MAJOR DEPRESSIVE DISORDER

MAJOR DEPRESSIVE DISORDER

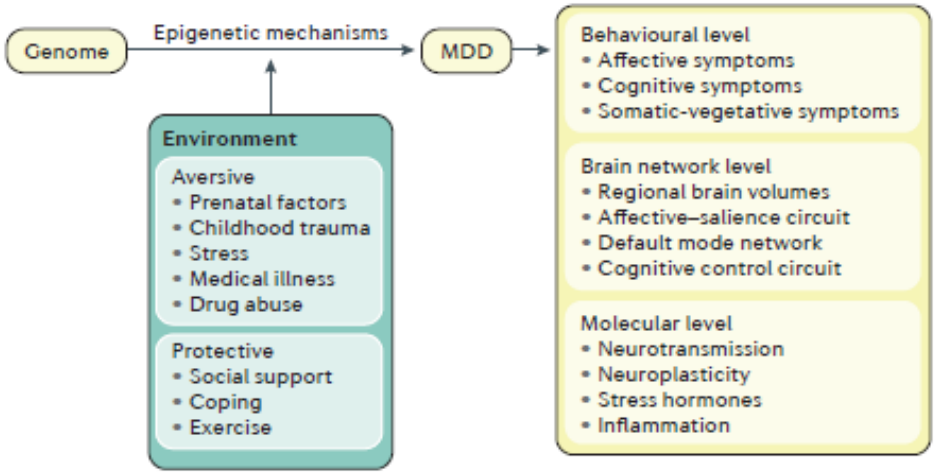
- Major depressive disorder (MDD) is a debilitating disease that is characterized by at least one discrete depressive episode lasting at least 2 weeks and involving clear-cut changes in mood, interests and pleasure, changes in cognition and vegetative symptoms
- MDD is a heterogeneous disorder, and is often associated with other psychiatric conditions, including anxiety, eating disorders and drug addiction

MAJOR DEPRESSIVE DISORDER

- The symptoms of depression include emotional and biological components. Emotional symptoms include
  - Emotional symptoms include
    - Low mood, excessive rumination of negative thought, misery, apathy and pessimism
    - Low self-confidence:
      - feelings of guilt
      - inadequacy
      - ugliness
    - Indecisiveness, loss of motivation
    - Anhedonia, loss of reward
  - Biological symptoms include
    - Retardation of thought and action
    - Loss of libido
    - Sleep disturbance and loss of appetite

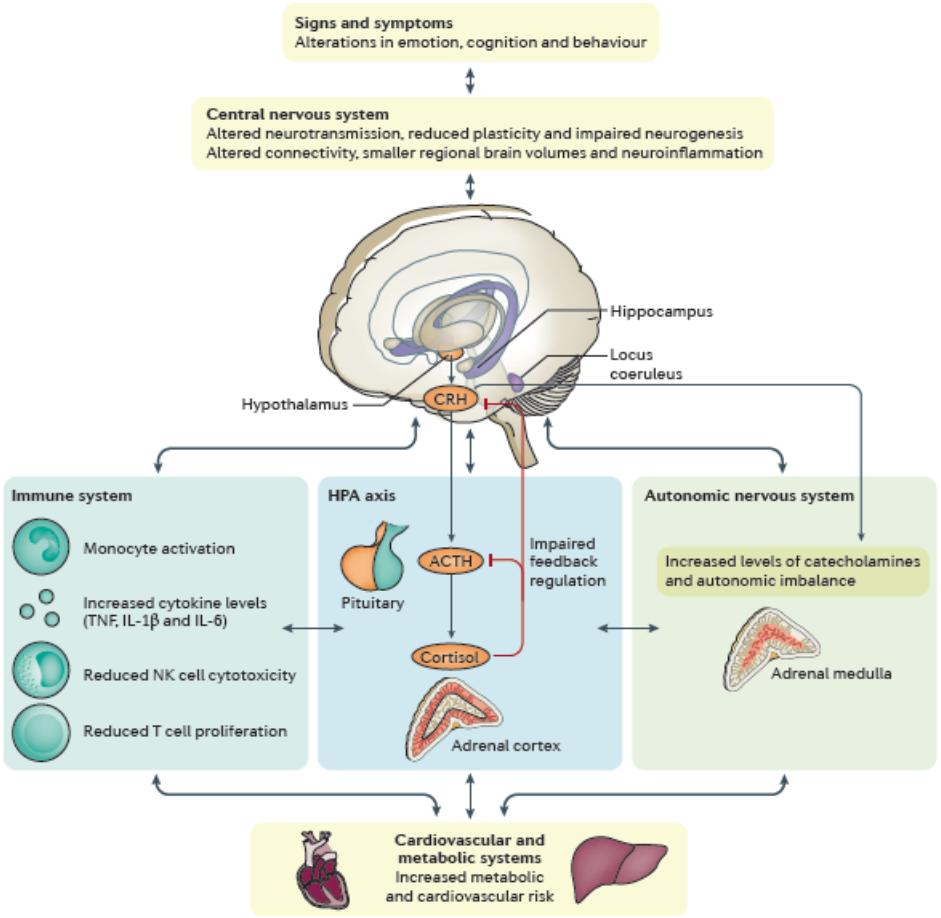
MAJOR DEPRESSIVE DISORDER

- Mechanisms/pathophysiology
  - Genetics
    - MDD is highly polygenic and involves many genes with small effects
  - Gene-environment interactions
    - The lack of consistent and replicated findings in genetic studies for MDD can at least partly be explained by the fact that relevant genetic variants confer an increased risk only in the presence of exposure to stressors and other adverse environmental circumstances
  - Environmental factors
    - There is a clear evidence of a dose–response relationship between the number and severity of adverse life events and the risk, severity and chronicity of MDD



MAJOR DEPRESSIVE DISORDER

- Mechanisms/pathophysiology
  - Biological systems involved in the pathophysiology of MDD
    - Clinical studies in MDD and relevant animal models have identified pathophysiology features in:
      - Central nervous system (CNS)
      - Hypothalamic-pituitary-adrenal axis (HPA)
      - Autonomic nervous system (ANS)
      - Immune system

