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

Antidepressant are use 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

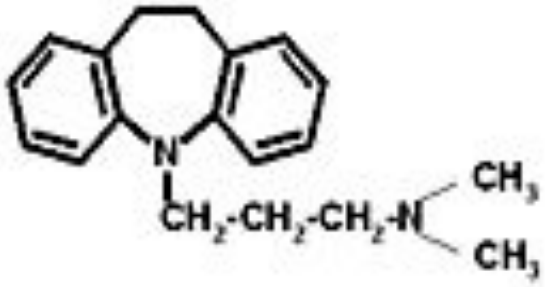
- Tricyclic and related antidepressants (TCA)
  - E.g. amitriptyline, imipramine, doxepin, mianserin, trazodone
- Monoamine-oxidase inhibitors (MAOI)
  - E.g. moclobemide, phenelzine, isocarboxazid, tranylcypromine
- Selective serotonin reuptake inhibitors (SSRI)
  - E.g. fluoxetine, paroxetine, sertraline,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

Tricyclic and related antidepressants (TCA)

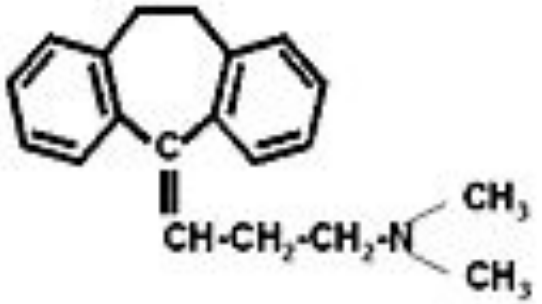
- Amitriptyline (Saroten®)
- Clomipramine (Anafranil®)
- Doxepin (Sinequan®)
- Imipramine (Tofranil®)
- Mianserin (Tolvon®)
- Nortriptyline (Nortrilen®)
- Trazodone (Trittico®)

Chemical structures of tricyclic antidepressants

Tertiary amines

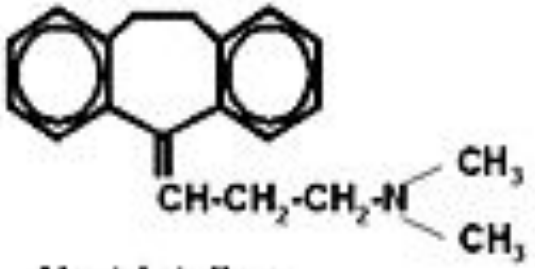


Imipramine

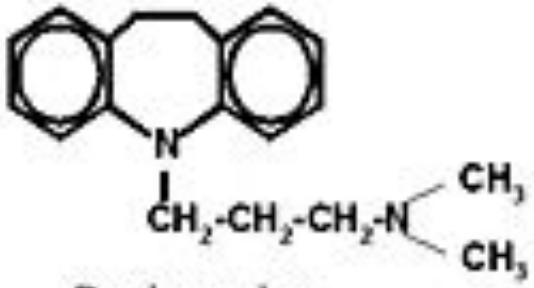


Amitriptyline

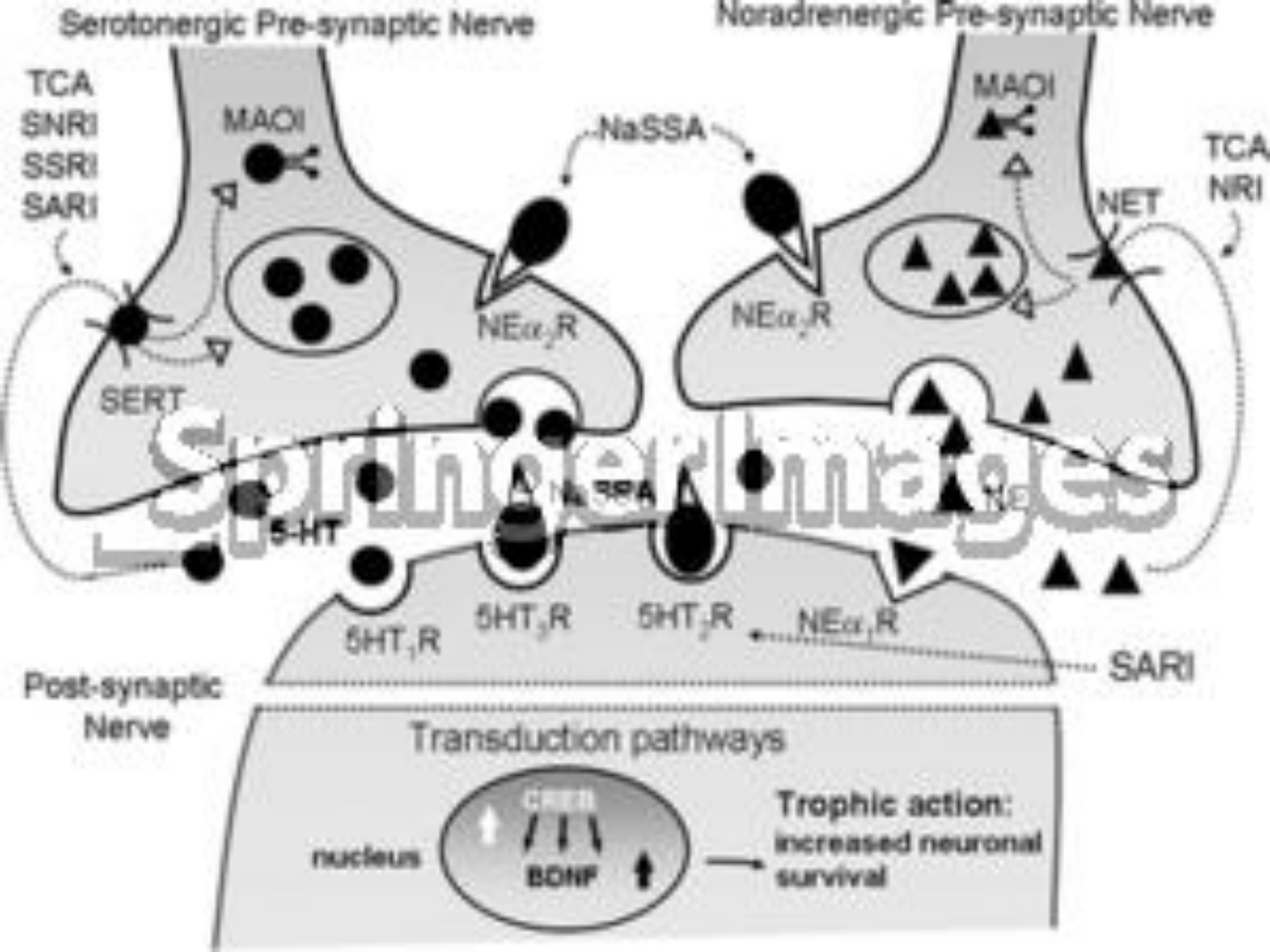
Secondary amines



Nortriptyline



Desipramine


Serotonergic Pre-synaptic Nerve
Noradrenergic Pre-synaptic Nerve
TCA
SNRI
SSRI
SARI
MAOI
NaSSA
MAOI
TCA
NRI
NET
NEα2R
NEα2R
SERT
5-HT
5HT1R
5HT2R
5HT2R
NEα1R
SARI
Post-synaptic
Nerve
Transduction pathways
nucleus
BDNF
Trophic action:
increased neuronal
survival

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).

