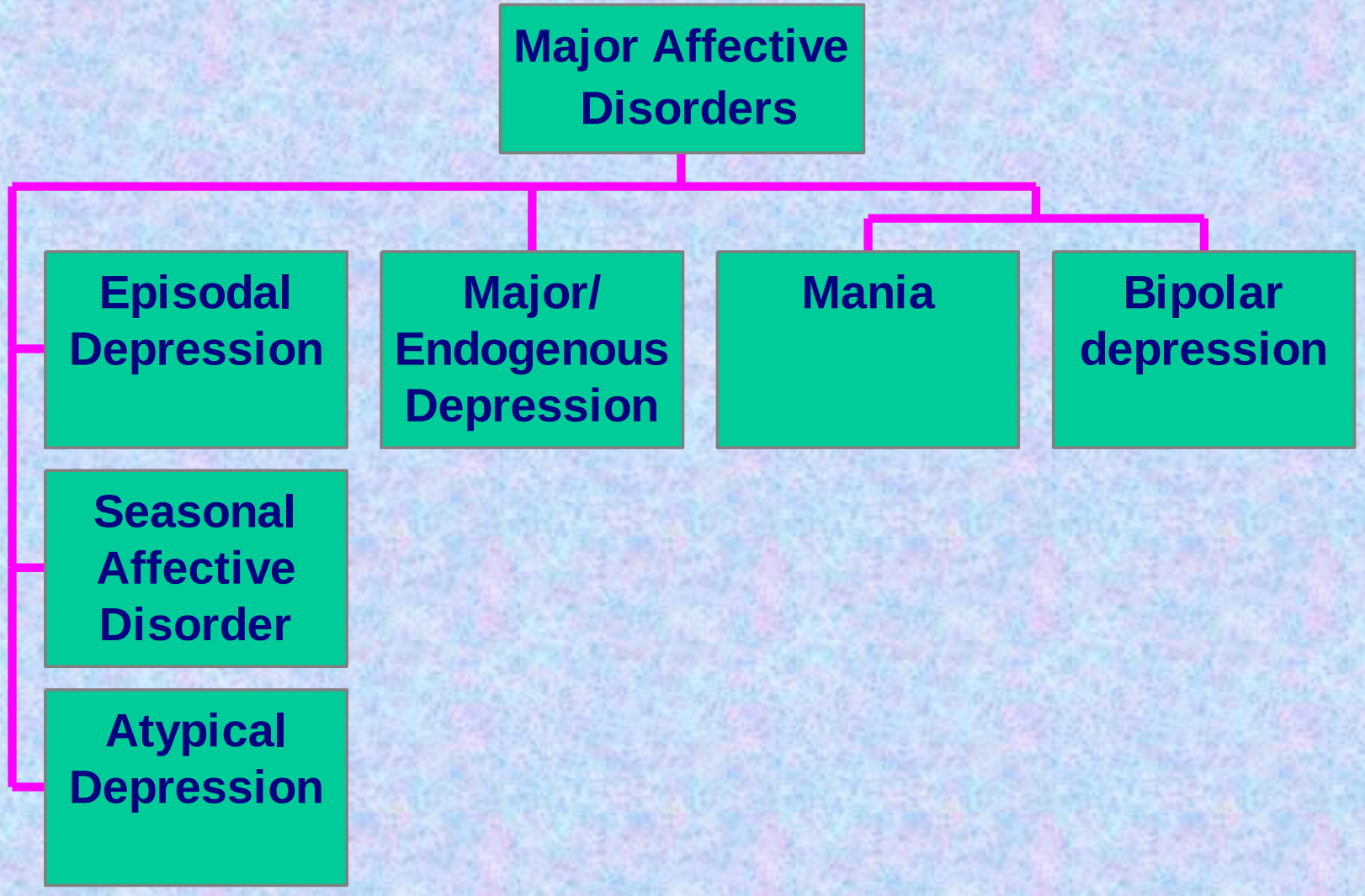

بسم الله الرحمن الرحيم

Antidepressant Drugs

Review & News

Classification of Major Affective Disorders



Depression

- Approximately 30 % of adults will have bouts with depression.
- Eighth leading cause of death in the US.
- $16 billion annual cost to society:
  - Lost productivity.
  - Treatment costs.
- Less than 25% of patients receive treatment.
- Less than 10 % receive adequate treatment.
- Risk of depression is higher (2-3 fold) in women & in first degree relatives.

Definition & Diagnostic Criteria

- **An affective disorder characterized by loss of interest or pleasure in almost all a person's usual activities or pastimes.**
- **At least five of the following symptoms have been present during the same 2 week depressed period.**
- **Symptoms:**
  - **Depressed mood, anhedonia & loss of interest in normal activities.**
  - **Weight loss or gain, Sleep disturbances, Psychomotor agitation.**
  - **Fatigue, Feelings of worthlessness or guilt, Lack of concentration.**
  - **Recurrent thoughts of suicide, Not acute response to situational events.**

Beck Inventory Scoring

- **Total score:** Levels of Depression.
- **1-10:** These ups and downs are considered normal.
- **11-16:** Mild mood disturbance.
- **17-20:** Borderline clinical depression.
- **21-30:** Moderate depression.
- **31-40:** Severe depression.
- **Over 40:** Extreme depression.

Pathophysiology of Depression

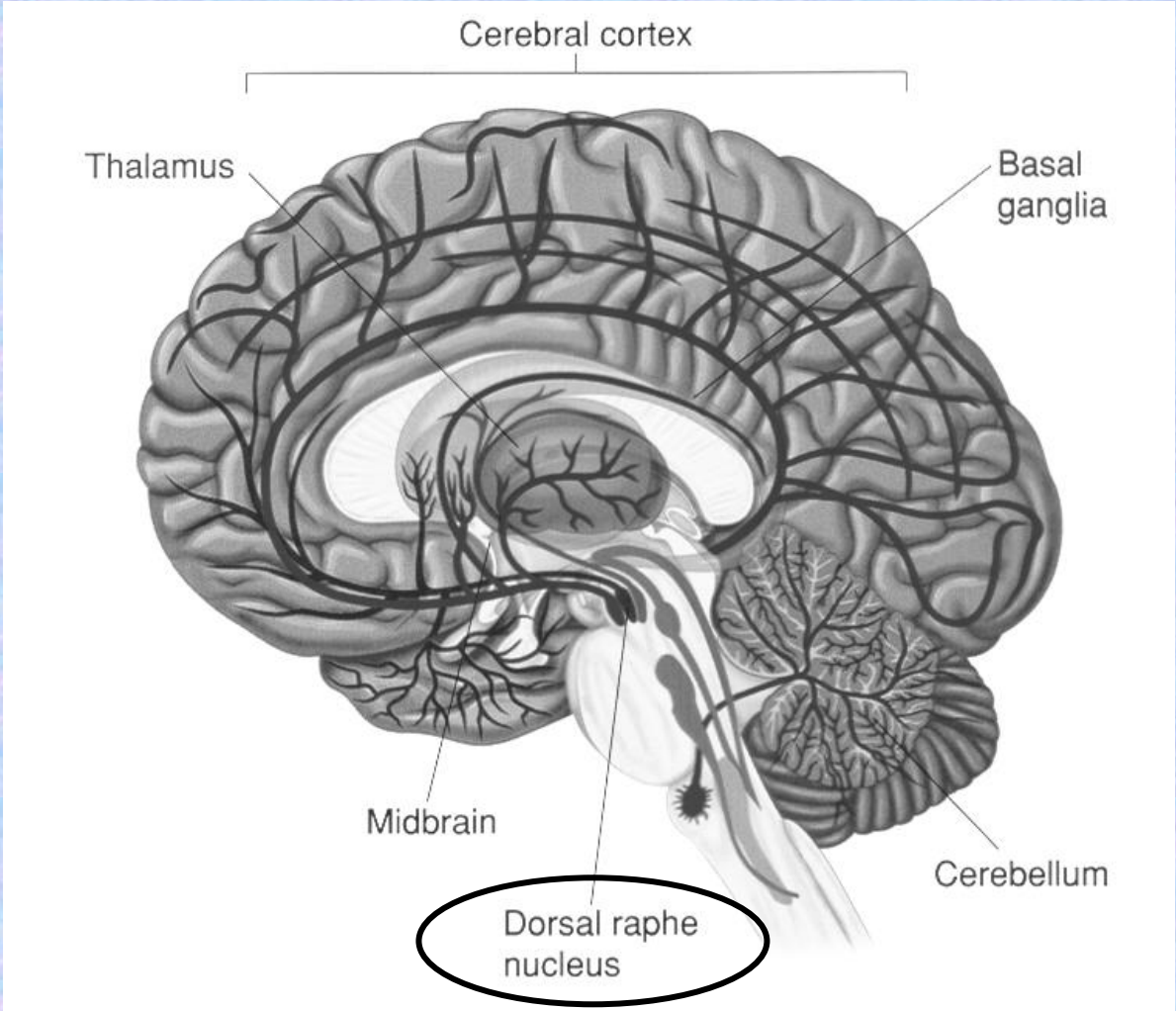
- **Biological factors:**
  - Neurotransmitter levels.
  - Disease states, drugs.
- Dysfunction in cortisol secretion.
- **Situational factors:**
  - Stress.
  - Adverse life events.
- **Example:**
  - Depression: ↓Norepinephrine, ↓serotonin.
  - Treatment: ↑Serotonin.