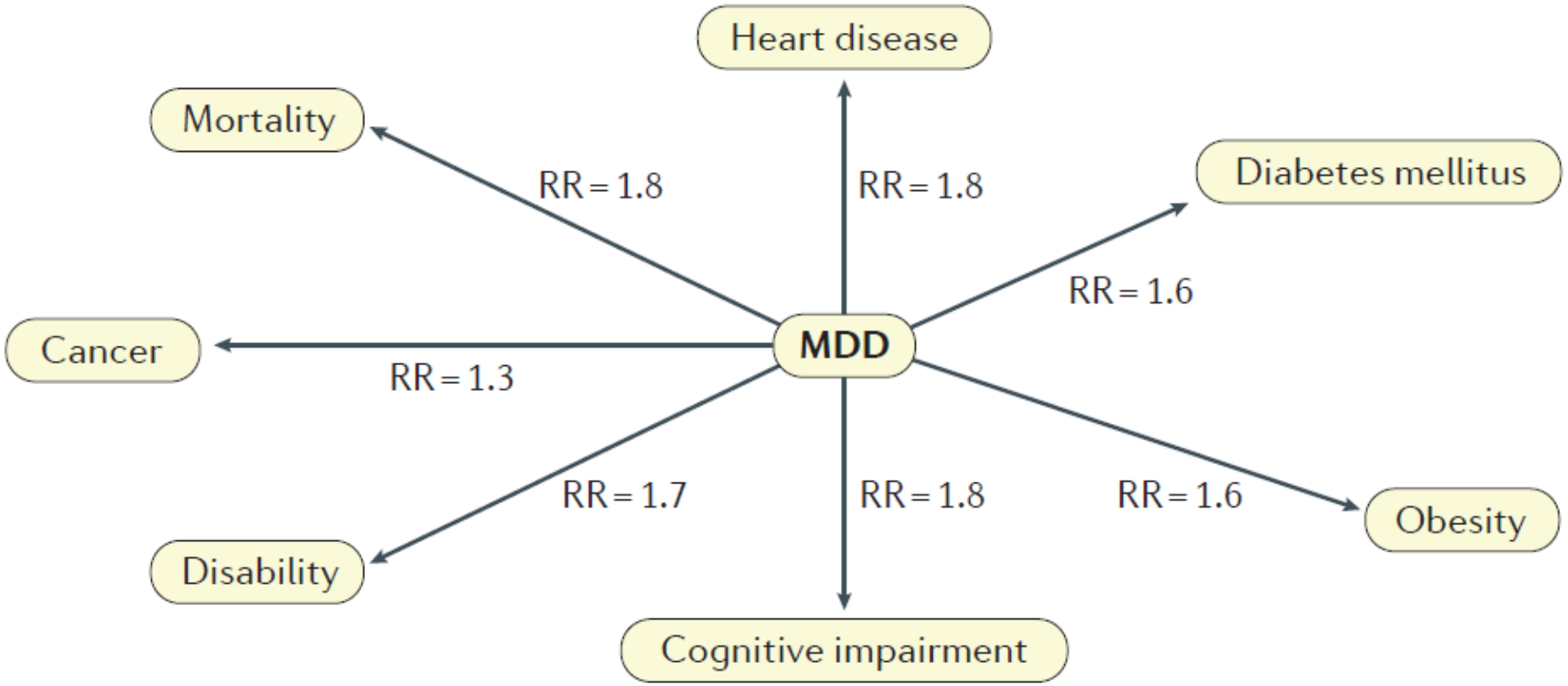


MAJOR DEPRESSIVE DISORDER

- Biological systems involved in the pathophysiology of MDD
  - CNS
    - Altered neurotransmission
    - Disrupting neuroplasticity and neurogenesis
      - These could underlie functional changes in relevant brain circuits (i.e. cognitive control and affective-salience networks)
      - Morphological changes in brain structure (i.e. hippocampus)
      - Neuroinflammation
      - Lower levels of the neurotrophin brain-derived neurotrophic factor (BDNF)
  - HPA axis
    - Impaired feedback regulation due to chronic hyperactivity
  - Immune system
    - Increased levels of circulating cytokines and low grade chronic activation of innate immune cells, including monocytes
    - Reduced natural killer (NK) cell cytotoxicity and T cell proliferative capacity
  - ANS
    - Cardiovascular and metabolic disease

MAJOR DEPRESSIVE DISORDER

- The somatic consequence of MDD



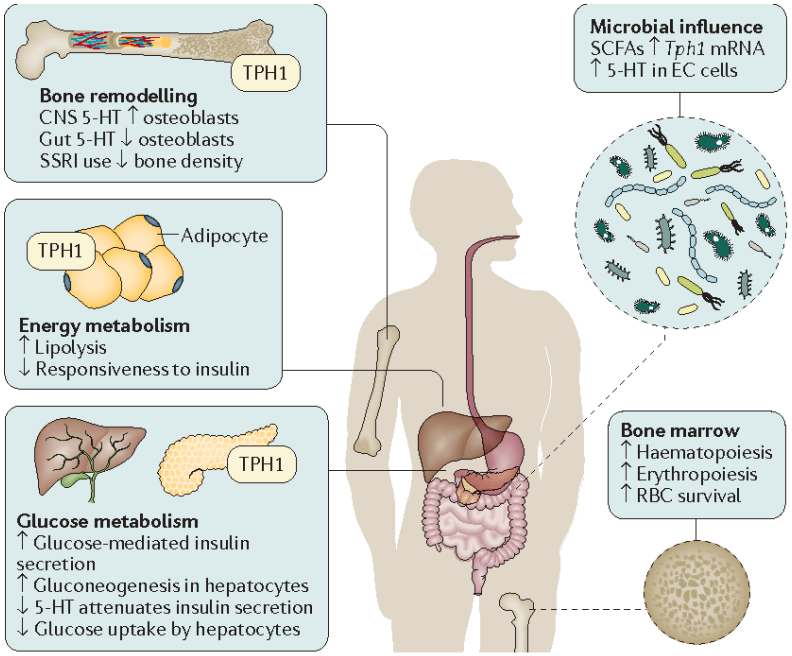
MAJOR DEPRESSIVE DISORDER

- Monoamine theory of depression (Reserpine)
  - The monoaminergic hypothesis of depression suggested that drugs capable of increasing the availability of extracellular monoamines were effective in the treatment of mood disorders. This hypothesis influenced the development of several generations of antidepressants, whose use was extended to other mood and anxiety disorders. The monoaminergic hypothesis was subsequently modified, according to more recent findings
  - The current version of the hypothesis, called neuroplasticity hypothesis of depression, it is based on the evidence that an increasing in extracellular monoamine levels induces adaptive changes:
    - In receptors
    - In several intracellular transduction pathways
    - In gene expression
      - Antidepressant therapies have been shown to normalize BDNF levels
    - In excitatory (glutamatergic) or inhibitory (GABAergic) transmission in the brain
  - This new hypothesis gives an explanation of the delayed antidepressant effect of drugs, which are not effective upon acute administration, but only after a few weeks of treatment

MAJOR DEPRESSIVE DISORDER

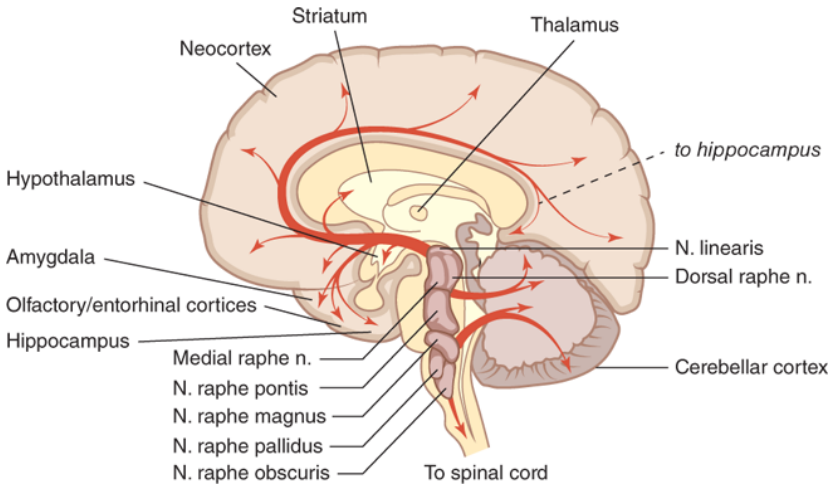
- Biological systems involved in the pathophysiology of MDD
  - CNS
    - Altered neurotransmission
      - Catecholaminergic transmission
      - Serotonergic transmission
      - Glutamatergic transmission