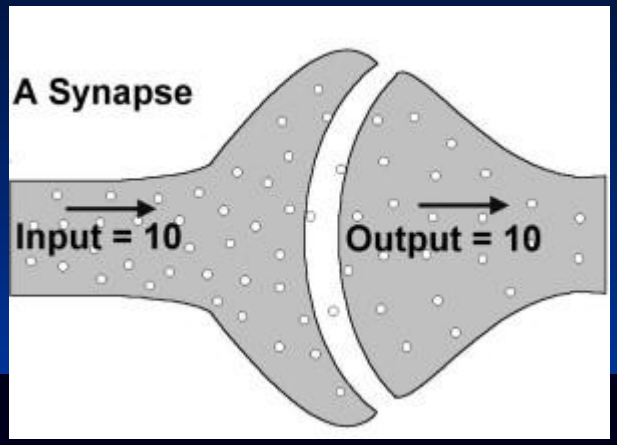
↓

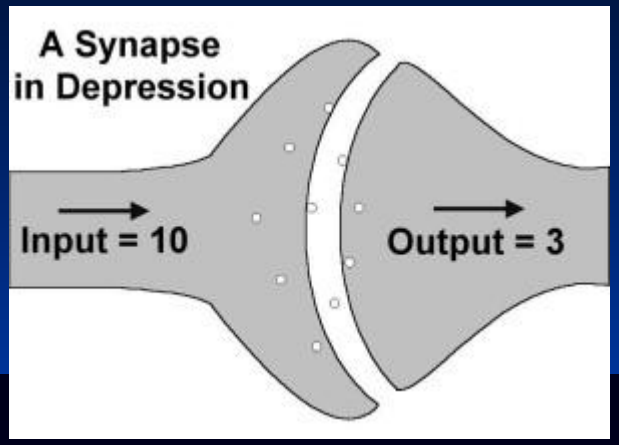
Increased activity of the cAMP signal transduction cascade indicates that the functional output of 5-HT and NE are up-regulated, even though levels of certain 5-HT and NE receptors are down-regulated.

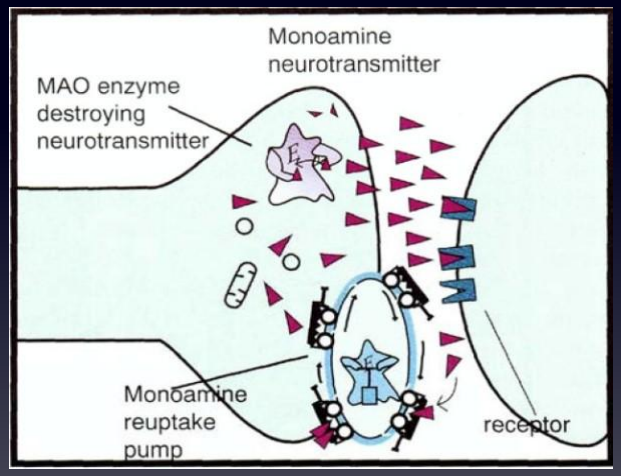
↓

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.

