



Antidepressants



Prof. Anatoly Kreinin MD, PhD

Director of University Psychiatric Department, Maale Carmel Mental Health Center,
Affiliated to Bruce Rappaport Medical Faculty, Technion, Haifa, Israel

Antidepressants are the second-most-prescribed-medication in the United States

- 15 million Americans are affected by depression each year
- 7% of all visits to the primary care doctors involve the doctor prescribing antidepressant medication
- \$10 billion dollars a year are spent on antidepressants

Antidepressants are used for the treatment of several different forms of depression and other psychological disorders.



Psychological disorders that may accompany, precede, or cause depression:

Bipolar Disorder, (OCD) obsessive compulsive disorder and (PTSD) Post Traumatic Stress Disorder

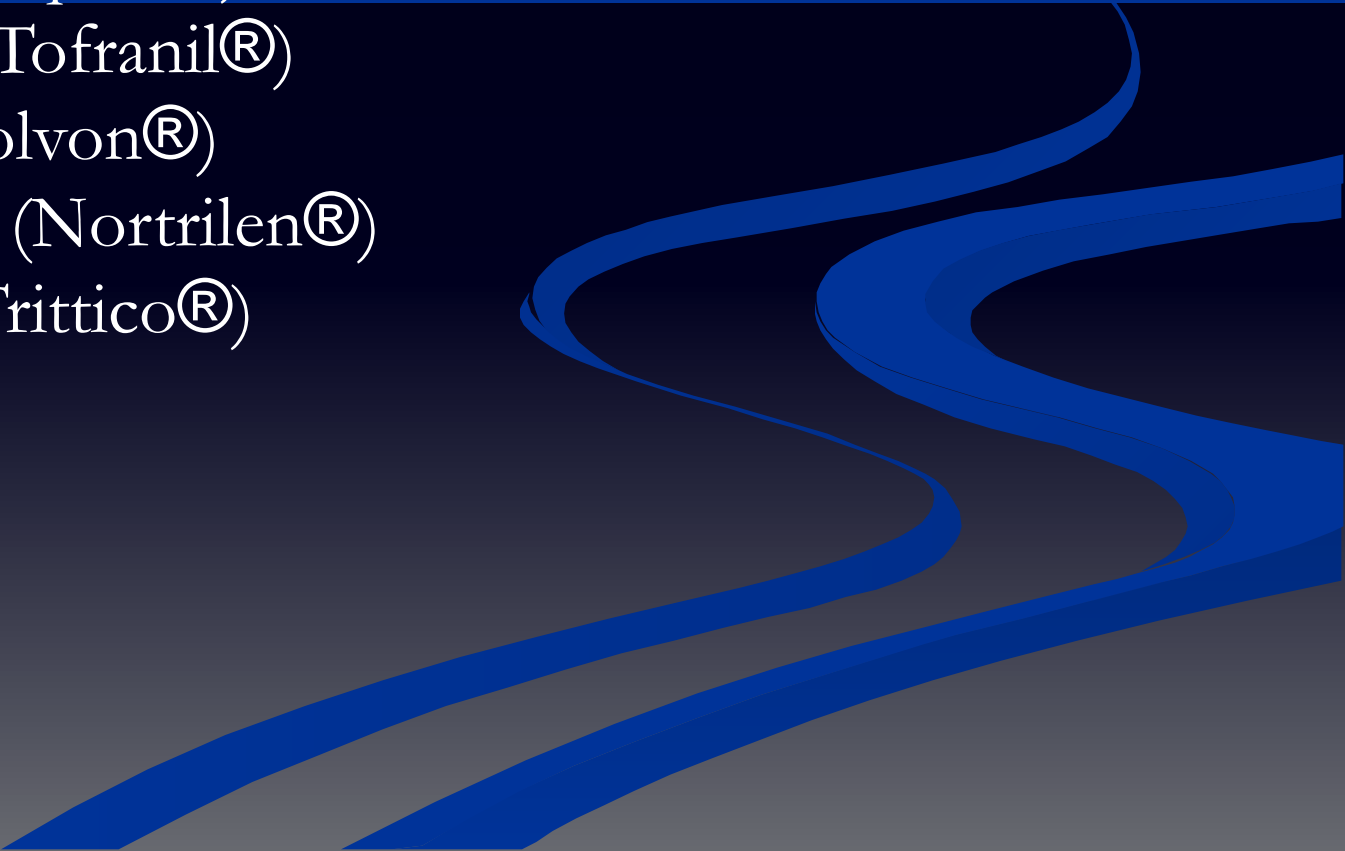
Depression is not uniform. Everyone does not experience the same the signs and symptoms. The severity, duration, and triggers of one's symptoms depend on the individual person and his or her illness.



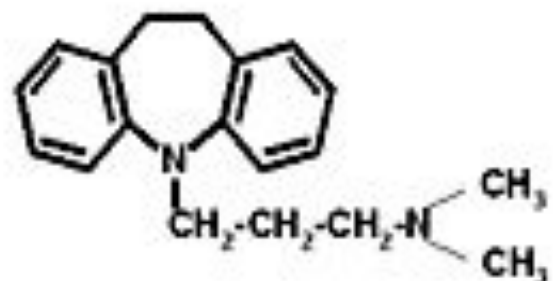
Antidepressants

- Tricyclic and related antidepressants (TCA)
 - E.g. amitriptyline, imipramine, doxepin, mianserin, trazodone
- Monoamine-oxidase inhibitors (MAOI)
 - E.g. moclobemide, phenelzine, isocarboxazid, tranylcypromine
- Selective serotonin reuptake inhibitors (SSRI)
 - E.g. fluoxetine, paroxetine, sertraline, citalopram
- Other antidepressants
 - E.g. mirtazapine, venlafaxine, duloxetine, flupentixol

Tricyclic and related antidepressants (TCA)

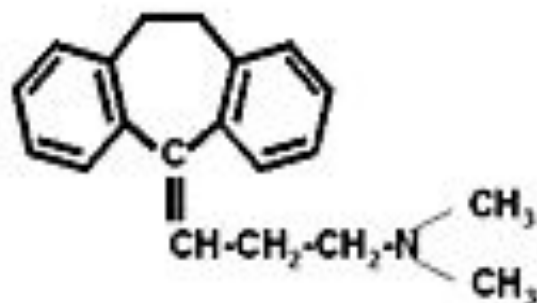
- Amitriptyline (Saroten®)
 - Clomipramine (Anafranil®)
 - Doxepin (Sinequan®)
 - Imipramine (Tofranil®)
 - Mianserin (Tolvon®)
 - Nortriptyline (Nortrilen®)
 - Trazodone (Trittico®)
- 
- A decorative graphic consisting of several thick, overlapping, wavy blue lines that flow from the bottom left towards the right side of the slide, creating a sense of movement and depth.

Chemical structures of tricyclic antidepressants



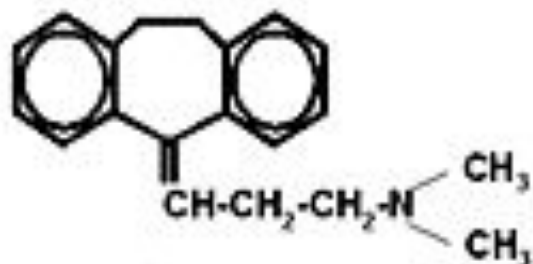
Imipramine

Tertiary amines

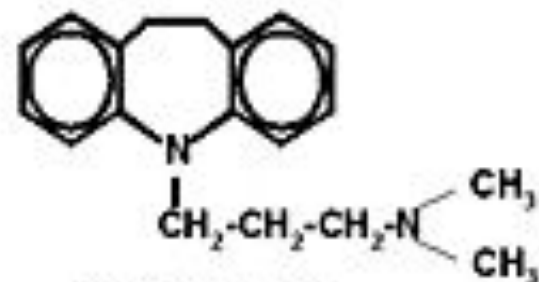


Amitriptyline

Secondary amines



Nortriptyline



Desipramine

Tricyclic and related antidepressants (TCA)

- Mechanism of action
 - Blocks neuronal uptake both norepinephrine and serotonin
 - Initial response develops in 1-3 weeks
 - Maximal response develops in 1-2 months
 - Older tricyclics
 - Marked anticholinergic Adverse effects
 - Risk of cardiotoxicity
 - Tricyclic-related drugs (e.g. trazodone)
 - Fewer anticholinergic adverse effects
 - Sedation, dizziness, priapism (persistent penile erection accompanied by pain and tenderness)

Antidepressant treatment causes inhibition of serotonin and norepinephrine reuptake or breakdown.

Short-term antidepressant treatment increase extracellular levels of serotonin and norepinephrine.



Long-term treatment leads to decrease in the function and expression of serotonin and norepinephrine receptors, to increase in the cAMP signal transduction and to increase in expression of CREB (cAMP response element binding).

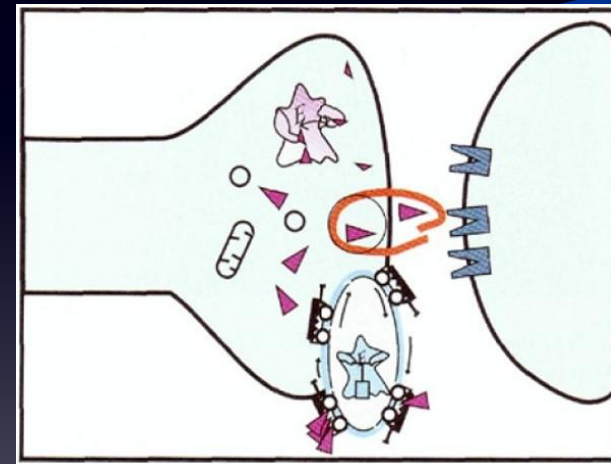
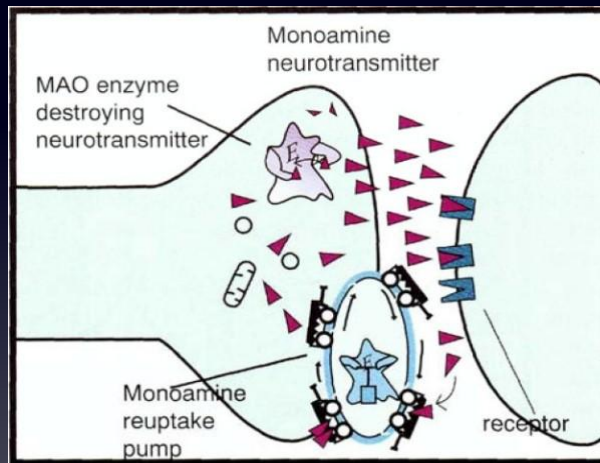
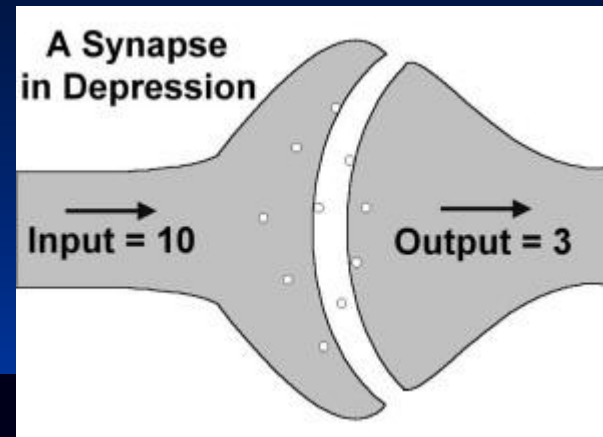
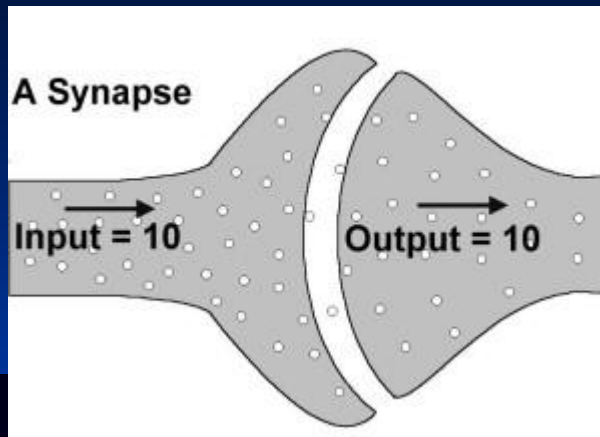


Increased activity of the cAMP signal transduction cascade indicates that the functional output of 5-HT and NE are up-regulated, even though levels of certain 5-HT and NE receptors are down-regulated.



Expression of BDNF and its receptor trkB is also increased by long-term antidepressant treatment, so increased neuronal survival, function, and remodelling of synaptic architecture are provided.

