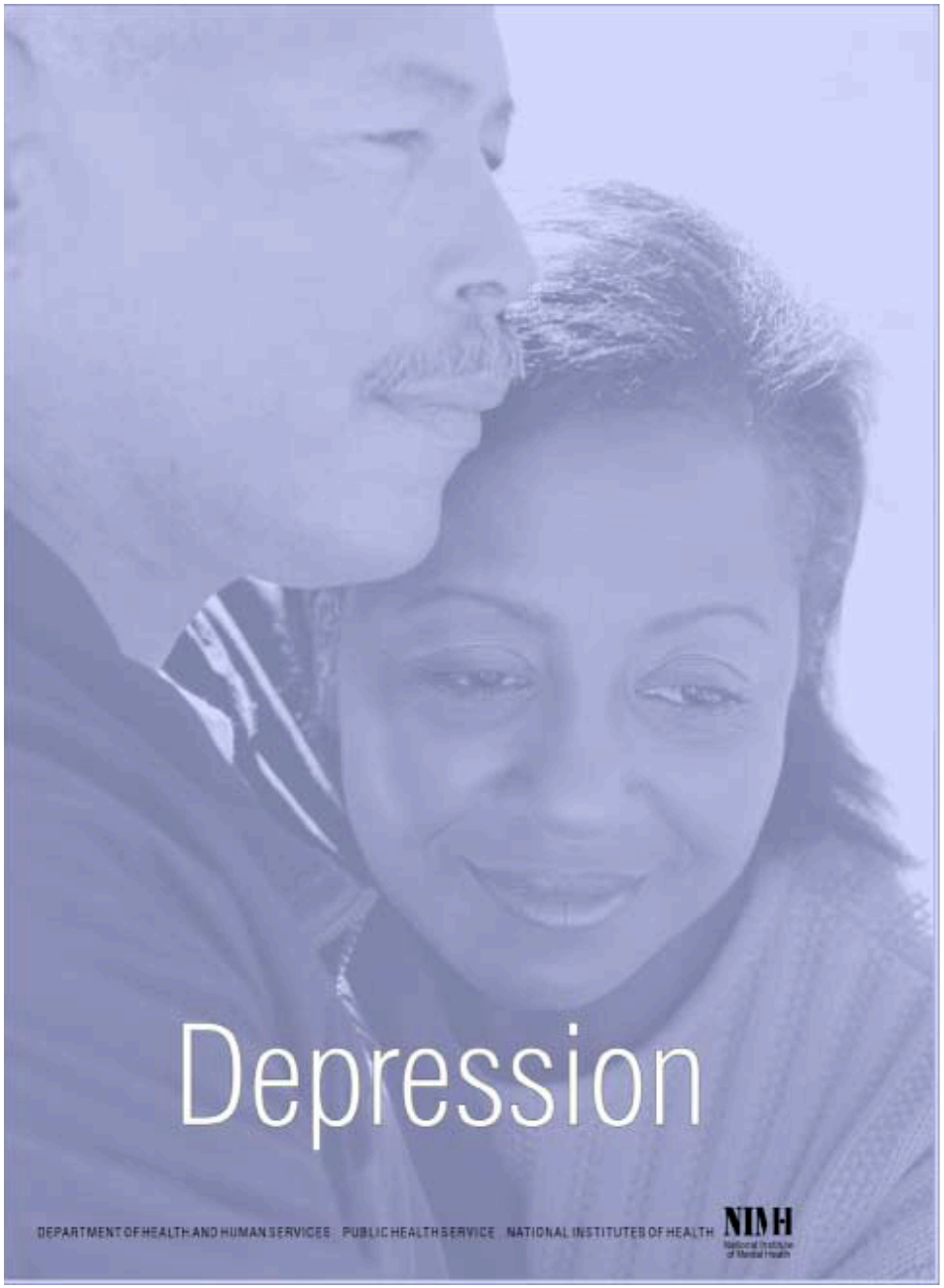


- In any given 1-year period, 9.5% of the USA population (about 20 million) suffer from a depressive illness.
- The economic cost for this disorder is high, but the cost in human suffering cannot be estimated.
- Depressive illnesses often interfere with normal functioning and cause pain and suffering not only to those who have a disorder, but also to those who care about them.

Emil Kraepelin (1856 - 1926)
Melancolia

Father of modern psychiatry

Kraepelin...pioneered psychopharmacology, which he virtually founded. He was the first to use experimental methods to study the effects of drugs, alcohol, nicotine, etc., on human behavior.

Kraepelin discovered schizophrenia and manic-depression. Kraepelin also jointly discovered Alzheimer's disease which he named after his colleague and co-discoverer, Dr. Alois Alzheimer

Albrecht Dürer (1471 - 1533)
Melancolia

"Grief and fear,when lingering, provoke melancholia."
Hippocrates, 460–377 BC

(μελανχηολια, from the Greek,'black bile') is the only condition whose original name survived from the Hippocratic classification of diseases based on the four humours.

Hippocrates thought that melancholia was caused by the humour 'black bile' and that treatment should consist of purging and removing of blood.

In the contemporary classification of psychiatric disorders (DSM-IV)1, melancholia is defined as a subtype of major depression.

What Is A Depressive Disorder?

- A depressive disorder is an illness that involves the body, mood, and thoughts.
- It affects the way a person eats and sleeps,
- the way one feels about oneself,
- and the way one thinks about things.

- **Depression is related to the normal emotions of sadness, but it does not remit when the external cause of these emotions dissipates, and it is disproportionate to their cause.**

- **Classic severe states of depression often have no external precipitating cause.**

- **Most people with a depressive illness do not seek treatment, although the great majority even those whose depression is extremely severe can be helped.**

- **There are now medications and psychosocial therapies such as cognitive/behavioral, that ease the pain of depression.**

Depression. It's not only a state of mind.

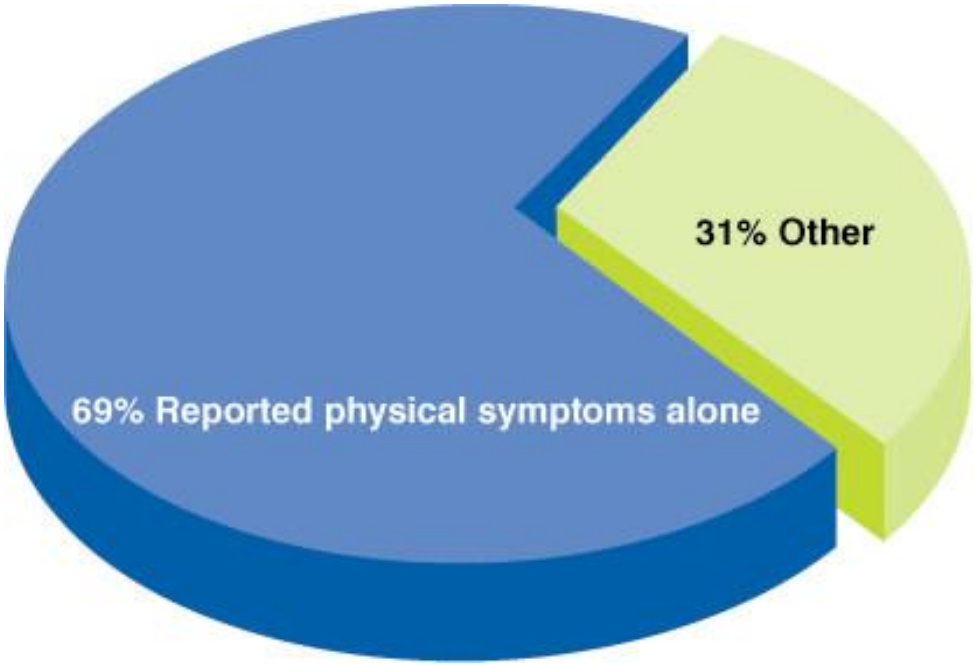
The symptoms of depression

Emotional Symptoms Include:	Physical Symptoms Include:
Sadness	Vague aches and pains
Loss of interest or pleasure	Headache
Overwhelmed	Sleep disturbances
Anxiety	Fatigue
Diminished ability to think or concentrate, indecisiveness	Back pain
Excessive or inappropriate guilt	Significant change in appetite resulting in weight loss or gain

Reference: Adapted from
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fourth Edition,Text Revision. Washington, DC; American Psychiatric Association. 2000:345-356,489.

