Antianxiety drugs

Dr.Leila kashani

Assistant professor of psychiatry

Anxiety

- I have a presentation
- I have a tough exam
- I have an important interview

Should I be anxious ?

What is anxiety ?

Physical and emotional distress which interfere with normal life.

What are different symptoms of anxiety ?

- **Psychic or emotional state.**
- **Somatic or physical symptoms.**

Common Emotional Symptoms of anxiety

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

Common Physical Symptoms of Anxiety

Sweating

Tachycardia

Stomach upset

Shortness of breath

Frequent urination or diarrhea

Sleep disturbances (Insomnia)

Fatigue

Types of anxiety

1. **Generalized anxiety disorder**
2. **Panic disorder**
3. **Phobia**

Generalized Anxiety Disorder (GAD)

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

Panic disorder

An disorder in which people have sudden and intense attacks of anxiety in certain situations.

Phobia

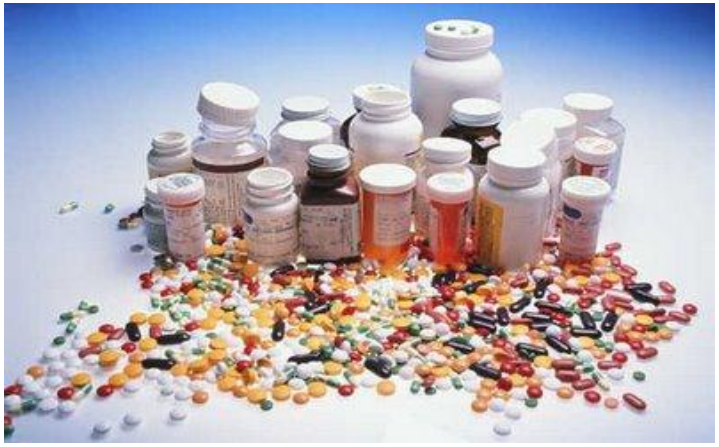
An intense, uncontrolled fear of a specific situation such as

open spaces & heights

Treatment of anxiety

- **Psychotherapy (cognitive behavioral therapy).**

- **Anxiolytics**



Antianxiety Drugs

- Benzodiazepine
  - Diazepam
  - Chlordiazepoxide
  - Oxazepam
  - Lorazepam
  - Alprazolam
- Azapirones
  - Buspirone
  - Gepirone
  - Ispapirone
- Others
  - Beta blocker- **Propranolol**
  - Antihistaminics- Hydroxyzine
  - SSRIs and other antidepressant drugs
  - (MAO inhibitors)

Benzodiazepines

Classifications of Benzodiazepines

- **Short acting: (3-5 hours): tria**zolam
- **Intermediate: (6-24 hours)**
  - **Alpra**zolam
  - **Lora**zepam
  - **Oxa**zepam
  - **Esta**zolam
  - **Tema**zepam