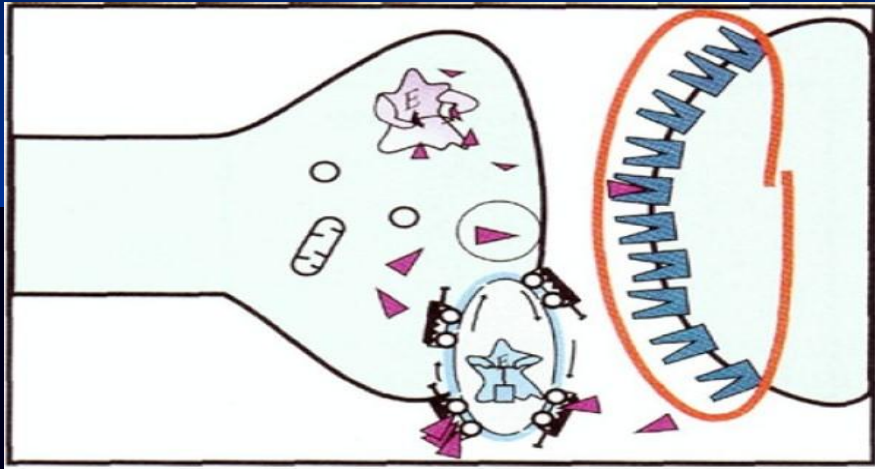
Down & Up-regulation's



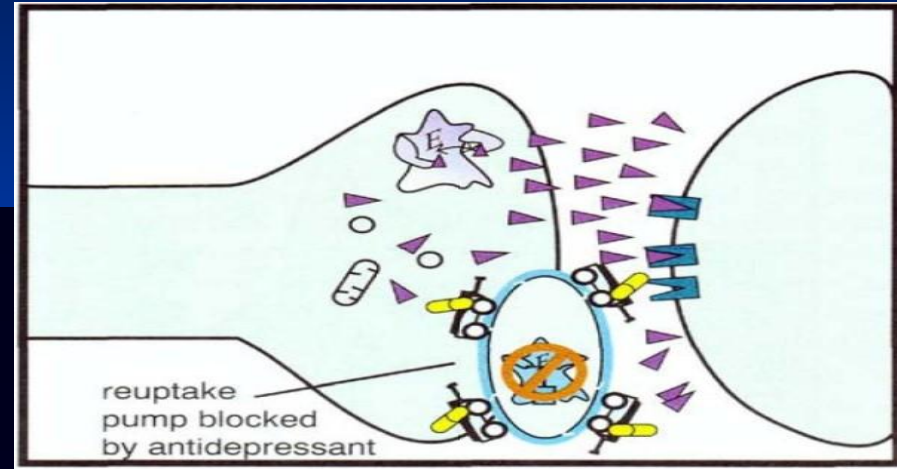
Normal synapse, no depression

Depression caused by neurotransmitter deficiency

Down & Up-regulation's

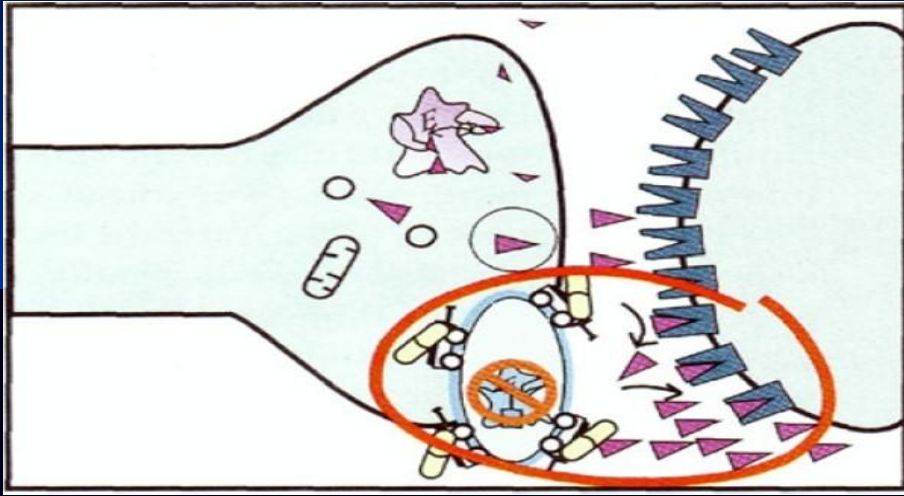


As a result of the depletion of neurotransmitters, the receptors increase ('upregulate')

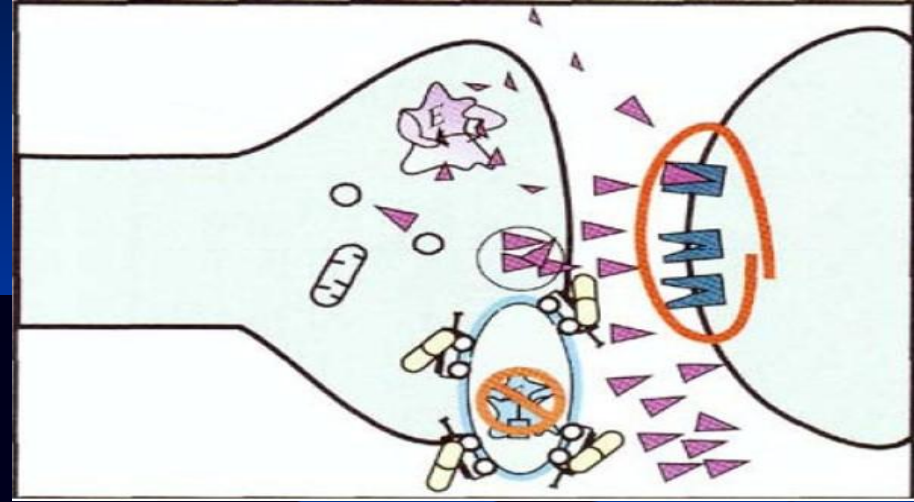


Reuptake blocking antidepressant (TCA, SSRI or SNRI) causes increase in neurotransmitters to normal state

Down & Up-regulation's



SSRI blocks the reuptake pump, causing more neurotransmitter to be in the synapse.



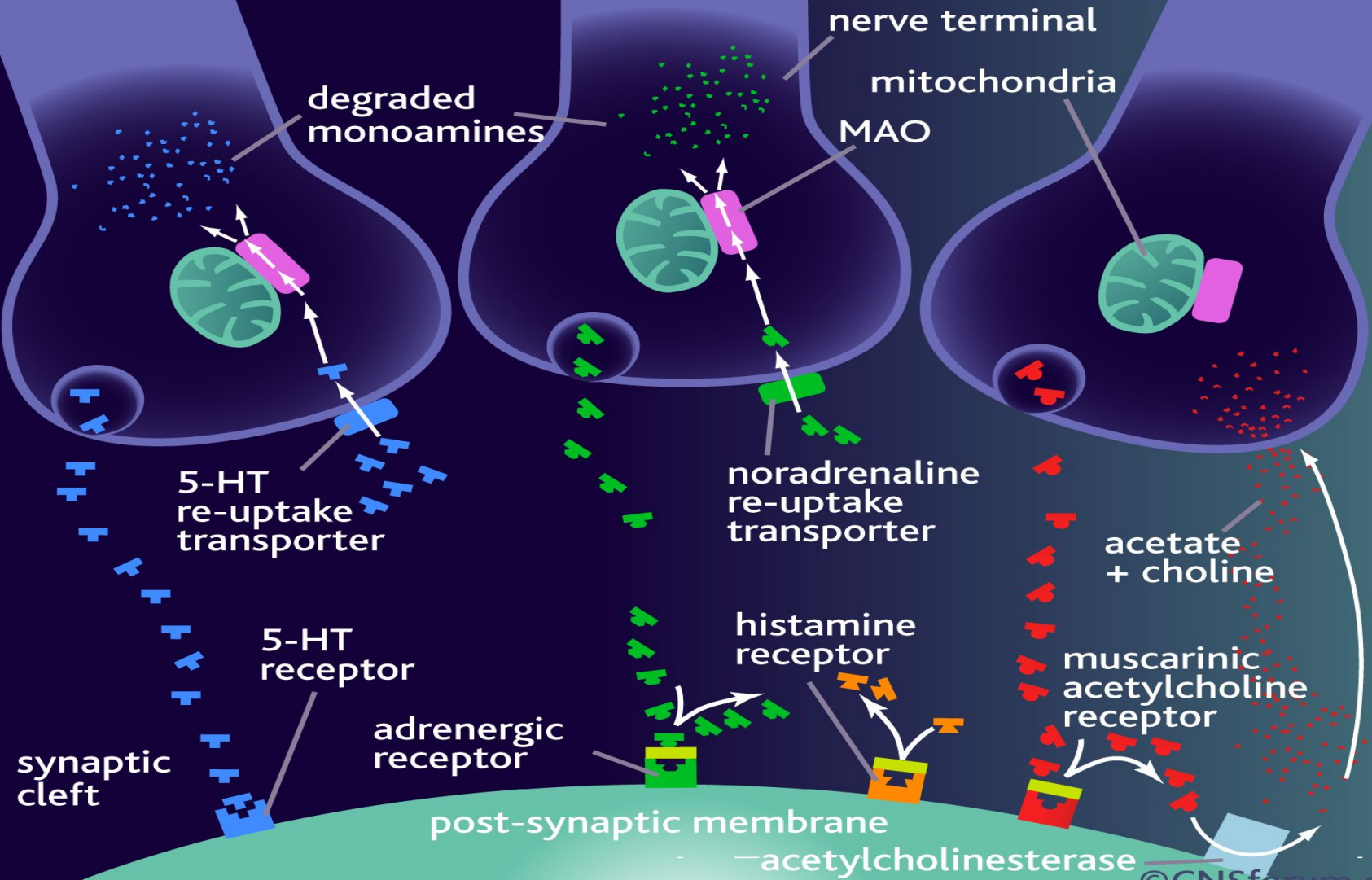
Increase in neurotransmitter causes receptors to down-regulate, eventually.

Tricyclic and related antidepressants (TCA)

■ Properties

- **Inexpensive, generic**
- Some with off-label use, e.g.
 - Neuropathy with amitriptyline
 - Refractory skin diseases with doxepin
- **Very dangerous in overdose**
 - Life threatening
 - Lethal dose only 8 times average daily dose
 - Acutely depressed patients should not be given more than 1-week TCA supply at one time

-  acetylcholine
-  5-HT
-  noradrenaline
-  histamine
-  tricyclic antidepressant



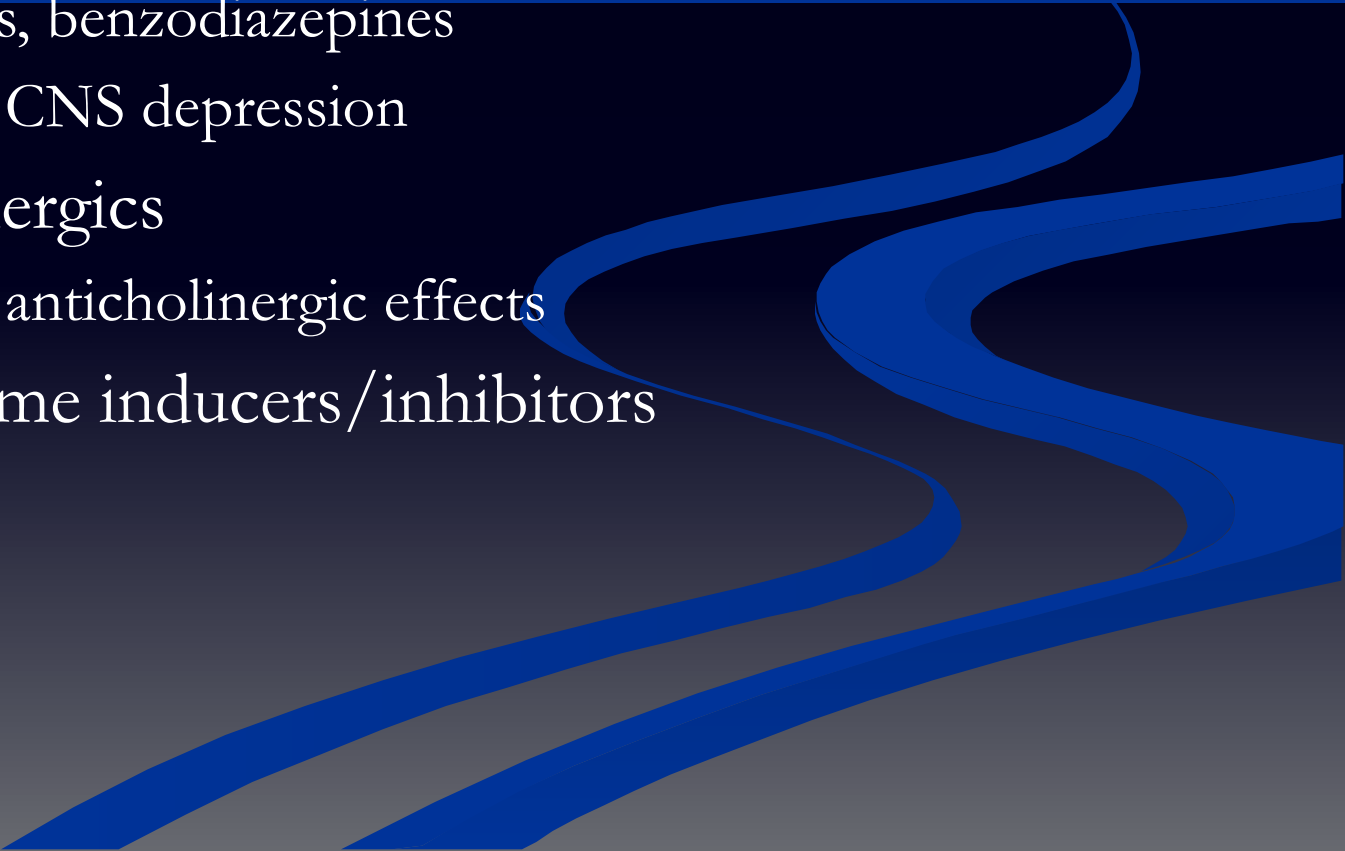
Tricyclic and related antidepressants (TCA)

- Adverse effects
 - Orthostatic hypotension
 - Reduced by moving slowly when assuming upright posture
 - Sit or lie down if symptoms (dizziness, lightheadedness) occur
 - Divided doses and slow titration
 - Anticholinergic effects
 - Dry mouth, blurred vision, photophobia, constipation, urinary retention, tachycardia
 - Tolerance may develop as treatment persists
 - Divided doses and slow titration
 - Sedation
 - Dose at bedtime

Tricyclic and related antidepressants (TCA)

- Adverse effects
 - Cardiac toxicity
 - Arrhythmias and heart block
 - ECG recommended before initiation
 - **Do not use in heart block!!!**
 - Seizures
 - Lowered seizure threshold
 - Hypomania (mild mania)
 - Elevated mood
 - Patient should be evaluated to determine dose reduction or bipolar disorder
 - Diaphoresis
 - Paradoxical effect

Tricyclic and related antidepressants (TCA)

- Drug interactions
 - CNS depressants
 - Narcotics, benzodiazepines
 - Additive CNS depression
 - Anticholinergics
 - Additive anticholinergic effects
 - P450 enzyme inducers/inhibitors
- 
- A decorative graphic consisting of several overlapping, wavy blue lines that flow from the right side of the slide towards the bottom left, creating a sense of movement and depth.