Depression – the physical presentation

In primary care, physical symptoms are often the chief complaint in depressed patients

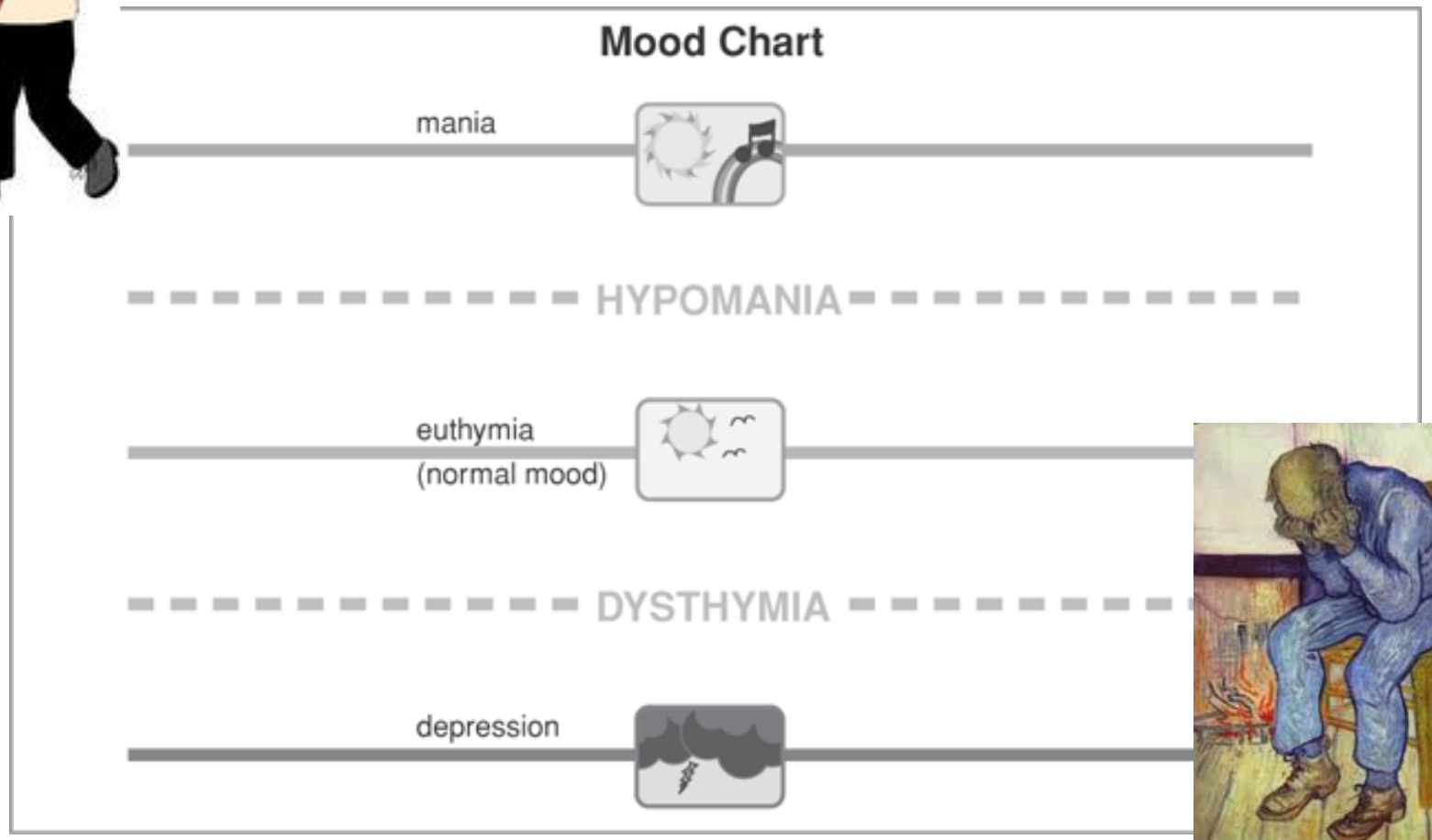


In a *New England Journal of Medicine* study, 69% of diagnosed depressed patients reported unexplained physical symptoms as their chief compliant

N = 1146 Primary care patients with major depression

Reference:
1. Simon GE, et al. *N Engl J Med*. 1999;341(18):1329-1335.

Types of Depression



1) Major depression 2) Dysthymia 3) Manic-depressive illness (Bipolar disorder)
The disease is carachterized by recurrent episodes

Symptoms of Depression and Mania

Mania

Abnormal or excessive elation
Unusual irritability
Decreased need for sleep
Grandiose notions
Increased talking
Racing thoughts
Increased sexual desire
Risk taking
Poor judgment
Distractible concentration

Inappropriate social behavior

Depression

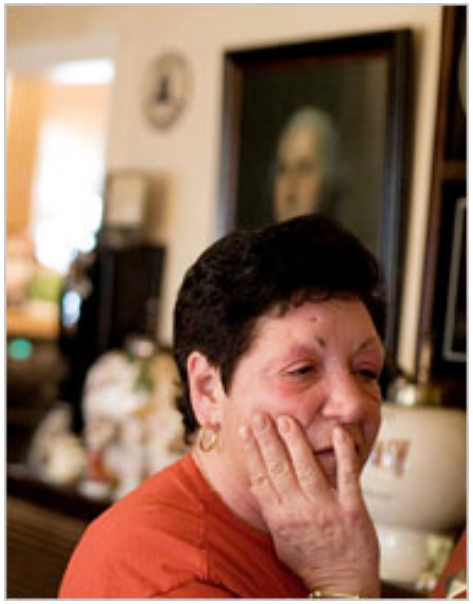
Persistent sad, anxious, or "empty" mood
Feelings of hopelessness, pessimism
Feelings of guilt, worthlessness, helplessness
Loss of interest or pleasure in hobbies and activities that were once enjoyed, including sex
Decreased energy, fatigue, being "slowed down"
Difficulty concentrating, remembering, making decisions
Insomnia, early-morning awakening, or oversleeping
Appetite and/or weight loss or overeating and weight gain
Thoughts of death or suicide; suicide attempts
Persistent physical symptoms that do not respond to treatment, such as headaches, digestive disorders, and chronic pain

Depression and Alcohol

Studies are finding a strong link between serious alcohol use and depression.

Does Depression Lead to Alcohol Abuse?
Nearly a third of people with major depression also have an alcohol problem, and depression may be the first to occur. Research shows that children who are depressed are more prone to develop alcohol problems once they reach adolescence.
Depression may be a particularly significant trigger for alcohol use in women, who are more likely than men to self-medicate with alcohol.

Does Alcohol Abuse Lead to Depression?
A number of studies have shown that alcohol abuse increases the risk for depression.