Classifications of Benzodiazepines

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

  Clonazepam

  Chlordiazepoxide

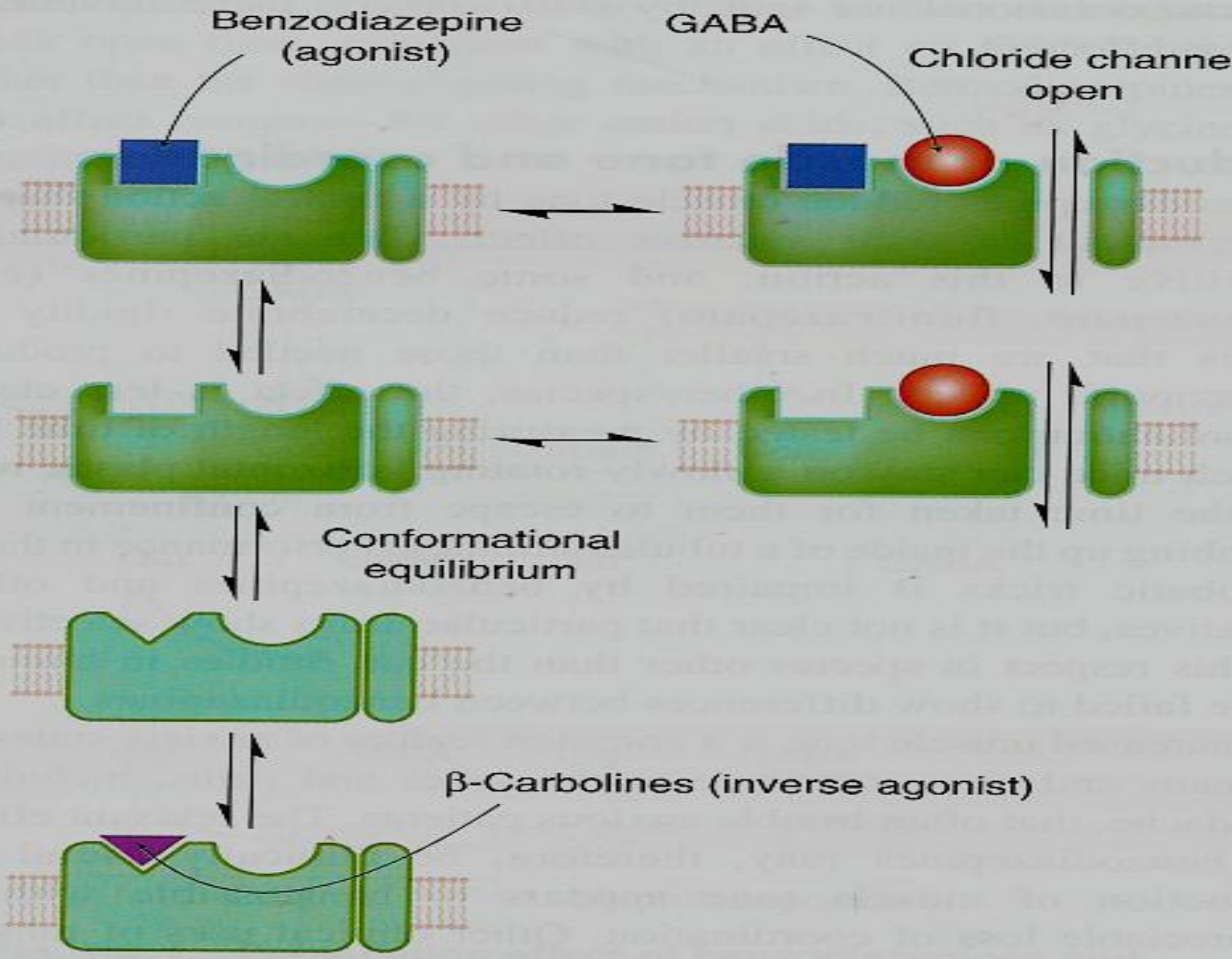
  Diazepam

  Flurazepam

Mechanism 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 → inhibition of brain.

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


Benzodiazepine
(agonist)
GABA
Chloride channel
open
Conformational
equilibrium
β-Carbolines (inverse agonist)

PHARMACOKINETICS

- are lipid soluble
- well absorbed orally,
- can be given parenterally
- Diazepam (IV only)
- 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).**
- **Redistribution from CNS to skeletal muscles, adipose tissue) (termination of action).**

Pharmacological Actions

- **Anxiolytic action.**
- **Depression of cognitive and psychomotor function**
- **Sedative & hypnotic actions**
- **Anterograde amnesia.**

Pharmacological Actions

- **Minimal depressant effects on**
  - **Cardiovascular system**
  - **Respiratory system**
- **Some have anticonvulsant effect:**
  - **clonazepam, diazepam.**

Therapeutic Uses

Anxiety disorders:

short term relief of severe anxiety
General anxiety disorder
Obsessive compulsive disorder
Panic attack with depression Alprazolam (antidepressant effect)

Sleep disorders (Insomnia).

- **Triazolam, Lorazepam, Flurazepam**

Therapeutic Uses

Treatment of epilepsy

Diazepam – clonazepam

In anesthesia

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

Adverse Effects

- **Ataxia (motor incoordination)**
- **Cognitive impairment.**
- **Hangover: (drowsiness, confusion)**
- **Tolerance & dependence**
- **Risk of withdrawal symptoms**

Rebound Insomnia, anxiety, agitation, tremors and convulsion.