SEROTONERGIC TRASMISSION



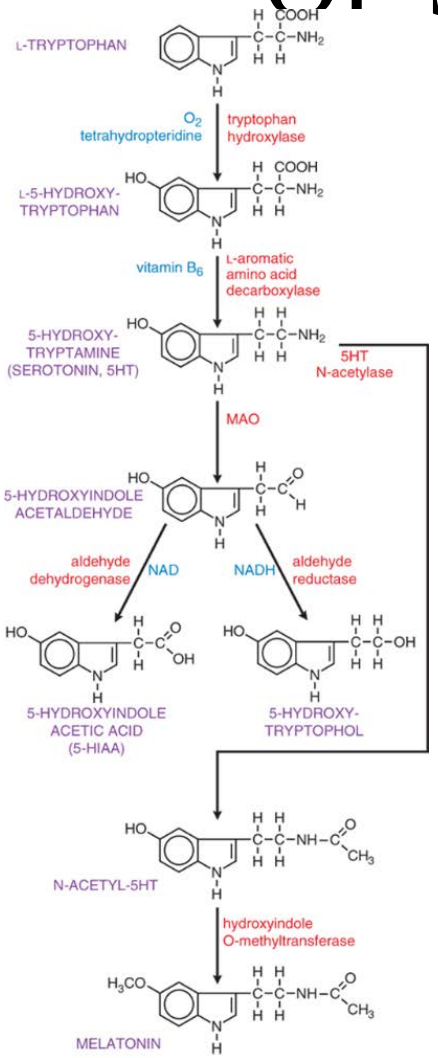
- Serotonin influences many peripheral tissues. Serotonin (5-HT) is involved in haematopoiesis by promoting the production of stem cells and the marrow microenvironment. In blood, 5-HT also supports erythropoiesis and lengthens the survival of red blood cells (RBCs). Energy and glucose metabolism are also affected by 5-HT. In pancreatic β cells, 5-HT contributes to insulin production and can promote glucose-mediated insulin secretion. In white adipocytes, 5-HT suppresses lipogenesis (increasing lipolysis) and impairs the insulin responsiveness. In bone, there is evidence for a role for 5-HT signalling in bone metabolism and remodelling via osteoblasts. Finally, bacteria in the gut can readily influence 5-HT synthesis via microbial by-products such as short-chain fatty acids (SCFAs)

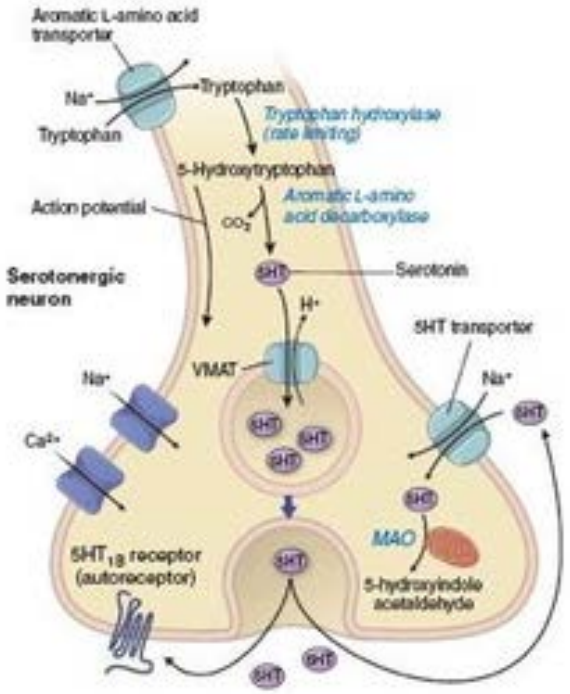
SEROTONERGIC TRASMISSION



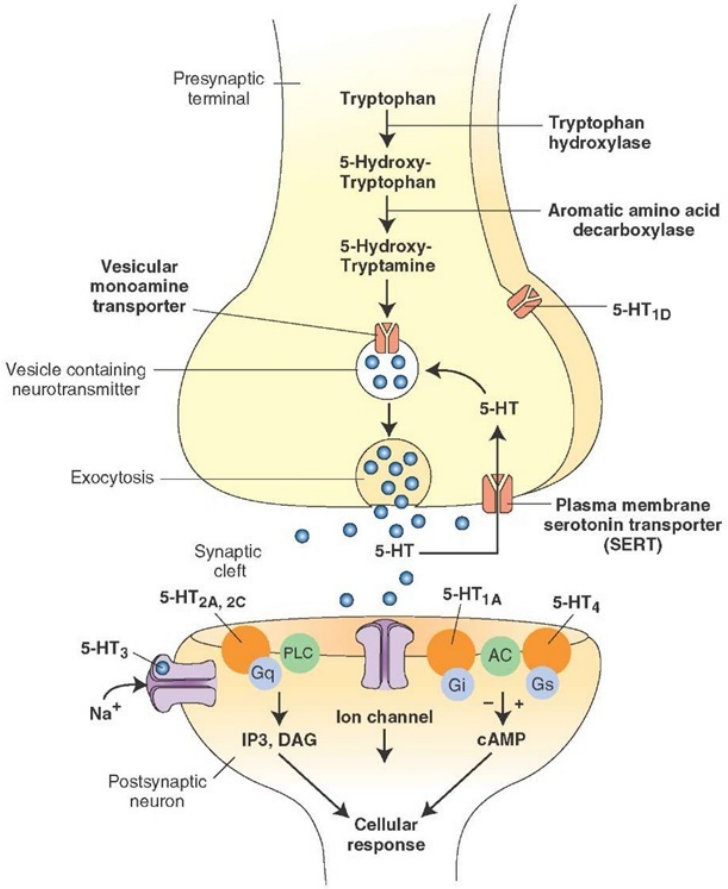
- Behavioural effects
  - Control of:
    - Mood
    - Memory
    - Aggression
    - Fear
    - Stress response
    - Appetite
    - Addiction
    - Sexuality
- Other CNS effects
  - Control of
    - Movement
    - Sleep/circadian rhythms
    - Vascular tone
    - Emesis
    - Respiratory centre
    - Body temperature