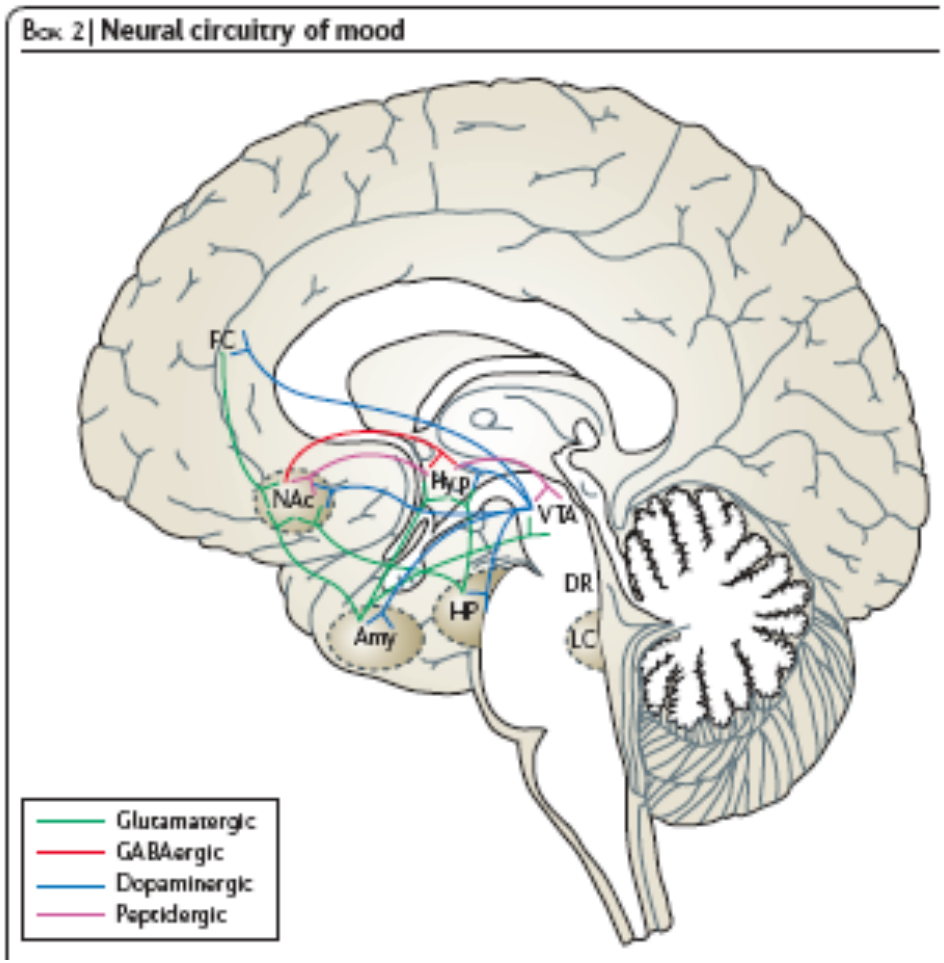
Depression Facts/Statistics

- **Clinical depression affects about 19 million Americans annually. About 5%-10% of women, and 2%-5% of men will experience at least one major depressive episode during their adult life.**
- **Depression affects people of all races, incomes, ages, ethnic and religious backgrounds.**
- **it is twice as common in women compared to men and three to five times more common in the elderly than in young people. Present also in children.**
- **It is estimated to contribute to half of all suicides.**

Table 1 | **Lifetime and annual rates and onset age for major depression, ages 18–64 years***

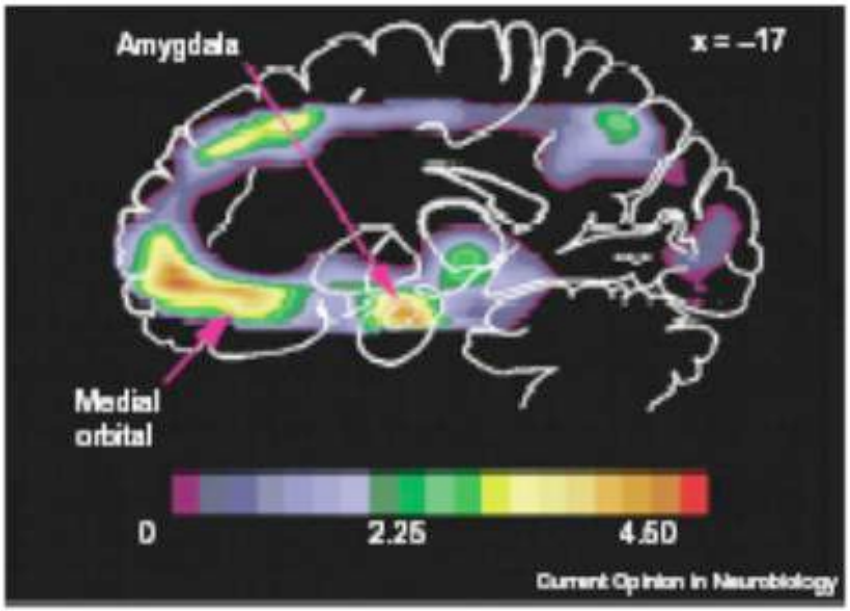
Country	Annual rate per 100 (SE)	Lifetime rate per 100 (SE)				
		Overall	Females	Males	Female ratio	Mean age at onset in years (SE)
United States	3.0 (0.18)	5.2 (0.24)	7.4 (0.39)	2.8 (0.26)	2.6 (0.11)	25.6 (0.30)
Edmonton, Alberta, Canada	5.2 (0.45)	9.6 (0.60)	12.3 (0.93)	6.6 (0.73)	1.9 (0.13)	24.8 (0.52)
Puerto Rico	3.0 (0.49)	4.3 (0.59)	5.5 (0.91)	3.1 (0.72)	1.8 (0.29)	29.5 (1.19)
Paris, France	4.5 (0.65)	16.4 (1.16)	21.9 (1.80)	10.5 (1.39)	2.1 (0.16)	29.2 (0.52)
West Germany‡	5.0 (1.13)	9.2 (1.50)	13.5 (2.46)	4.4 (1.56)	3.1 (0.39)	29.7 (1.18)
Florence, Italy	Not available	12.4 (1.33)	18.1 (2.16)	6.1 (1.40)	3.0 (0.26)	34.8 (1.12)
Beirut, Lebanon	Not available	19.0 (1.76)	23.1 (2.63)	14.7 (2.25)	1.6 (0.19)	25.2 (1.00)
Taiwan	0.8 (0.09)	1.5 (0.12)	1.8 (0.19)	1.1 (0.16)	1.6 (0.17)	29.3 (1.04)
Korea	2.3 (0.22)	2.9 (0.24)	3.8 (0.38)	1.9 (0.29)	2.0 (0.18)	29.3 (0.88)
Christchurch, New Zealand	5.8 (0.70)	11.6 (0.96)	15.5 (1.51)	7.5 (1.14)	2.1 (0.18)	27.3 (0.58)

*Figures standardized to US age and sex distribution. ‡Data from former Federal Republic of Germany (West Germany) based on ages 26 to 64 years. (SE, standard error)
(Adapted with permission from REF. 9 © (1996) American Medical Association.)



The broad range of symptoms suggests that many brain regions might be involved (prefrontal and cingulate cortex, hippocampus, striatum, amygdala and thalamus).

- **Cortex and hippocampus** might mediate cognitive aspects, such as memory impairments and feelings of worthlessness, hopelessness, guilt, doom and suicidality.
- The **ventral striatum or nucleus accumbens, and amygdala** are important in mediating aversive and rewarding responses to emotional stimuli, and mediate the anhedonia, anxiety and reduced motivation.
- The **hypothalamus** may be responsible for too much or too little sleep, appetite and energy, as well as a loss of interest in sex and other pleasurable activities.
- The VTA provides dopaminergic input to the NAc as well as to most of the other brain areas.
- Noradrenaline, from the LC, and serotonin, from the DR innervate all of the regions shown in the panel.



Altered blood flow and glucose metabolism in limbic and prefrontal cortical structures

* **Increased activation in amygdala, orbital cortex, medial thalamus, anterior cingulate**
* **Decreased activation in dorsomedial/dorsal anterolateral PFC, portions of the anterior cingulate cortex**

Biologic mechanisms of depression (Hypothesis)