Adverse Effects

- **Toxic effects: respiratory & cardiovascular depression in large doses.**

Drug interactions

	Examples
CNS depressants	Alcohol & Antihistaminics ↑ effect of benzodiazepines
Cytochrome P450 (CYT P450) inhibitors	Cimetidine & Erythromycin ↑ $t_{1/2}$ of benzodiazepines
CYT P450 inducers	Phenytoin & Rifampicin ↓ $t_{1/2}$ of benzodiazepines

Dose should be reduced in

- **Liver disease**
- **Old people.**

Precaution

Should not used in

- **pregnant women or breast-feeding.**
- **People over 65.**

Benzodiazepines

Adverse effects

- Sedation
- Light headedness
- Psychomotor impairment
- Cognitive impairment
- Vertigo
- Confusional state
- Increased weight
- Impaired sexual functions
- Potential to produce dependence

Benzodiazepines (Individual drugs)

Chlordiazepoxide

- First BZD
- Long lasting effect
- Chronic anxiety
- Safe in pregnancy
- Long lasting withdrawal

Diazepam

- Has two phase of metabolism
- Broken in to active metabolites
- Long duration of action

Oxazepam

- Penetration In brain is slow
- No active metabolite
- Used in short lasting anxiety state

Lorazepam

- Less lipid soluble
- Slow entry in brain
- No active metabolite
- IM

Alprazolam-

high potency, mood elevating in depressed pt. less drowsiness

$5HT_{1A}$ agonists
Buspirone

- acts as agonist at brain $5HT_{1A}$ receptors
- *Partial agonist on 5HT1A (pre-synaptic) and antagonist on 5HT postsynaptic receptors*
- rapidly absorbed orally.
- Slow onset of action (delayed effect)
- T½ : (2 – 4 h).
- liver dysfunction → ↓ its clearance.
- Drug Interactions with CYT P450 inducers and inhibitors.

Buspirone

- Relieves mild to moderate generalized anxiety
- Effects develop slowly (not used for acute)
- Presynaptic auto-receptors stimulated leading to reduced activity of dorsal raphe serotonergic neurones
- Also has weak D2 blocking effect

Buspirone

- Only anxiolytic
- No hypnotic effect.
- Not muscle relaxant.
- Not anticonvulsant.
- No potentiation of other CNS depressants.
- Minimal psychomotor and cognitive dysfunctions.
- Does not affect driving skills.
- Minimal risk of dependence.
- No withdrawal signs.

Uses of buspirone

- As anxiolytic in mild anxiety & generalized anxiety disorders.
- Not effective in severe anxiety/panic disorder.
- better effect on decrease concentration
- Interfere with MAO.I is dangerous

Buspirone

- Does not produce sedation, cognitive impairment,
- Does not interact with BZD receptor or modify GABAergic transmission
- No tolerance
- No physical dependence
- No muscle relaxant
- No anticonvulsant property

Hydroxazine

- H1 antihistaminic
- Sedative, anti -emetic and spasmolytic
- Anti - Pruritus

Propranolol

- Reduces sympathetic symptoms like rise in BP, Tremors, sweating etc.
- Performance or situational anxiety

(like examination fear, social phobia, public lecture)

Beta Blockers

- **Propranolol – atenolol**

act by blocking peripheral sympathetic system.

- **Reduce somatic symptoms of anxiety.**
- **Decrease BP & slow HR.**
- **Used in social phobia.**
- **are less effective for other forms of anxiety**
- Atenolol is better in respiratory disorder and liver disfunction.
- Side effect:depressin, fatigue, night mare,sexual dysfunction, increase WT,…

Tricyclic Antidepressants (TCAs)

Imipramine represents the class (Prototype)

Inhibit monoamine reuptake (serotonin and noradrenalin)

Increase the concentration of ***Serotonin and NA*** at synapse and potentiate the action (therapeutic effects)

Other receptors acted (Adverse effects)

- **Muscarinic- Anticholinergic side effects (dryness etc.) #**
- **Alpha- alpha blocking actions (postural hypotension etc.) #**
- **Histamine-Antihistaminic (sedation) #**
- ***Dopamine- antipsychotic (amoxapine,)***

- Pharmacokinetics:

  - Lipophilic with High protein binding; basic in nature, metabolized in liver.

- Nowadays, this group of antidepressants became less popular than it was, due to the unwanted effects.

