






Drugs used in anxiety and panic disorders

- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE



Objectives

-  Identify different types of anxiety disorders.
-  Classification of the antianxiety agent groups.
-  Identify the specific clinical applications of each class of anti-anxiety drugs
-  Pharmacological mechanisms of each group; examples.
-  Discussing pharmacokinetic differences, pharmacodynamic potentials, indications, contraindications and side effects.

Anxiety

Anxiety: physical & emotional distress which interferes with normal life.

Symptoms:

Psychological or Emotional

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

Physical or Somatic

Due to : over stimulation of the sympathetic system

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

Boys Dr: Know the types of anxiety and drug of choice for each type

Types of Anxiety

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 repetitively/excessively.
Post-Traumatic Stress Disorder (PTSD)	An anxiety disorder that affects people who have experienced a severe emotional trauma, such as rape, dramatic car accident, or even war.
Phobia	An intense, uncontrolled fear of a specific situation such as open spaces & heights.
Panic Disorder	<ul style="list-style-type: none"> ○ Sudden, intense, and acute attacks of anxiety in certain situations. ○ Panic attacks cannot be predicted. <i>May associated with history of GAD or PTSD</i>

Treatment of Anxiety

Anxiolytics
relieve anxiety without interfering with mental or physical function.

Psychotherapy (Cognitive behavioral therapy)
(talk therapy)

Benzodiazepines (BDZ)

5-HT reuptake inhibitors

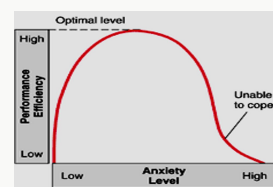
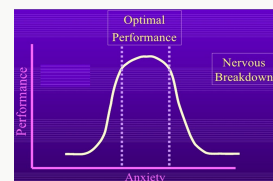
5-HT_{1A} agonists

Antidepressants

MAO inhibitors

β-adrenergic blockers

Pregabalin



Benzodiazepines (BDZ)

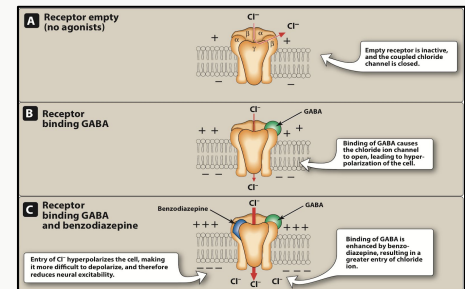
Overview

- They have the suffix **-zolam** or **-zepam**.
- They are classified according to duration of action:
 - **Short-acting** (3-8 h): **"TO"** = **T**riazolam + **O**xazepam (mnemonic: **"Tri = 3hrs Only"**)
 - **Intermediate-acting** (10-20 h) **"LATE"** = **L**orazepam + **A**lprazolam + **I**emazepam + **E**stazolam
 - **Long-acting** (24-72 h): Chlordiazepoxide, Diazepam, Flurazepam, Clorazepate, Quazepam

M.O.A

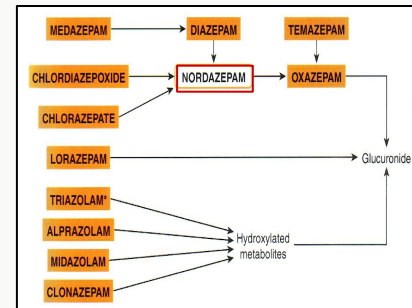
- Act by binding to **BDZ receptors** in the brain (different binding site than GABA)
 - **enhance GABA* (inhibitory NT) action** on the brain → chloride channels opening → **↑ chloride influx** to the cell → hyperpolarization → more difficult to depolarize → **↓ neural excitability** and inhibition of the brain

*γ-aminobutyric acid



P.K

- Lipid-soluble → can cross BBB
- Well-absorbed orally;
 - **Chlordiazepoxide - Diazepam (IV only NOT IM)**
- Widely-distributed
- **Cross placental barrier (fetal respiratory depression)**
- **Excreted in milk (neonatal depression)**
- Metabolized in the liver to active metabolites (long D.O.A - **cumulative effect**) & excreted in urine (Liver disease: Lorazepam has no active metabolite and is preferred)
- **The metabolism of BDZ:** Nordiazepam is formed from a number of benzodiazepines and is important because it is biologically active with a very long 1/2 life.