SYNTHESIS, STORAGE, REUPTAKE AND CATABOLISM OF SEROTONIN





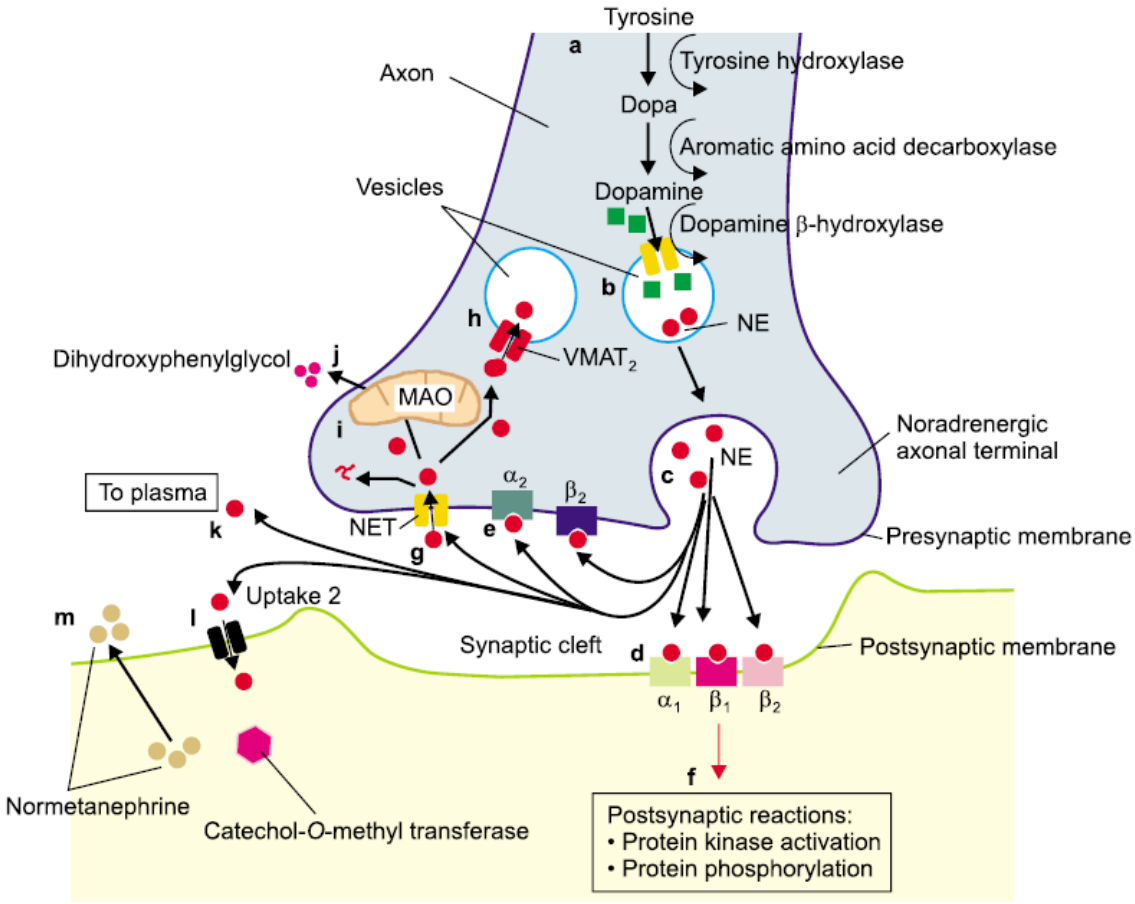
SERTONIN RELEASE



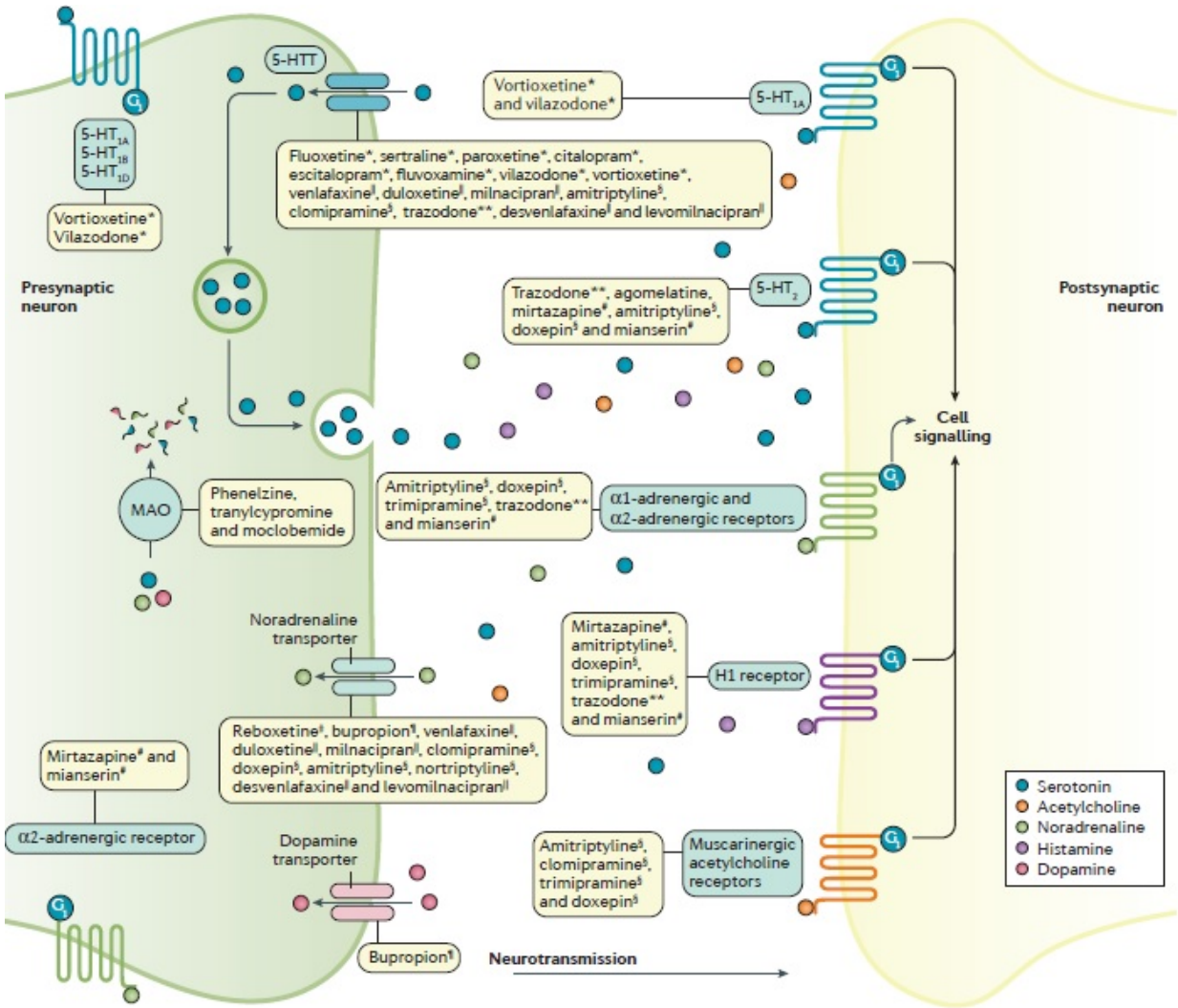
SEROTONIN RECEPTORS

SUBTYPE	SIGNALING EFFECTOR	LOCALIZATION	FUNCTION	AGONISTS	ANTAGONISTS
$5HT_{1A}$	↓ AC	Raphe nuclei, cortex, hippocampus	Somatodendritic autoreceptor	8-OH-DPAT, buspirone	WAY 100135
$5HT_{1B}$	↓ AC	Subiculum, globus pallidus, substantia nigra	Presynaptic autoreceptor	Sumatriptan, CP94253	GR-55562
$5HT_{1D}$	↓ AC	Cranial vessels, globus pallidus, substantia nigra	Presynaptic autoreceptor, vasoconstriction	Sumatriptan	SB 714786
$5HT_{1E}$	↓ AC	Cortex, striatum	—	—	—
$5HT_{1F}$	↓ AC	Dorsal raphe, hippocampus, periphery	—	LY334370	—
$5HT_{2A}$	↑ PLC, PLA_2	Platelets, smooth muscle, cerebral cortex	Aggregation, contraction, neuronal excitation	α-CH_3-5HT, DOI, MCPP	Ketanserin, LY53857
$5HT_{2B}$	↑ PLC	Stomach fundus	Smooth muscle contraction	α-CH_3-5HT, DOI	LY53857
$5HT_{2C}$	↑ PLC, PLA_2	Choroid plexus, substantia nigra, basal ganglia	CSF production, neuronal excitation	α-CH_3-5HT, DOI	LY53857, mesulergine
$5HT_3$	Cations	Parasympathetic nerves, solitary tract, area postrema, GI tract	Neuronal excitation	2-CH_3-5HT, quipazine	Ondansetron, tropisetron
$5HT_4$	↑ AC	Hippocampus, striatum, GI tract	Neuronal excitation	Renzapride	GR 113808
$5HT_{5A}$	↓ AC	Cortex, hippocampus	Unknown	—	SB-699551
$5HT_{5B}$	Unknown	—	Pseudogene in humans	—	—
$5HT_6$	↑ AC	Hippocampus, striatum, nucleus accumbens	Neuronal excitation	WAY-181187	SB-271046
$5HT_7$	↑ AC	Hypothalamus, hippocampus, GI tract	Smooth muscle relaxation	5-CT, LP-12	SB-269970