Serotonin System

- **Located in the pons and midbrain (in groups known as raphe nuclei) send their projections diffusely to areas implicated in depression such as the cortex, hippocampus, amygdala, hypothalamus, thalamus, etc.**
- **This system is also involve in:**
  - **Anxiety.**
  - **Sleep.**
  - **Sexual behavior.**
  - **Rhythms (Suprachiasmatic nucleus).**
  - **Temperature regulation.**
  - **CSF production.**

Serotonin Deficiency

- Depressed mood.
- Anxiety.
- Panic.
- Phobia.
- Obsessions and compulsions.
- Food craving, bulimia.
- Sleep disruption.

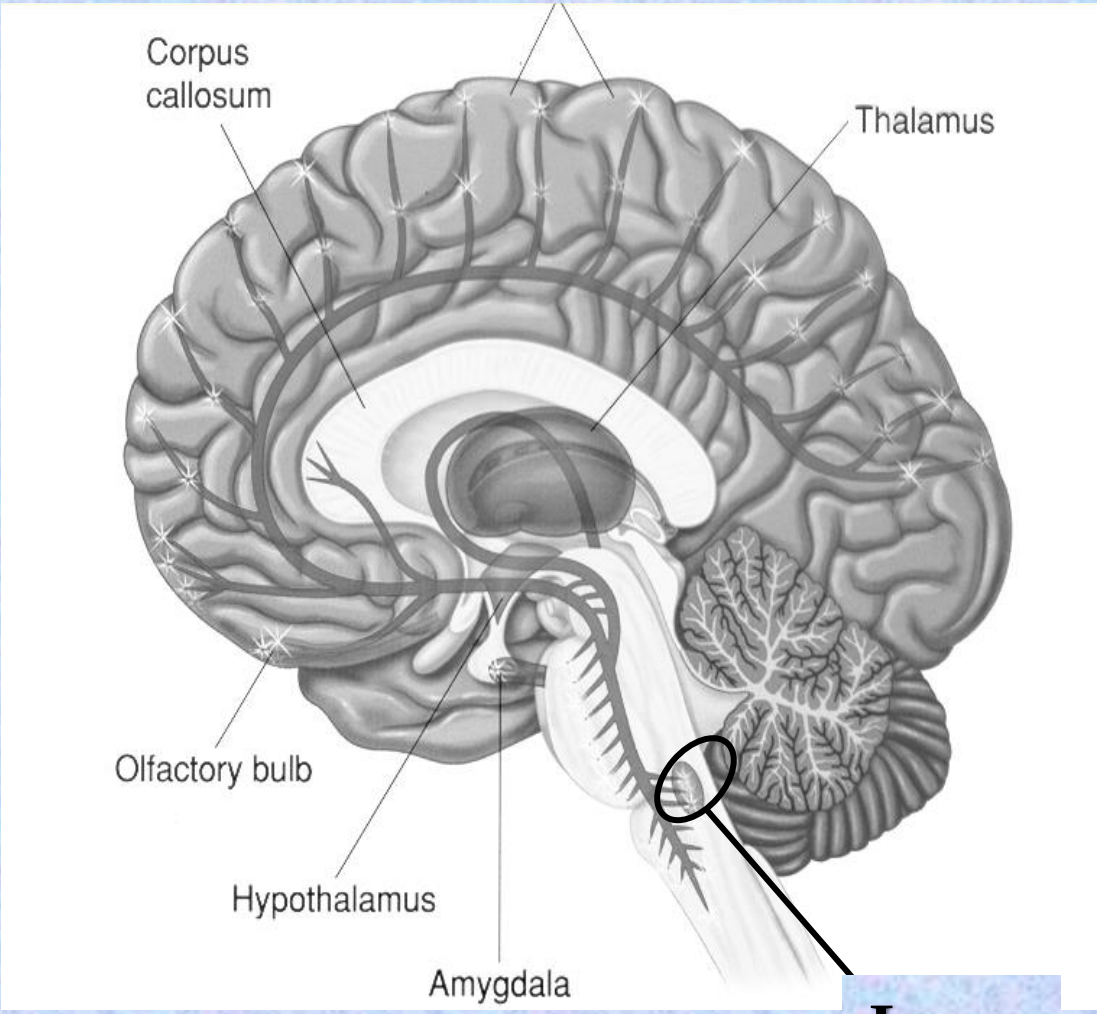


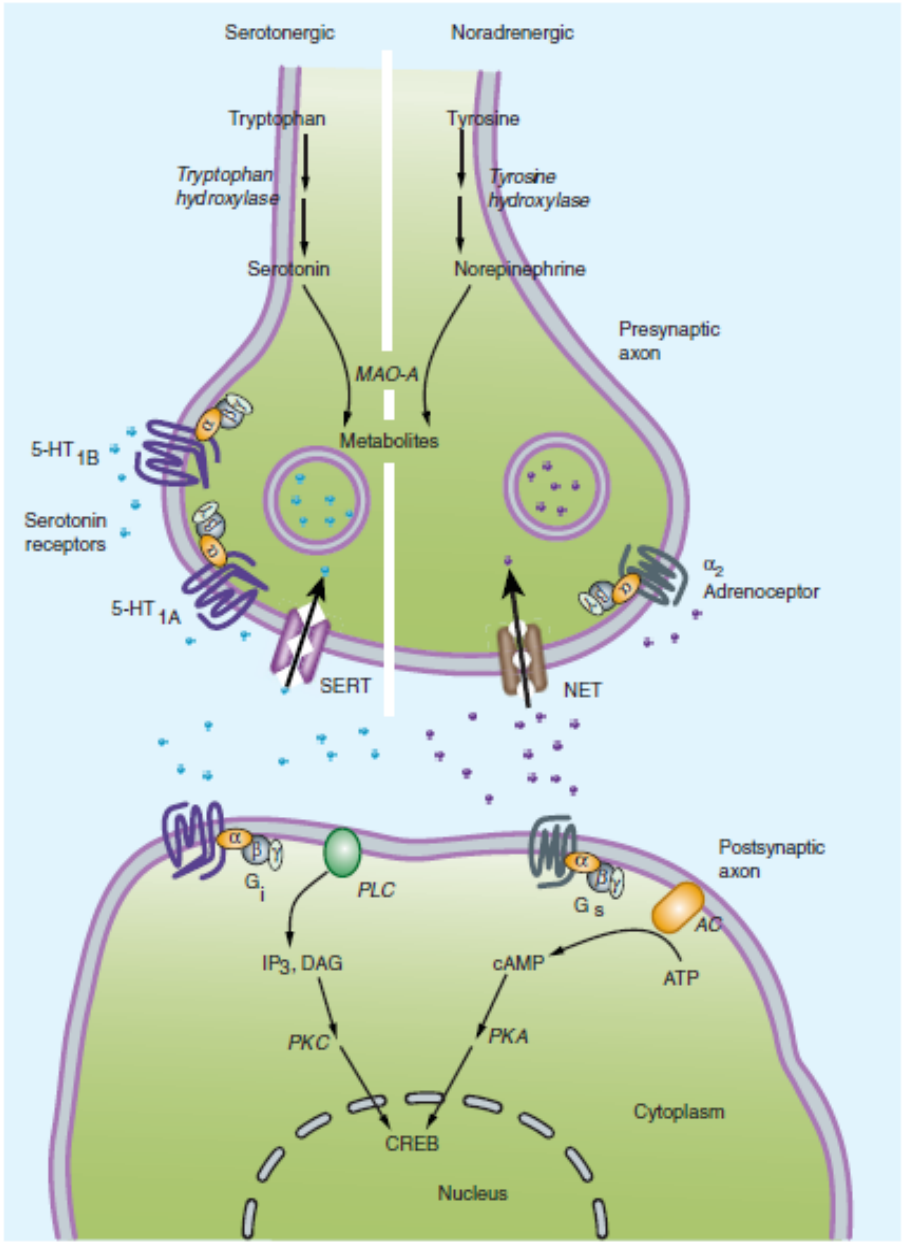
Norepinephrine System

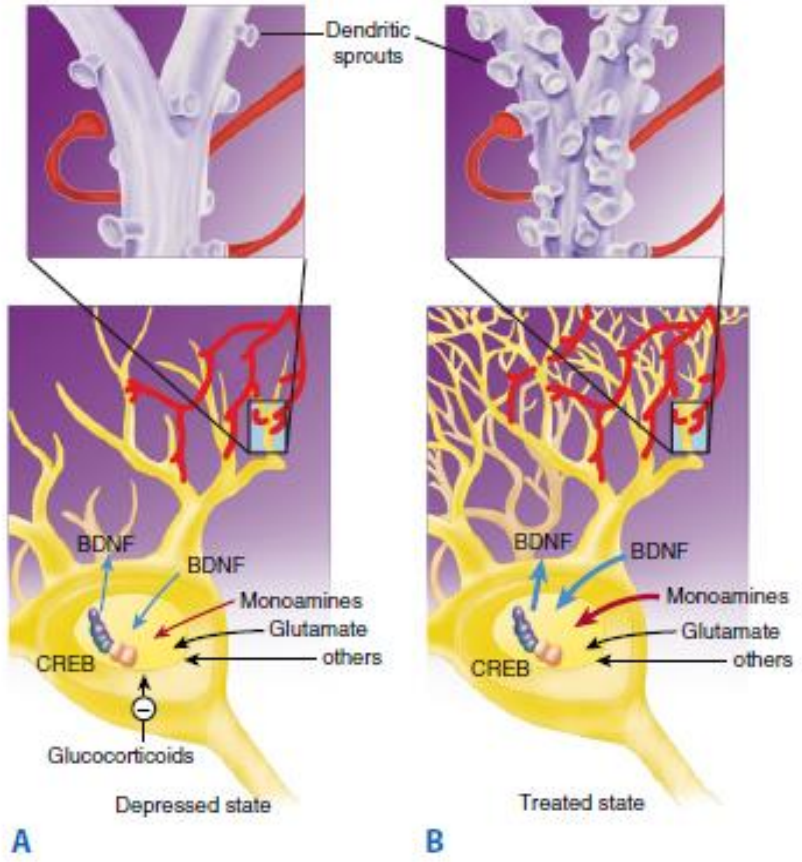
- **Origination the locus coereleus in the midbrain & projection diffusely to the cortex, cerebellum and limbic areas (hippocampus, amygdala, hypothalamus, thalamus).**
  - **Mood & Cognitive function: Higher functions performed by the cortex.**
  - **Drive and motivation: Function of brainstem.**
  - **Memory and emotion: Function of the hippocampus and amygdala.**
  - **Endocrine response: Function of hypothalamus.**

NE Deficiency

- Impaired attention.
- Concentration and memory problems.
- Slow processing of information.
- Depressed mood.
- Psychomotor retardation.
- Fatigue.




Serotonergic
Noradrenergic
Tryptophan
Tyrosine
Tryptophan hydroxylase
Tyrosine hydroxylase
Serotonin
Norepinephrine
Presynaptic axon
MAO-A
Metabolites
5-HT 1B
Serotonin receptors
5-HT 1A
α2 Adrenoceptor
SERT
NET
Postsynaptic axon
Gi
PLC
Gs
AC
IP3, DAG
cAMP
ATP
PKC
PKA
CREB
Cytoplasm
Nucleus