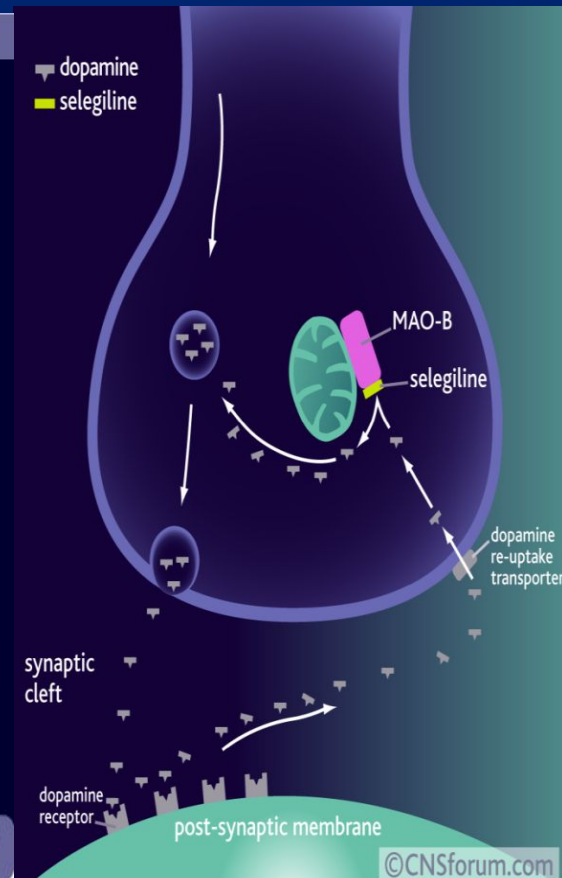
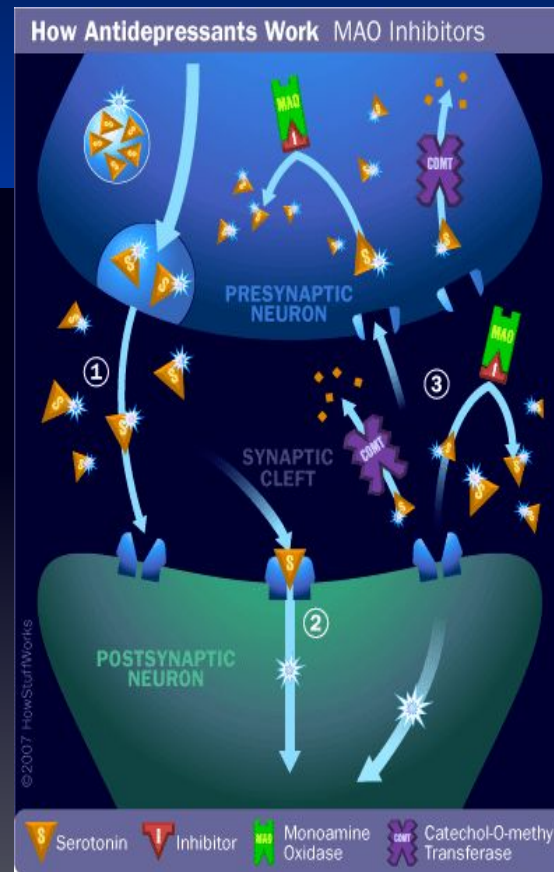
Monoamine-oxidase inhibitors (MAOI)

- Moclobemide (Aurorix®) (RIMAs - Reversible Inhibitors of Monoamine Oxidase)
 - Phenelzine
 - Isocarboxazid
 - Tranylcypromine
- 
- A decorative graphic consisting of several overlapping, wavy blue lines that flow from the right side of the slide towards the bottom left, creating a sense of movement and depth.

Monoamine-oxidase inhibitors (MAOI)

Mechanism of action

- Inhibit both MAO-A and MAO-B
 - Phenelzine, tranylcypromine
- Selective & reversible inhibitor of MAO-A
 - Moclobemide



Monoamine-oxidase inhibitors (MAOI)

■ Properties

- Useful in atypical depression (somnolence and weight gain), refractory disorders and certain types of anxiety disorders
- Less prescribed than tricyclics, SSRIs and other antidepressants
 - **Danger of dietary and drug interactions**

Monoamine-oxidase inhibitors (MAOI)

■ Properties

■ Drug interactions

- Other antidepressants should not be started for **2 weeks after MAOI has been stopped (3 weeks for clomipramine or imipramine)**
- MAOI should not be started for **7-14 days after a tricyclic or related antidepressant (3 weeks for clomipramine or imipramine)**
- MAOI should not be started for at **least 2 weeks after a previous MAOI**

Monoamine-oxidase inhibitors (MAOI)

- Adverse effects

- Hypertensive crisis


- Severe occipital headache, photophobia, palpitation, sharply increased in BP due to additive effect between MAOI and adrenergic stimulants

- Tyramine-rich food e.g. cheese, wine (), smoked/aged/picked meat or fish, alcohol
 - Amphetamins
 - Pseudoephedrine

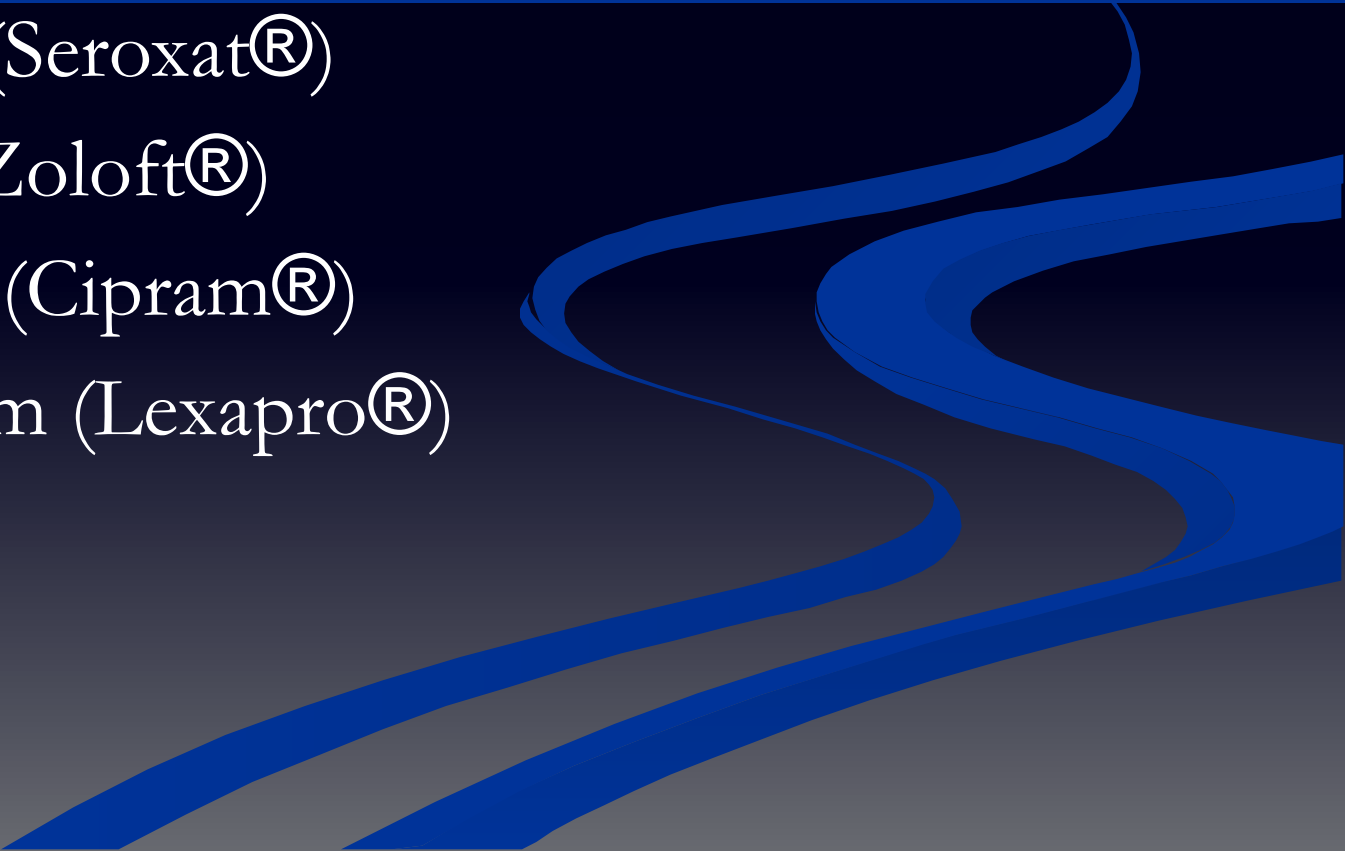
Monoamine-oxidase inhibitors (MAOI)

- Adverse effects
 - Hypertensive crisis
 - Severe occipital headache, photophobia, palpitation, sharply increased in BP due to additive effect between MAOI and adrenergic stimulants
 - Tyramine-rich food e.g. cheese, wine (*Chianti*), smoked/aged/picked meat or fish, alcohol
 - Amphetamins
 - Pseudoephedrine

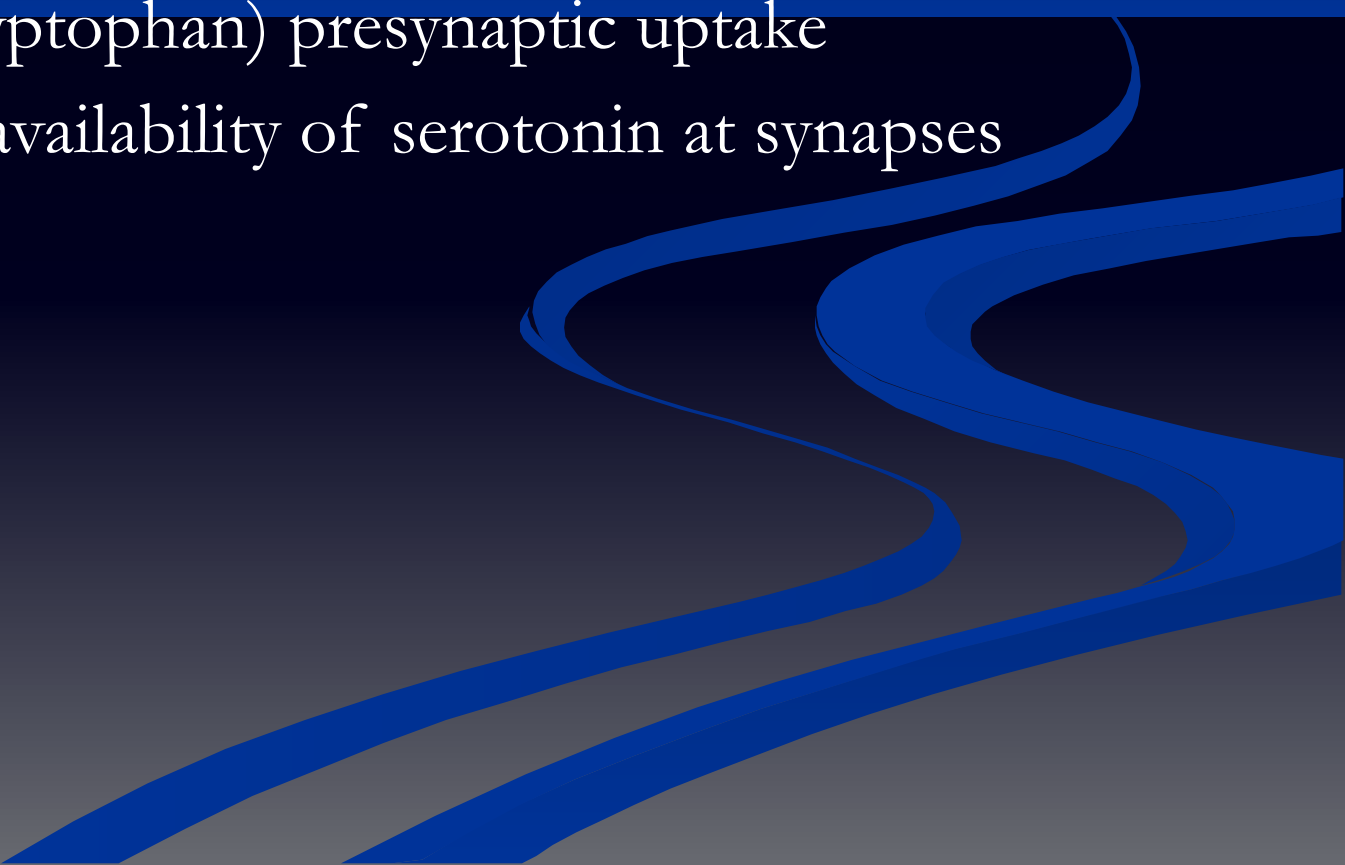
Monoamine-oxidase inhibitors (MAOI)

- Adverse effects
 - Orthostatic hypotension
 - Insomnia
 - Weight gain
 - Sexual dysfunction
- 
- A decorative graphic consisting of several overlapping, wavy, blue lines that flow from the right side of the slide towards the bottom left. The lines vary in thickness and create a sense of movement and depth against the dark blue background.