- Genetic
- The Monoamine-DeficiencyHypothesis
- Stress, the Hypothalamic–Pituitary–Adrenal Axis, and Growth Factors

heritability

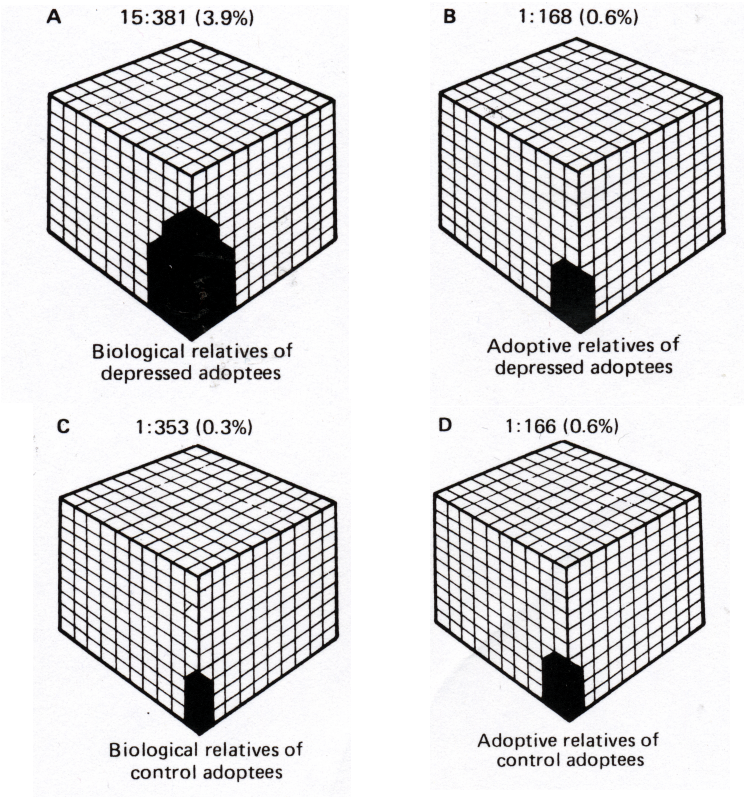
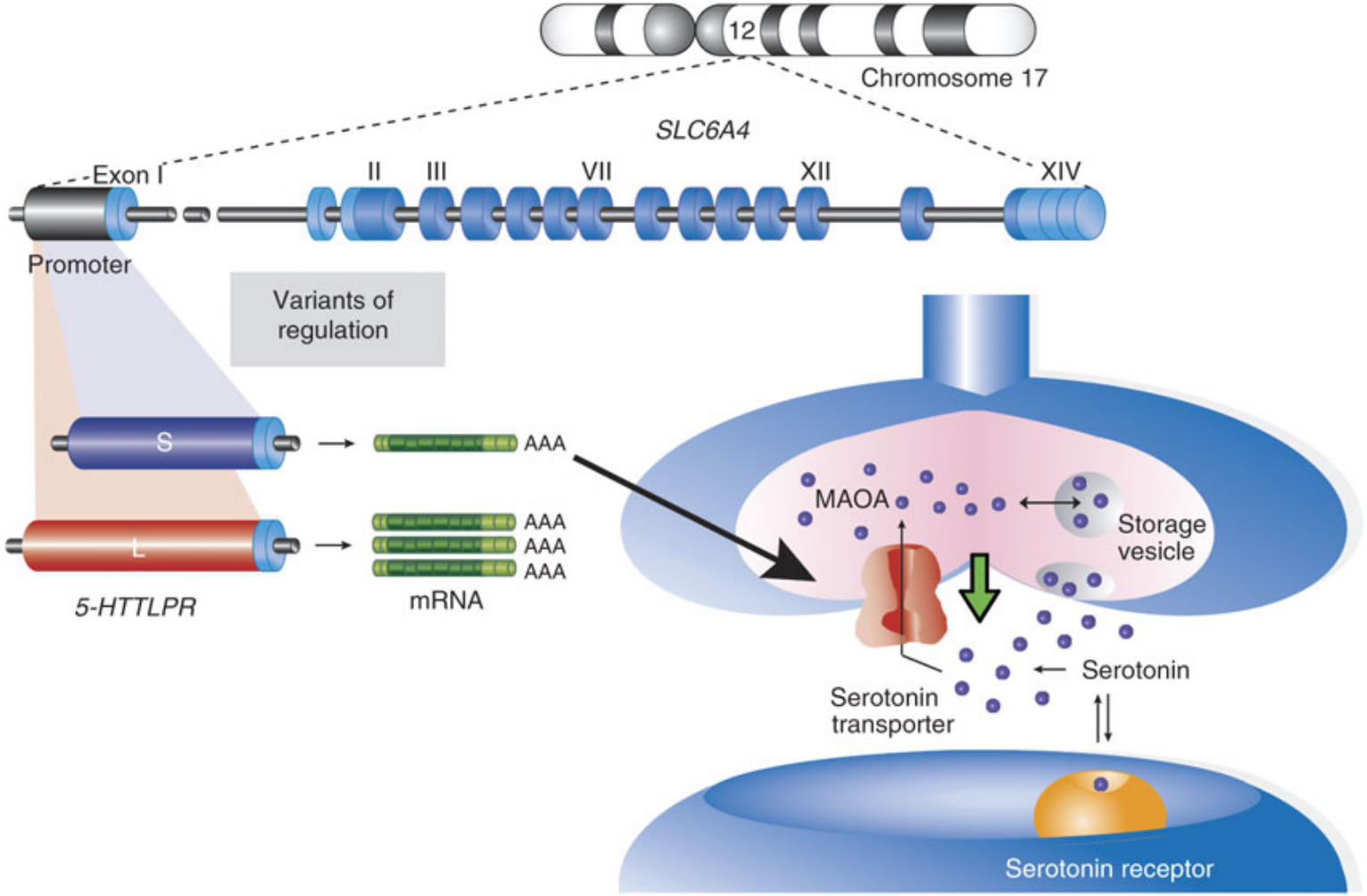


FIGURE 56–1
Incidence of suicides among biological and adoptive relatives of depressed patients. There is a higher incidence of suicide among biological relatives of adoptees who suffered from bipolar depression **(A)** than among their adoptive relatives **(B)**. The rates in the adoptive relatives of depressed patients are similar to those of both the biological **(C)** and adoptive **(D)** relatives of mentally healthy adoptees. Each ratio shows the number of relatives who committed suicide with respect to the total number of relatives. (Adapted from Kety, 1979.)

- **Concordance rates for major depression suggest a heritability of about 15 % between dizygotic and 55% between monozygotic twins**
- **The heritability of bipolar disorder is much higher (70%)**
- **Depression is not caused by any single gene but is a disease with complex genetic features**
- **No single chromosomal region has been replicated in every family study of genetic linkage in depression**
- **Some environmental factors could confer a predisposition to depression by affecting the genome epigenetically — e.g., increased maternal care in rodents causes an epigenetic change in the promoter region of the glucocorticoid-receptor gene.**
- **Environment influence: since 1940 onset has become younger (28 : 35) and incidence in depressed families has increased**

heritability

The short (S) *5-HTTLPR* variant (purple) of the 5-HTT gene (*SLC6A4*) produces significantly less 5-HTT mRNA and protein, as indicated by the green arrow, than the long (L) variant (red), leading to higher concentrations of serotonin in the synaptic cleft. The short variant is associated with anxiety-related personality traits such as neuroticism, which are risk factors for affective spectrum disorders. MAOA, monoamine oxidase A; SSRI, selective serotonin reuptake inhibitor



Allelic variation of 5-HTT is not specific of depression since it appears also in other disorders of emotion regulation (eg.: anxiety-related personality disorders)

Science 18 July 2003:
Vol. 301. no. 5631, pp. 386 – 389

Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene

A. Caspi et al.

…we tested why stressful experiences lead to depression in some people but not in others. A functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene was found to moderate the influence of stressful life events on depression. Individuals with one or two copies of the short allele of the 5-HTT promoter polymorphism exhibited more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events than individuals homozygous for the long allele. This epidemiological study thus provides evidence of a gene-by-environment interaction, in which an individual's response to environmental insults is moderated by his or her genetic makeup.