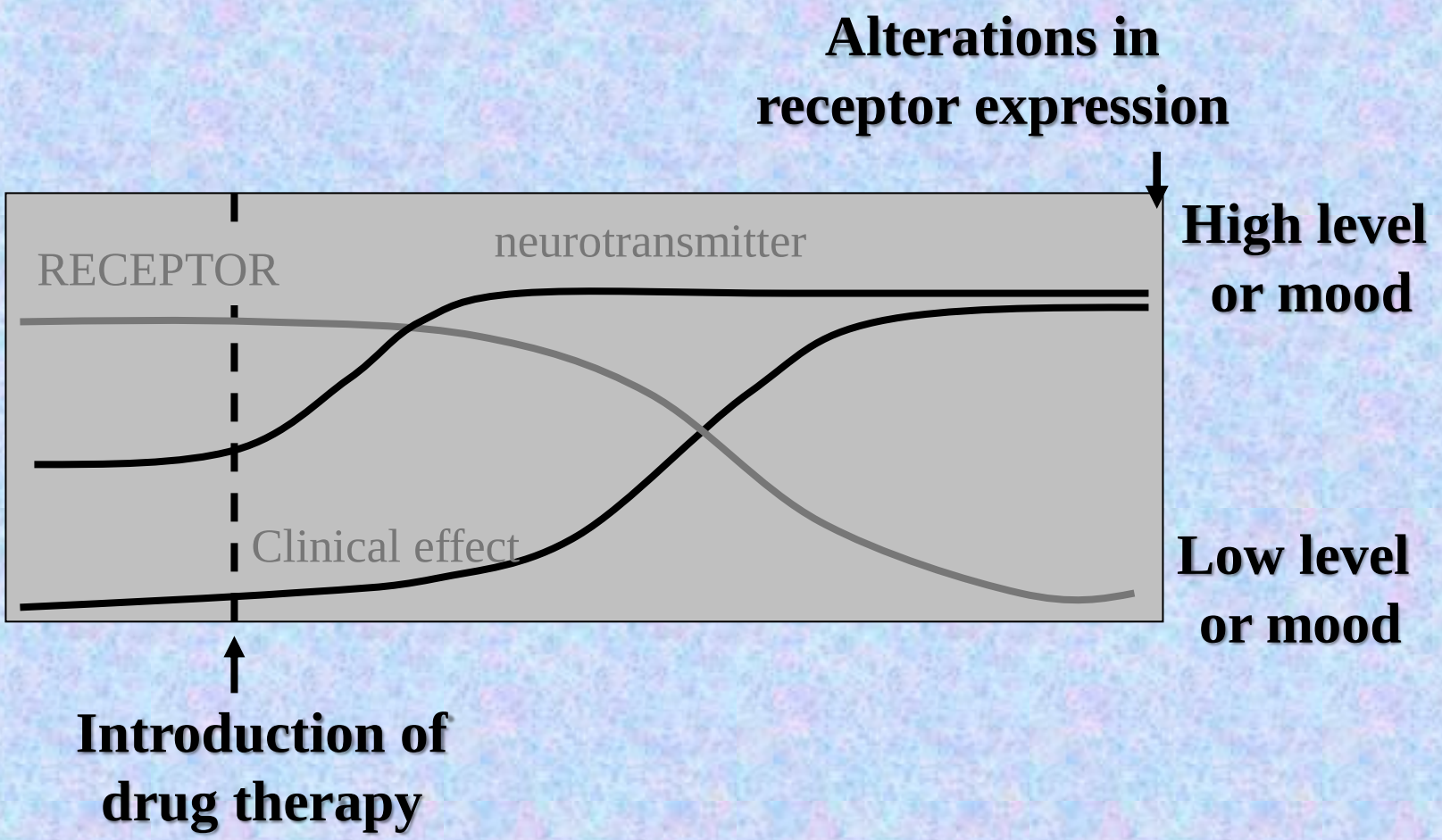

Dendritic sprouts
BDNF
BDNF
Monoamines
Glutamate
others
CREB
Glucocorticoids
Depressed state
A
BDNF
BDNF
Monoamines
Glutamate
others
CREB
Treated state
B

Target Genes Altered In Depression And By Stress

- **Biogenic amine induced gene expression is abnormal (second messenger system).**
- **BDNF (brain-derived neurotrophic factor) helps maintain neurons especially in the hippocampus; protect and/or facilitate neuronal function.**
- **ADs may activate these neurotrophic factor genes.**

ADs → Desensitization or down regulation of post synaptic receptors

→ Delayed onset of clinical effect compared to increase in NT level



Treatments of depressive disorder

- Tricyclic antidepressants.
- Selective serotonin reuptake inhibitors.
- Monoamine oxidase (MAO) inhibitors.
- Atypical antidepressants.
- Electroconvulsive shock therapy.
- Counseling; in less severely depressed patients.
- Adverse effects and potential drug interactions are prominent; the choice of an antidepressant is based on tolerability.
- Abuse, addiction, dependence are not issues.

Antidepressants

1. **Tricyclic anti-depressants (TCAs):**

   Imipramine, nortriptyline, amytriptiline, doxepin.

2. **Monoamine oxidase inhibitors (MAOIs):**

   Isocarboxacid, phenelzine, tranylcypromine.

3. **Selective serotonin reuptake inhibitors (SSRIs):**

   Fluoxetine, Sertraline, Paroxetine, Fluvoxamine, Citalopram.

4. **Selective serotonin norepinephrine reuptake inhibitors (SNRIs):**

   Duloxetine, Milnacipran,Venlafaxine

5. **Serotonin modulator and stimulators (SMSs): Vilazodone, Vortioxetine.**

6. **5-HT2 antagonists: Trazodone, Nefazodone.**

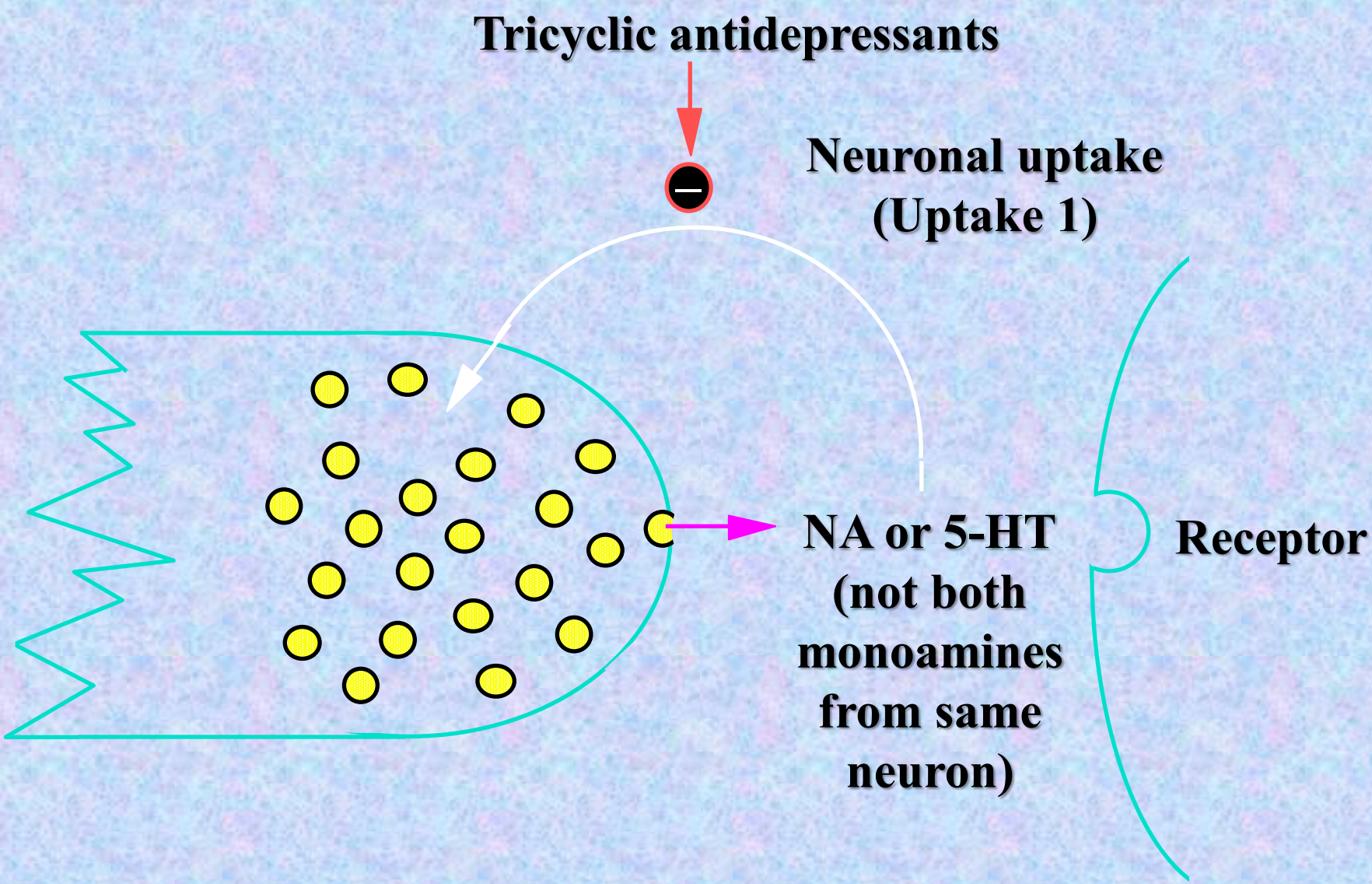
7. **Tetracyclics and unicyclic:**

   amoxapine, bupropion, alprazolam, maprotiline, nomifensine, mianserin.

