#7

Drugs used in anxiety and panic disorders

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.
- Discuss the different characteristics of antianxiety drugs.

Color index:

- Drugs names
- Doctors notes
- Important
- Extra

Introduction

Anxiety

Physical and emotional distress which interferes with normal life.

Emotional or psychological symptom

- Feeling tense
- Trouble concentrating
- Irrational (without reason) and excessive fear and worry
- Irritability
- Restlessness

Physical or somatic symptoms

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

Types of anxiety

Generalized anxiety disorder (GAD)

Patients are usually and constantly worried about **every thing**, health, money, work with **no** apparent reason.

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.

Phobias

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.

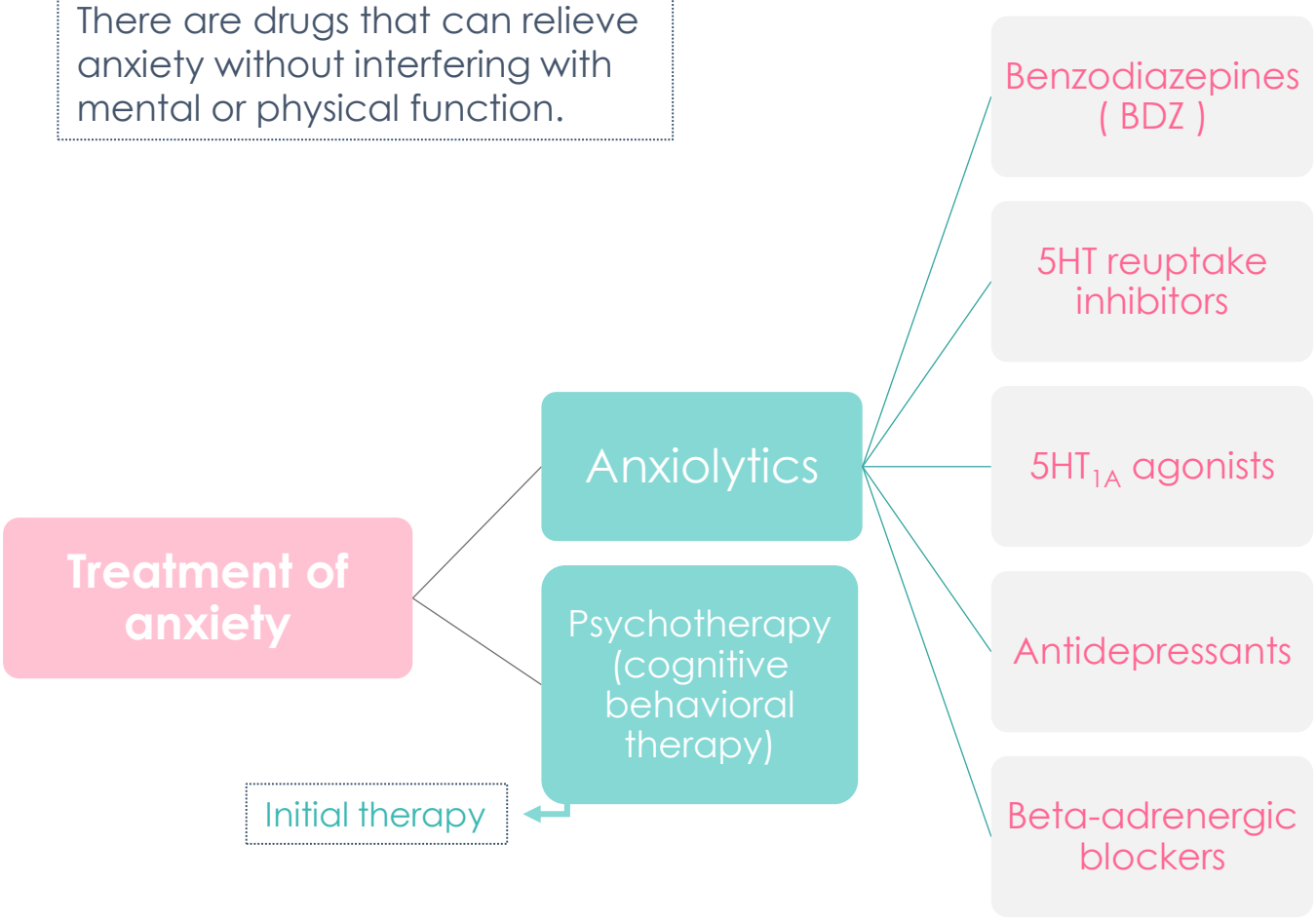
Obsessive-compulsive disorder (OCD)

An anxiety disorder in which people cannot prevent themselves from unwanted thoughts or behaviors that seem impossible to stop e.g. **washing their hands**

Overview of anxiety treatment

4:05 min

There are drugs that can relieve anxiety without interfering with mental or physical function.