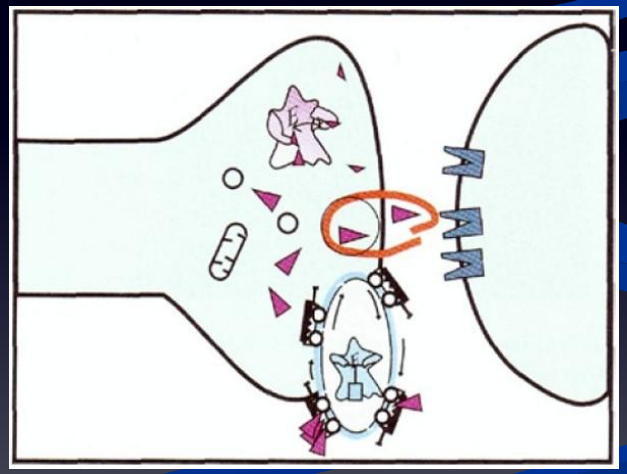
Down&Up-regulation's





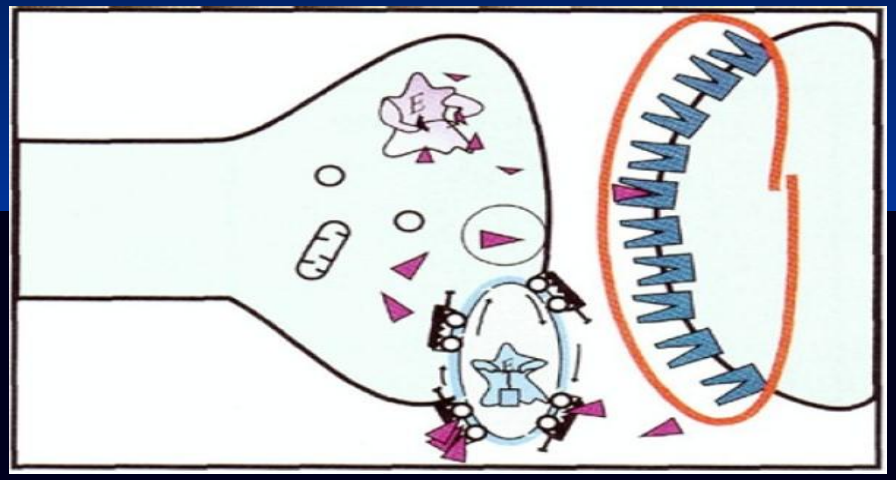


Normal synapse, no depression

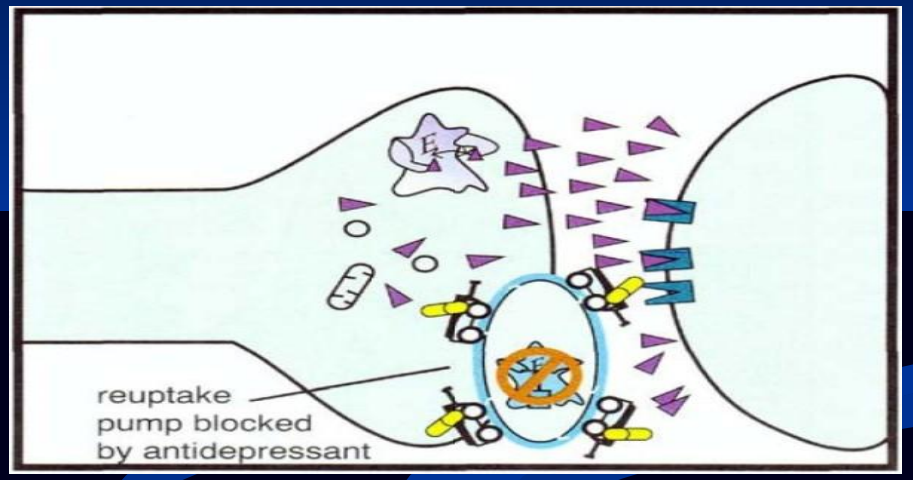


Depression caused by neurotransmitter deficiency

Down&Up-regulation's

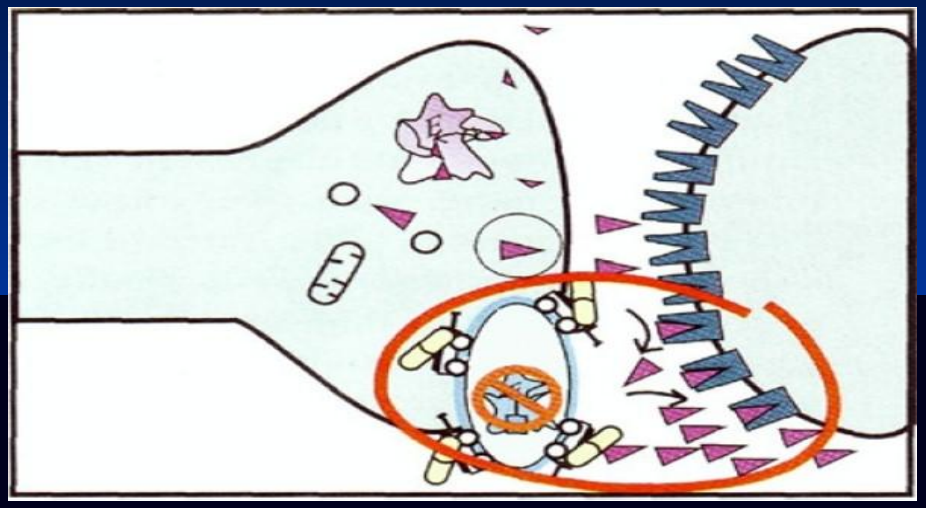


As a result of the depletion of neurotransmitters, the receptors increase ('upregulate')

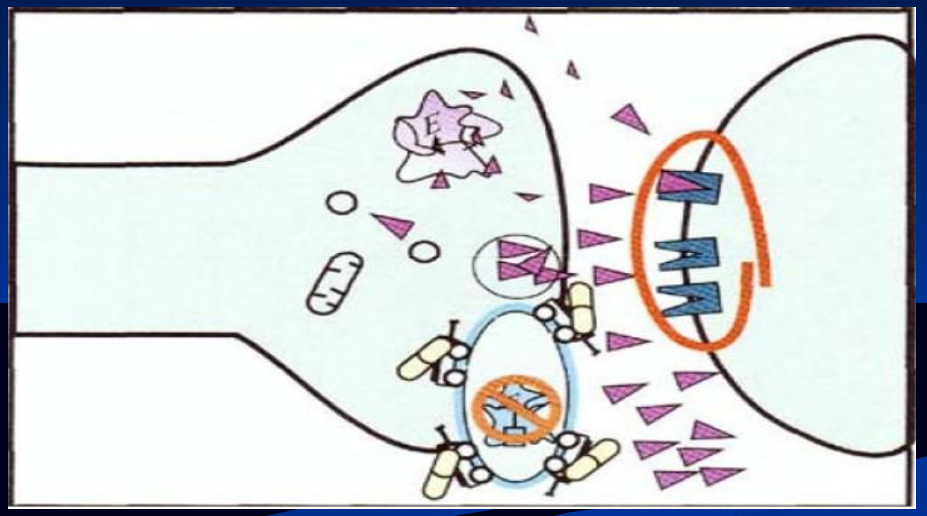


Reuptake blocking antidepressant (TCA, SSRI or SNRI) causes increase in neurotransmitters to normal state

Down&Up-regulation's



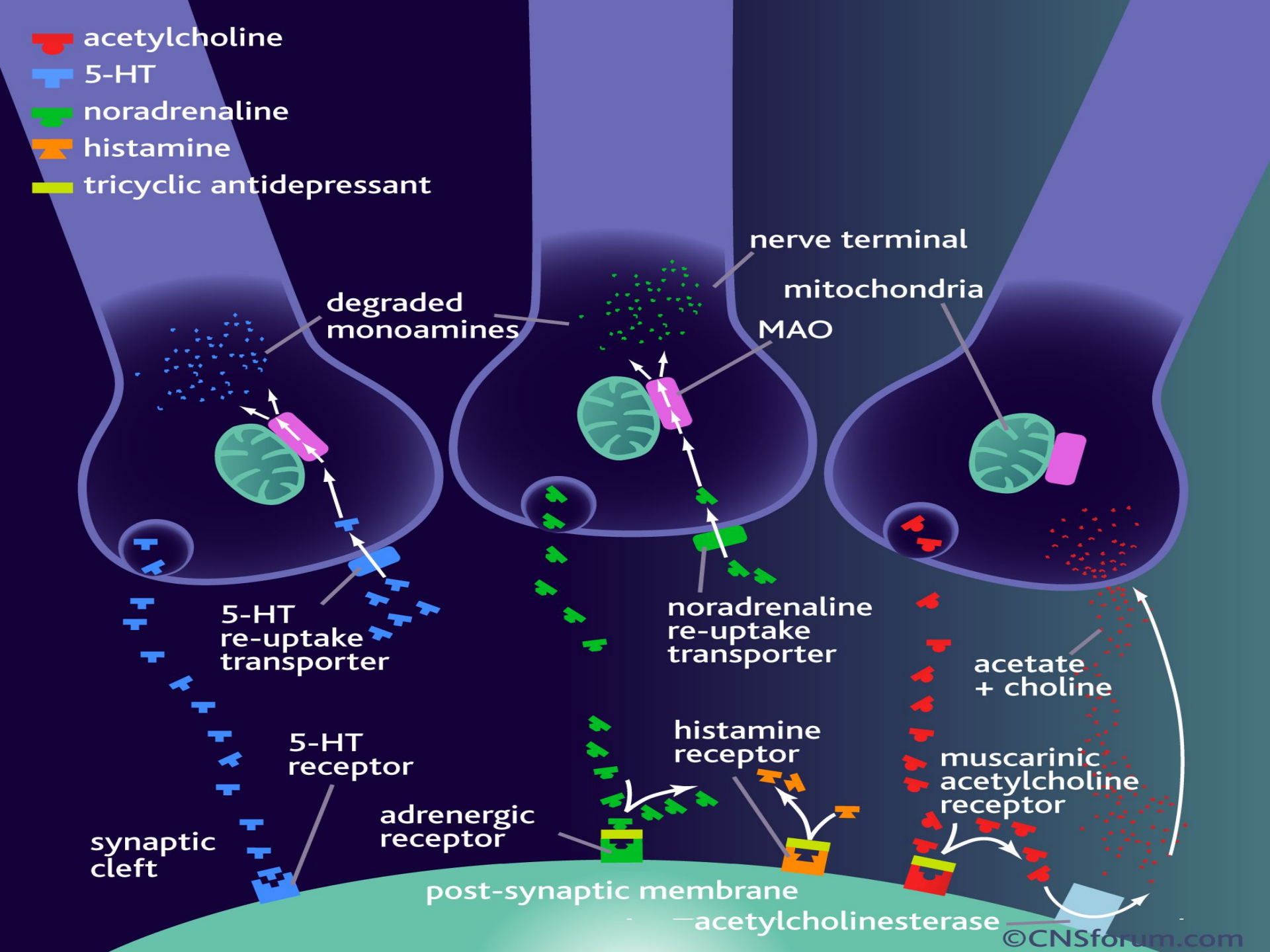
SSRI blocks the reuptake pump, causing more neurotransmitter to be in the synapse.