Other Uses for Antidepressants

- **Anxiety disorders including GAD , Panic disorder, Obsessive-compulsive disorder, Social phobia, Post-traumatic stress disorder.**
- **Premenstural dysphoric disorder & menopause.**
- **ADHD and enuresis in children.**
- **Bulimia.**
- **Neuropathic & Chronic pain.**
- **Narcolepsy.**
- **Smoking cessation.**

Postulated Mode Of Action Of Tricyclic Antidepressant Drugs



Time-course Of Antidepressant Action Of TCA

- **Week 1:**
  - **Alleviation of insomnia, anxiety.**
- **Week 2:**
  - **Increase in energy, interest.**
  - **Somatic complaints eased.**
- **Week 2-4:**
  - **Onset of antidepressant action.**

Tricyclic Antidepressants (TCAs)

3° Amines: **Imipramine, Amitriptyline**

⇓ ⇓

2° Amines: **Desipramine, Nortriptyline**

Selectivity: **2º Amines -- NE ≥ 5-HT**

3º Amines -- 5-HT ≥ NE

TCAs; Kd

	Muscarinic receptor	Histamine H_1 receptor	Adrenergic α_1 receptor
Desipramine	**200**	**110**	**130**
Imipramine	**91**	**11**	**91**
Nortriptyline	**150**	**10**	**59**
Amitriptyline (sedative)	**18**	**1.1**	**27**
Doxepin	**83**	**0.24**	**24**

Side Effects of TCAs (Antimuscarinic & Antihistaminic)

- Drowsiness, dizziness.
- Anxiety, restlessness followed by myoclonus, tonic-clonic seizures and coma.
- Nausea, dry mouth, constipation, urinary retention or difficulty with urination.
- Cognitive and memory difficulties.
- Blurred vision, photophobia.
- ↑ HR, arrythmias.
- ↑ Intraocular pressure in glaucoma
- Weight gain.
- ↓ Sweating.
- Elderly more susceptible.
- Administration in bipolar disorder may precipitate acute mania or rapid cycling.
- **Antidote:**
  - Cholinesterase inhibitor (Physostigmine).

Other Side Effects of TCAs

- **Blockade of norepinephrine reuptake:**
  - **Tremor, tachycardia.**
  - **Atrial arrhythmias (Managed with physostigmine).**
  - **Ventral arrhythmias;**
    - **Managed with anti-arrhythmic drugs;**
      - **Lidocaine, procainamide & phenytoin.**
- **Blockade of serotonin reuptake:**
  - **Tremor.**
- **Blockade of alpha-1 adrenergic receptors:**
  - **Orthostatic hypotension w/reflex tachycardia, sedation nystagmus, slurred speech, confusion, altered consciousness, delirium, hyperpyrexia, coma, respiratory failure.**
  - **Sexual dysfunction, including loss of libido, impaired erection and ejaculation and anorgasmia.**

. …↓ Compliance

Important Differences Among Tricyclics

- **Imipramine, amitriptyline are strongly sedating and have strong anticholinergic effects.**
- **Desipramine, nortriptyline are less sedating, less anticholinergic effects; better tolerated in elderly.**
- **Desipramine has greatest cardiotoxicity.**
- **Start low and go slow.**

Medical Contraindications To Use Of TCAs

- Seizure disorder.
- Bipolar disorder.
- High risk for suicide.
- Congestive heart failure.
- Orthostatic hypotension.
- Advanced cardiovascular disease.

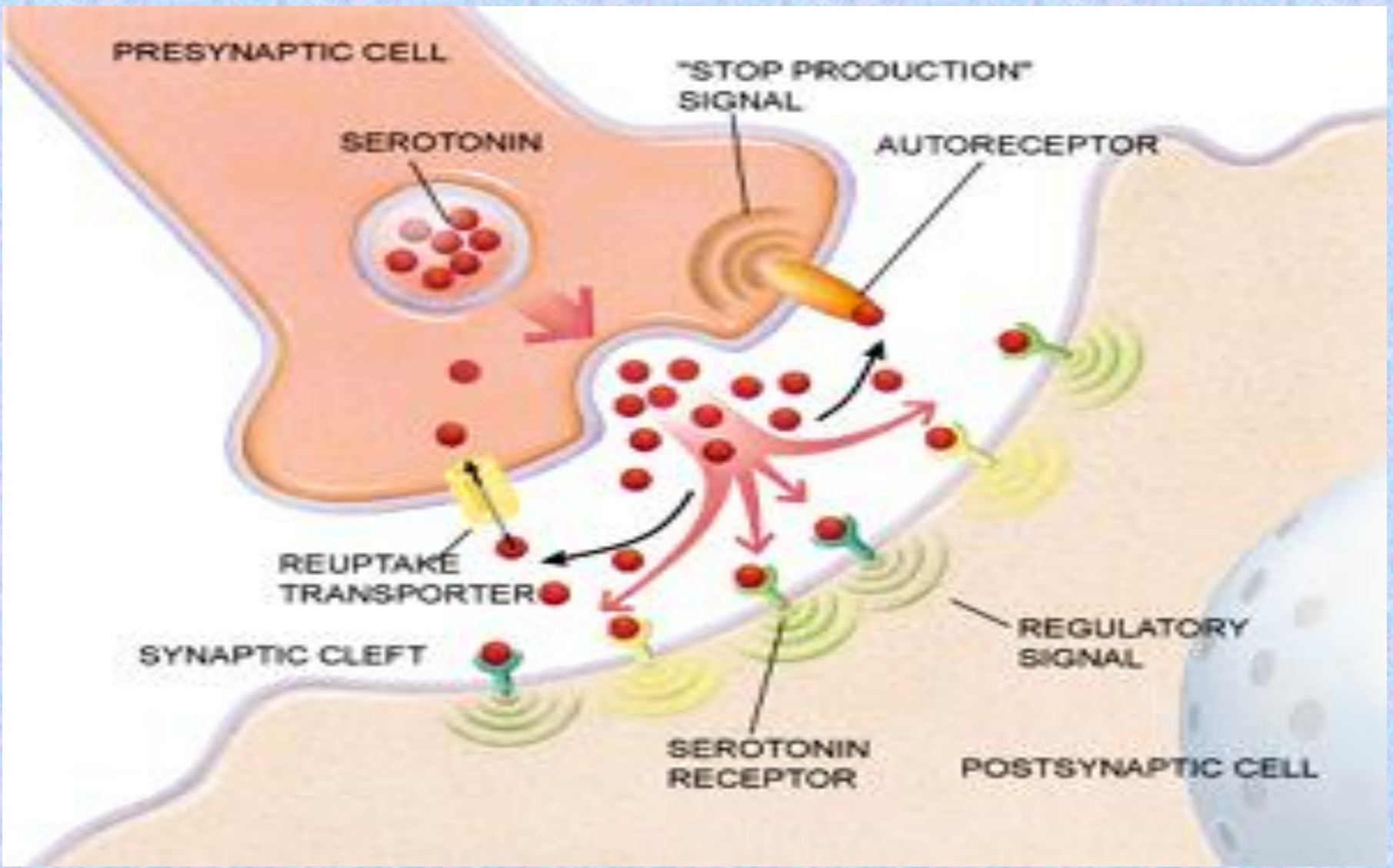
Drug Interactions With TCAs

- **CNS Depressants.**
- **Antihypertensive agents.**
- **Antiarrhythmic agents.**
- **Anticholinergic agents.**
- **Numerous drugs inhibit metabolism of tricyclic antidepressants.**
- **A few drugs enhance metabolism of tricyclic antidepressants.**
- **Tricyclic antidepressants inhibit action of other drugs:**
  - **Clonidine.**