Don't forget to revise this summary after you finish studying this lecture ☺

CLASSES OF ANXIOLYTICS	USES	Adverse effects
Benzodiazepines	Generalized anxiety disorders, OCD, phobia, panic attack.	Ataxia, confusion, dependence, tolerance, withdrawal symptoms.
SSRIs (**Fluoxetine**)	Generalized anxiety disorders, Obsessive-compulsive disorder, phobia, panic attack.	Sexual dysfunction, atropine like actions.
Tricyclic antidepressants (**doxepin, imipramine**)	Anxiety with depression panic attacks.	Weight gain, sexual dysfunction, atropine like actions, arrythmia.
5HT1A agonists (**Buspirone**)	Mild anxiety Not effective in panic attack.	Minimal adverse effects.
Beta blockers (**propranolol, atenolol**)	Phobia (social Phobia).	Hypotension

Benzodiazepines

suffix "zolam" or "zepam"

"Classifications according to duration of action"

Short acting (3-8hrs) **TO**
- *Triazolam*
- *Oxazepam*

Intermediate (10-20hrs) "**LATE**"
- ***L**orazepam*
- ***A**lprazolam*
- ***T**emazepam*
- ***E**stazolam*

Long acting (24-72hrs)
- *Diazepam*
- *Chlordiazepoxide*
- *Flurazepam*
- *Clorazepate*
- *Quazepam*

Benzodiazepines

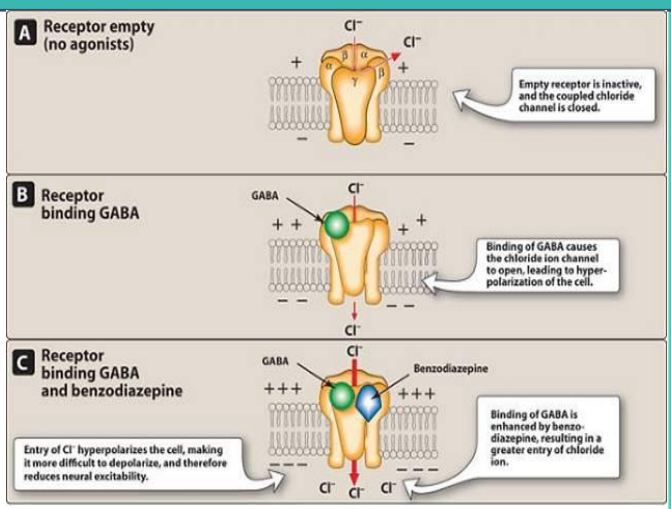
Mech. of action

1) Benzodiazepines binds to BZ receptor in the brain.

2) enhance GABA action on brain **$GABA_A$ (γ-aminobutyric acid)**: is an inhibitory neurotransmitter

3) chloride channels opening leading to **increase Cl^- influx** to the cell (hyperpolarization)

4) more difficult to depolarizes which will lead to → **reduction of neural excitability**.



Pharmacology Recall (page 78-79):
Benzodiazepines bind to specific receptors that are separated from but adjacent to the $GABA_A$ receptor, they potentiate the binding of GABA to its own receptor. The binding of GABA to its own receptor results in increased Cl^- conduction, cell membrane hyperpolarization, & decreased initiation of action potentials.
Remember benzodiazepines do not bind to GABA receptors, they bind adjacent to them.

P.K

- **Lipid** soluble → widely distributed.
- Well absorbed **orally**
- ***Chlordiazepoxide*** - ***Diazepam*** (IV only **NOT** IM)

- cross placental barrier (Fetal depression).
- excreted in milk (neonatal depression).
- metabolized in **liver** to **active** metabolites (Nordazepam) (long duration of action, **cumulative effect**) & excreted in **urine**.