MAJOR DEPRESSIVE DISORDER



MAJOR DEPRESSIVE DISORDER

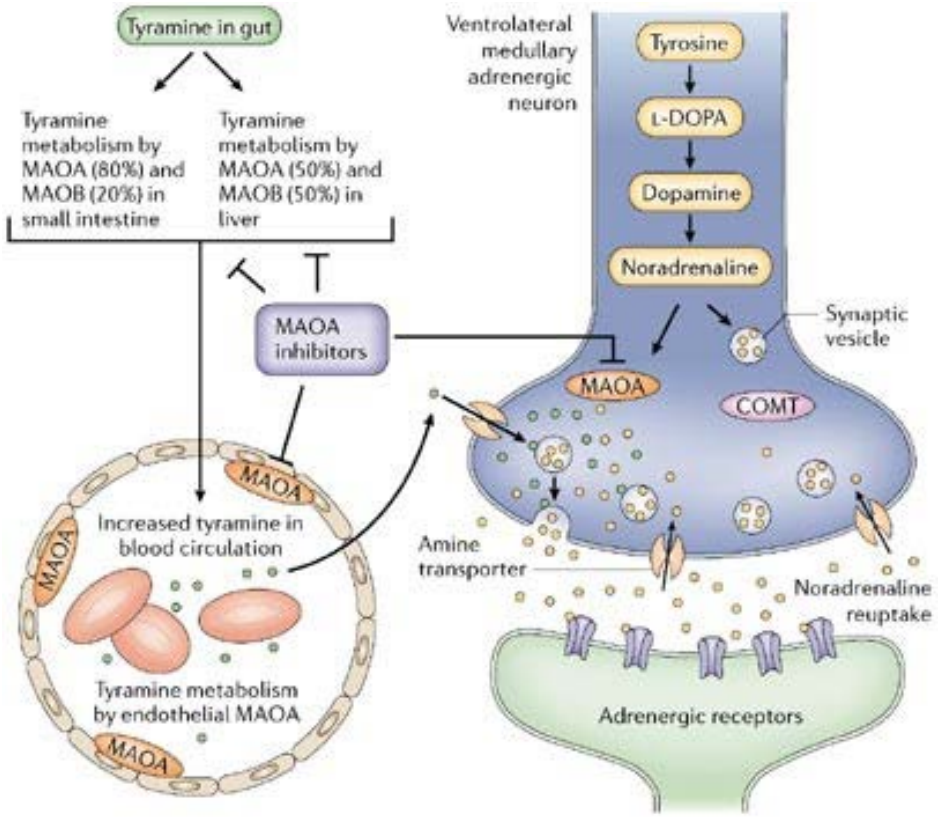


MAJOR DEPRESSIVE DISORDER

- Monoamine Oxidase (MAO)
  - This enzyme is found in nearly all tissues, mostly associated with mitochondria
    - Within nerve terminals, MAO regulates the free intraneuronal concentration of noradrenaline, 5-HT and dopamine
    - MAO in the gut wall is important in the inactivation of endogenous and ingested amines such as tyramine that would otherwise produce unwanted effects
    - This enzyme exists in two similar molecular forms coded by separate genes
      - MAO-A oxidizes preferentially epinephrine, norepinephrine, serotonin
      - MAO-B oxidizes preferentially phenylethylamine and dopamine

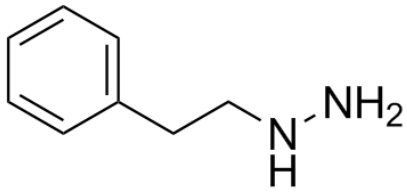
MAJOR DEPRESSIVE DISORDER

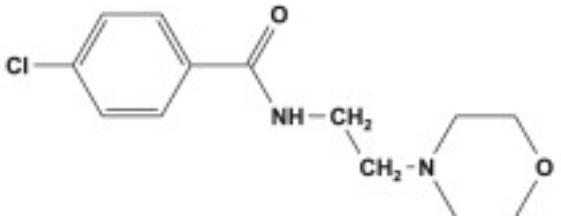
- Monoamine Oxidase Inhibitors (IMAO)
  - Irreversible and non selective inhibitors
    - MAO-A, MAO-B
      - Phenelzine
      - Tranylcypromine
      - Iproniazid
  - Reversible and selective inhibitor
    - MAO-A
      - Moclobemide
  - Irreversible and selective inhibitor
    - MAO-B
      - Selegiline
  - Clinical studies have shown clearly that antidepressant activity, as well as the main side effects of MAOIs, is associated with MAO-A inhibition

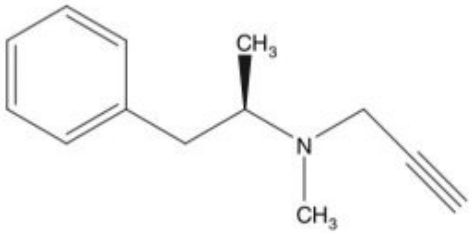


MAJOR DEPRESSIVE DISORDER

- Monoamine Oxidase Inhibitors (IMAO)
  - Monoamine oxidase inhibitors are substrate analogues with a phenylethylamine-like structure, that enables the inhibitor to bind covalently to the enzyme, resulting in a non-competitive and long-lasting inhibition
  - Recovery of MAO activity after inhibition takes several weeks with most drugs
  - Moclobemide acts as a reversible competitive inhibitor







MAJOR DEPRESSIVE DISORDER

- Monoamine Oxidase Inhibitors (IMAO)
  - Pharmacological effects
    - Monoamine oxidase inhibitors cause a rapid and sustained increase in the 5-HT, noradrenaline and dopamine content of the brain, 5-HT being affected most and dopamine least. Similar changes occur in peripheral tissues such as heart, liver and intestine, and increases in the plasma concentrations of these amines are also detectable
    - The main effect of MAOIs is to increase the cytoplasmic concentration of monoamines in nerve terminals, without greatly affecting the vesicular stores that are releasable by nerve stimulation. The increased cytoplasmic pool results in an increased rate of spontaneous leakage of monoamines
    - MAOIs do not increase the response of peripheral organs, such as the heart and blood vessels, to sympathetic nerve stimulation
      - Bretylium-like mechanism
        - Prevent the release of norepinephrine from sympathetic nerve endings, a mechanism that could account for orthostatic hypotension

MAJOR DEPRESSIVE DISORDER

- Monoamine Oxidase Inhibitors (IMAO)
  - Side effects
    - Postural hypotension (sympathetic block)
    - Atropine-like effects
    - Weight gain
    - CNS stimulation
      - Restlessness
      - Insomnia
      - Neurotoxicity
      - Convulsion (over dose)
    - ‘Cheese reaction’, i.e. severe hypertensive response to tyramine-containing foods (e.g. cheese, beer, wine, well-hung game, yeast or soy extracts). Such reactions can occur up to 2 weeks after treatment is discontinued

MAJOR DEPRESSIVE DISORDER

- Monoamine Oxidase Inhibitors (IMAOs)
  - Side effects
    - Hypotension is a common side effect. The possible explanations for this effect – the opposite of what might have been expected – are
      - Dopamine accumulates more than other amines within peripheral sympathetic nerve terminals displacing noradrenaline from the storage vesicles, thus reducing noradrenaline release associated with sympathetic activity
      - Bretylium-like mechanism
      - Clonidine-like mechanism
        - Increasing stimulation of presynaptic alpha-2 receptors in the cardiovascular center in the brainstem (similar to the alpha-2 agonist clonidine).
    - Atropine-like side effects
      - MAOIs exhibit anticholinergic effects due to an increase of sympathetic activity
    - Weight gain
      - Overeating or inactivity as a result of depression can cause weight gain.
      - Some people lose weight as part of their depression. In turn, an improved appetite associated with improved mood may result in increased weight