TCAs on other systems

ANS

- *Potent anticholinergic*
  (dry mouth, blurring of vision,, constipation, urinary hesitancy)
- Weak alpha 1 blocking
  (postural hypotension, impairment of ejaculation,)
- H1 antihistaminic
  (sedation)

CVS

- Tachycardia
- Postural hypotension
- Cardiac *arrhythmias*
  (T wave suppression or inversion) due to intra ventricular conduction interference due to NA and Anti cholinergic actions

Tolerance to Anticholinergic and hypotensive actions develop latter on

TCAs (Pharmacokinetics)

- Good oral absorption
- Highly bound to Proteins (plasma and tissue)
- Metabolized in liver (oxidation, glucuronide conjugation and CYP2D6, CYP3A4, CYP1A2
- Many active metabolites may be produced
- Mostly can be given once a day (at bed)
- Have *Therapeutic Window* phenomenon (50-200ng/ml of imipramin)

TCAs Adverse effects

- ***Anticholinergic***- dry moth, bad taste, constipation, epigastric fullness, urinary retention (more common in elderly male), blurred vision, palpitation
- **Sedation**, mental confusion, weakness
- Increased appetite and weight
- Sweating, fine tremors
- Precipitation of seizures
- **Postural hypotension: less in nortriptyline**
- **Cardiac arrhythmias:less in nortriptyline**
- Rashes and jaundice

TCAs (Acute Poisoning)

- Usually suicidal attempt

- Presents as
  - Excitement
  - delirium,
  - Anticholinergic symptoms like atropine poisoning
  - Muscle spasm
  - Convulsions
  - Respiratory depression
  - Coma

- Treatment
  - Gastric lavage
  - I.V. line
  - Oxygen
  - Maintenance of BP and Temperature
  - Diazepam iv
  - Propranolol

Table 1: Effects of tricyclic antidepressants on Reuptake and 5-HT_2

Tricyclic antidepressants	5-HT reuptake	Noradrenaline reuptake	5-HT2 antagonism
Tricyclic antidepressants			
Amitriptyline	+ +	+	+
Clomipramine	+	-	?
Desipramine	?	++	-
Dothiepin	-	+	-
Doxepin	+	+	+
Imiprmine	+	+	-
Lofipramine	-	+	-
Nortriptyline		+	+

Table 2: Side Effects of Tricyclic antidepressants

	Relative Side effects				Reuptake inhibition	
	Sedation	**Cardio-toxicity**	**Hypotension**	**Anti-Cholinnergic**	**NE**	**5-HT**
Amitriptyline	+++	+++	+++	+++	++	+++
Amoxapine	++	+	+	++	+++	+
Clomipramine	++	+++	++	++	+/-	+++
Desipramine	+	+++	+	++	++++	+/-
Dothiepin	+++	+++	++	++	+	+
Doxepin	+++	++	++	++	+	+
Imipramine	++	+++	+++	+++	+	+++
Lofepramine	+	+	+	+	++++	+
Nortriptyline	+	++	0/+	++	+++	+
Protriptyline	-	+++	+	++	++++	+
Trimipramine	+++	+++	++	++	+	+

Selective Serotonin Uptake Blockers (SSRI)

- e.g. Fluoxetine; Fluvoxamine; Paroxetine; Sertraline; Citalopram (see table 3).
- Pharmacological Activities:

MOA : Selective uptake of 5-HT in the presynaptic cleft.

Why they are better choice as compared to TCA?

Selective Serotonin Reuptake Inhibitors (SSRIs)

Limitations of TCAs

- Anticholinergic effects
- Alpha blocking action
- Cardio toxicity
- Sedation, seizures
- Low safety margin
- Weight gain
- Therapeutic window
- Overdose poisoning common
- Lag of 1 month period
- Incomplete response to Tt

Answers may be given by SSRIs

- **Selectively inhibit membrane associated SERT (serotonin transporter)**
- **More tolerability and better acceptability**
- **Used in in anxiety ,OCD, phobias**
- **No sedation, No seizure**
- **No alpha blocking action**
- **Less chances of arrhythmia**
- **No weight gain**
- **Now 1st choice for OCD, Panic disorders, Social Phobia, Premenstrual syndrome, Post traumatic stress**

SSRIs

Side effects

- Gastric upset
- Nausea
- Interfere with ejaculation
- Nervousness
- Restlessness
- Insomnia
- Anorexia
- Headache
- Diarrhea
- Epistaxis
- Ecchymosis

Others

- ***Inhibit*** **cytochrome enzymes** and elevate the plasma level of other drugs
- Other serotonergic drug (MAOIs) is taken may precipitate **Serotonin Syndrome** manifesting as agitation, restlessness, sweating, twitching, convulsions

Selective serotonin reuptake inhibitors (SSRIs)

Fluoxetine:

- acts by blocking uptake of 5HT
- Orally
- Delayed onset of action (weeks).
- Used for panic disorder – OCD depression- Generalized anxiety disorders - phobia.