Benzodiazepines

actions

CNS depressants:
- Anxiolytic action.
- Sedation.
- **Hypnotic action**. = sleeping pills
- Anterograde amnesia.→ temporary impairment of memory

- Depression of cognitive and psychomotor function
- Some have skeletal muscle relaxing effect (*diazepam*) → by increasing presynaptic inhibi- tion in the spinal cord
- Some have anticonvulsant effect e.g. *clonazepam*, *diazepam*, *lorazepam*.
- Therapeutic doses have minimal depressant effects on: cardiovascular system & respiratory system

Therapeutic uses

1. Anxiety disorders:
Short term relief of severe anxiety, General anxiety disorder, OCD (Obsessive-Compulsive Disorder) , Panic disorder with depression ***Alprazolam*** (antidepressant effect)
- Benzodiazepines are **fast acting** typically bringing relief within (30mins – hour).

2. Sleep disorders (Insomnia): ***Triazolam***, ***Lorazepam***, ***Flurazepam***.
→ They tend to decrease the latency to sleep onset and increase Stage II of NREM sleep.

3. Treatment of epilepsy: ***Diazepam*** – ***Lorazepam***.

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

5. Alcohol withdrawal syndrome: (***diazepam***)

What Are Benzodiazepines and Why Are They Abused? (Duration 6:10min)

GABA Receptor (BZD) - Structure and Mechanism of Action (Duration 3:00min)

ADRs

- Cognitive impairment.
- Ataxia (motor incoordination) w\ ↑ dose
- Impairment of driving ability.
- Anterograde amnesia.
- Hangover: (excess sedation, **drowsiness, confusion**)
- Tolerance and dependence.
- 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** & **old people**.

Drug interactions

Drugs	Examples
CNS depressants e.g. ***alcohol & antihistamin*** (1st generation)	↑ effect of benzodiazepines **(Additive effect)**
Cytochrome P450 inhibitors e.g. ***cimetidine & erythromycin***	↑ $t_{½}$ of benzodiazepines → by inhibition of metabolism
CYT P450 inducers ***phenytoin & rifampicin***	↓ $t_{1/2}$ of benzodiazepines (all epileptic drugs are inducers)

Drug: Flumazenil

P.D
- Selective, competitively to GABA receptors, displacing benzodiazepine → **antagonise them**.

P.K
- Injection (IV only) - **Short plasma** half life so **repeated dosing is required**.

Uses
- Benzodiazepines overdose (**antidote**)
- Can precipitate **withdrawal symptoms** in benzodiazepines **addicts**.

	5-HT1A agonists (5-hydroxytryptamine)	Selective serotonin reuptake inhibitors (SSRIs)
Drug	**Buspirone**	**Fluoxetine**
MOA	Acts as a partial agonist at brain, presynapticaly inhibiting 5HT release.	Acts by **blocking uptake of 5-HT**
Receptor	$5HT_{1A}$ receptors, Weak D_2 action	/
Rout of Administration	Rapidly absorbed **orally**.	Given **orally**
Onset of Action	**Slow onset** of action (delayed effect)	Delayed onset of action (weeks).
P.K	- $T_{1\backslash2}$: 2 – 4 h - Undergoes extensive **hepatic metabolism** → so its clearance is reduced by **liver dysfunction**.	Has long half life
Actions of drug	1) Only anxiolytic **2) No hypnotic effect**. 3) No muscle relaxant effect. **4) No anticonvulsant action**. 5) **No alcohol additive effect**. 6) it **doesn't impair memory and coordination**. **7) Does not affect driving skills**. **8) Minimal risk of dependence**. 9) No withdrawal symptoms 10) No potentiation of other CNS depressants 11) Minimal psychomotor & cognitive dysfunctions	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**.
Indications	- As anxiolytic in generalized anxiety disorders. **(Mild situation)**	
Disadvantages \ Side Effects	1) Slow onset of action (delayed effect) 2) GIT upset, **dizziness, drowsiness** 3) Not effective in severe anxiety/panic disorders 4) Drug interactions with CYT P450 inducers and inhibitors	1- Delayed onset of action (weeks). 2- Nausea, diarrhea → GIT upset 3- SSRIs may cause **weight gain or loss, Fluoxetine cause weight Loss**. 4- Sexual dysfunction 5- Dry mouth 6- Sleep disturbance or insomnia 7- Seizures
Drug interactions	- **CYP450 3A4 Inhibitors** (**verapamil**, **diltiazem**) → ↑ buspirone level - **CYP450 3A4 Inducers** (**Rifampin**) → 10 folds ↓ **buspirone** level. - MAOIs → increase BP.	
Precautions	- **Pregnant** women or **breast-feeding**. - Old people (>65) - Dose reduction is recommended in liver disease.	