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
nerve terminal
mitochondria
degraded monoamines
MAO
5-HT re-uptake transporter
noradrenaline re-uptake transporter
acetate + choline
histamine receptor
muscarinic acetylcholine receptor
5-HT receptor
adrenergic receptor
synaptic cleft
post-synaptic membrane
acetylcholinesterase
©CNSforum.com

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

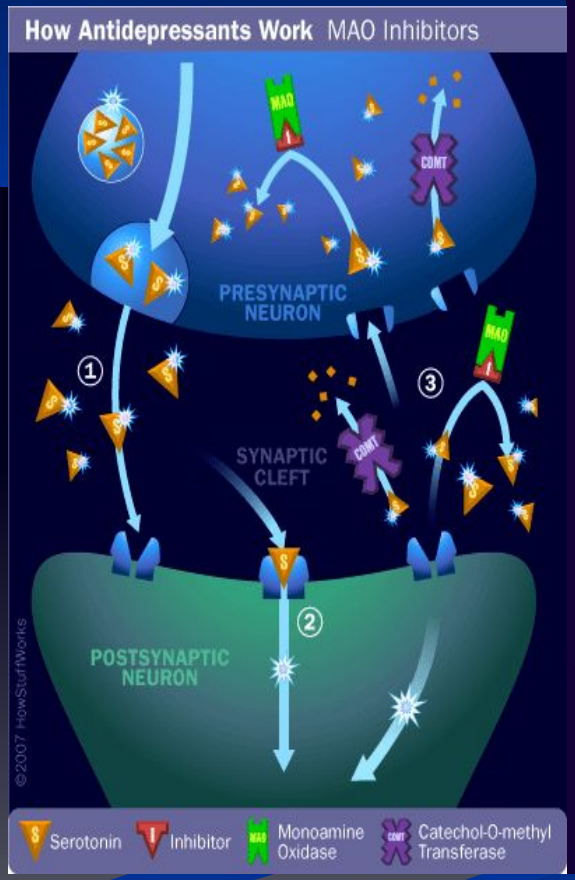
Monoamine-oxidase inhibitors (MAOI)

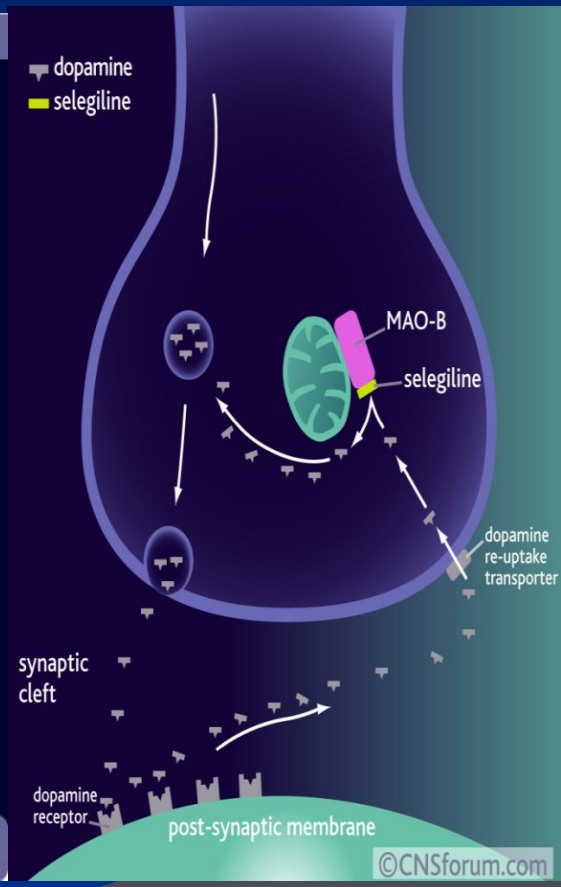
- Moclobemide (Aurorix®) (RIMAs - Reversible Inhibitors of Monoamine Oxidase)
- Phenelzine
- Isocarboxazid
- Tranylcypromine

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)

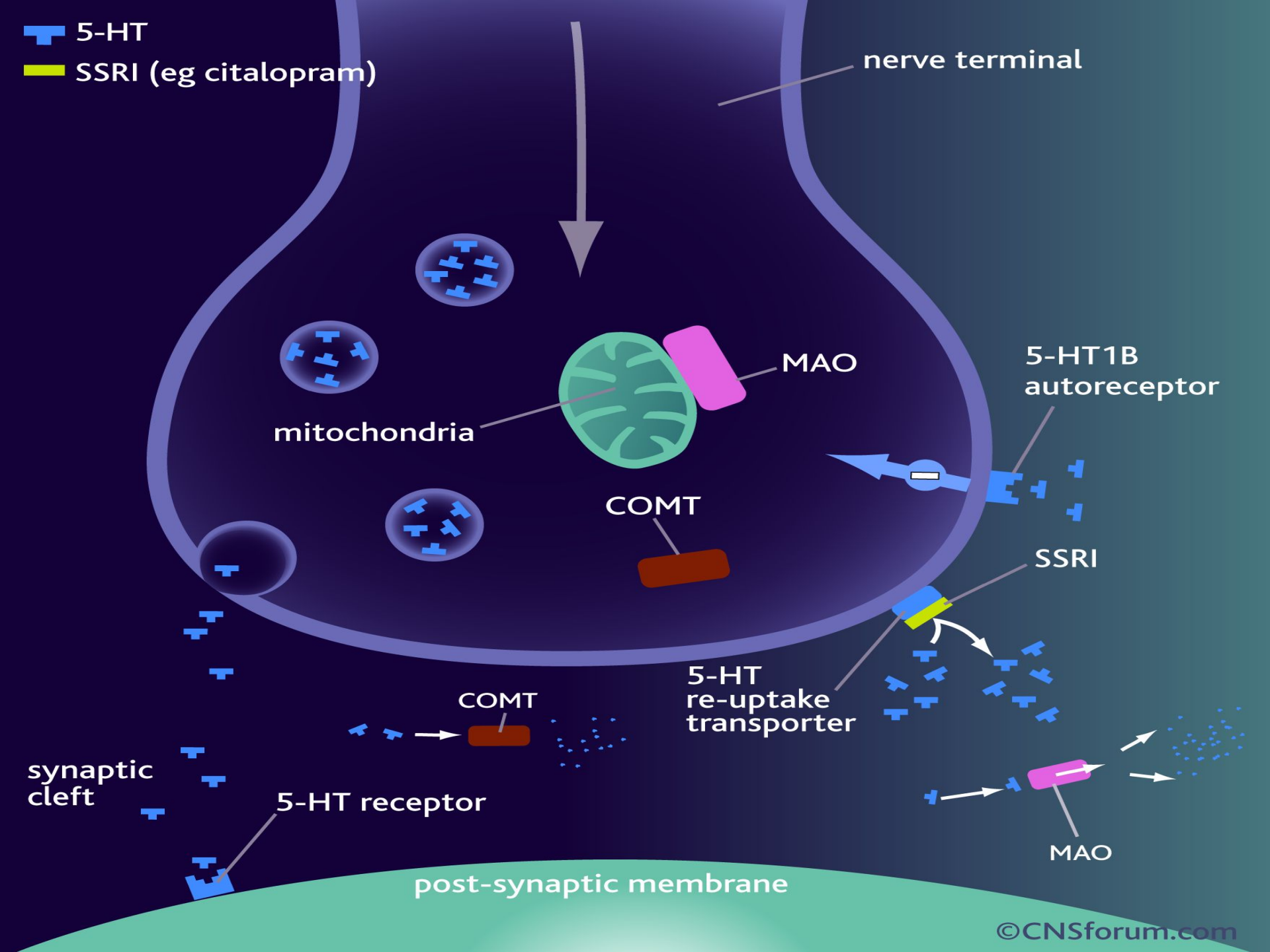
- Adverse effects
  - Orthostatic hypotension
  - Insomnia
  - Weight gain
  - Sexual dysfunction