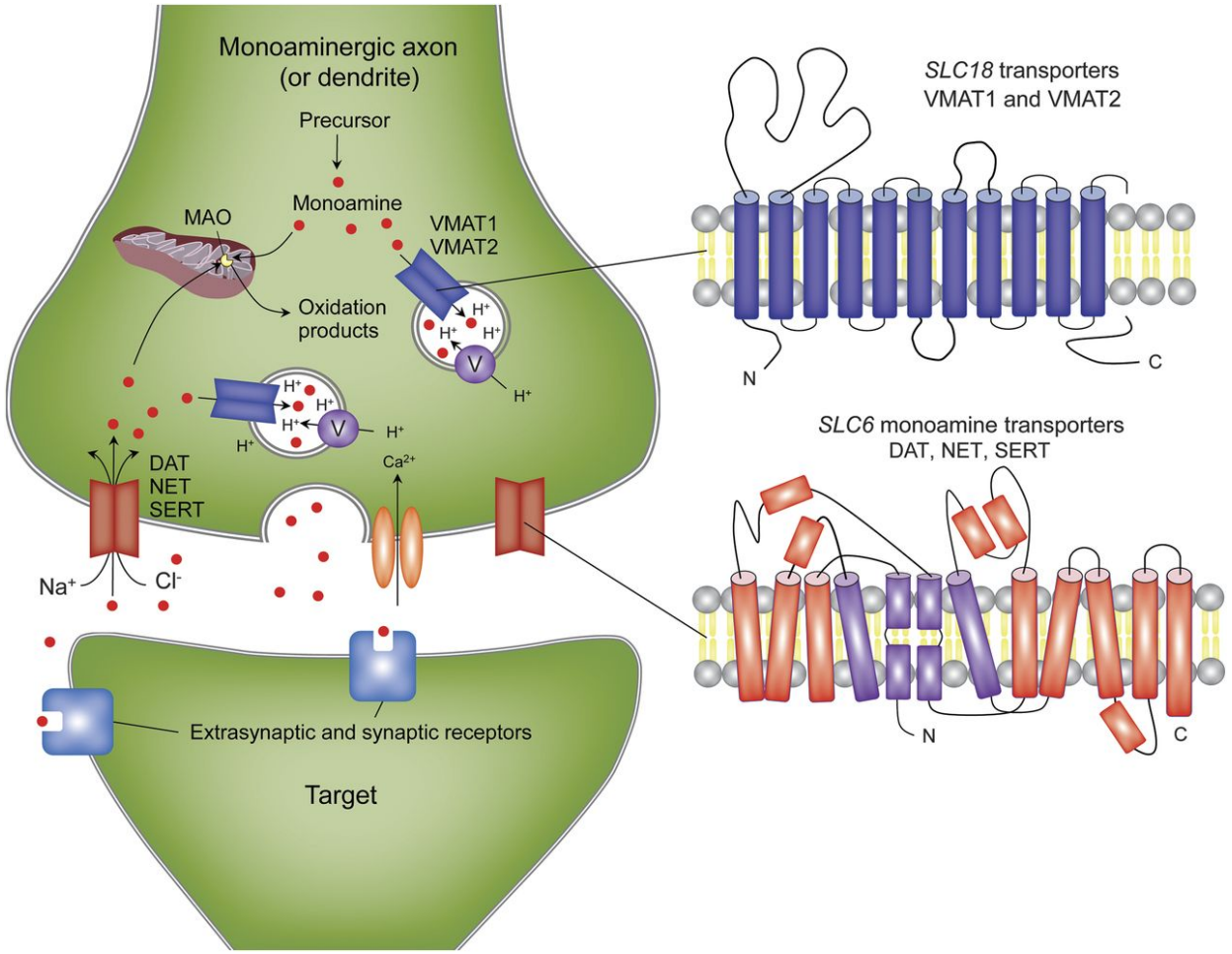
MAJOR DEPRESSIVE DISORDER

- Monoamine Oxidase Inhibitors (IMAO)
  - Interaction with other drugs and food
    - Interaction with other drugs and foods is the most serious problem with MAOIs and is the main factor that caused their clinical use to decline. The special advantage claimed for the new reversible MAOIs, such as moclobemide, is that these interactions are reduced
    - The ‘cheese reaction’ is a direct consequence of MAO inhibition and occurs when normally innocuous amines (mainly tyramine) produced during fermentation are ingested. Tyramine is normally metabolised by MAO in the gut wall and liver, and little dietary tyramine reaches the systemic circulation. MAO inhibition allows tyramine to be absorbed, and also enhances its sympathomimetic effect. The result is acute hypertension, giving rise to a severe throbbing headache and occasionally even to intracranial haemorrhage
    - Administration of indirectly acting sympathomimetic amines (e.g. ephedrine – a nasal decongestant – or amphetamine – a drug of abuse) also causes severe hypertension in patients receiving MAOIs
    - Moclobemide, a specific MAO-A inhibitor, does not cause the ‘cheese reaction’, probably because tyramine can still be metabolised by MAO-B

MAJOR DEPRESSIVE DISORDER

- Monoamine Oxidase Inhibitors (IMAO)
  - Pharmacokinetics
    - Oral administration
    - Peak plasma concentration are attained 30-150 minutes after the ingestion
    - Half-lives of 1.5–4 hours
    - Extensive bound to the plasma protein
    - Large volume of distribution
    - Extensive first pass metabolism by acetylation
    - Urinary excretion is low

MAJOR DEPRESSIVE DISORDER



MAJOR DEPRESSIVE DISORDER

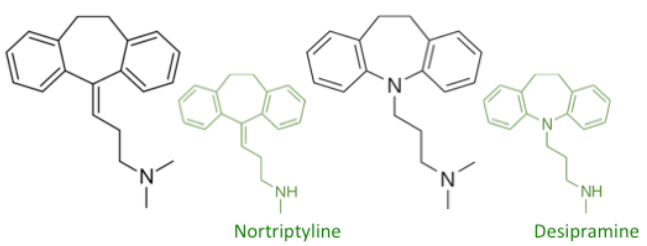
- Norepinephrine serotonin and dopamine transporters (NETs, SERTs and DATs) belong to a family of sodium-chloride-dependent transporters (SLC6)
- The SLC6 family is a diverse set of transporters that mediate solute translocation across cell plasma membranes by coupling solute transport to the cotransport of sodium and chloride down their electrochemical gradients
- The catecholamine transporter first binds a sodium ion, followed by serotonin, and then a chloride ion. The transporter then flips inside the cell, releasing serotonin. A potassium ion binds, and the transporter flips back out, ready to receive another serotonin molecule

MAJOR DEPRESSIVE DISORDER

- Monoamine Uptake Inhibitors
  - Tricyclic Antidepressant Drugs (TCA)
    - Mechanism of action
      - The main immediate effect of TCAs is to block the uptake of amines by nerve terminals, by competition for the binding site of the amine transporters. Most TCAs inhibit noradrenaline and 5-HT uptake but have much less effect on dopamine uptake
      - In addition to their effects on amine uptake, most TCAs affect other receptors, including muscarinic acetylcholine receptors, histamine receptors and 5-HT receptors. The antimuscarinic effects of TCAs do not contribute to their antidepressant effects but are responsible for various side effects

MAJOR DEPRESSIVE DISORDER

- Monoamine Uptake Inhibitors
  - Tricyclic Antidepressant Drugs (TCA)
    - TCAs are closely related in structure to the phenothiazines
      - Amitriptyline
      - Desipramine
      - Doxepin
      - Imipramine
      - Nortriptyline
      - Protriptyline
      - Trimipramine