Tricyclic Antidepressants

Drug	**Doxepin - Imipramine - Desipramine**
MOA	Act by **reducing uptake of 5HT & NE** (not selective)
Onset of Action	**Delayed** onset of action (weeks).
Indications	1- Used for **anxiety** especially associated with **depression** 2- Effective for **panic** attacks.
ADRs	1. Atropine like actions (dry mouth-blurred vision, tachycardia, urinary retention). 2. α-blocking activity (**Postural hypotension**). 3. Sexual dysfunction. 4. **Weight gain**.

Beta Blockers

Drug	**Propranolol** (non-selective) **– atenolol**
MOA	1. Act by **blocking peripheral sympathetic system**. 2. → Reduce **somatic** symptoms of anxiety. 3. Decrease BP & slow heart rate.
Indications	- Used in **performance or social anxiety**. - Are **less effective** for other forms of anxiety.
ADRs	- Should be used with **caution** in asthma, cardiac failure, peripheral vascular disorders. → because of beta2 effects.

Do not forget to revise the quick summary in page **2**

Summary-1

Drug	Benzodiazepines	$5HT_{1A}$ agonists
	Alprazolam-Estazolam-Triazolam-Lorazepam-Oxazepam-Temazepam-Diazepam-Flurazepam-Chlordiazepoxide	Buspirone
Mech. 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 → difficulty to depolarize → reduction of neural excitability	Acts as a partial agonist at brain **$5HT_{1A}$** receptors.
P.K	• Lipid soluble Chlordiazepoxide-Diazepam (IV only NOT IM) • Metabolized in the liver (long duration of action) • Excreted in urine	• rapidly absorbed orally • Slow onset of action (delayed effect) • T½ : (2 – 4 h)
Actions	• CNS depressants • Anxiolytic action • Sedation • Hypnotic action • Skeletal muscle relaxing (**diazepam**) • Anticonvulsant effect (**clonazepam**, **diazepam**, **lorazepam**)	• Only anxiolytic • No hypnotic effect • No muscle relaxant effect • No anticonvulsant action • No alcohol additive effect • No impairment of memory and coordination. • Does not affect driving skills • Minimal risk of dependence • No withdrawal symptoms
ADRs	• ↓cognitive and psychomotor function • Ataxia • Anterograde amnesia • Hangover: (excess sedation, drowsiness, confusion) • Tolerance • Psychological & physical dependence • Risk of withdrawal symptoms: (Rebound insomnia, anorexia, anxiety, agitation, tremors & convulsion). • Respiratory & CVS depression in large doses only (toxic effects)	• 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
Uses	• Anxiety disorders • Sleep disorders • Epilepsy • Anesthesia • Alcohol withdrawal	As anxiolytic in **generalized anxiety disorders**

Summary-2

Drug	SSRIs	Tricyclic Antidepressants	Beta Blockers
	Fluoxetine	**Doxepin- imipramine- Desipramine**	**Propranolol – Atenolol**
MOA	Block uptake of 5-HT	Reduce uptake of 5HT & NA	Block peripheral sympathetic system
P.K	• Given orally • Long ½ life • Delayed onset of action (weeks)	Delayed onset of action (weeks)	• ↓ somatic symptoms of anxiety • ↓ BP & heart rate
ADRs	• Nausea • Diarrhea • Weight gain or loss • Sexual dysfunction • Dry mouth • Sleep disturbance or insomnia • Seizures	- Atropine-like actions: • (dry mouth, blurred vision, tachycardia, urinary retention) - α-blocking activity: **(Postural hypotension)** - Sexual dysfunction - Weight gain	Hypotension
C.I	First line of treatment for most anxiety disorders (**well tolerated, have low risk for dependency and abuse and low potential for overdose**)	• Used for anxiety especially associated with **depression** • Effective for panic attacks	Used in performance or **social anxiety** (less effective for other forms of anxiety)
Indication			Used w/ **caution** in: • Asthma • Cardiac failure • Peripheral vascular disorders

Summary-3

Drug	Flumazenil
P.D	- Selective benzodiazepine receptor **antagonist**.
P.K	- Injection (IV only) - **Short plasma** half life so **repeated dosing is required**.
Uses	- Benzodiazepines overdose (**antidote**) - Can precipitate **withdrawal symptoms** in benzodiazepines **addicts**.