Selective serotonin reuptake inhibitors (SSRI)

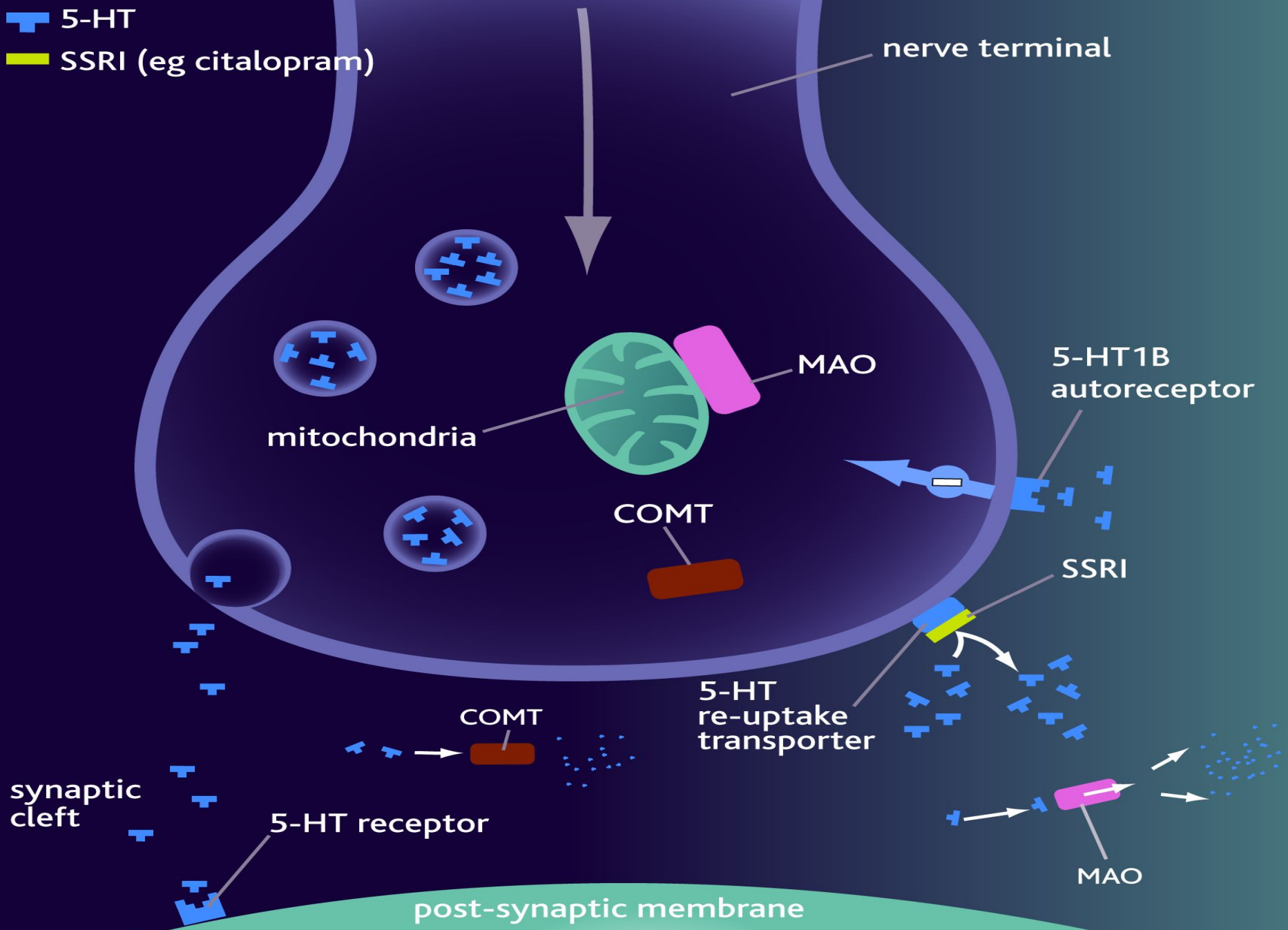
- Fluoxetine (Prozac®)
 - Fluvoxamine (Faverin®)
 - Paroxetine (Seroxat®)
 - Sertraline (Zoloft®)
 - Citalopram (Cipram®)
 - Escitalopram (Lexapro®)
- 
- A decorative graphic consisting of several thick, wavy blue lines that flow from the bottom left towards the right side of the slide, creating a sense of movement and depth.

Selective serotonin reuptake inhibitors (SSRI)

- Mechanism of action
 - Inhibits reuptake of serotonin (5-HT - hydroxytryptophan) presynaptic uptake
 - Increases availability of serotonin at synapses
- 
- The bottom half of the slide features several thick, wavy, blue lines that flow from the right side towards the left, creating a sense of movement and depth against the dark blue background.

5-HT

SSRI (eg citalopram)



nerve terminal

mitochondria

MAO

5-HT1B autoreceptor

COMT

SSRI

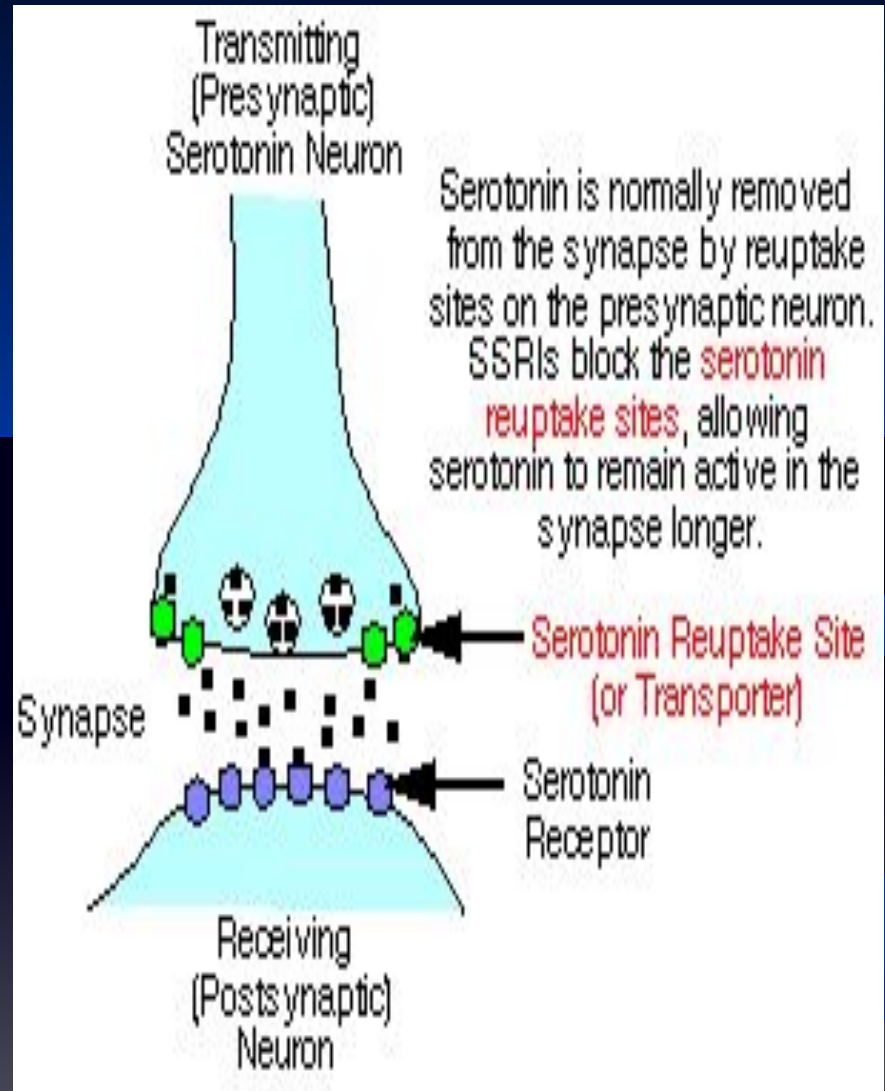
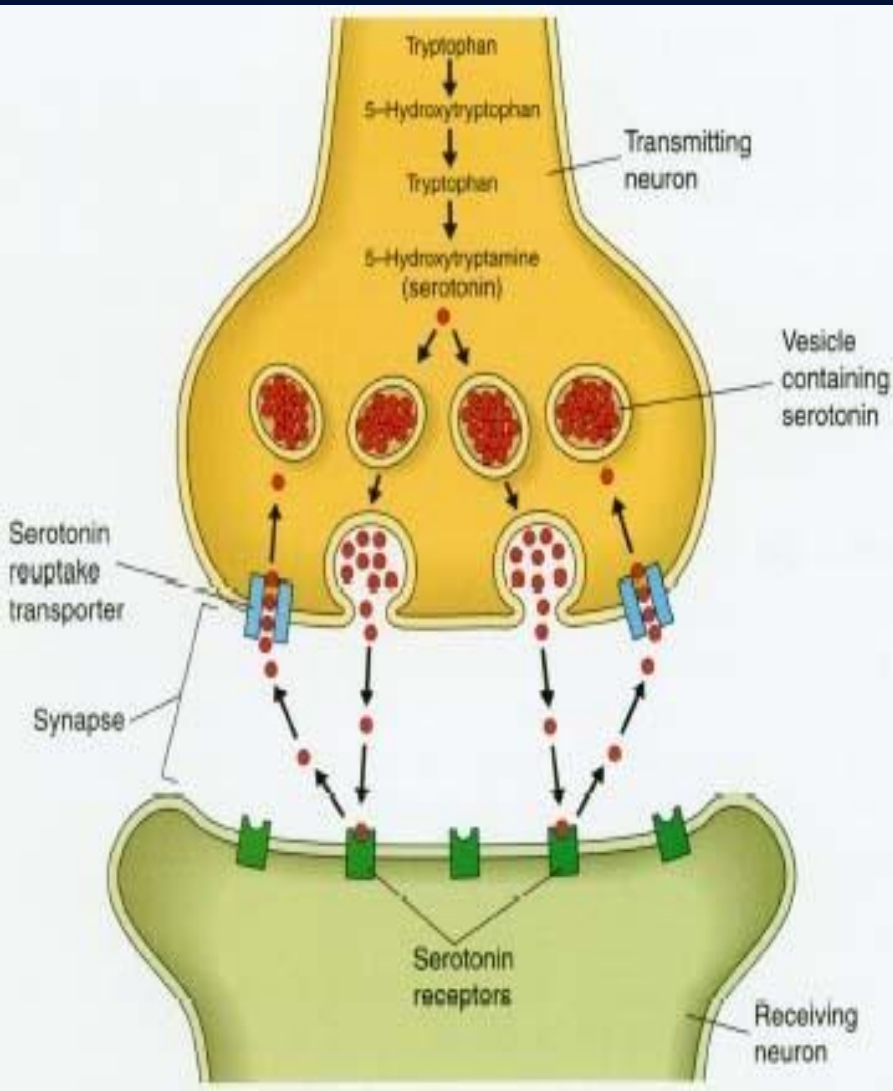
5-HT re-uptake transporter

synaptic cleft

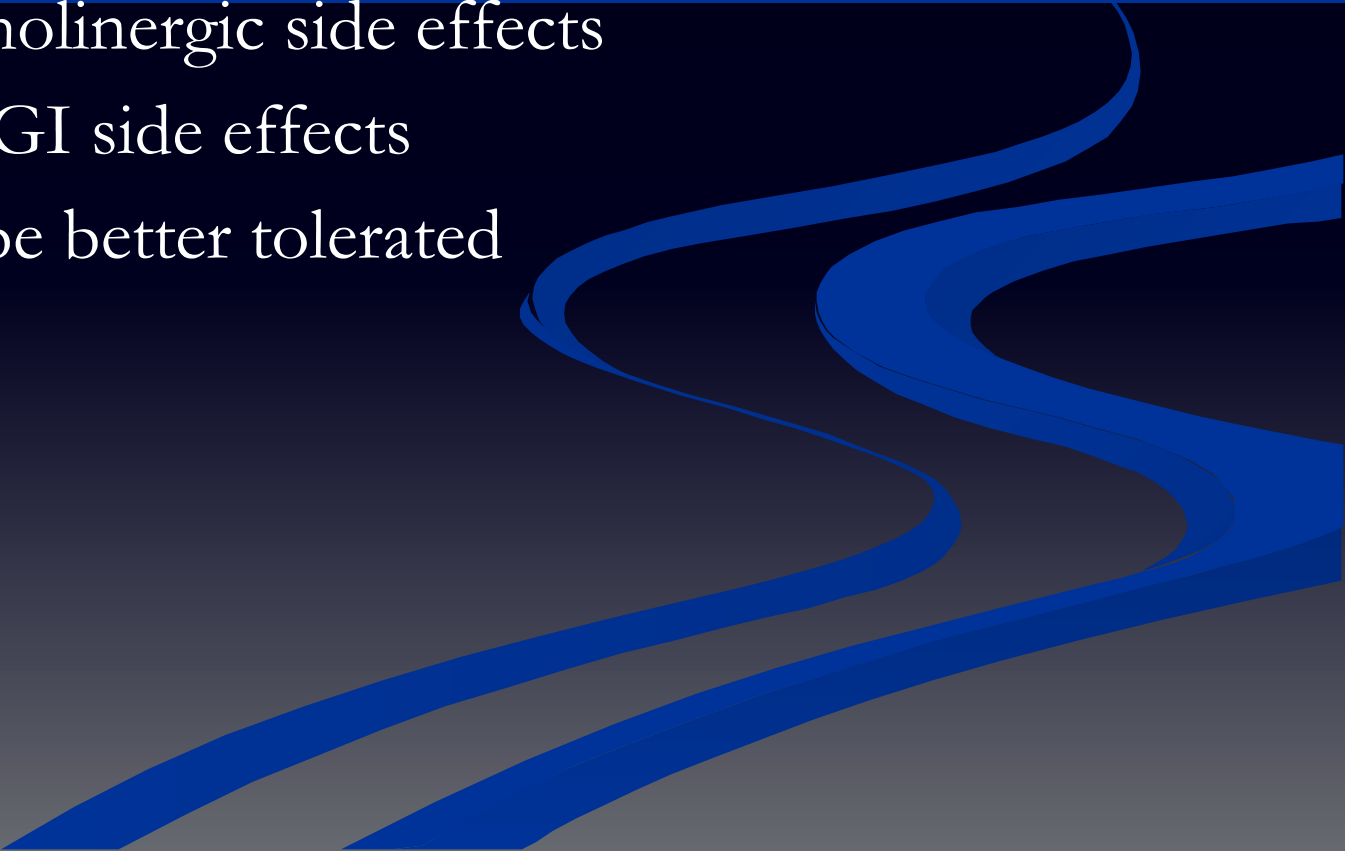
5-HT receptor

post-synaptic membrane

MAO



Selective serotonin reuptake inhibitors (SSRI)