Monoamine hypothesis

- Postulates a deficiency in 5HT or NA neurotransmission in the brain
- Inhibitors of MAO were discovered to have antidepressant properties. Such inhibition could be expected to increase the availability of 5HT or NA .
- Early antidepressants blocked the reuptake of 5HT or NA by the presynaptic neuron. This increases the availability of 5HT or NA in the synapse
- These discoveries led to this hypothesis
- Numerous studies of 5HT or NA metabolites in plasma, urine, and cerebrospinal fluid, as well as postmortem studies of the brains of patients with depression, have yet to identify the purported deficiency

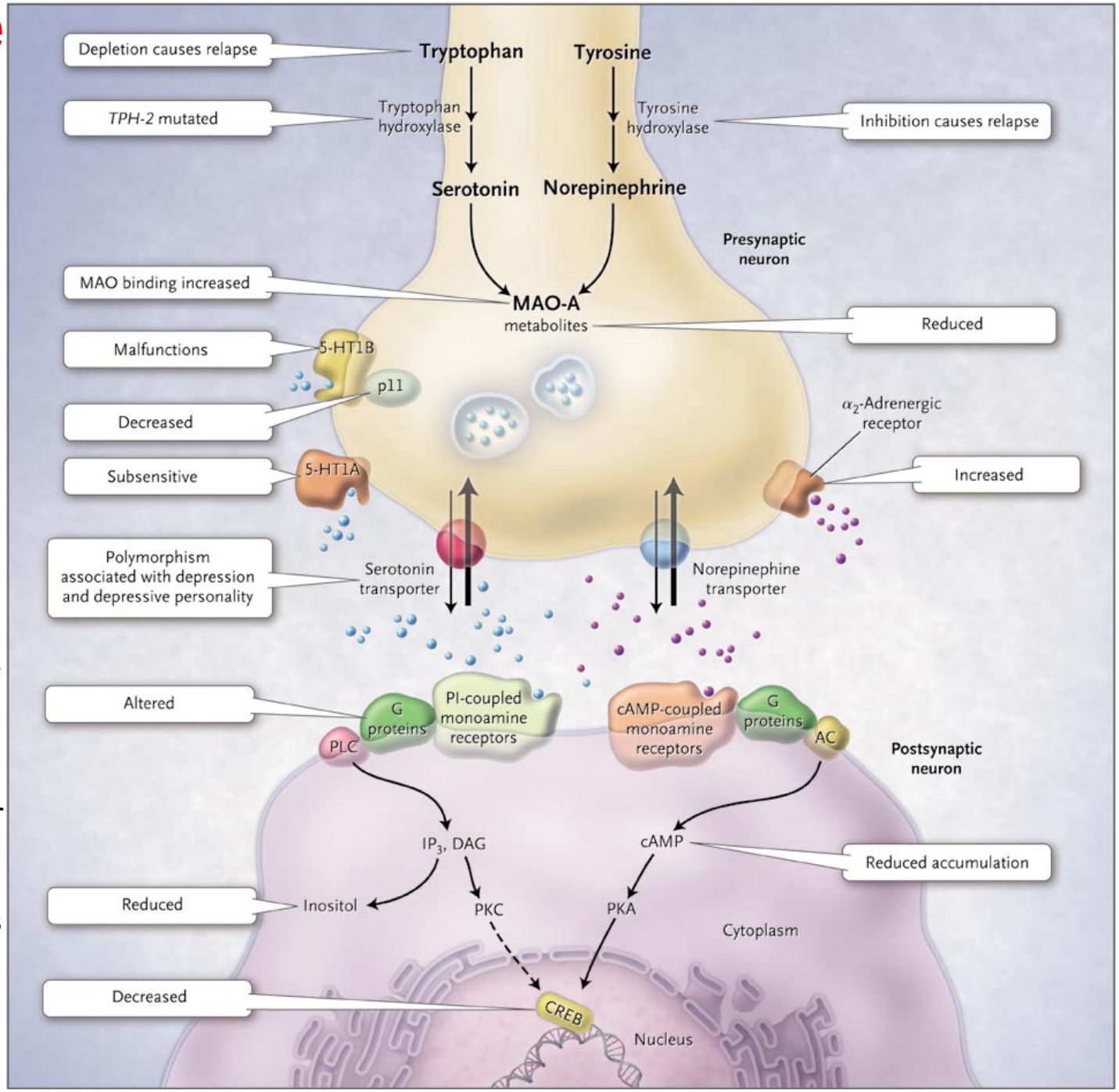


Fig 1. The Monoamine-Deficiency Hypothesis Extended.

The monoamine hypothesis of depression postulates a deficiency in 5HT or NA neurotransmission in the brain. Monoaminergic neurotransmission is mediated by 5HT or NA released from presynaptic neurons (serotonergic neuron, shown on the left side, and noradrenergic neuron, shown on the right side [condensed virtually]).

5HT is synthesized from tryptophan, with the first step in the synthetic pathway catalyzed by tryptophan hydroxylase;

NA is synthesized from tyrosine, with the first step catalyzed by tyrosine hydroxylase.

Both monoamine transmitters are stored in vesicles in the presynaptic neuron and released into the synaptic cleft, thereby affecting both presynaptic and postsynaptic neurons.

Cessation of the synaptic action of the neurotransmitters occurs by means of both reuptake through the specific 5HT and NA transporters and

feedback control of release through the presynaptic 5-HT1A and 5-HT1B regulatory autoreceptors for 5HT and

the a2 autoreceptors for NA.

MAO-A catabolizes monoamines presynaptically and thereby indirectly regulates vesicular content. The protein p11, which interacts with 5-HT1B receptors, increases their function.

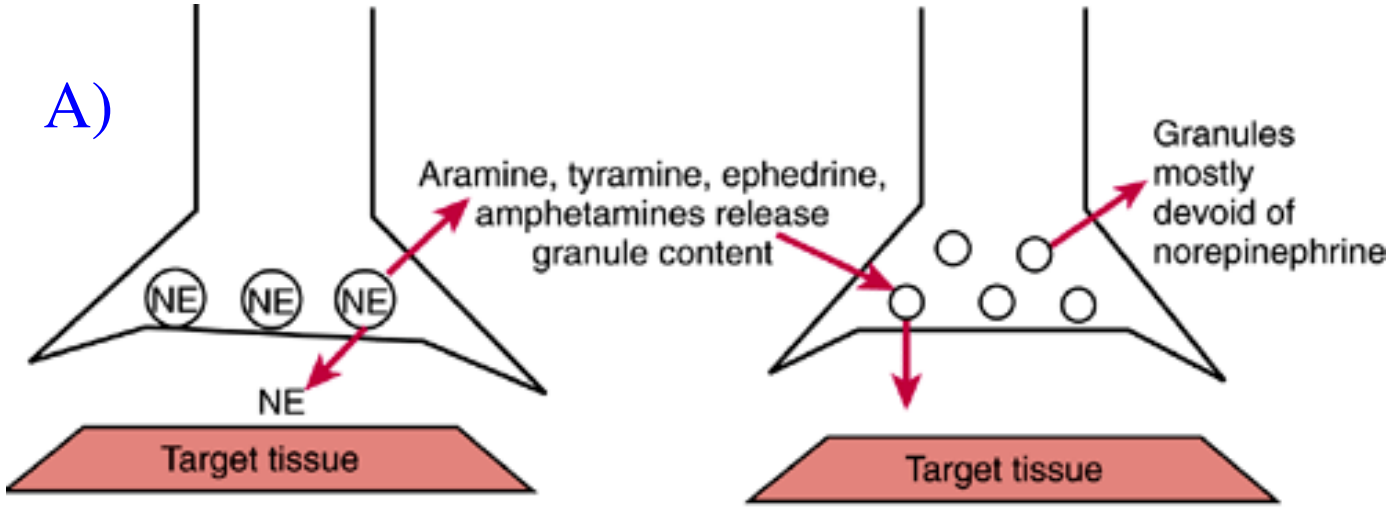
Postsynaptically, both 5HT and NA bind two kinds of GPCRs: cAMP)–coupled receptors, which activate adenylate cyclase (AC) to generate cAMP, and phosphatidylinositol (PI)–coupled receptors, which activate phospholipase C (PLC). PLC generates IP_3) and DAG; cAMP activates PKA, and IP_3 and DAG activate PKC.

The two protein kinases affect CREB.

Findings in patients with depression that support the monoamine-deficiency hypothesis include a relapse of depression with inhibition of tyrosine hydroxylase or depletion of dietary tryptophan, an increased frequency of a mutation affecting the brain-specific form of tryptophan hydroxylase (TPH-2), increased specific ligand binding to MAO-A, subsensitive 5-HT1A receptors, malfunctioning 5-HT1B receptors, decreased levels of p11, polymorphisms of the serotonin-reuptake transporter associated with depression, an inadequate response of G proteins to neurotransmitter signals, and reduced levels of cAMP, inositol, and CREB in postmortem brains.

Evidence supporting Monoamine theory

A)



Cocaine and amphetamines are releasers of monoamines into the synapse and inhibitors of reuptake. Their mood-elevating effects are immediate, but in patients with severe depression they cause agitation rather than relief of depression. This finding could reflect the ability of these stimulants to deplete the presynapse of monoamines and thus cause a "crash" into depression.