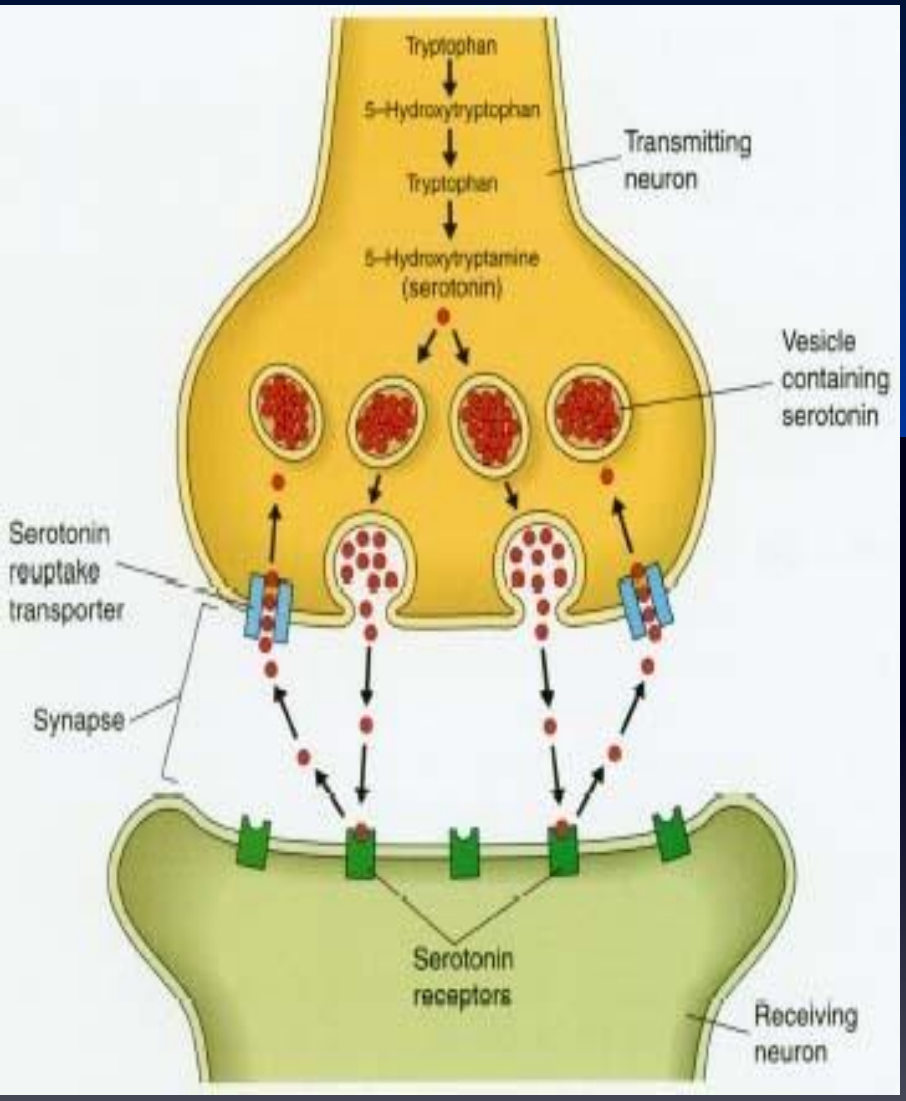
Selective serotonin reuptake inhibitors (SSRI)

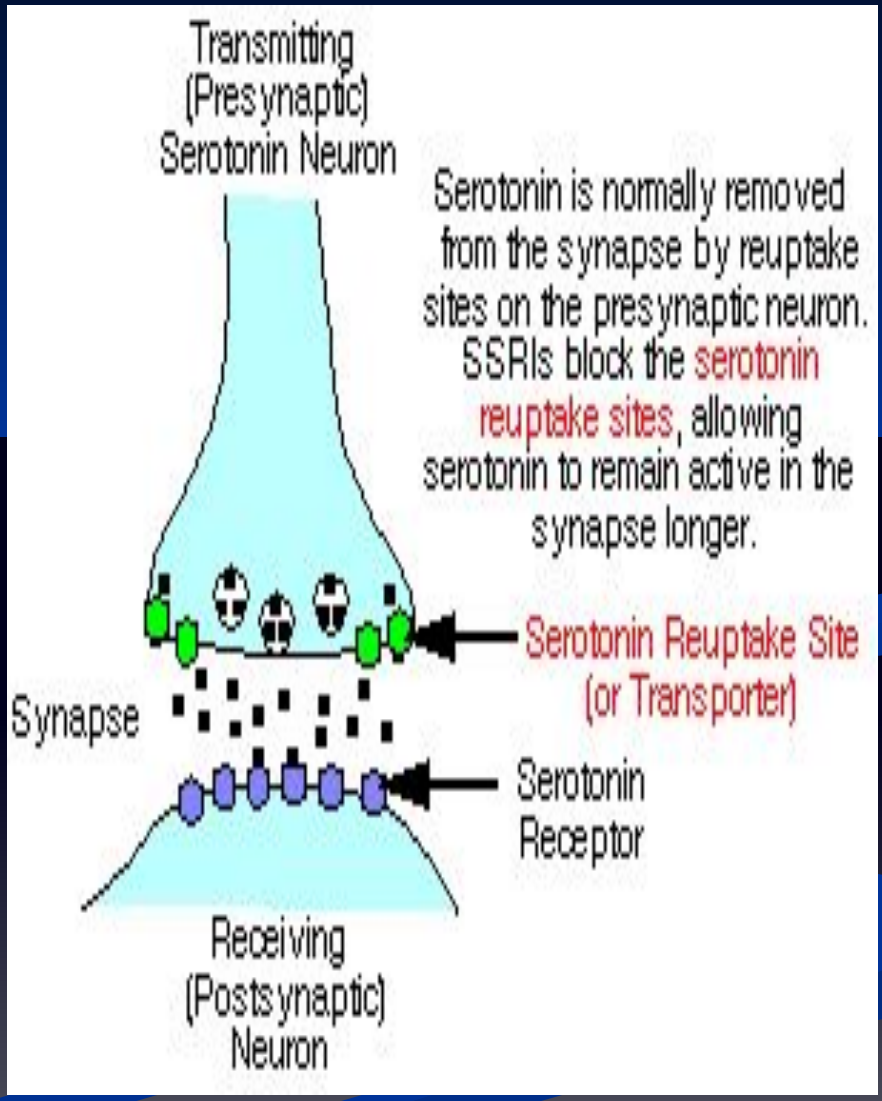
- Fluoxetine (Prozac®)
- Fluvoxamine (Faverin®)
- Paroxetine (Seroxat®)
- Sertraline (Zoloft®)
- Citalopram (Cipram®)
- Escitalopram (Lexapro®)