Selective Serotonin Reuptake Inhibitors (SSRIs)

- **Fluoxetine.**
- **Paroxetine.**
- **Fluvoxamine, Less hepatotoxic than most other antidepressants.**
- **Sertraline.**
- **Citalopram.**

SSRIs


PRESYNAPTIC CELL
"STOP PRODUCTION" SIGNAL
SEROTONIN
AUTORECEPTOR
REUPTAKE TRANSPORTER
SYNAPTIC CLEFT
REGULATORY SIGNAL
SEROTONIN RECEPTOR
POSTSYNAPTIC CELL

SSRI Adverse Effects; Paroxetine

- **Endocrine effects:** **Sexual dysfunction in men.**
- **Weight gain, anticholinegric & drowsiness.**
- **Has a short half life compared to other SSRIs and the most prone to causing withdrawal effects whenever a dose is missed.**

SSRI Adverse Effects; Fluoxetine

- **Rashes & dermatologic reactions.**
- **Akathisia and agitation, extrapyramidal symptoms.**
- **Insomnia.**

SSRI Adverse Effects; Sertraline

- **Highest risk of psychiatric side effects (e.g. mania, suicidal behavior/ideation, psychosis, Insomnia etc).**
- **Has slight but clinically significant inhibitory effects on dopamine reuptake.**
- **GI toxicity: Mostly diarrhea.**

Cardiac Toxicity; Citalopram

- **Prolonged QT interval:**
  - **EKG abnormality linked to cardiac arrhythmia.**
  - **Potentially dangerous, even fatal.**
  - **High affinity for 5-HT_{2B} receptors.**
- **Human potassium channel:**
  - **High affinity for potassium channel also linked to propensity for drugs to produce cardiotoxicity.**

Drug	Anticholinergic	Drowsiness	Insomnia/agitation	Orthostatic hypotension	QTc prolongation*	Gastrointestinal toxicity	Weight gain
Selective serotonin reuptake inhibitors (SSRIs) ¶							
Citalopram	0	0	1+	1+	1+ Δ	1+ (all SSRIs: see ¶)	1+
Escitalopram	0	0	1+	1+	1+	1+	1+
Fluoxetine	0	0	2+	1+	1+	1+	1+
Fluvoxamine	0	1+	1+	1+	0 to 1+	1+	1+
Paroxetine	1+	1+	1+	2+	0 to 1+	1+	2+
Sertraline	0	0	2+	1+	0 to 1+	2+ ◊	1+

Serotonin inconveniences

- **Serotonin Syndrome:**
  - **Fever, agitation, hypertension, hyperthermia, rigidity, myoclonus; Can lead to seizure, coma, death.**
  - **Always get complete list of drugs prior to starting therapy.**
  - **Must have "washout" period between meds (1-3 months).**
- **Serotonin withdrawal syndrome:**
  - **With discontinuation of any SSRI; onset of withdrawal symptoms occur within a few days and can persist 3-4 weeks.**
  - **Symptoms: Disequilibrium, gastrointestinal problems, flu-like symptoms, sensory & sleep disturbances.**

TABLE 16–4 Characteristics of serotonin syndrome and other hyperthermic syndromes.

Syndrome	Precipitating Drugs	Clinical Presentation	Therapy[1]
Serotonin syndrome	SSRIs, second-generation antidepressants, MAOIs, linezolid, tramadol, meperidine, fentanyl, ondansetron, sumatriptan, MDMA, LSD, St. John's wort, ginseng	Hypertension, hyperreflexia, tremor, clonus, hyperthermia, hyperactive bowel sounds, diarrhea, mydriasis, agitation, coma; onset within hours	**Sedation (benzodiazepines), paralysis, intubation, and ventilation;** consider 5-HT_2 block with cyproheptadine or chlorpromazine
Neuroleptic malignant syndrome	D_2-blocking antipsychotics	Acute severe parkinsonism; hypertension, hyperthermia, normal or reduced bowel sounds, onset over 1–3 days	**Diphenhydramine** (parenteral), cooling if temperature is very high, sedation with benzodiazepines
Malignant hyperthermia	Volatile anesthetics, succinylcholine	Hyperthermia, muscle rigidity, hypertension, tachycardia; onset within minutes	**Dantrolene,** cooling

SSRI Drug Interactions

- **The Serotonin Syndrome: SSRI in combination with MAO inhibitors, St. John's Wort, pseudoephedrine.**
- **Sertraline & Citalopram with less drug interactions.**
- **Fluoxetine and paroxetine are inhibitors of CYP2D6 enzymes; potential adverse interactions with:**
  - **TCAs, digoxin, antiarrhythmics, warfarin, theophylline, β-blockers, opioid analgesics.**
  - **Are inhibitors of CYP3A4 enzymes; potential adverse interactions with: Ca2+blockers, antifungal , alprazolam, TCAs, digoxin, antiarrhythmics, warfarin, theophylline.**

Atypical/Heterocyclic

2nd Generation heterocyclics:

- Amoxapine
- Maprotiline
- Trazodone
- Bupropion

★ Similar to TCAs

★ ⇑NE output

★ α2-AR antagonist

★ 5-HT antagonists

★ SSRI-like

Third Generation heterocyclics:

- Mirtazapine
- Venlafaxine
- Nefazodone

Clomipramine

- **Structurally a TCA but exerts inhibitory effects on 5-HT reuptake.**

- **Used to treat OCD, depression, panic disorder and phobic disorders.**

Venlafaxine

- **Dual function:**

  - Low doses: ↑5-HT activity.

  - Higher doses: ↑ NE activity.
- **Advantage to other antidepressants for severe depressions.**
- **Hypertension in high doses.**

Duloxetine

- No cause dose-dependent hypertension as a common adverse effect.
- More hepatotoxic than most other antidepressants.
- The analgesic properties in the treatment of diabetic neuropathy and central pain syndromes such as fibromyalgia are believed to be due to sodium ion channel blockade.

Bupropion

- **Dual function:** ↑5-HT activity &↑ NE & DA activity.
- One of few antidepressants that does not cause sexual dysfunction.
- In patients who have not responded to other SSRIs.
- **Contraindication:** Epileptic seizures or other conditions that lower the seizures threshold, such as anorexia nervosa, bulimia nervosa, active brain tumors, or concurrent alcohol and/or benzodiazepine use and/or withdrawal.

Mirtazapine

- ↑5-HT activity &↑ NE activity with different mechanism of other antidepressants.
- Effective in severe or resistant to treatment of depressions.
- Increased appetite, and weight gain, sleepiness.
- α2–AR antagonists.

