effect
3. No anticonvulsant action
4. No alcohol additive effect

5.it doesn't impair memory and coordination

6. Minimal risk of dependence and because of that it has no withdrawal symptoms

Side effects:

1. GIT upset, dizziness, drowsiness
2. Because it is effective only on mild GAD we can't use it in sever anxiety/panic disorders

3 .Drug interactions with CYT P450 inducers and inhibitors (because it metabolized in the liver)

Selective serotonin reuptake inhibitors (SSRIs)

Fluoxetine

Act on :	acts by blocking uptake of 5-HT
Administration :	Given orally
Half life :	Long half life

Uses :

It is the most common drug (first line of treatment) which use to treat (panic disorder, OCD, GAD, PTSD, phobia) Because of :

1. It is well tolerated
2. It have low risk for dependency and abuse and low potential for overdose

Side effects :

1. Nausea, diarrhea
2. Weight gain بعضهم يسبب خساره للوزن لكن الاغلب يسببون زياده بالوزن
3. Sexual dysfunction
4. Sleep disturbance or insomnia

5.Seizures

6.Atropin like actions

Slow onset of action (delayed effect , weeks)

tricyclic antidepressants & Monoamine oxidase inhibitors & Beta Blockers

tricyclic antidepressants

Doxepin- imipramine		Uses :	Side effects :
Act on :	The serotonin (5HT) & noradrenalin (NA) receptors by reducing their uptake	1. anxiety especially associated with depression. 2. panic attacks	1. Atropine like actions • dry mouth • blurred vision • Tachycardia • urinary retention 2. α-blocking activity (Postural hypotension) اللي يصير لما نوقف 3. Sexual dysfunction 4. Weight gain
Action :	Delayed onset of action (weeks)		

Monoamine oxidase inhibitors (MAOIs)

Phenelzine		Uses :	Side effects :
Act on :	Act on MAO enzymes by blocking its action (which increase the level of 5HT and NA)	panic attacks and phobia	1. Dry mouth 2. Constipation 3. Diarrhea 4. Restlessness 5. Dizziness
Requirement & avoidance	•It requires dietary restriction •Avoid wine, beer, fermented foods as old cheese that contain tyramine*		

Beta Blockers

Propranolol – atenolol		Uses :	Side effects :
Act on :	PNS by blocking it	Used in performance or social anxiety	Hypotension
Effects :	1. Reduce somatic symptoms of anxiety . 2. Decrease BP & slow heart rate		
Caution :	should be used with caution in : •Asthma (because it cause vasoconstriction) •cardiac failure •peripheral vascular disorders (because it will cause vasoconstriction)		

*tyramine is an indirect sympathomimitcs which inrease releasing of NA = cause hypertensive crisis

❑tricyclic antidepressants are nonselective antidepressants
❑SSRIs are selective antidepressants

Summary

Drug	Benzodizepam Triazolam - Alprazolam – Lorazepam - Diazepam	SSRI Fluoxetine	TCA Doxepin - Imipramine	5HT1a agonist Buspirone	MAOI Phenelzine	B-blockers Propranolol-Atenolol
Mechanism	Enhance GABA > Hyper-polarization >Dec. neuronal excitability.	Block the reuptake of 5HT.	Block the reuptake of 5HT & NA.	Partial agonist at brain 5HT1a receptor	Block the action of MAO enzyme > Inc. 5HT & NA levels.	Blocking Beta receptors in peripheral sympathetic system
Action	CNS depressant Anxiolytic Sedative - Hypnotic Sk. Ms. Relaxant Anticonvulsant Anterograde Amnesia	Anti-depressant No dependence or withdrawal symptoms	Anti-depressant	Anxiolytic	-	Control somatic activity Dec. BP & HR
Uses	Generalized anxiety Obsessive compulsive anxiety Panic Disorder + Phobia Epilepsy	1st line: Most types of Anxiety	Anxiety with depression Panic disorder	Mild anxiety (GAD)	Panic disorder Phobia	Social anxiety performance
Side Effects	• Respiratory & CVS depression (Toxic dose) Cognitive & Psychomotor impairment • Ataxia & confusion • Tolerance & Dependence Withdrawal syndrome	• Sexual dysfunction • Weight gain • Insomnia • Seizure Xerostomia-nausea & diarrhea	• Atropine-like action • Postural hypotension • Sexual dysfunction • Weight gain	• Dizziness • Drowsiness • GIT upsets	Xerostomia Constipation Diarrhea Restlessness dizziness	Hypotension

Cont' Summary

Drug	Benzodizepam Triazolam - Alprazolam – Lorazepam - Diazepam	SSRI Fluoxetine	TCA Doxepin - Imipramine	5HT1a agonist Buspirone	MAOI Phenelzine	B-blockers Propranolol-Atenolol
Drug interaction	1. With CNS depressants > Inc. the efficacy 2. With CP450 inhibitors > Inc. T1/2 3. With CP450 inducers > Dec. T1/2	-	-	1. With CP450 inducers & inhibitors	-	-
Precaution	• Pregnant women or breast feeding • Reduce the dosage > Liver disease Elderly	-	-	-	Require restricted diet	-

Quiz yourself

1-first line of treatment for most anxiety disorders disorder?

A)Fluoxetine

B) propranolol

C) doxepin

2-Patient has a fear of high places which drug is most appropriate ?

A) Propranolol

B) Phenelzine

C) Buspirone

3-Drug that cause a sexual dysfunction ?

A)Buspirone

B)Atenolol

C)Doxepin

4-Anti-axity drug that induces anesthesia ?

A)Lorazepam

B)Midazolam

C)Erythromycin

5-Drug with minimal risk of dependence ?

A)Buspirone

B)Propranolol

C)Fluoxetine

6-Drug used in social anxiety ?

A)propranolol

B)doxepin

C)Benzodiazepines

7-A patient with sleep disorder which anti-axity drug is the most a propriate ?

A)Triazolam

B)Buspirone

C)Imipramine

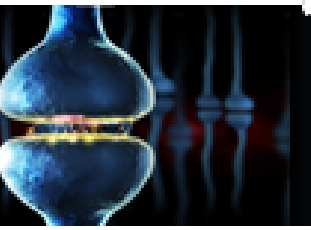
8-Anti-axity drug that cause dependence ?

A)Benzodiazepine

B)imipramine

C)Fluoxetine

Answers: **1-A 2-B 3-C 4-B 5-A 6-A 7-A 8-A**



CNS Block

PHARMACOLOGY 433

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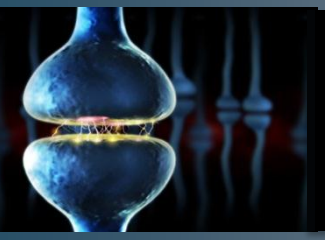
We hope that we made this lecture easier for you

Good Luck !



CNS Block