- Properties
 - Overdose less likely to be fatal
 - Less anticholinergic side effects
 - But more GI side effects
 - Seems to be better tolerated
- 
- A decorative graphic consisting of several overlapping, wavy blue lines that flow from the right side of the slide towards the bottom left, creating a sense of movement and depth.

Selective serotonin reuptake inhibitors (SSRI)

■ Properties

■ Fluoxetine

- Most stimulating SSRI
- Indicated for Premenstrual Dysphoric Disorder (PMDD) (as Sarafem®)(?)
- Long half-life, ensure 5 week washout before MAOI (2 week for other SSRI)

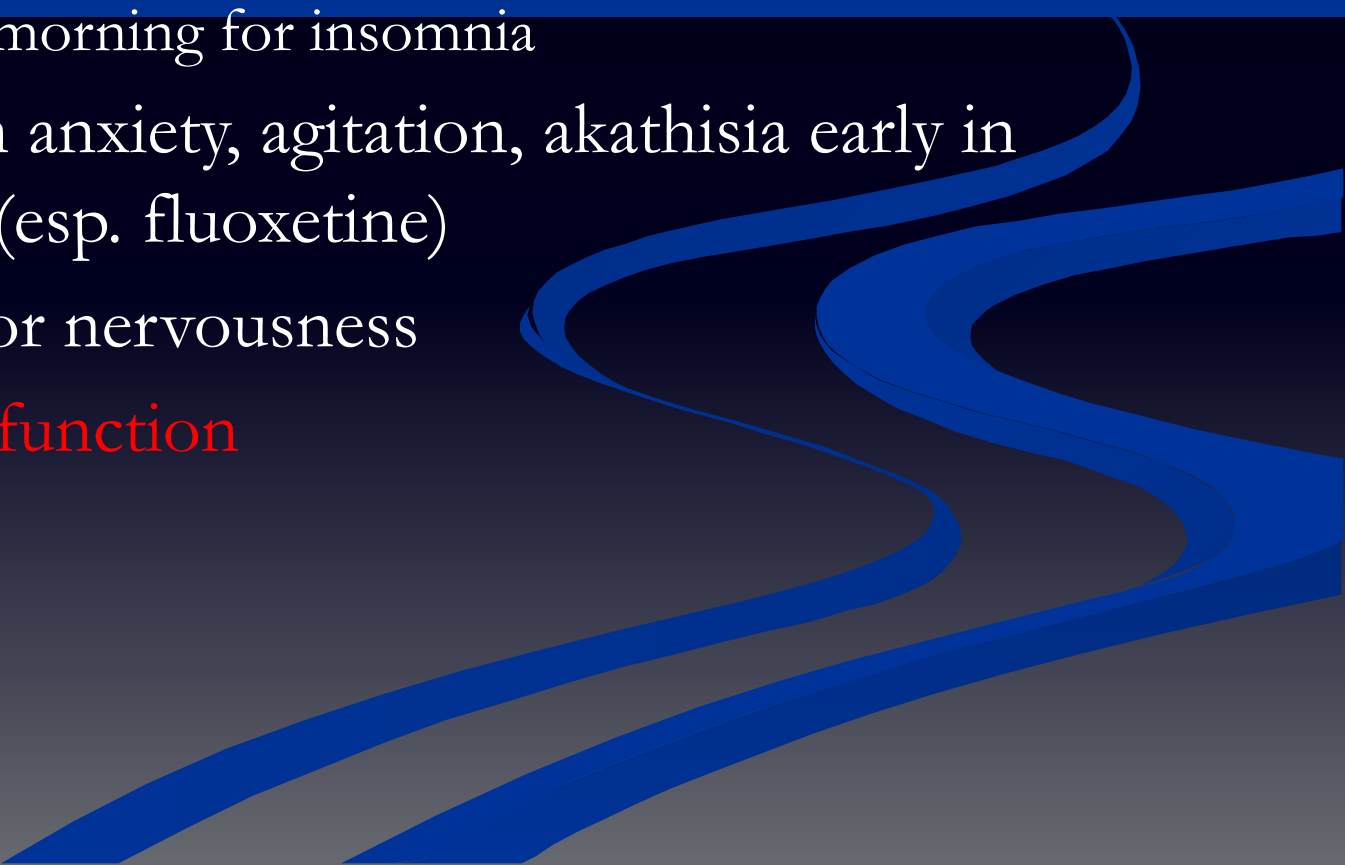
■ Some SSRIs also indicated for

- Obsessive-compulsive disorder (OCD)
- Panic disorder
- Eating disorders
- Social phobia
- Post traumatic stress disorder (PTSD)

Selective serotonin reuptake inhibitors (SSRI)

- Adverse effects
 - Headache
 - GI
 - Nausea, diarrhoea, loss of appetite
 - Titrate dose to minimize side effect
 - May be taken with food
 - Anticholinergic Adverse effects
 - Fever than TCA
 - Tend to see more with Paroxetine

Selective serotonin reuptake inhibitors (SSRI)

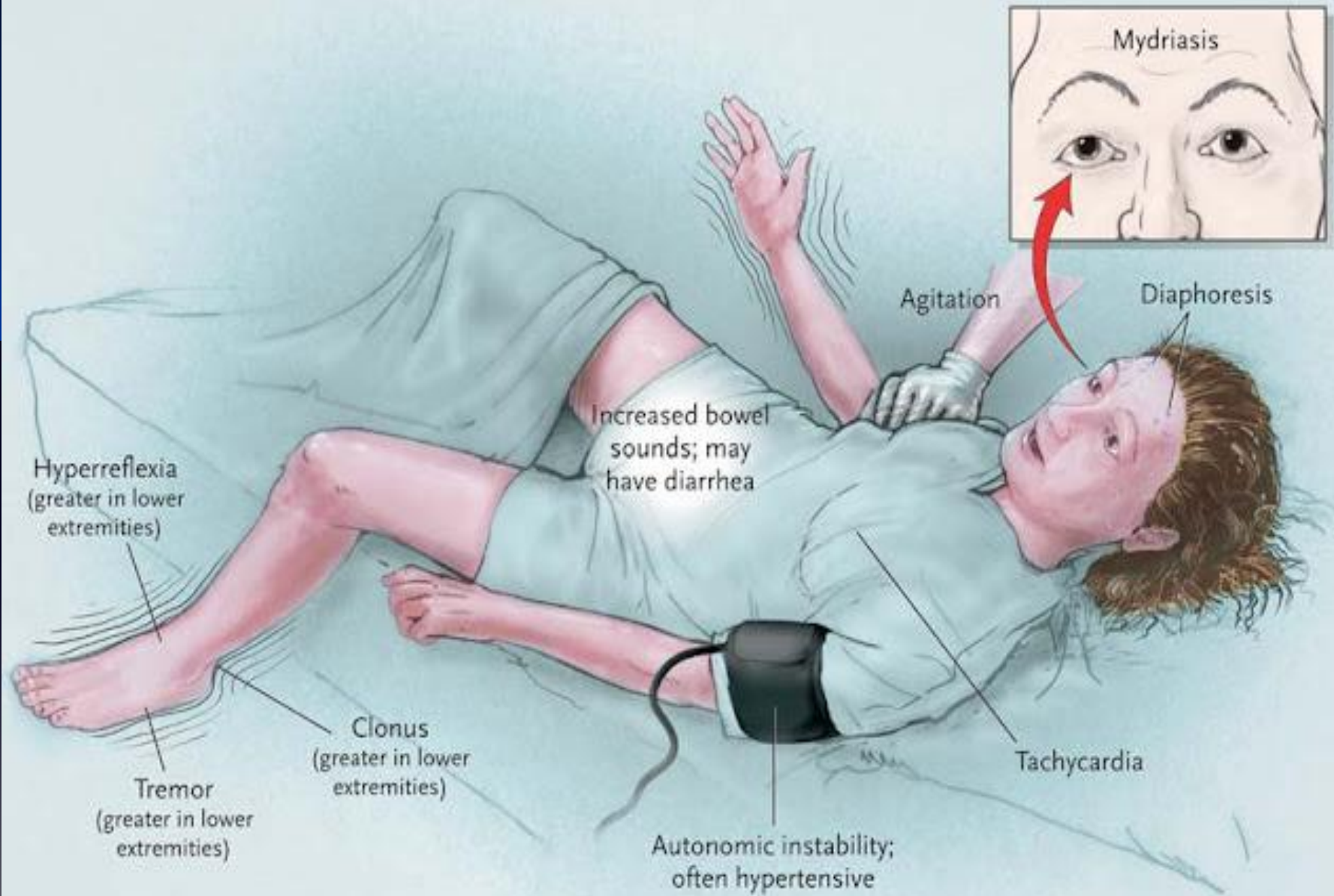
- Adverse effects
 - Somnolence or insomnia
 - Dose in morning for insomnia
 - Increase in anxiety, agitation, akathisia early in treatment (esp. fluoxetine)
 - Agitation or nervousness
 - **Sexual dysfunction**
- 

Selective serotonin reuptake inhibitors (SSRI)

- Adverse effects
 - Serotonergic syndrome

Aetiology - SSRI or MAOI + something else
(usually with sl. Different serotonin action)

- Rare but potentially fatal interaction between 2 or more drugs that enhance serotonin
- Confusion, Anxiety, shivering, diaphoresis, tremor, hyperflexia, clonus, autonomic instability (BP, pulse) tachycardia, flushing
- Fatal if malignant hyperthermia - **ICU**
- Management
 - Mild: resolve in 24-48 hours after discontinuing offending agent
 - Severe: 5-HT antagonist, cyproheptidine, propranolol, methysergide, dantrolene (hyperthermia)



Mydriasis

Agitation

Diaphoresis

Increased bowel sounds; may have diarrhea

Hyperreflexia (greater in lower extremities)

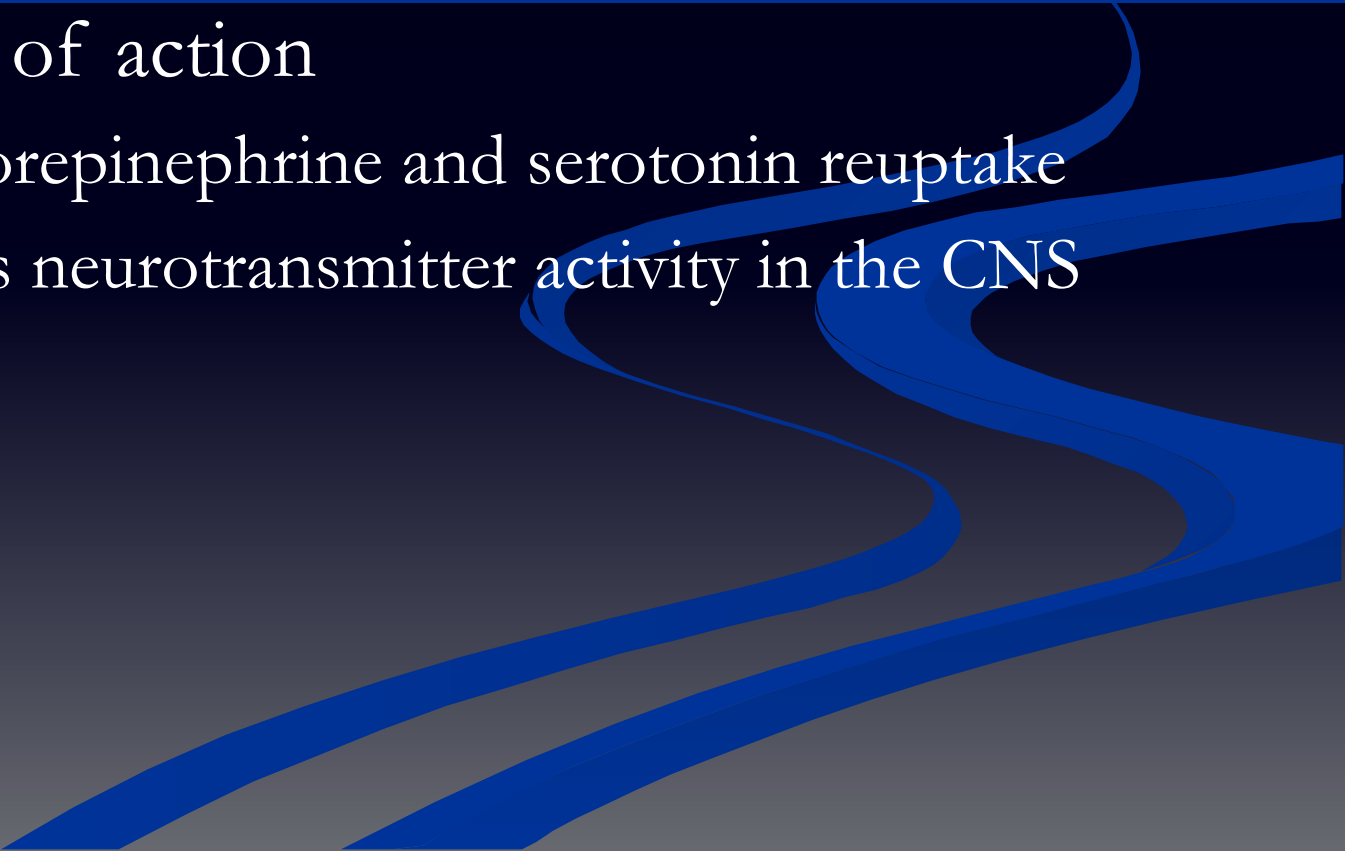
Clonus (greater in lower extremities)