Selective serotonin reuptake inhibitors (SSRI)

- Mechanism of action
  - Inhibits reuptake of serotonin (5-HT - hydroxytryptophan) presynaptic uptake
  - Increases availability of serotonin at synapses


5-HT
SSRI (eg citalopram)
nerve terminal
MAO
5-HT1B
autoreceptor
mitochondria
COMT
SSRI
5-HT
re-uptake
transporter
COMT
synaptic
cleft
5-HT receptor
MAO
post-synaptic membrane
©CNSforum.com


Tryptophan
5-Hydroxytryptophan
Tryptophan
5-Hydroxytryptamine (serotonin)
Transmitting neuron
Vesicle containing serotonin
Serotonin reuptake transporter
Synapse
Serotonin receptors
Receiving neuron


Transmitting (Presynaptic) Serotonin Neuron
Serotonin is normally removed from the synapse by reuptake sites on the presynaptic neuron. SSRIs block the serotonin reuptake sites, allowing serotonin to remain active in the synapse longer.
Serotonin Reuptake Site (or Transporter)
Synapse
Serotonin Receptor
Receiving (Postsynaptic) Neuron

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

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

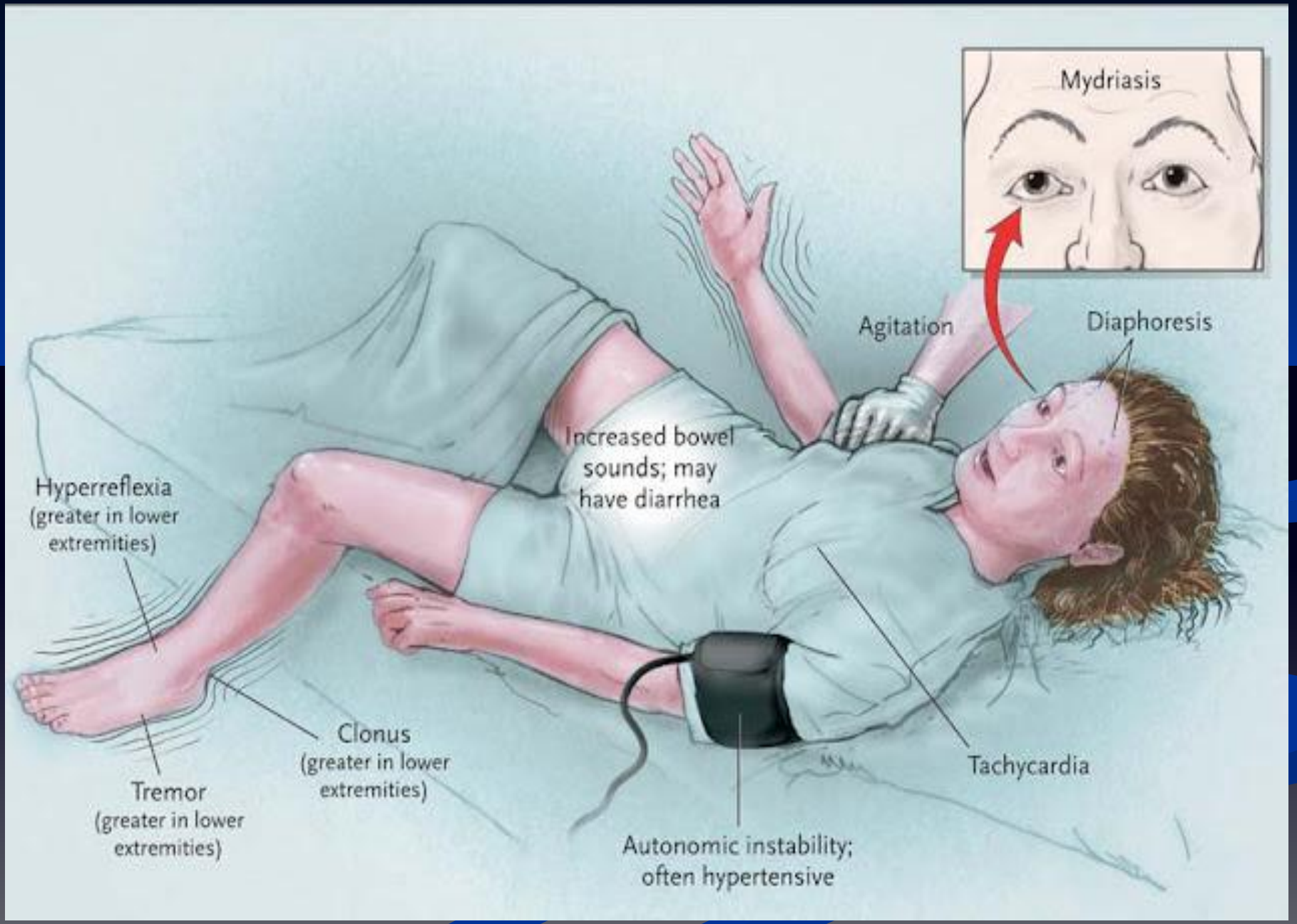
Selective serotonin reuptake inhibitors (SSRI)