Amitriptyline Imipramine Chlorpromazine (phenothiazine)

MAJOR DEPRESSIVE DISORDER

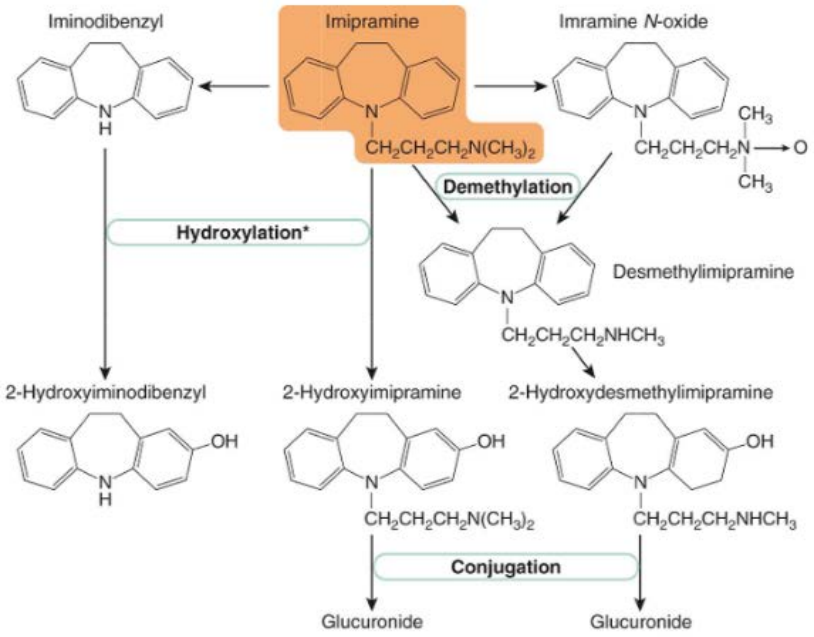
- Monoamine Uptake Inhibitors
  - Tricyclic Antidepressant Drugs (TCA)
    - Side effects
      - Muscarinic M_1 receptor antagonism
        - Anticholinergic effects
          - Dry mouth
          - Blurred vision
          - Constipation
          - Urinary retention
          - Impotence
      - Histamine H_1 receptor antagonism
        - Sedation and weight gain
      - Adrenergic α receptor antagonism in medullary vasomotor centre in the brainstem
        - Postural hypotension
      - TCAs, particularly in overdose, may cause ventricular dysrhythmias associated with prolongation of the QT interval. Usual therapeutic doses of TCAs increase, slightly but significantly, the risk of sudden cardiac death

Antidepressant Drugs

- Monoamine Uptake Inhibitors
  - Tricyclic Antidepressant Drugs (TCA)
    - Interactions with other drugs
      - TCAs are particularly likely to cause adverse effects when given in conjunction with other drugs. They rely on hepatic metabolism by microsomal cytochrome P450 (CYP) enzymes for elimination, and this may be inhibited by competing drugs
      - TCAs potentiate the effects of alcohol and anaesthetic agents, for reasons that are not well understood, and deaths have occurred as a result of this, when severe respiratory depression has followed about of drinking. TCAs also interfere with the action of various antihypertensive drugs

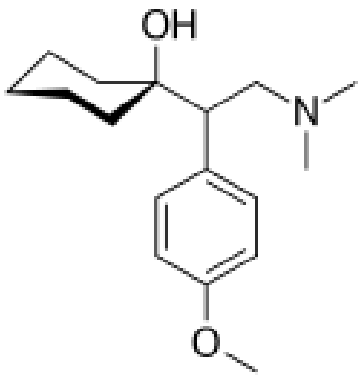
MAJOR DEPRESSIVE DISORDER

- Monoamine Uptake Inhibitors
  - Tricyclic Antidepressant Drugs (TCA)
    - Pharmacokinetics
      - Oral administration
      - Half-lives of 10–80 hours
      - Extensive binding to the plasma proteins
      - Large volume of distribution
      - Extensive first pass metabolism by N-demethylation and ring hydroxylation
        - Hydroxylation catalyzed by CYP2D6
        - Both the demethyl and the hydroxylated metabolites commonly retain biological activity. During prolonged treatment with TCAs, the plasma concentration of these metabolites is usually comparable to that of the parent drug
      - Low urinary excretion after the glucuronide conjugation

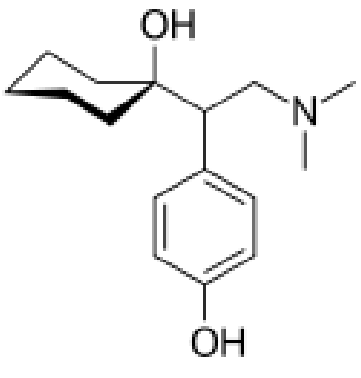


MAJOR DEPRESSIVE DISORDER

- Monoamine Uptake Inhibitors
  - Serotonin and Noradrenaline Uptake Inhibitors (SNRIs)
    - Venlafaxine
    - Desvenlafaxine
    - Duloxetine



venlafaxine



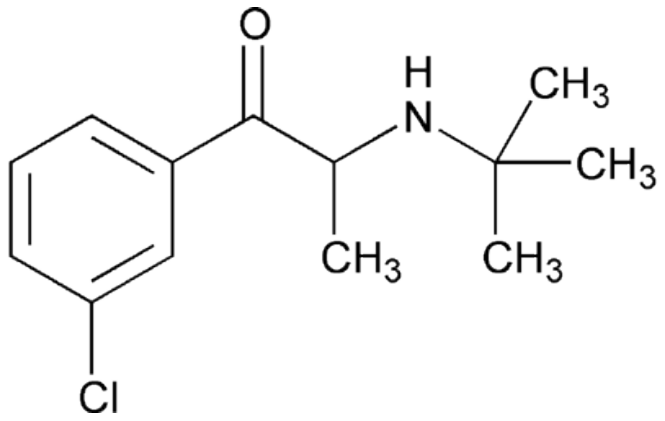
desvenlafaxine

MAJOR DEPRESSIVE DISORDER

- Monoamine Uptake Inhibitors
  - Serotonin and Noradrenaline Uptake Inhibitors (SNRIs)
    - Mechanism of action
      - The main immediate effect of SNRIs is to block the uptake of NA and 5-HT by nerve terminals, by competition for the binding site of the NA and 5-HT transporters
    - Side effects
      - Less risk of cardiac effects, so safer in overdose than tricyclic antidepressants
    - Pharmacokinetics
      - Oral administration
      - Extensive first pass metabolism
        - Venlafaxine and duloxetine are metabolised by CYP2D6. Venlafaxine is converted to desvenlafaxine, which shows greater inhibition of noradrenaline reuptake

MAJOR DEPRESSIVE DISORDER

- Monoamine Uptake Inhibitors
  - Dopamine and Noradrenaline Uptake Inhibitors
    - Bupropion