Maprotiline

- **Strong effects as a norepinephrine reuptake inhibitor.**
- **A strong initial sedation (first 2 to 3 weeks of therapy) and is therefore indicated to treat agitated patients or those with suicidal risks.**
- **Neuropathic pain.**
- **Side effects: Anticholinergic, antihistamine.**
- **Contraindications: Psychotic conditions like schizophrenia.**

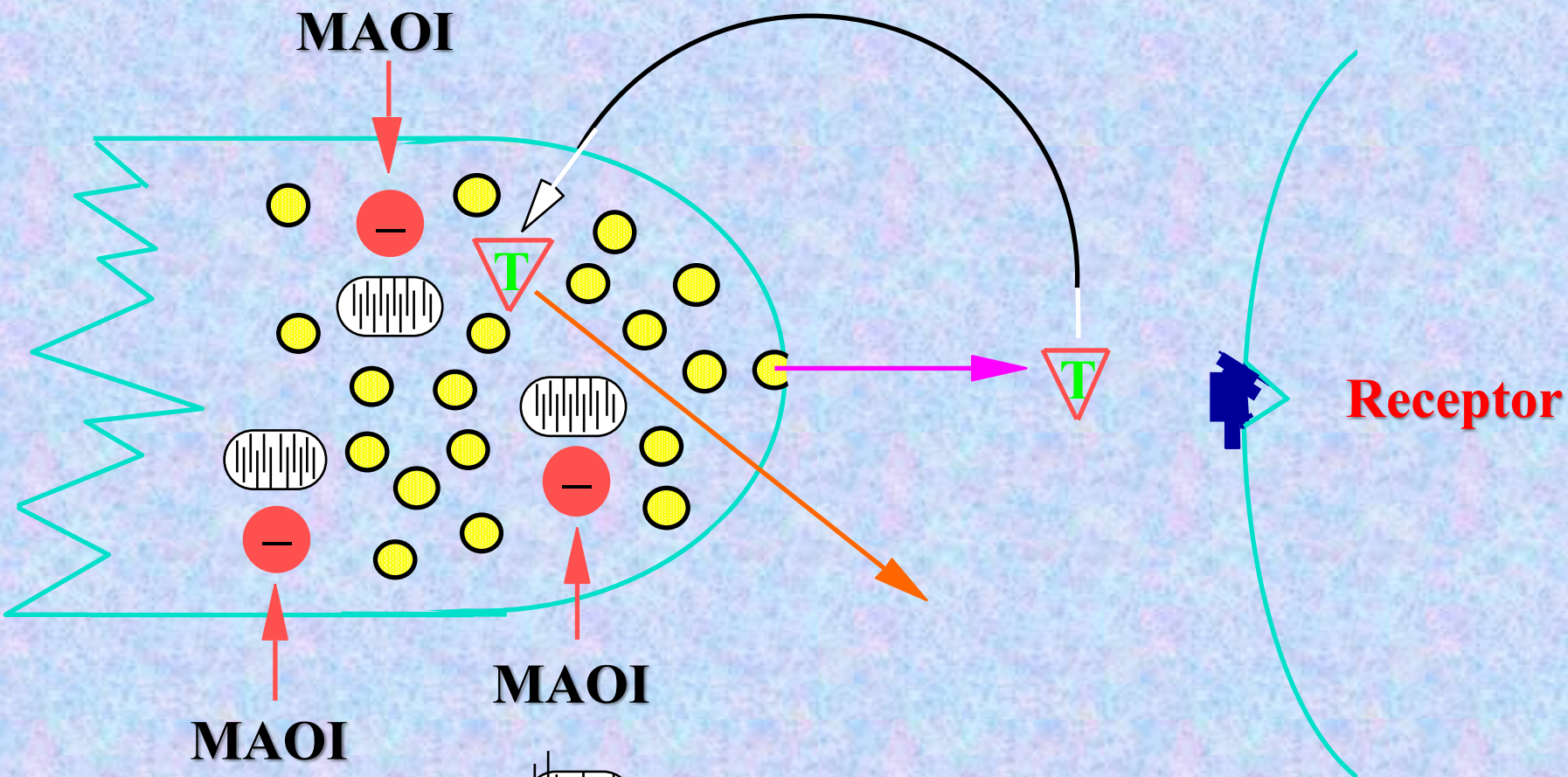
Nefazodone & Trazodone

- **Severe sleepiness.**
- **Nefazodone: Hepatic failure, strong inhibitor of CYP3A4.**
- **Useful for insomnia.**

Monoamine Oxidase Inhibitors

- **Two types:**
  - **MAO-A: Inhibition causes antidepressant activity (NE, 5-HT, Tyramine).**
  - **MAO-B: Inhibition causes side effects (DA).**

Monoamine Oxidase Inhibitors (Cont)



e.g.. Phenelzine, tranylcypromine, iproniazid

= Mitochondrion
MAO = On mitochondrial membrane

T = NA or 5-HT

MAOI = Monoamine oxidase inhibitor

Irreversible MAOI's

- **Nonselective:** Block both A and B types.
- Form a permanent chemical bond with part of the MAO enzyme → Enzyme function returns only as new enzyme is biosynthesized.
- **Ex:** Phenelzine, Tranylcypomine, Isocarboxazid.

Reversible MAOI's

- Not available in the U.S. yet.
- Highly selective in inhibiting MAO-A.
- Much safer than irreversible MAOI's.
- Side effects are minimal.
- Ex: Brofaromine, Pirlindole, Toloxatone, and Moclobemide.
- Inhibitors of MAO-B:

  - Deprenyl, Selegiline.