Action

- **CNS depressants**
- Sedation
- Hypnotic action* (could be used in treating insomnia)
- Anxiolytic action (1/3 hypnotic dose)
- Anterograde amnesia: ↓ ability to retain new info
- Depression of cognitive & psychomotor function
- Some have skeletal muscle relaxing effect (**Diazepam**) (centrally acting spasmolytic #MSK)
- Some have anticonvulsant effect (**Clonazepam, Diazepam, Lorazepam**)
- ★ **Therapeutic doses** have minimal depressant effects on:
 - Cardiovascular and **Respiratory systems**

* cannot be given to patients that have jobs require critical thinking, long drives or work with machines that require precision

Benzodiazepines

Drug	Diazepam	Midazolam	Lorazepam	Triazolam, Flurazepam	Alprazolam
Uses	<ul style="list-style-type: none"> Anxiety disorders: <ul style="list-style-type: none"> Benzodiazepines are fast-acting, typically bringing relief within 30 min to an hour. Short term relief of severe anxiety (NOT for long term because it leads to dependence) GAD (general anxiety disorder) OCD (obsessive compulsive disorder) 				
	<ul style="list-style-type: none"> Treatment of epilepsy Preanesthetic medication Alcohol withdrawal syndrome 	IV, Induction of anesthesia	<ul style="list-style-type: none"> Treatment of epilepsy Sleep disorders (insomnia) 	Sleep disorders (insomnia)	Panic disorder with depression (antidepressant effect)
ADRs	<ul style="list-style-type: none"> Cognitive impairment Ataxia (motor incoordination) Impairment of driving ability Anterograde amnesia Hangover (excess sedation, drowsiness, confusion) especially with old ages due to supersensitivity → not given long acting drugs. Tolerance Stop gradually Psychological & physical dependence with continuous use Risk of withdrawal symptoms: rebound insomnia, anorexia, anxiety, agitation, tremors & convulsion Respiratory & CVS depression in large doses only (toxic effects) 				
Drug-interaction (for all)	BDZ + CNS depressant (e.g alcohol, antihistamine) = ↑ effect of BDZ (additive effect)		BDZ + CYT P450 inhibitors (Cimetidine In peptic ulcer (Antihistamine), Erythromycin Antibiotic) = ↑ t 1/2 of BDZ		BDZ + CYT P450 inducers (e.g Phenytoin, Rifampicin) = ↓ t 1/2 of BDZ
Precaution	<ul style="list-style-type: none"> Pregnant or breastfeeding women. BDZ are considered D category in pregnancy, which is dangerous Dose reduction is recommended in: 1-Liver disease 2-Old people 				

BDZ Antagonist

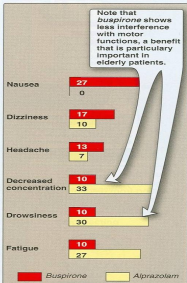
Flumazenil

M.O.A.	Selective benzodiazepine receptor antagonist.
P.K.	given by injection, Short half-life → repeated dosing is required
Uses	★ Benzodiazepines overdose (antidote)
ADRs	Can precipitate withdrawal symptoms in benzodiazepine addicts.

5-HT_{1A} Agonists

Buspirone

M.O.A.	Acts as a partial agonist at brain 5-HT _{1A} receptors	
P.K.	<ul style="list-style-type: none"> ○ Rapidly absorbed orally ○ Slow onset of action (delayed effect) (disadvantage) if pt. complains of no effect after a few days, tell them to continue use ○ t 1/2 = 2-4 h ○ Undergoes extensive hepatic metabolism; its clearance is reduced by liver dysfunction 	
Actions	<ul style="list-style-type: none"> ○ Only anxiolytic ○ No hypnotic effect ○ No muscle relaxant effect ○ No anticonvulsant action ○ No alcohol additive effect 	<ul style="list-style-type: none"> ○ Doesn't impair memory & coordination ○ Doesn't affect driving skills (least sedative effect) (439: <u>bus</u> driver uses <u>buspirone</u>) ○ Minimal risk of dependence ○ No withdrawal symptoms <p>○ Less interference with motor function which is particularly important in elderly patients.</p>
Uses	As anxiolytic in mild anxiety & generalized anxiety disorders. First line	
ADRs	<ul style="list-style-type: none"> ○ GIT upset ○ Dizziness & drowsiness ○ Not effective in severe anxiety/panic disorders because of delayed effect Increases serotonin, may cause serotonin syndrome 	
DDI	CYP450 3A4 Inhibitors (Verapamil, Diltiazem) → ↑ Buspirone levels	CYP450 3A4 Inducers (Rifampin) → ↓ Buspirone level
Precaution	<ul style="list-style-type: none"> ○ Pregnant or breastfeeding women. ○ people over 65 ○ Dose reduction is recommended in: 1-Liver disease 2-Old people 	