Extra summary

Subclass and Examples	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
BENZODIAZEPINES • Alprazolam • Chlordiazepoxide • Clorazepate • Clonazepam • Diazepam • Estazolam • Flurazepam • Lorazepam • Midazolam • Oxazepam • Quazepam • Temazepam • Triazolam	Bind to specific $GABA_A$ receptor subunits at central nervous system (CNS) neuronal synapses facilitating frequency of GABA-mediated chloride ion channel opening—enhance membrane hyperpolarization	Dose-dependent depressant effects on the CNS including sedation and relief of anxiety • amnesia • hypnosis • anesthesia • coma and respiratory depression	Acute anxiety states • panic attacks • generalized anxiety disorder • insomnia and other sleep disorders • relaxation of skeletal muscle • anesthesia (adjunctive) • seizure disorders	Half-lives from 2–40 h • oral activity • Hepatic metabolism—some active metabolites • *Toxicity:* Extensions of CNS depressant effects • dependence liability • *Interactions:* Additive CNS depression with ethanol and many other drugs
BENZODIAZEPINE ANTAGONIST • Flumazenil	Antagonist at benzodiazepine binding sites on the $GABA_A$ receptor	Blocks actions of benzodiazepines and zolpidem but not other sedative-hypnotic drugs	Management of benzodiazepine overdose	IV • short half-life • *Toxicity:* Agitation • confusion • possible withdrawal symptoms in benzodiazepine dependence
5-HT-RECEPTOR AGONIST • Buspirone	Mechanism uncertain: Partial agonist at 5-HT receptors but also affinity for D_2 receptors	Slow onset (1–2 weeks) of anxiolytic effects • minimal psychomotor impairment—no additive CNS depression with sedative-hypnotic drugs	Generalized anxiety states	Oral activity • forms active metabolite • short half-life • *Toxicity:* Tachycardia • paresthesias • gastrointestinal distress • *Interactions:* CYP3A4 inducers and inhibitors

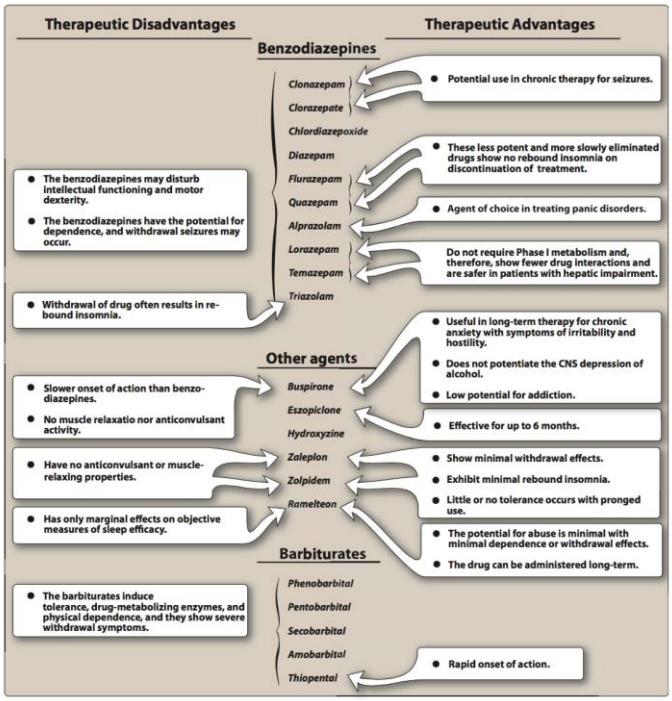


Figure 9.12
Therapeutic disadvantages and advantages of some anxiolytic and hypnotic agents. CNS = central nervous system.

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Thank you for checking our team!

Pharmacology 435

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ملاك اليحيا
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محمد ابونيان
محمد السحيباني
يوسف الصامل

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4- Basic & Clinical Pharmacology by Katzung. Chapter 22, 12th edition

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