MAJOR DEPRESSIVE DISORDER

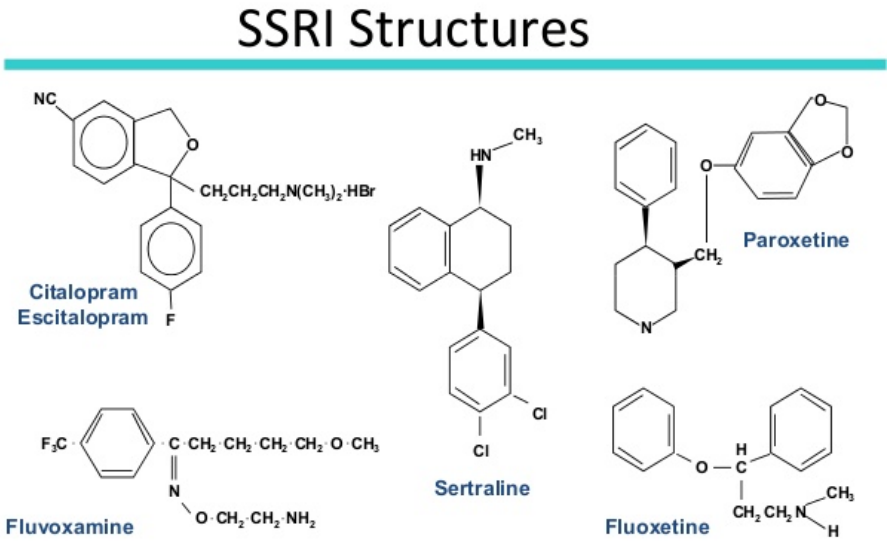
- Monoamine Uptake Inhibitors
  - Dopamine and Noradrenaline Uptake Inhibitors
    - Mechanism of action
      - Bupropion inhibits both noradrenaline and dopamine (but not 5-HT) uptake but, unlike cocaine and amphetamine does not induce euphoria and has so far not been observed to have abuse potential. It is metabolised to active metabolites. It is also used to treat nicotine dependence. At high doses it may induce seizures

MAJOR DEPRESSIVE DISORDER

- Monoamine Uptake Inhibitors
  - Selective 5-Hydroxytryptamine Uptake Inhibitors (SSRIs)
    - Mechanism of action
      - The main immediate effect of SSRIs is to block the uptake of serotonin by nerve terminals, by competition for the binding site of the serotonin transporters. All SSRIs inhibit 5-HT uptake
      - In addition to their effects on amine uptake, novel SSRIs have also a partial agonist activity at 5-HT_{1A} and 5-HT_{1B} receptors and are antagonists at 5-HT_{3A} and 5-HT_{7} receptors
      - They are less likely than TCAs to cause anticholinergic side effects and are less dangerous in overdose. In contrast to MAOIs, they do not cause ‘cheese reactions’

MAJOR DEPRESSIVE DISORDER

- Monoamine Uptake Inhibitors
  - Selective 5-Hydroxytryptamine Uptake Inhibitors (SSRIs)
    - Fluoxetine
    - Fluvoxamine
    - Paroxetine
    - Citalopram
    - Escitalopram
    - Sertraline
    - Vortioxetine



MAJOR DEPRESSIVE DISORDER

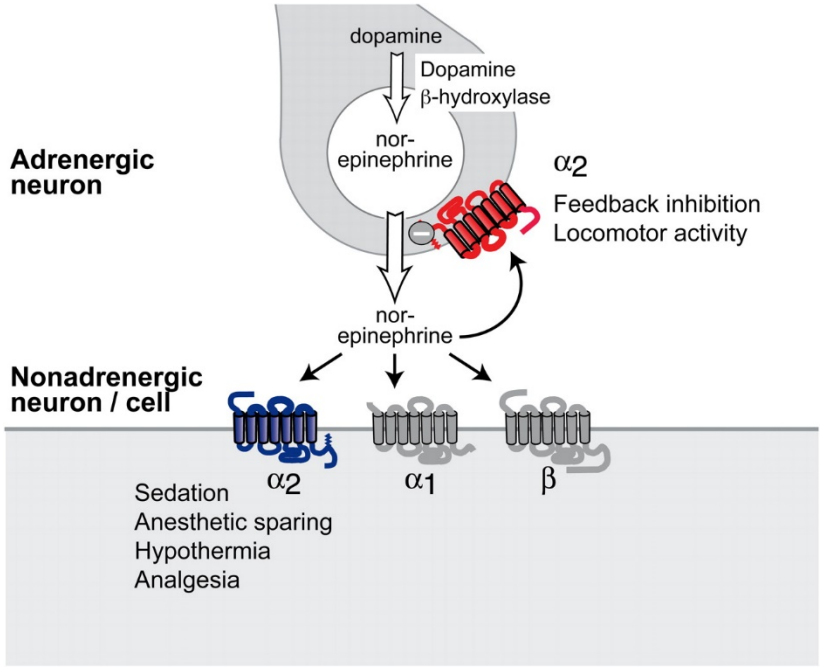
- Monoamine Uptake Inhibitors
  - Selective 5-Hydroxytryptamine Uptake Inhibitors (SSRIs)
    - Side effects
      - Some of the side effects result from the enhanced stimulation of postsynaptic 5-HT receptors as a result of the drugs increasing the levels of extracellular 5-HT. This can be either stimulation of the wrong type of 5-HT receptor (e.g. $5\text{-}HT_2$, $5\text{-}HT_3$ and $5\text{-}HT_4$ receptors) or stimulation of the same receptor that gives therapeutic benefit (e.g. postsynaptic $5\text{-}HT_{1A}$ receptors) but in the wrong brain region (i.e. enhanced stimulation of 5-HT receptors can result in both therapeutic and adverse responses)
        - Nausea
        - Anorexia
        - Insomnia
        - Loss of libido
        - Failure of orgasm

MAJOR DEPRESSIVE DISORDER

- Monoamine Uptake Inhibitors
  - Selective 5-Hydroxytryptamine Uptake Inhibitors (SSRIs)
    - Pharmacokinetics
      - The SSRIs are well absorbed when given orally, and most have plasma half-lives of 18–24 h (fluoxetine is longer acting: 24–96 h). Paroxetine and fluoxetine are not used in combination with TCAs, whose hepatic metabolism they inhibit through an interaction with CYP2D6, for fear of increasing TCA toxicity

MAJOR DEPRESSIVE DISORDER

- Monoamine Receptor Antagonists
  - α_2 adrenoreceptors
    - Pre-synaptic activation of α_2-adrenoceptors in sympathetic nerve endings and noradrenergic neurons leads to inhibition of norepinephrine release. Central nervous system activation of post-synaptic α_2-adrenoceptors inhibits sympathetic activity, which results in hypotension and bradycardia as well as sedation
  - 5-HT_{2A} and 5-HT_3 receptors



MAJOR DEPRESSIVE DISORDER

- Mirtazapine blocks not only α_2 adrenoreceptors but also other receptors, including 5-HT_{2C} receptors, which may contribute to its antidepressant actions. Block of α_2 adrenoceptors will not only increase noradrenaline release but will also enhance 5-HT release; however, by simultaneously blocking 5-HT_{2A} and 5-HT_3 receptors it will reduce unwanted effects mediated through these receptors (e.g. sexual dysfunction and nausea) but leave intact stimulation of postsynaptic 5-HT_{1A} receptors. It also blocks histamine H_1 receptors, which may cause sedation

MAJOR DEPRESSIVE DISORDER

- Other Clinical Uses of Antidepressant Drugs
  - To some extent, the term ‘antidepressant drug’ is misleading, as many of these drugs are now used to treat disorders other than depression. These include:
    - Neuropathic pain
      - amytriptyline
      - nortryptyline
      - duloxetine
    - Anxiety disorders
      - SSRIs
    - Fibromyalgia
      - SSRIs
      - TCAs
    - Bipolar disorder
      - Fluoxetine in conjunction with olanzapine
    - Smoking cessation
      - Buproprion
    - Attention deficit/hyperactivity disorder
      - Atomoxetine

BIPOLAR DISORDER

- Understanding Bipolar Disorder – YouTube
- Lithium's Hypothetical Mechanism of Action - YouTube