Selective Serotonin Reuptake Inhibitors (SSRIs)

Fluoxetine (Prozac)

M.O.A.	Acts by blocking uptake of 5-HT (↑ serotonin in the brain)	
P.K.	<ul style="list-style-type: none"> ○ Given orally ○ Long half-life ○ Delayed onset of action (weeks) 	
Uses	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.	
ADRs	<ul style="list-style-type: none"> ○ With delayed onset, increase in anxiety symptoms, insomnia, or headache in the first days or weeks of treatment may ↓ compliance delayed action → trust issues (patient become less compliant to doctor's orders) ○ Nausea & diarrhea ○ Weight gain ○ Sexual dysfunction ○ Dry mouth (Atropine-like anticholinergic effect; present in most antidepressants) ○ Sleep disturbance or insomnia ○ Seizures 	

Tricyclic Antidepressants

Drugs	Doxepin	Imipramine	Desipramine
M.O.A.	Acts by reducing uptake of 5-HT & NA		
P.K.	Delayed onset of action (weeks)		
Uses	<ul style="list-style-type: none"> ○ Used for anxiety especially associated with depression ○ Effective for panic attacks 		
ADRs	<ul style="list-style-type: none"> ○ Atropine-like actions (muscarinic blocking actions) (dry mouth, blurred vision, tachycardia, urinary retention) ○ α-blocking activity (postural hypotension) ○ Sexual dysfunction ○ Weight gain 		

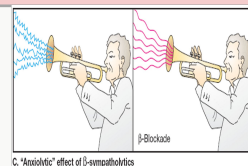
Monoamine Oxidase Inhibitors (MAOIs)

Phenelzine

M.O.A.	Acts by blocking the action of MAO enzymes
P.K.	Require dietary restriction: avoid wine, beer, fermented foods as old cheese that contain tyramine \uparrow NA release (Sympathomimetic) \rightarrow hypertensive crisis
Uses	<ul style="list-style-type: none"> ○ Used for panic attacks & phobias ○ Reserved for patients who have not responded to, or proved intolerant of, other treatments
ADRs	Dry mouth & constipation (Atropine-like), diarrhea, restlessness, dizziness

Beta-Blockers

Drugs	Propranolol (Inderal)	Atenolol
M.O.A.	<ul style="list-style-type: none"> ○ Act by blocking peripheral sympathetic system don't act on CNS ○ Reduce somatic symptoms of anxiety (physical NOT mental,) ○ Decrease BP & slow heart rate 	
Uses	<ul style="list-style-type: none"> ○ Performance or social anxiety (event-based anxiety) ○ Less effective for other forms of anxiety 	
#	Should be used with caution in: <ul style="list-style-type: none"> ○ Asthma B2 blocker \rightarrow Bronchoconstriction ○ Cardiac failure ○ Peripheral vascular disorders 	



Pregabalin (Lyrica)

M.O.A	Modulates <ol style="list-style-type: none">1. calcium channels in CNS (\downarrowCa²⁺ influx)2. release of neurotransmitters (\downarrow)
P.K.	<ul style="list-style-type: none">○ Onset occurs in first days of treatment○ Excreted unchanged in urine
Uses	<ul style="list-style-type: none">○ Effective in treatment & prevention of relapse of GAD (1st line as SSRIs)○ Used in epilepsy & neuropathic pain (pain that is usually caused by chronic, progressive nerve disease, and or as a result of injury or infection)
ADRs	<ul style="list-style-type: none">○ Dizziness & somnolence○ Withdrawal symptoms may occur but less severe than benzodiazepines