B)

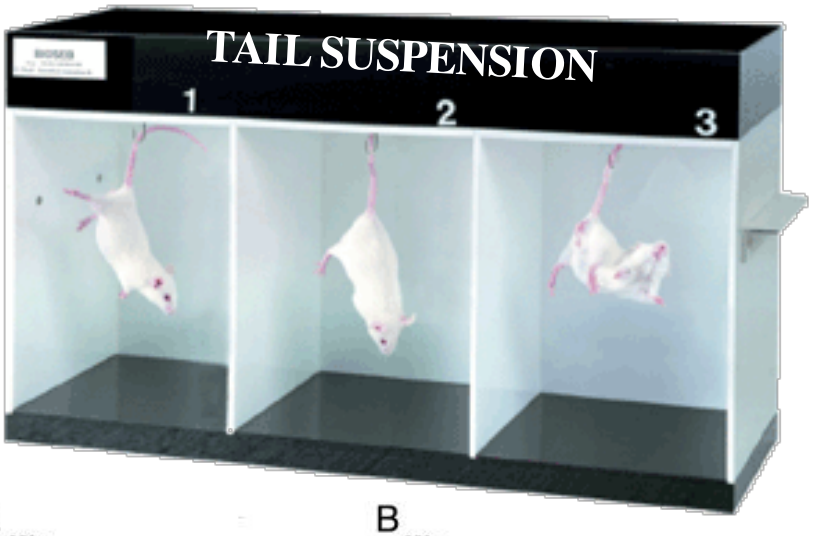
C) **Almost every compound that has been synthesized for the purpose of inhibiting norepinephrine or serotonin reuptake has been proved to be a clinically effective antidepressant.**

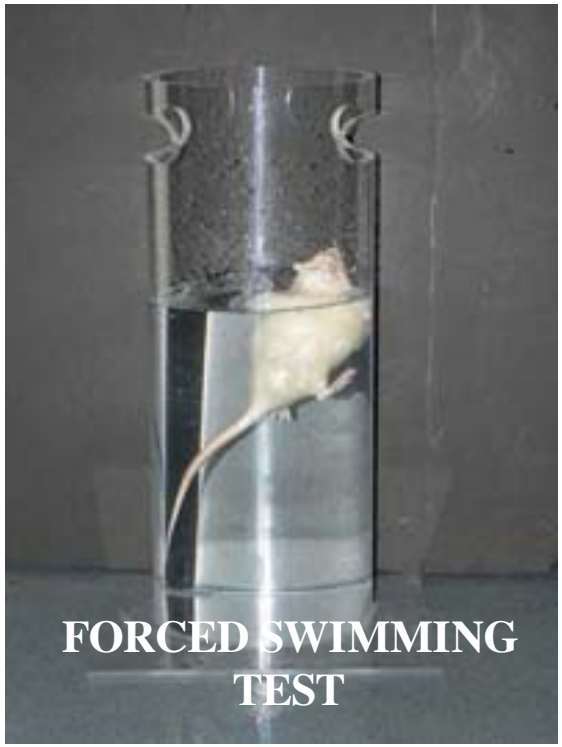
The role of dopamine deficiency

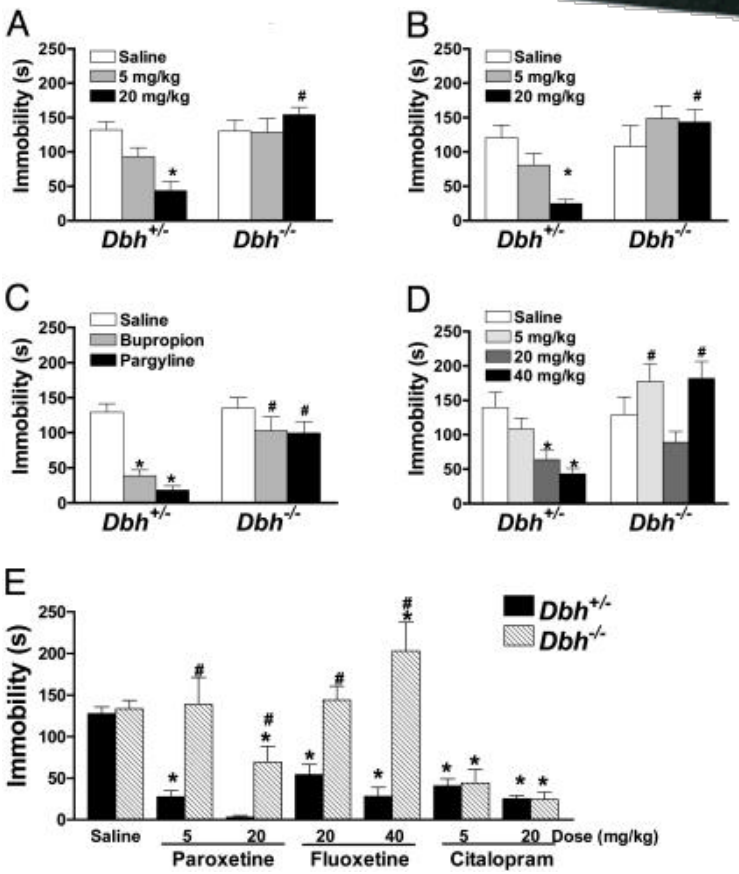
The role of dopamine deficiency in depression is suggested by the frequency of depression in patients with Parkinson's disease and the effect of reserpine, which depletes 5HT and NE, and dopamine, causing a hypoactive state in animals.

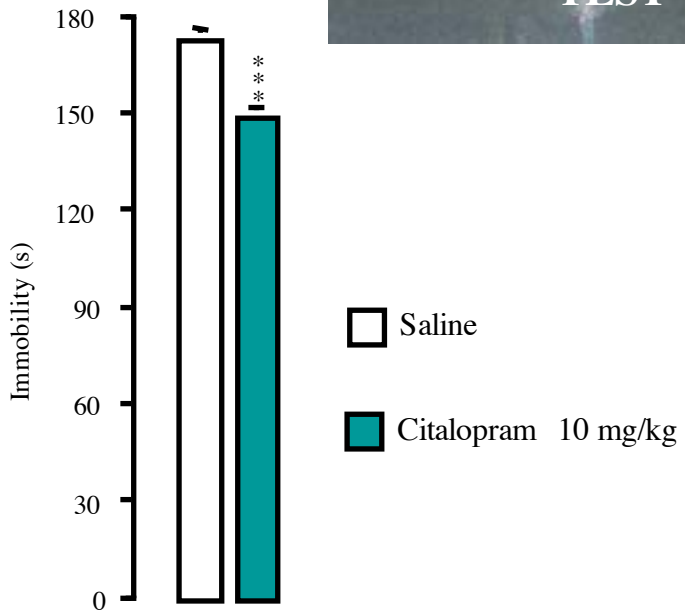
Not Supporting: delay of CLINICAL RESPONSE