Tremor (greater in lower extremities)

Tachycardia

Autonomic instability; often hypertensive

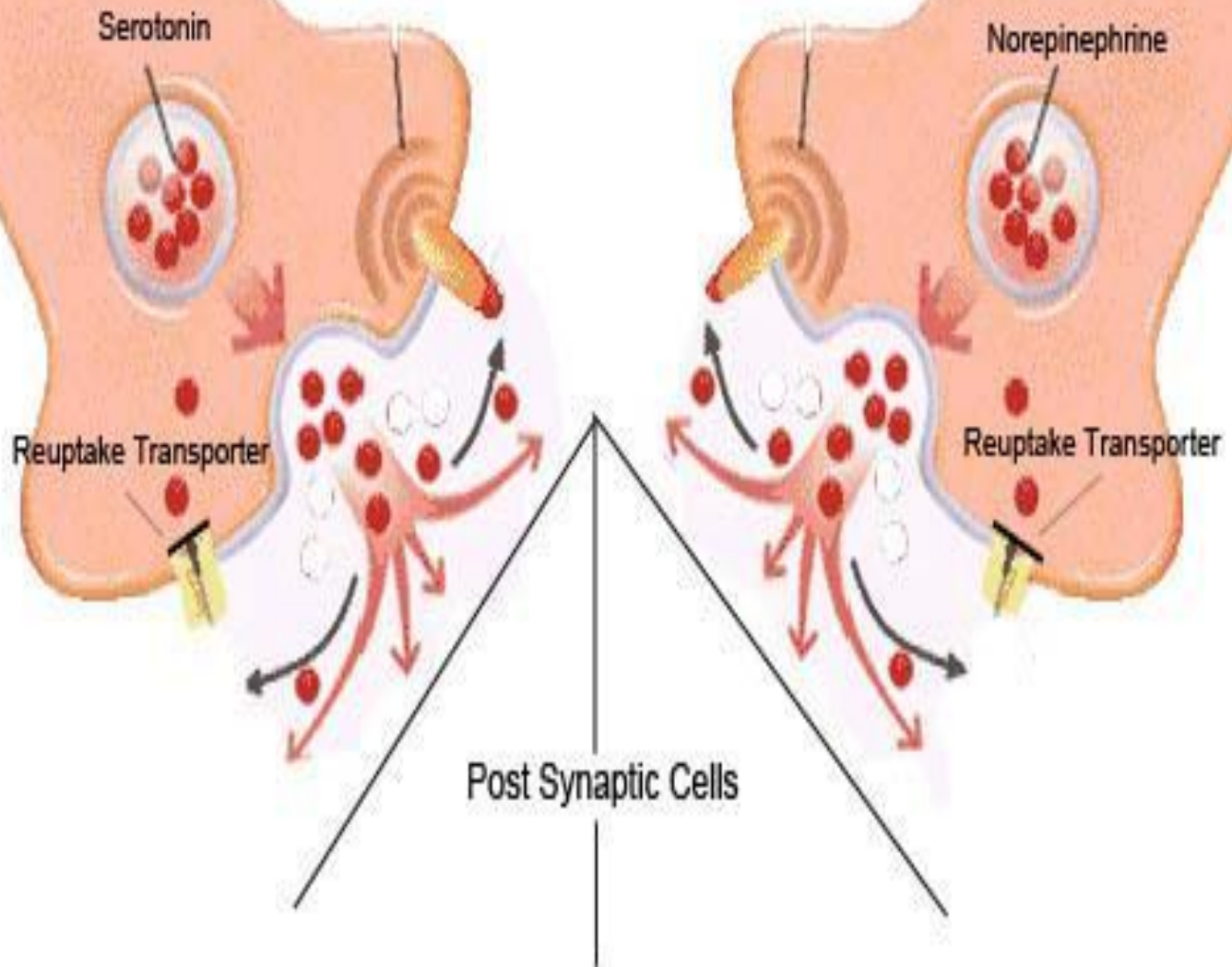
Serotonin norepinephrine reuptake inhibitor (SNRI)

- Duloxetine (Cymbalta®)
 - Venlafaxine (Efexor®, Efexor XR®)
 - Mechanism of action
 - Inhibits norepinephrine and serotonin reuptake
 - Potentiates neurotransmitter activity in the CNS
- 
- A decorative graphic consisting of several thick, wavy blue lines that flow from the right side of the slide towards the bottom left, creating a sense of movement and depth.

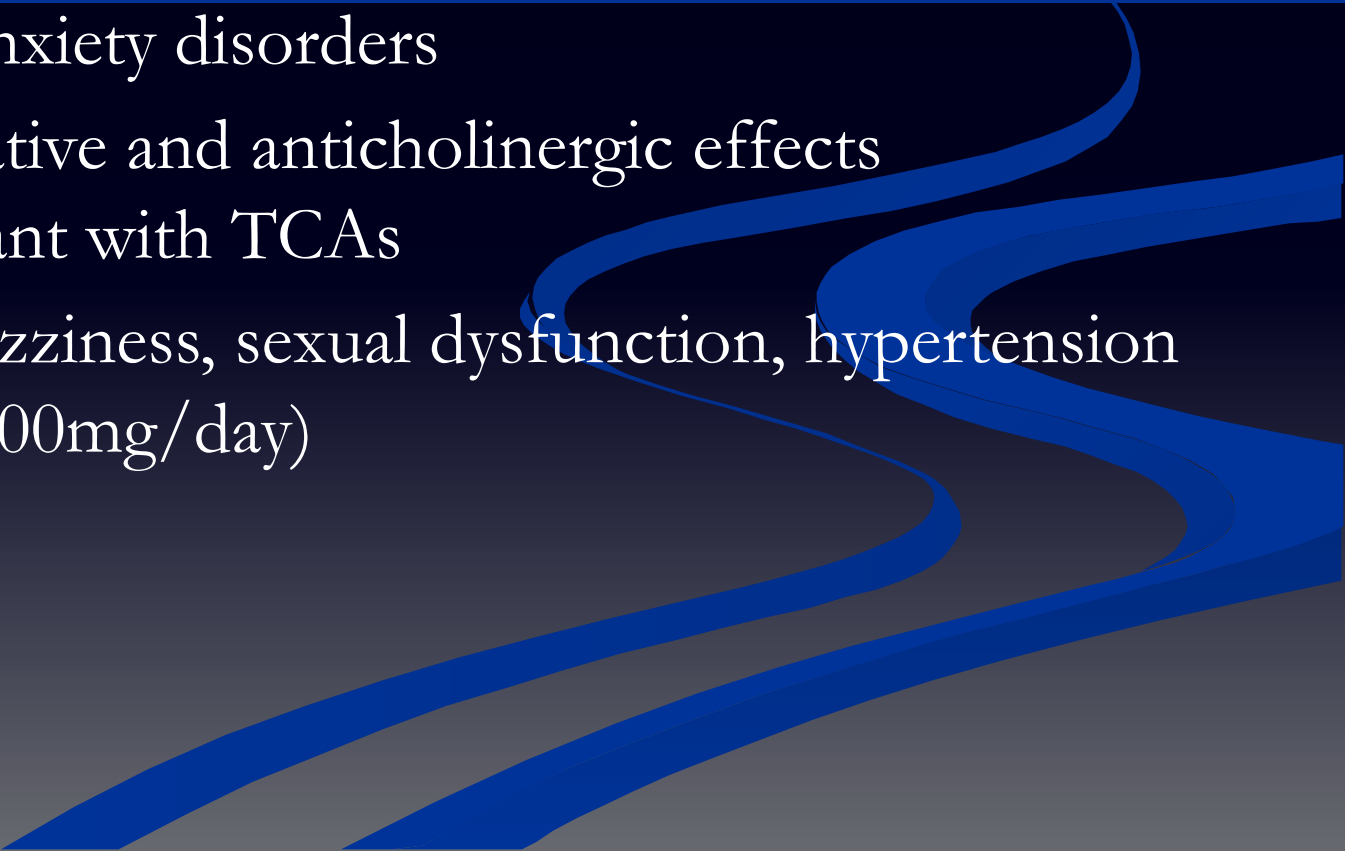
SNRI Mechanism of Action

Serotonergic Neuron

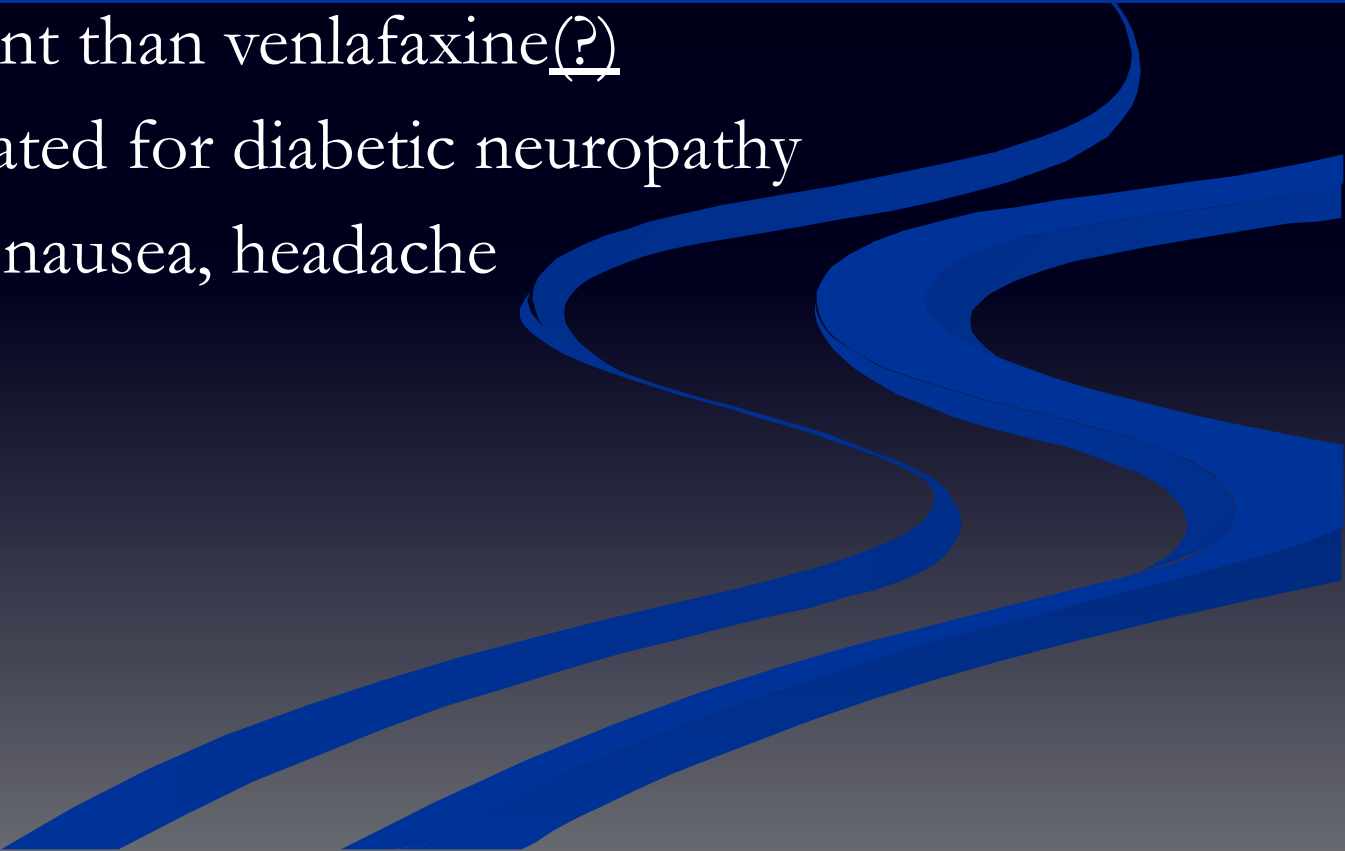
Adrenergic Neuron



Serotonin norepinephrine reuptake inhibitor (SNRI)

- Venlafaxine (Efexor®), Efexor XR®
 - Properties and Adverse effects
 - Also for anxiety disorders
 - Lacks sedative and anticholinergic effects predominant with TCAs
 - Nausea, dizziness, sexual dysfunction, hypertension (when > 300mg/day)
- 
- A decorative graphic consisting of several thick, wavy blue lines that flow from the right side of the slide towards the bottom left, creating a sense of movement and depth.