- Adverse effects
  - Serotonergic syndrome

Aetiology - SSRI or MAOI + something else

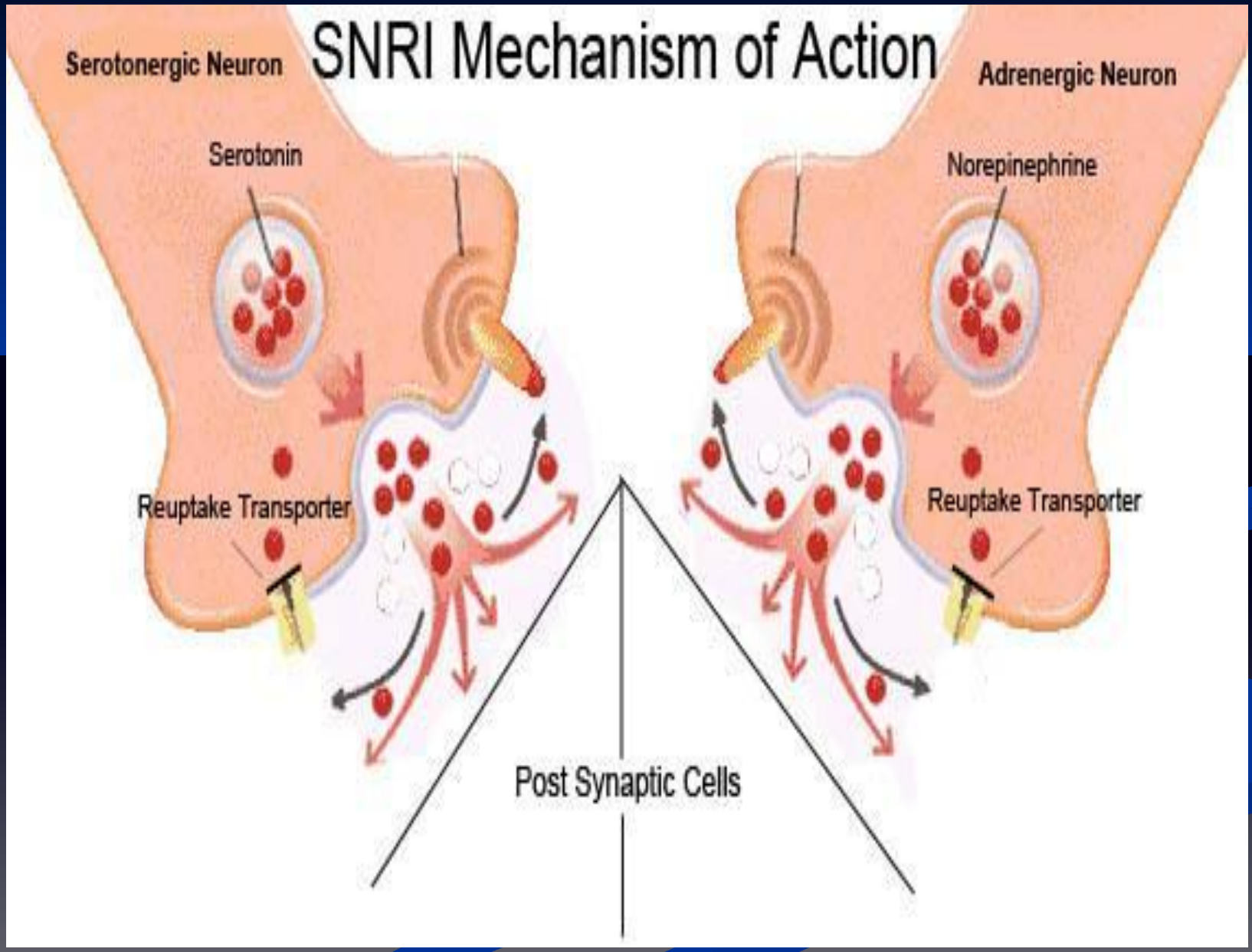
(usually with sl. Different serotonin action)

- 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


SNRI Mechanism of Action
Serotonergic Neuron
Adrenergic Neuron
Serotonin
Norepinephrine
Reuptake Transporter
Reuptake Transporter
Post Synaptic Cells

Serotonin norepinephrine reuptake inhibitor (SNRI)

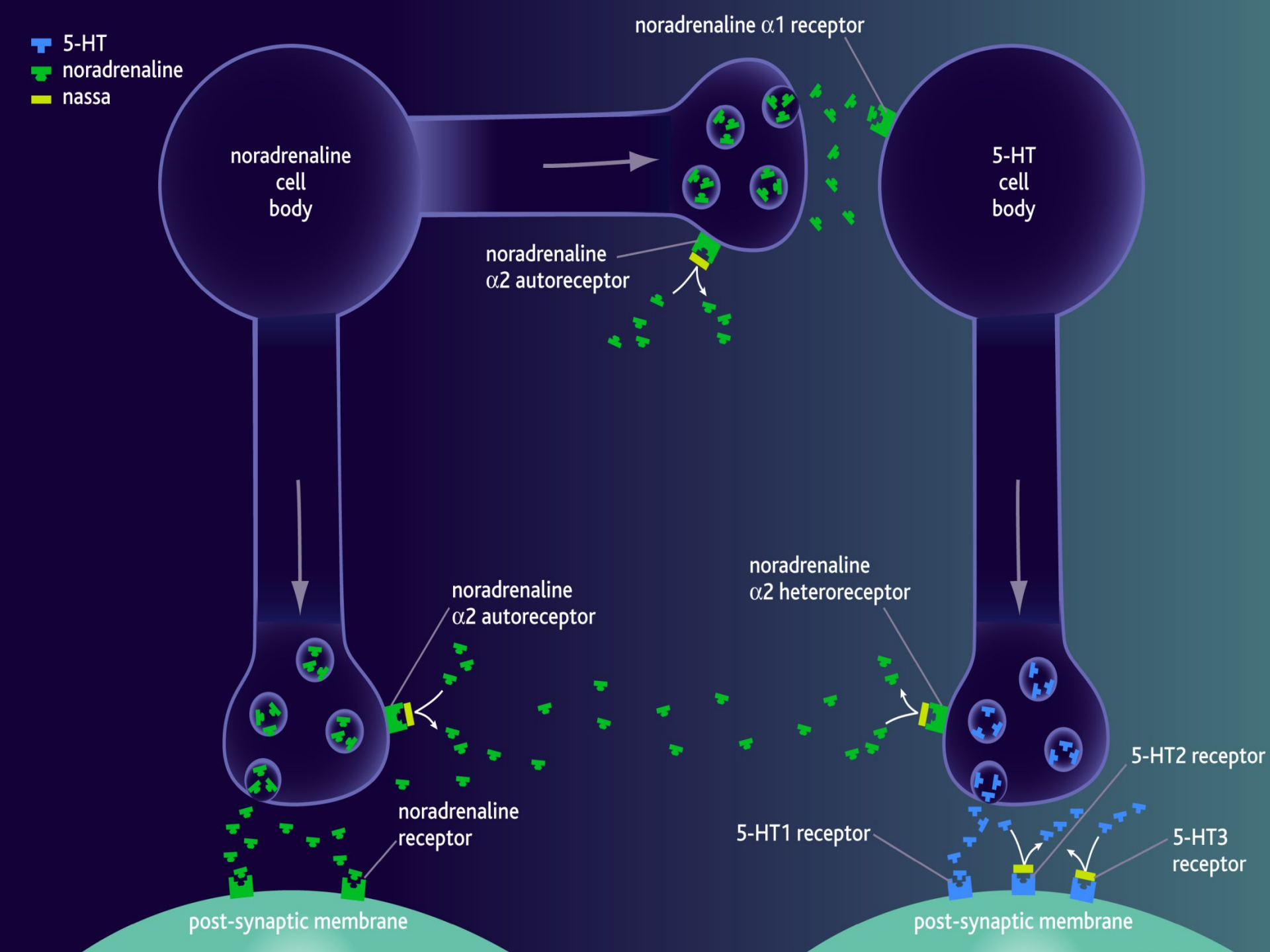
- Venlafaxine (Efexor®, Efexor XR®)
- Properties and Adverse effects
  - Also for anxiety disorders
  - Lacks sedative and anticholinergic effects predominant with TCAs
  - Nausea, dizziness, sexual dysfunction, hypertension (when > 300mg/day)

Serotonin norepinephrine reuptake inhibitor (SNRI)

- Duloxetine (Cymbalta®)
- Properties and Adverse effects
  - More potent than venlafaxine(?)
  - Also indicated for diabetic neuropathy
  - Insomnia, nausea, headache