Pregabalin is a new synthetic molecule and a structural derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Remember: preGABAin. **It doesn't affect the release of GABA.**



Summary

(From the slides)

Boys Dr: Know the drug of choice for each type of anxiety

Classes of Anxiolytics	MOA	★ Uses	ADRs
Benzodiazepines e.g. Diazepam	Act by binding to BDz receptors in the brain	<ul style="list-style-type: none"> ● GAD ● OCD ● phobia ● panic attack 	Ataxia, confusion, dependence, tolerance, withdrawal symptoms
SSRIs e.g. Fluoxetine	Acts by blocking uptake of 5-HT		<ul style="list-style-type: none"> ● Sexual dysfunction ● Weight gain ● Dry mouth Atropine like action
Tricyclic Antidepressants e.g. Doxepin	Acts by reducing uptake of 5-HT & NA	<ul style="list-style-type: none"> ● Anxiety with depression ● Panic attacks 	Weight gain, sexual dysfunction, atropine like actions, arrhythmia
5-HT_{1A} Agonists e.g. Buspirone	Acts as a partial agonist at brain 5-HT _{1A} receptors	<ul style="list-style-type: none"> ● Mild anxiety ● Not effective in panic attack 	Minimal ADRs
β-blockers e.g. Propranolol, atenolol	Act by blocking peripheral sympathetic system	Event-based anxiety e.g. phobias (social phobia)	Hypotension
MAO inhibitors e.g. Phenelzine	Block action of MAO enzyme	<ul style="list-style-type: none"> ● Panic attack ● Phobia 	Dry mouth & constipation diarrhea, restlessness, dizziness



MCQ

1. Which one of the following drug cause muscle relaxant ?			
A. Triazolam	B. Lorazepam	C. Diazepam	D. Alprazolam
2. Which one of the following drugs is used in performance and social anxiety?			
A. Lorazepam	B. Fluoxetine	C. Imipramine	D. Propranolol
3. Which one of the following is considered the 1st line of treatment in most anxiety disorders ?			
A. Triazolam	B. Fluoxetine	C. Buspirone	D. Atenolol
★ Which one of the following is used as an antidote to benzodiazepines overdose ?			
A. Flumazenil	B. Atenolol	C. Fluoxetine	D. Buspirone
5. A 58 years old female presents to the doctor with mild anxiety and she wants a drug with lowest sedative effect?			
A. Buspirone	B. Diazepam	C. Lorazepam	D. Flurazepam
6. Which of the following drug of Benzodiazepines used in panic attack with depression?			
A. Alprazolam	B. Lorazepam	C. Diazepam	D. Flurazepam
7. Which of the following may cause hypertensive crisis if used with avoid wine, beer, fermented food?			
A. Flumazenil	B. Buspirone	C. Phenezine	D. Doxepin



SAQ

01

Lulu is a 15-years-old female came to see a psychologist with her parents, her parents explain to the doctor that she has no friends and always set alone in her room which seemed normal until they force her to attend a family gathering where they noticed that she started sweating and breathing fast then she locked herself in the bathroom.

Which drug would be the most helpful to this patient ?
What is the mechanism of action of this drug ?

-Propranolol or atenolol
-beta blockers-blocking peripheral sympathetic system.

02

A 40-years-old male with history of anxiety associated with depression, in the last visit to his psychologist he told him that he noticed that since he started taking the medication he gain a lot of weight and feels dizzy when he stand up.

Which anxiolytic drug he most likely taking that cause that symptoms ?

Doxepin - Imipramine - Desipramine

03

Hussam a 36 year-old patient came to ER with trouble breathing and depressed cardiac function, PMH revealed that he is on Diazepam. History taking showed that he drinks alcohol frequently. Which drug would help him in this case ?

Flumazenil

04

Muneerah is a 32 years old teacher who came into the clinic complaining of stress that is disruptive but not affecting her daily tasks. The psychiatrist told her that she has mild anxiety. Which drug should the psychiatrist prescribe for Muneerah?

Buspirone

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