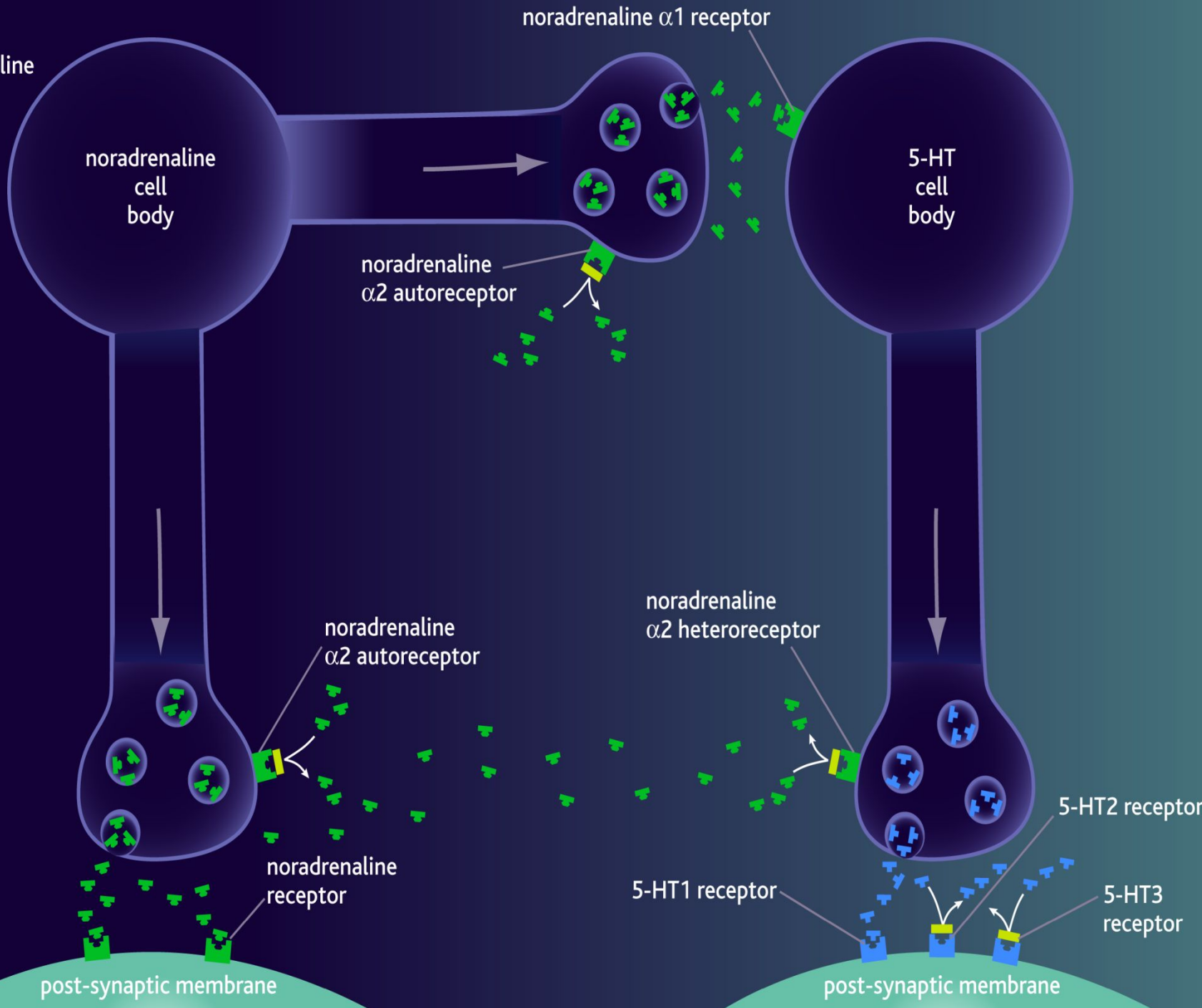
Serotonin norepinephrine reuptake inhibitor (SNRI)

- Duloxetine (Cymbalta®)
 - Properties and Adverse effects
 - More potent than venlafaxine(?)
 - Also indicated for diabetic neuropathy
 - Insomnia, nausea, headache
- 
- A decorative graphic consisting of several thick, wavy blue lines that flow from the right side of the slide towards the bottom left, creating a sense of movement and depth.

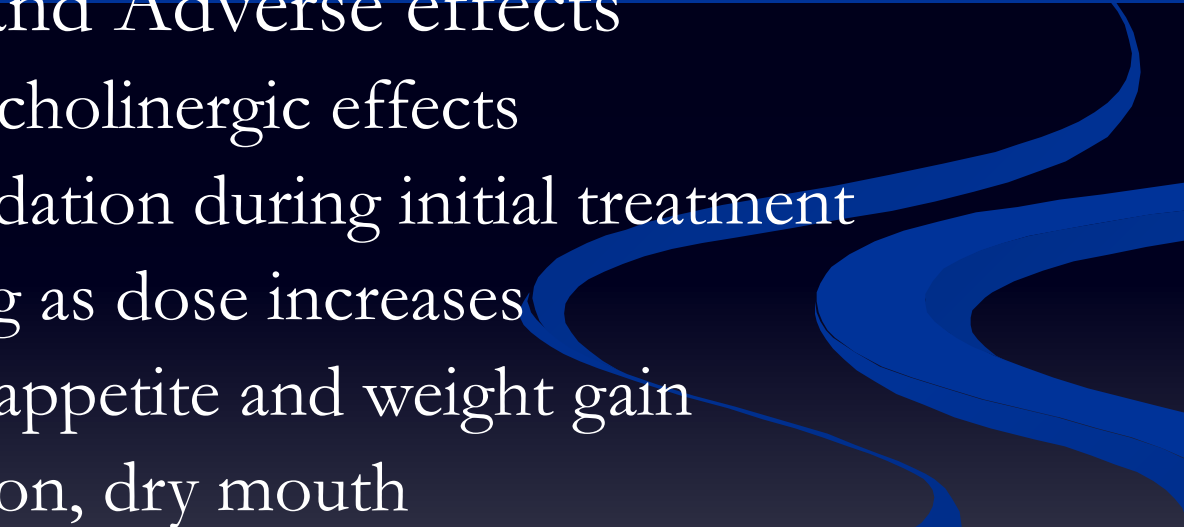
Mixed serotonin norepinephrine effects

- Mirtazapine (Mirtazon®), Remeron®, Remeron SolTab®)
Tetracyclic antidepressant (Noradrenergic and Specific Serotonergic Antidepressants - NaSSAs).
- Mechanism of action
 - NaSSAs bind to and inhibit both noradrenaline α_2 -autoreceptors and noradrenaline α_2 -heteroreceptors. This action prevents the negative feedback effect of synaptic noradrenaline on 5-HT and noradrenaline neurotransmission, and neurotransmission sustained.
 - have a dual mechanism of action that increases the concentration of 5-HT and noradrenaline in the synaptic cleft to within the normal range.
 - NaSSAs also block 5-HT₂ and 5-HT₃ receptors on the post-synaptic membrane, which causes enhanced 5-HT₁ mediated neurotransmission.
 - Increases central noradrenergic and serotonergic neurotransmission