Animal models can predict clinical efficacy

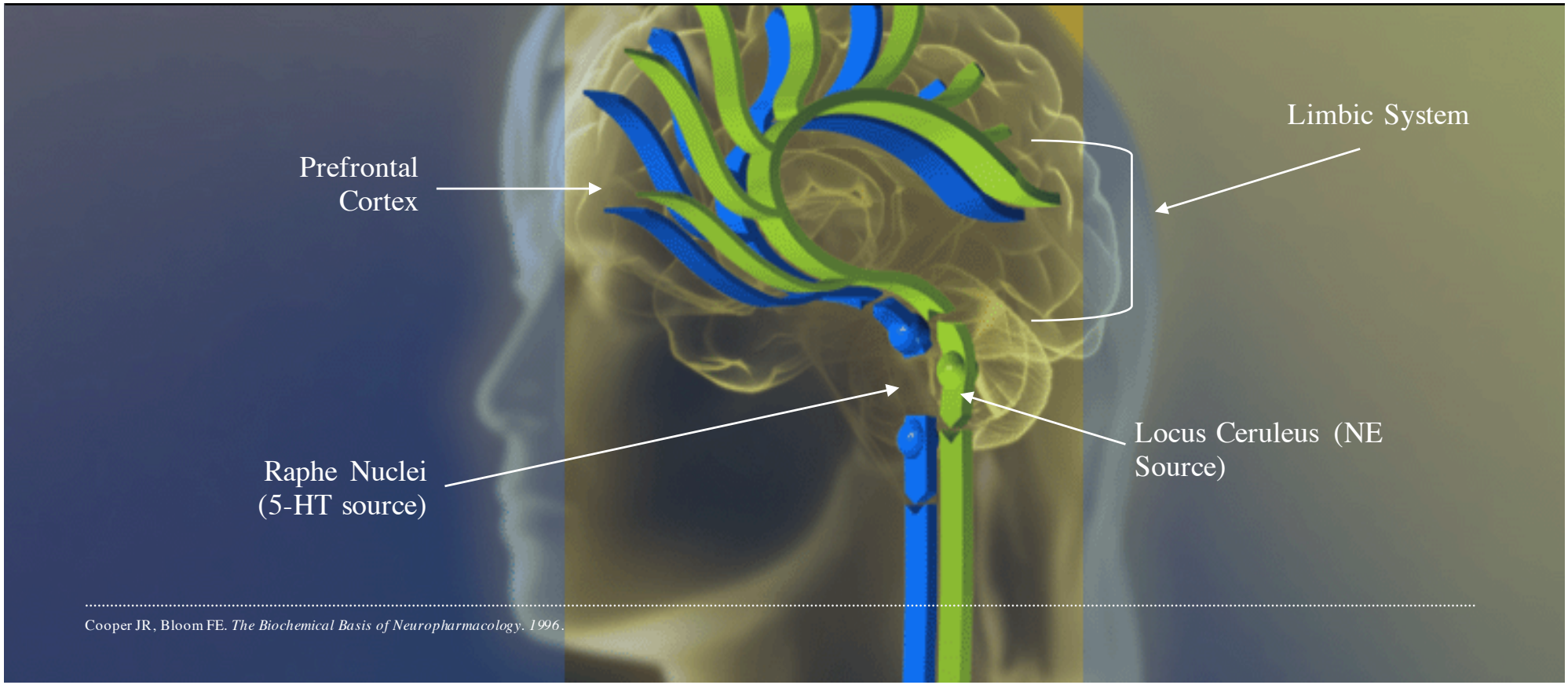




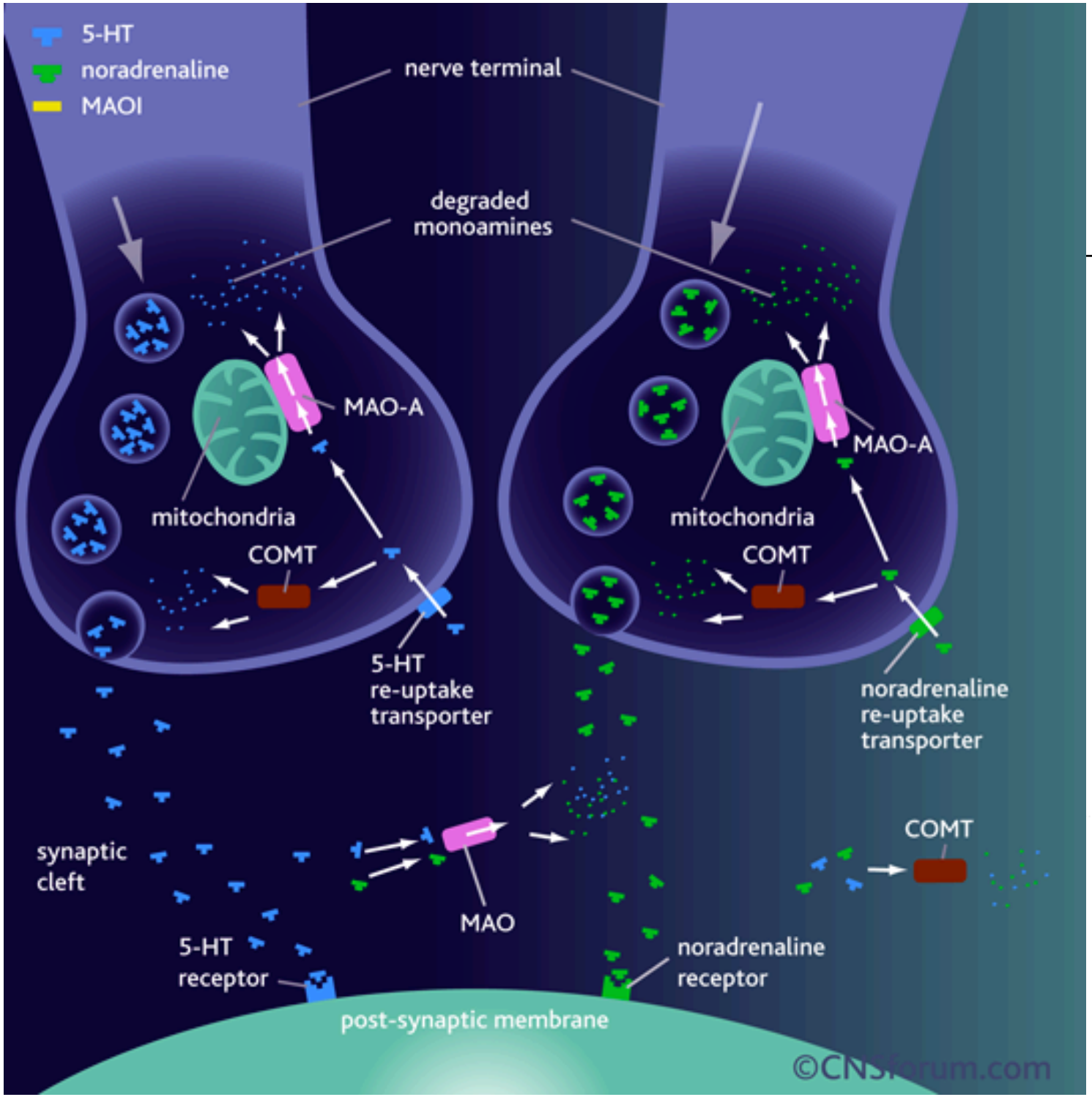




Serotonin^{5HT} and Norepinephrine^{NE} in the brain
origin and distribution of 5HT & NE innervation



5HT and NE are believed to be key neurotransmitters in the etiology of depression