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 a2-autoreceptors and noradrenaline a2-heteroeceptors. 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

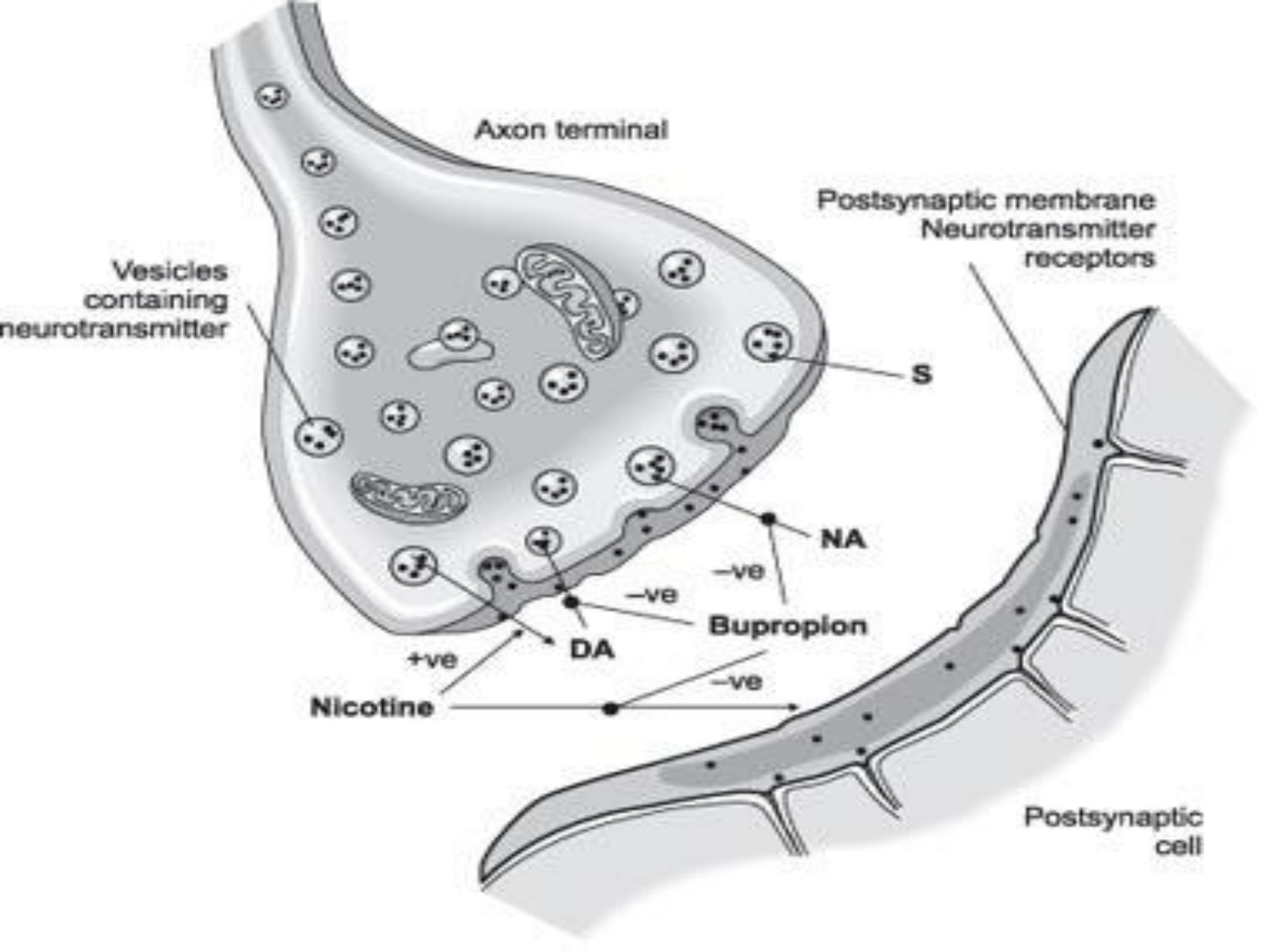

5-HT
noradrenaline
nassa
noradrenaline α1 receptor
noradrenaline cell body
5-HT cell body
noradrenaline α2 autoreceptor
noradrenaline α2 autoreceptor
noradrenaline α2 heteroreceptor
noradrenaline receptor
5-HT2 receptor
5-HT1 receptor
5-HT3 receptor
post-synaptic membrane
post-synaptic membrane

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

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


Axon terminal
Postsynaptic membrane
Neurotransmitter
receptors
Vesicles
containing
neurotransmitter
S
NA
–ve
–ve
Bupropion
DA
+ve
–ve
Nicotine
Postsynaptic
cell

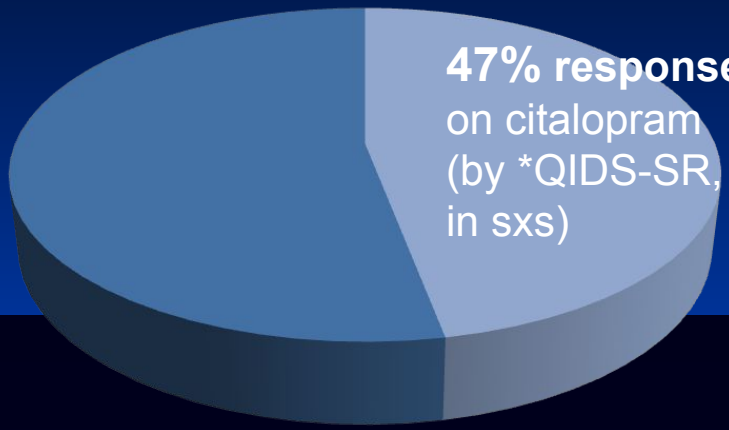
Norepinephrine dopamine reuptake inhibitor (NDRI)

- 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®)

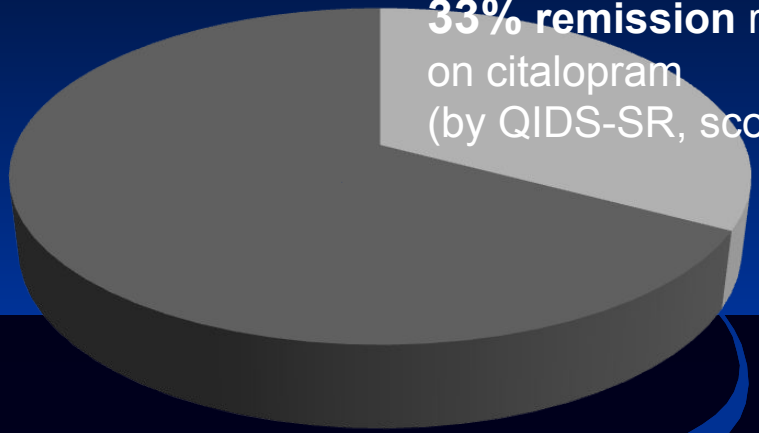
Other antidepressants

- 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)



47% response rate on citalopram (by *QIDS-SR, 50% ↓ in sxs)



33% remission rate on citalopram (by QIDS-SR, score <5)

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/

Trivedi MH et al, *Am J Psychiatry*. 2006 Jan;163(1):28-40

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

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