- 5-HT
- noradrenaline
- nassa

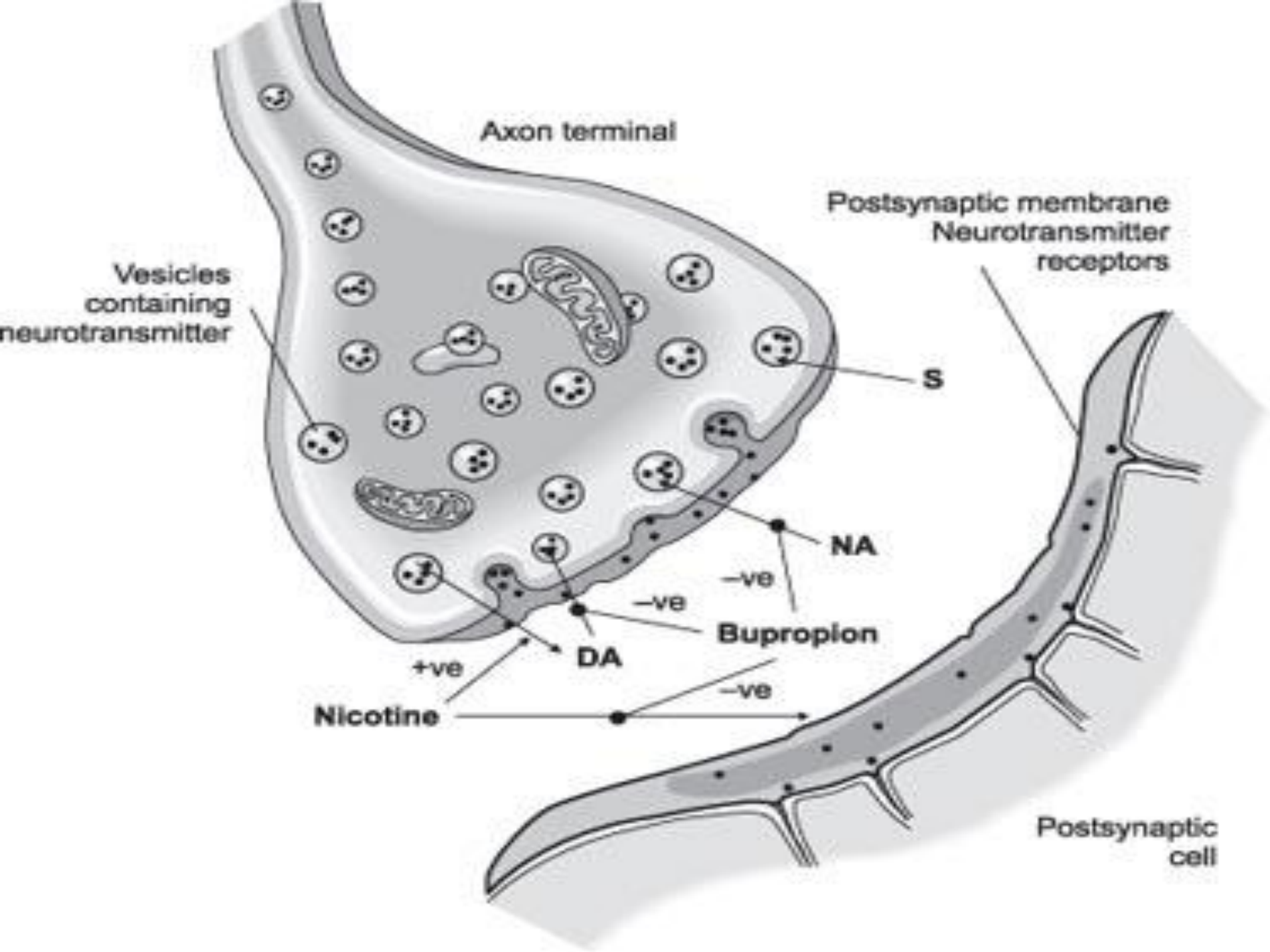


Mixed serotonin norepinephrine effects

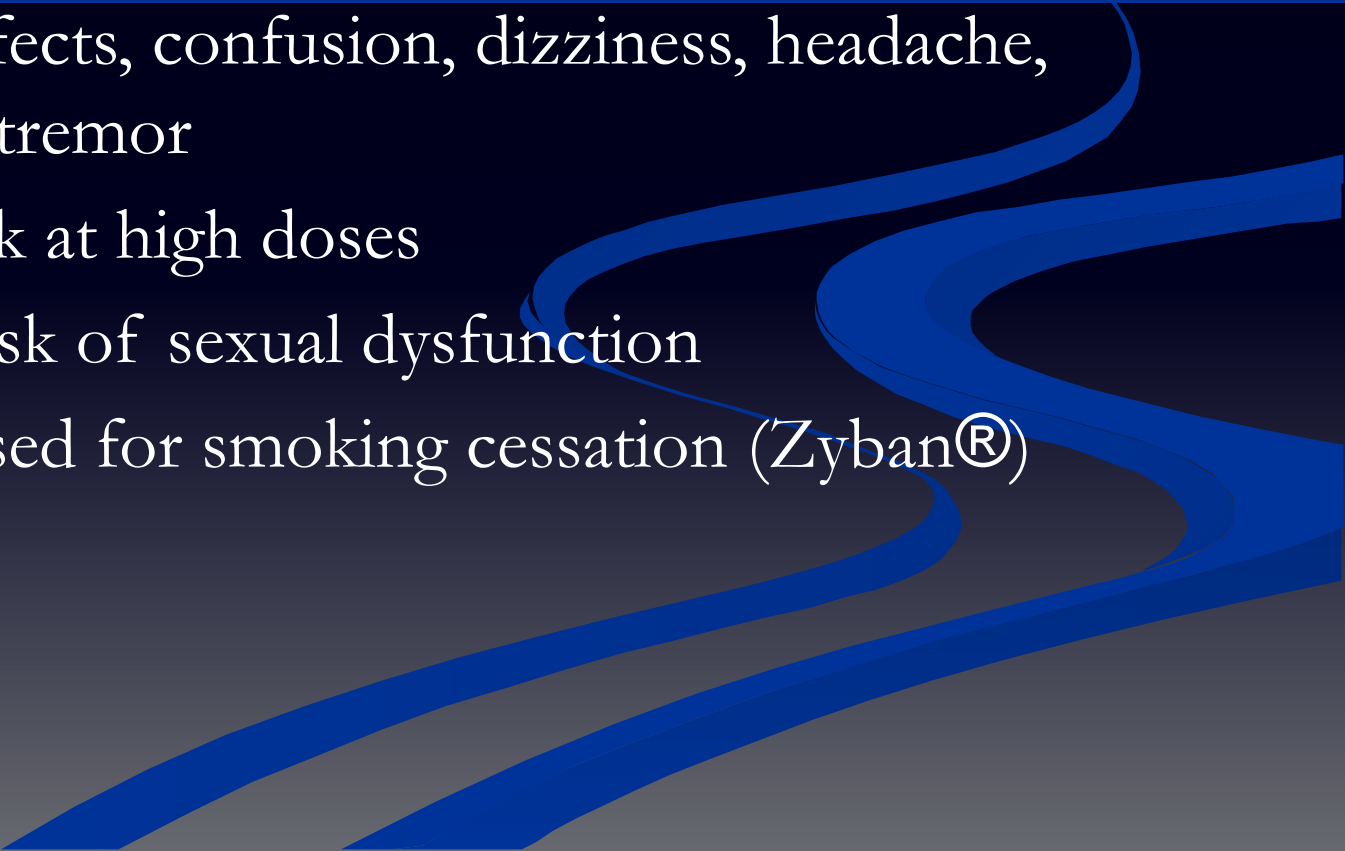
- Mirtazapine (Mirtazon®), Remeron®, Remeron SolTab®)
 - Properties and Adverse effects
 - Fewer anticholinergic effects
 - Marked sedation during initial treatment
 - Stimulating as dose increases
 - Increased appetite and weight gain
 - Constipation, dry mouth
- 
- A decorative graphic consisting of several thick, wavy blue lines that flow from the right side of the slide towards the bottom left, creating a sense of movement and depth.

Norepinephrine dopamine reuptake inhibitor (NDRI)

- Bupropion (Wellbutrin SR®)
- Mechanism of action
 - Inhibits weakly the neuronal uptake of dopamine, norepinephrine and serotonin
 - Does not inhibit monoamine oxidase
 - Also acts as a nicotinic acetylcholine receptor antagonist



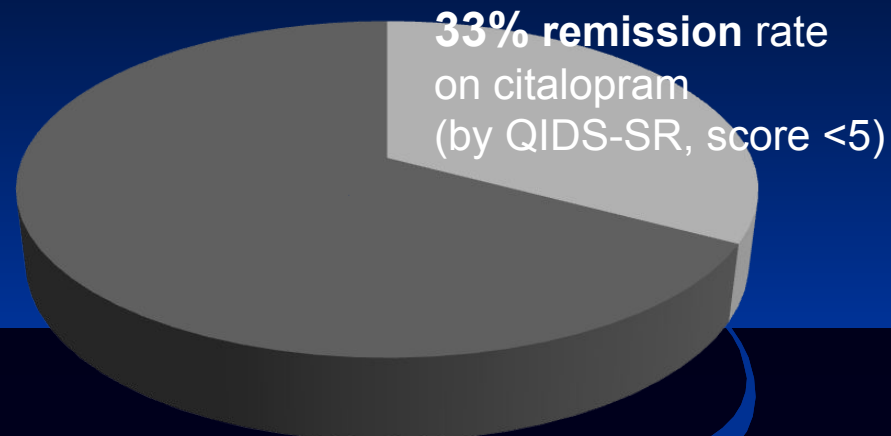
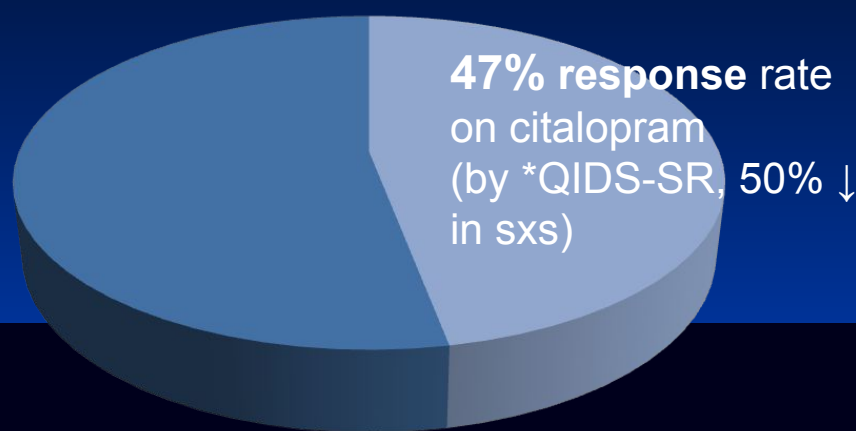
Norepinephrine dopamine reuptake inhibitor (NDRI)

- Bupropion (Wellbutrin SR®)
 - Properties and side effects
 - GI side effects, confusion, dizziness, headache, insomnia, tremor
 - Seizure risk at high doses
 - Minimal risk of sexual dysfunction
 - Also licensed for smoking cessation (Zyban®)
- 

Other antidepressants

- Flupenthixol (Fluanxol®)
 - Typical antipsychotic
 - Antidepressant effect at low doses
 - Antipsychotic dose: 3-9mg twice daily
 - Antidepressant dose: 1-3mg daily
 - Combined with another antidepressant as Deanxit®
 - Flupenthixol 0.5mg + melitracen 10mg
 - For depression and anxiety
 - Trazodone, ~~Nefazodone~~ - Serotonin antagonists and reuptake inhibitors (SARIs)

Sequenced Treatment Alternatives for the Relief of Depression (STAR*D), n = 2,876 (qualifying pts)



Rx choice:

- according to side effects (SE's), comorbid condn's / risks (GMC & Ψ), ?FmRxHx
- 6-8wk trials each (preferable)
- augmentation v. switch?

*QIDS-SR = Quick Inventory of Depressive Symptomatology, Self-Report (range 0-27)

<http://www.ids-qids.org/>

Antidepressants in depression

- Choice of agents
 - *All are equally efficacious for depression*
 - Selection based on
 - Side effect profile
 - Potential drug interaction
 - Response failure to an antidepressant does not predict response to another drug class or another drug within class

Antidepressants in depression

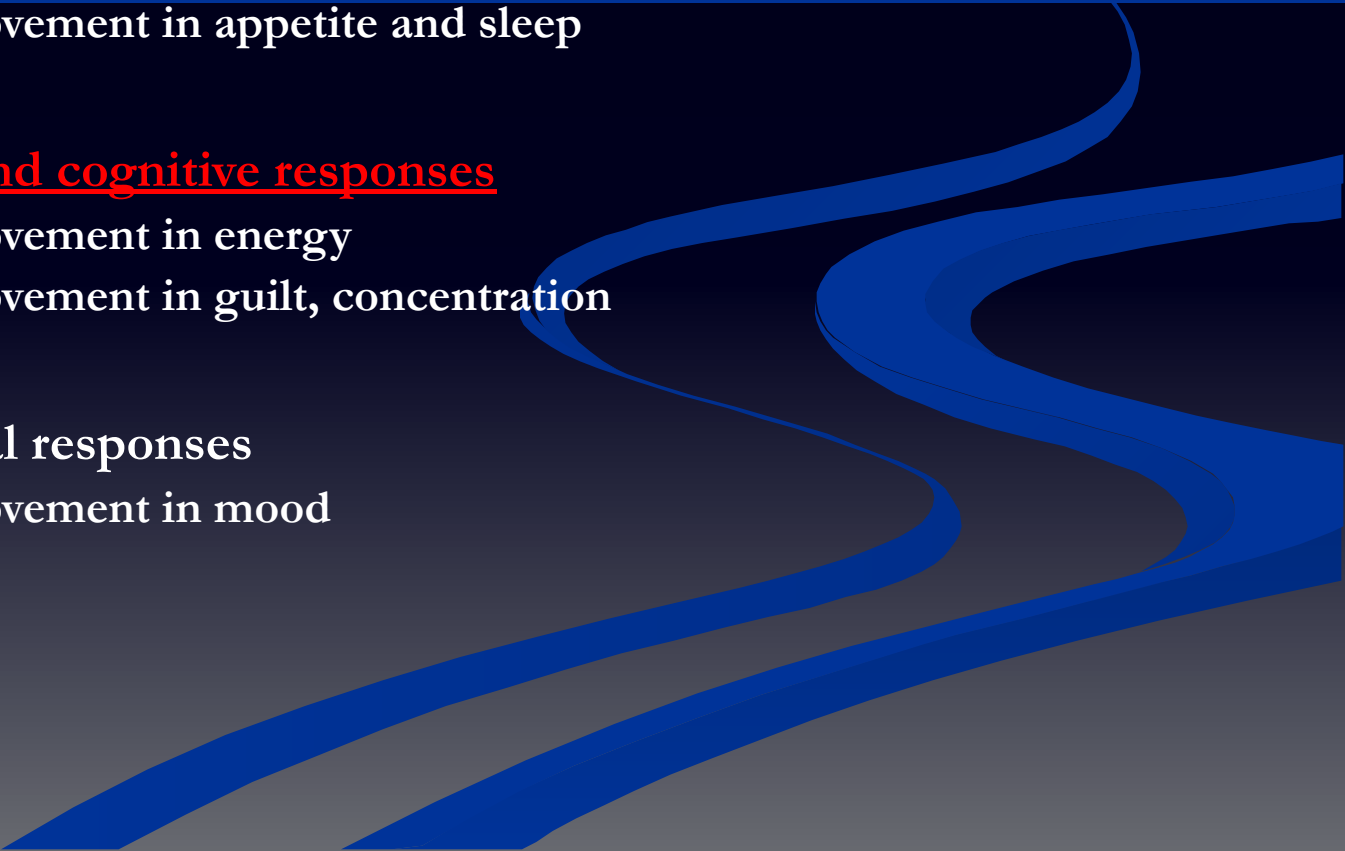
■ Geriatrics

- Reduce initial dose by half
- Gradual dose titration
 - Risk of dizziness and syncope
 - **Hyponatremia**

■ Pediatrics

- Decrease initial dose by half
- Recent evidence links SSRIs with suicide in adolescents(?)

Antidepressants in depression

- Treatment response
 - Weeks 1-2
 - Physical responses
 - Improvement in appetite and sleep
 - Weeks 3-4
 - Energy and cognitive responses
 - Improvement in energy
 - Improvement in guilt, concentration
 - Weeks 5-6
 - Emotional responses
 - Improvement in mood
- 
- A decorative graphic consisting of several overlapping, wavy blue lines that flow from the top right towards the bottom left, creating a sense of movement and depth against the dark blue background.

Antidepressants in depression

- Continuation therapy
 - To prevent relapse
 - **4-9 months after complete remission of symptoms**
 - **At therapeutic doses**
- Lifelong maintenance therapy
 - Recommended by some investigators for patients at greater risk or reoccurrence
 - < 40 years with ≥ 2 prior episodes
 - Any age with ≥ 3 prior episodes

Antidepressant Discontinuation

Neuro

Dizziness / confusion

agitation or anxiety,

tremor

sensory disturbances

paraesthesia

electric shock sensations),

sleep disturbances (including intense dreams),

Somatic

Nausea

sweating,

headache,

diarrhoea

Usually resolve within 2 weeks but lasts 2-3 months for some

- Taper if previous hx.
- **Worst TCA, venlafaxine, paroxetine (incl. flu like illness)**

SSRI side effects

Sexual

A. Anorgasmia or delayed orgasm

B. Reduced libido

C. Ejaculatory dysfunction esp.
retarded/delayed ejaculation

D. Erectile dysfunction

Pregnancy and TCAs

| | |
|----------------|---|
| Generally safe | BUT: anticholinergic withdrawal post delivery (irritability, fever, colic) |
| Doxepin | NO: reports of malformations |
| Clomipramine | NO: Premature delivery and subsequent convulsions (abated by a single dose of clomipramine) |
| Nortriptyline | May be particularly good because blood levels can be monitored |

Risks of SSRIs and Pregnancy

| | | |
|---------------------------------------|------------------|--|
| Postpartum withdrawal/toxicity | Over-excitement | Jitteriness Irritability tremor Hyperreflexia vomiting Seizures |
| | Under-excitement | Floppiness Hypotonia Feeding difficulty |
| | Medical problems | Jaundice Cyanosis Apnoea Respiratory distress Hypoglycaemia Temperature instability |

Risks of SSRIs and Pregnancy

| | |
|---------------------------------------|---|
| Birth defects 1st trimester | 4% paroxetine vs 2% usual (US) 60% increase all SSRIs (Danish) 2% VSD (ventricular septal defect) paroxetine vs 1% usual |
|---------------------------------------|---|

Non-antidepressants in depression

- Anxiolytics
- Antipsychotics
 - Use may mask the true diagnosis
 - Used with caution
 - But are still useful adjuncts in agitated patients
- Lithium and thyroid
 - To potentiate effect of antidepressants in refractory cases
 - Lithium: plasma level 0.4-0.8mEq/L
 - Thyroid supplement: 25mcg/day