Side Effects:

- Weight gain, sexual dysfunction, dry mouth
- **Sertraline:**
- Safe in breastfeeding
- **Paroxetine:**
- Severe withdrawal syndrome

Table 3: Effect of SSRIs on Reuptake and 5-HT2

	5-HT reuptake	Noradrenaline reuptake	5-HT2 antagonists
Selective serotonin reuptake inhibitors			
Citalopram	+	-	-
Fluoxetine	+	-	-
Fluvxamine	+	-	-
Paroxetine	+	-	-
Sertraline	+	-	-

Side Effects of SSRI (see Table 4)

- Almost have no cardiovascular manifestations as compared to TCA.
- Nausea and vomiting and decrease appetite
- Insomnia and anxiety (with Fluoxetine; but not with Paroxetine
- Impotence and sexual dysfunction (in male and female)

Decrease weight.

Table 4: Side effects of SSRIs

Drug	Cardiotoxicty	Nausea	Anticholinergic effects	Sedation
Citalopram	?	++	=	=
Fluoxetine	-	++	=	=
Fluvoxamine	=	+++	=	+
Paroxetine	=	++	+	+
Sertraline	–	++	–	–

α_2 – adrenoceptors antagonists

:Mirtazepine

act by increasing the release of 5-HT and NE

Via……

Differ from SSIR in

Increase appetite (good for patients taking cancer chemotherapy) NO N/V

No Sexual dysfunction ;

sedation. Also, produces constipation and rarely leads to agranulocytosis

Other non classified Antidepressants

- Venlavaxine (Effexor^{R}): Act by blocking 5-HT and NE uptake but it has side effects profile similar to SSRI. However, it may produce seizure and constipation.

Desvenlafaxine PristiqR (metabolite of Venlavaxine)

- Suitable for diabetes

- Trazodone: Selective blocker of 5-HT uptake but has significant α- blocking effect (hypotension and sedation); Blocks 5-HT2 receptors (Priapism)

Table 6: Side effects of atypical antidepressants

Drug	Toxicity	Sedation	Hypotension	Anticholinergic effects
Mianserin	-	++	-	+
Mirtazepine	-	++	-	+
Nefazodone	-	+	+	-
Trazodone	+	+++	+++	-
Venlafaxine	+	++	-	+

Classifications of MAOIs

- **Either:**
  - **Hydralazine Derivatives (Phenelzine)**
  - **Non –hydralazine DER.(Tranylcypramine)**
- **Or as irreversible non –selective (Phenlizine and Tranylcypramine) vs reversible selective (Mclobemide)**
- **Side Effects:↑ appetite (Phenelzine like) ↓ appetite (Tranylcypramine; hepatotoxicity; SLE like;**
- **Drug and Food interactions (very important).**
- **Hypertension crysis**

	Drug	Sedation	Anticholinergic effects	Hypotensin
Non-selective irreversible	Isocarboxazid	+	++	+
	Phenelzine	+	++	+
	Tranylcypromine	-	+	+
Selective reversible	Moclobemide	-	-	-

MONOAMINE OXIDASE INHIBITORS

Phenelzine

- Acts 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.

Side effects

Dry mouth, constipation, diarrhea, restlessness, dizziness.

Conclusion of anxiolytics

CLASSES OF ANXIOLYTICS	USES
Benzodiazepines	Generalized anxiety disorders, OCD, phobia, panic attack
SSRIs (sertraline-citalopram)	Generalized anxiety disorders, OCD, phobia, panic attack
Tricyclic antidepressants (doxepin, imipramine-nortriptyline)	anxiety with depression. panic attacks
5HT1A agonists (Buspirone)	Mild anxiety Not effective in panic attack
Beta blockers (propranolol, atenolol)	Phobia (social Phobia)
MAO inhibitors Phenelzine	Panic attack, phobia

Conclusion of anxiolytics

CLASSES OF ANXIOLYTICS	Adverse effects
Benzodiazepines	Ataxia, confusion, dependence, tolerance, withdrawal symptoms,
SSRIs (setralin-citalopram)	weight gain, sexual dysfunction Dry mouth
Tricyclic antidepressants (doxepin, imipramine)	weight gain, sexual dysfunction, atropine like actions
5HT1A agonists (Buspirone)	Minimal adverse effects
Beta blockers (propranolol, atenolol)	Hypotension


در پناه حق