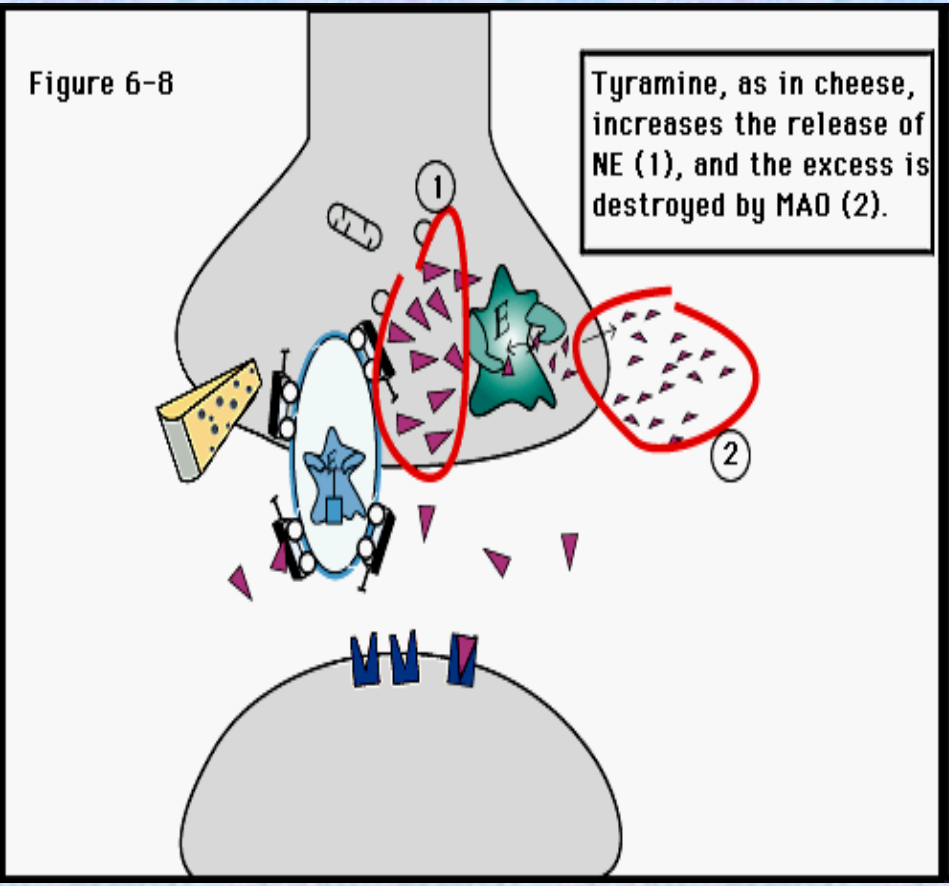
MAOI's; Pharmacotherapeutics

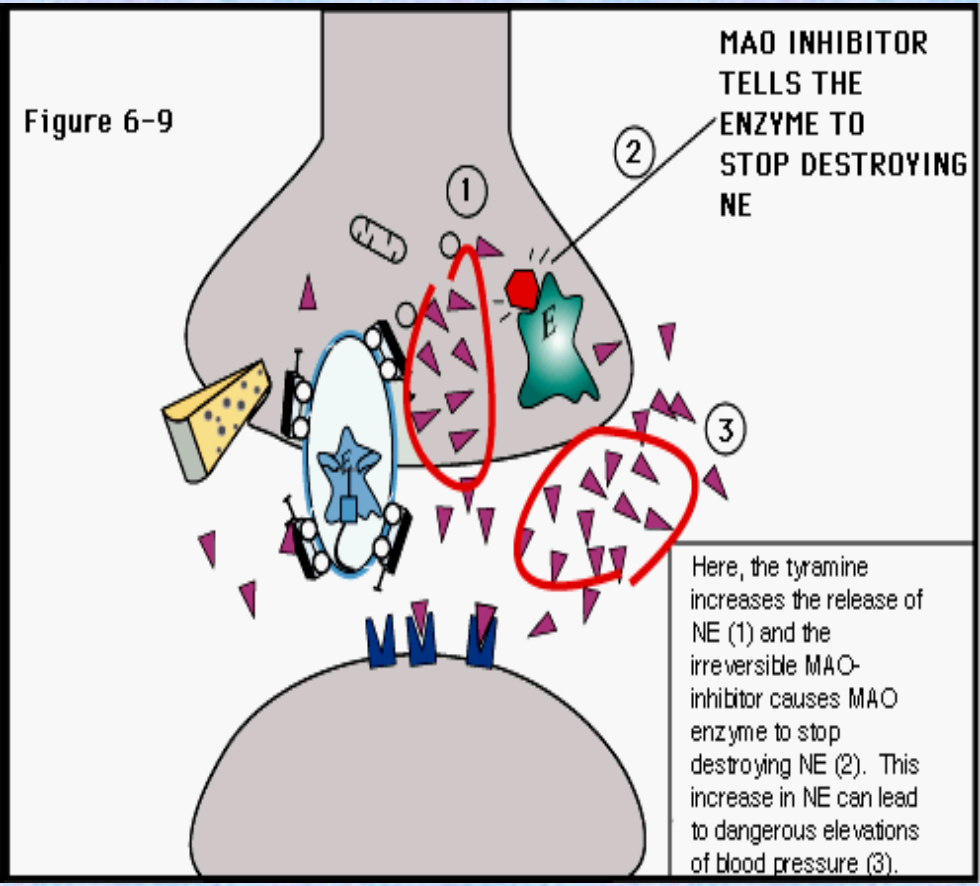
- **Treatment of choice for atypical depression (signs opposite of typical depression - weight gain, lacks suicidal tendencies, increased sexual drive).**
- **Also used to treat: Typical depression when other treatments are unsuccessful.**
- **Obsessive compulsive disorder, Phobic anxiety disorders, Bulimia.**

MAOIs; Adverse Effects

- Severe headache.
- Diaphoresis, nausea & vomiting, dry mouth and constipation hepatotoxicity.
- Agitation, hallucination, hyperreflexia, tremors, CNS stimulation, anxiety, agitation, increased risk of seizures.
- Impotence.
- Orthostatic hypotension (alpha-1 blockade), Hypertensive crisis (life-threatening).
- Hyperpyrexia with meperidine, dextromethorphan, TCAs.
- Phenelzine can produce a peripheral neuropathy, which can be treated with vitamin B6.

The Tyramine Cheese Effect





General Therapeutic Principles For Use Of Antidepressants

- An initial episode of major depression will be treated for at least one year.
- Choice of agent:
  - Tolerability of side effects.
  - Potential for drug interactions.
  - Other medical conditions.
  - Economics.
- First line agents include: SSRIs, non-sedating TCAs, bupropion.

General Therapeutic Principles For Use Of Antidepressants (Cont)

- **Three phases:**
  - **Phase 1:** Weeks 1-12;
    - Evaluations, dosage adjustments at 3-4 week intervals.
    - At least 6-8 weeks before switching meds.
  - **Phase 2:** Weeks 13-52; Continuation phase.
  - **Maintenance phase:** By taper or continue based on risk factors and other considerations.

Alternative Therapies

- **No way of a *priori* knowing which therapy will be best for a patient.**
  - **Light Therapy.**
  - **Psychological Treatment.**
  - **ECT.**
  - **St. John's Wort.**

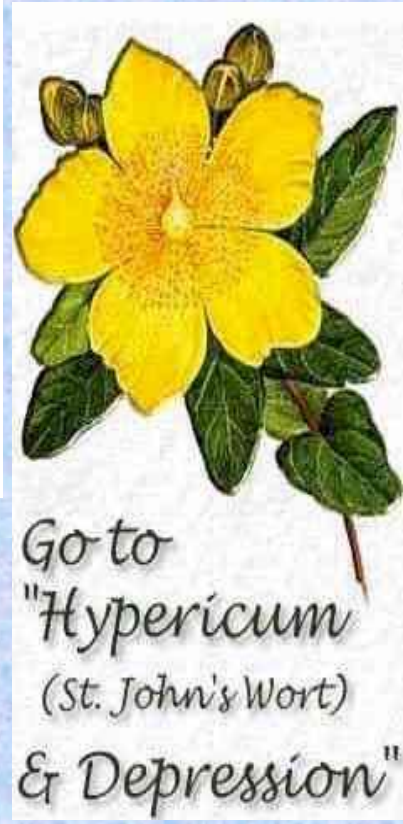
Electroconvulsive Therapy

- Often effective in drug non-responders.
- Modern medical approaches eliminated the horror of early use of ECT.
- Mechanism:

– In animals, causes many of the same receptor down-regulation events seen with antidepressant drugs.

St. John's Wort

- **Data suggest similar efficacy to TCAs in short term Rx of mild-moderate depression.**
- **Well tolerated:**
  - **Mild GI upset.**
  - **Photosensitivity.**
- **Potential drug interactions:**
  - **w/SSRIs: Mild Serotonin Syndrome.**
  - **From induction of P 450 enzymes: Decreased levels of digoxin and theophylline, OC's.**



- بیمار مردی 48 ساله است که به پاروکستین خوب پاسخ داده، وی دو ماه پس از شروع مصرف احساس کرد توانایی جنسی خود را از دست داده، بهترین اقدام برای وی که می باید داروی خود را ادامه دهد، چیست؟

الف) پاروکستین را به سرترالین تغییر دهیم.

ب) دوز پاروکستین را کاهش دهیم.

ج) بوپرونورفین را به درمان کنونی بیافزاییم.

د) سیلدانافیل را تجویز کنیم.

- بیمار دانشجویی 21 ساله و مبتلا به دوره حاد افسردگی ماژور با علائم شدید است. گرچه علائم وی پس از 8 هفته درمان با ونلافاکسین بهبود پیدا کرده است، او در حال حاضر دچار گیجی و درد در ناحیه پاهایش است. محتمل ترین توضیح برای این مشکل ایجاد شده چیست؟

الف) سندرم ضعف عضلانی ائوزینوفیلی

ب) سندرم سروتونین

ج) سندرم ترک ضد افسردگی های مهار گر بازجذب سروتونین

د) حمله قلبی

ه) سندرم بدخیم نورولپتیک


Thanks so much
for your attention