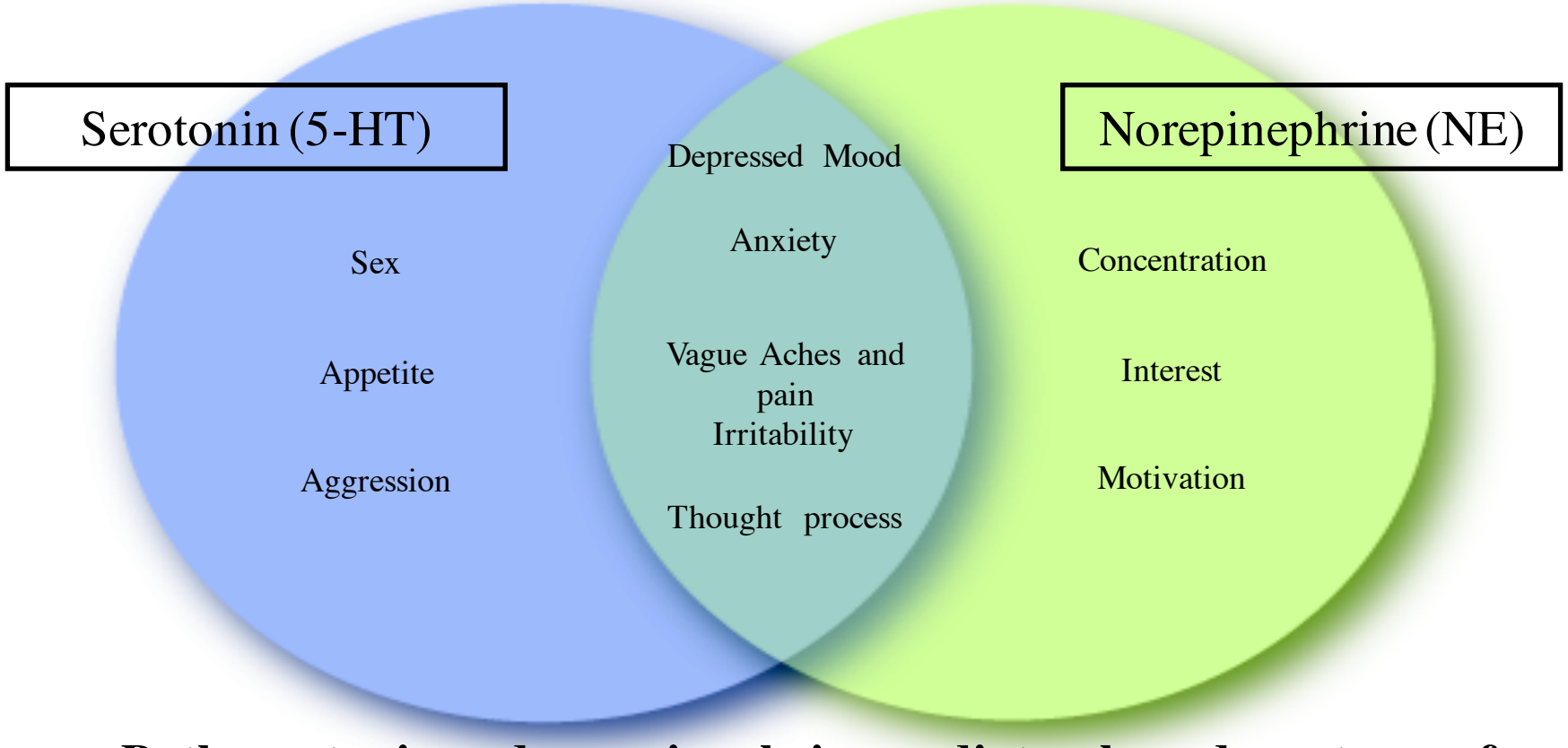


5-HT and NA neurotransmission

- When a nerve impulse arrives at a 5-HT or NA nerve terminal the NT is released from the synaptic vesicle into the synaptic cleft.
- NT bind to their specific receptors on the post-synaptic membrane and the nerve impulse is propagated or inhibited, depending on the receptor type.
- 5-HT and NA are then released from their receptors and
- taken back into the nerve terminal via either the 5-HT or NA re-uptake transporters.
- 5-HT and NA are degraded by MAO and COMT, these enzymes are found in both the synaptic cleft and in the nerve terminal.

There are at least two sides to the neurotransmitter story

Functional domains of Serotonin and Norepinephrine[1-4]



- **Both serotonin and norepinephrine mediate a broad spectrum of depressive symptoms --- also dopamine plays a role**

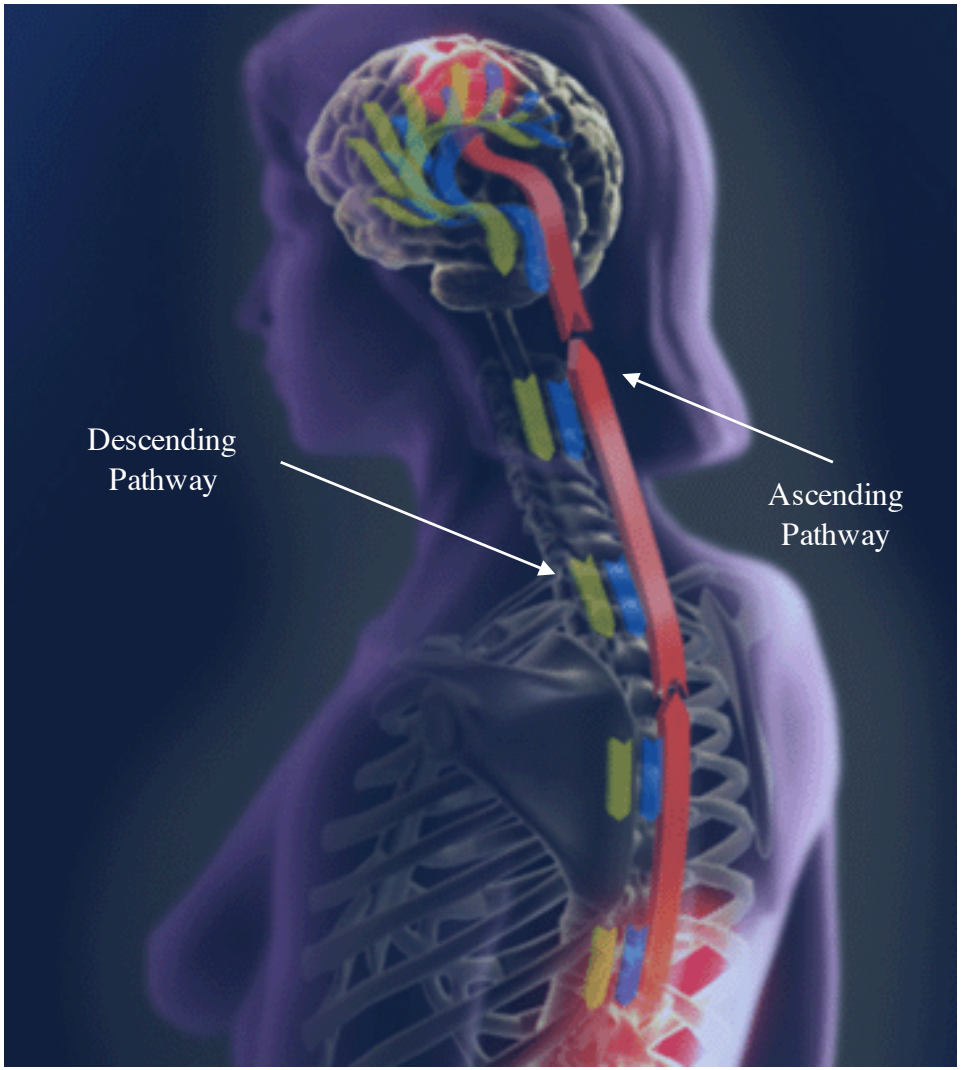
References:

1. Adapted from: Stahl SM. In: *Essential Psychopharmacology: Neuroscientific Basis and Practical Applications: 2nd ed*. Cambridge University Press 2000.
2. Blier P, et al. *J Psychiatry Neurosci*. 2001;26(1):37-43.
3. Doraiswamy PM. *J Clin Psychiatry*. 2001;62(suppl 12):30-35.
4. Verma S, et al. *Int Rev Psychiatry*. 2000;12:103-114.

The neurotransmitter pathway story

It's not all in your head

- **Dysregulation of Serotonin (5HT) and Norepinephrine (NE) in the brain are strongly associated with depression**
- **Dysregulation of 5HT and NE in the spinal cord may explain an increased pain perception among depressed patients[1-3]**
- **Imbalances of 5HT and NE may explain the presence of both emotional and physical symptoms of depression.**



Adapted from References:

1. Stahl SM. *J. Clin Psych*. 2002;63:203-220.
2. Verma S, et al. *Int Rev Psychiatry*. 2000;12:103-114.
3. Blier P, et al. *J Psychiatry Neurosci*. 2001;26(1):37-43.

MONOAMINE-RELATED GENE KOs THAT AFFECT DEPRESSION-RELATED BEHAVIOUR IN MICE

Table 1. Monoamine-Related Gene Knockouts That Affect Depression-Related Behavior in Mice.*

Gene or Protein	Function	Depression-Related Changes	Corroboration of Monoamine-Deficiency Hypothesis	Other Behavior Elicited by Knockout of Gene
sert	Serotonin transporter	Increased depressive behavior, reduced serotonin level, desensitized postsynaptic 5-HT1AR, and reduced presynaptic 5-HT1AR function[32]	No	Excessive anxiety[32]
net	Norepinephrine transporter	Reduced depressive behavior, prolonged norepinephrine clearance, elevated extracellular norepinephrine levels[33]	Yes	Increased locomotion response to amphetamines and cocaine[33]
5-ht1ar	Serotonergic 1A receptor (presynaptic autoreceptor and postsynaptic)	Reduced depressive behavior, normal serotonin level and release, impaired SSRI-induced neurogenesis[32]	No	Excessive anxiety, impaired hippocampal learning[32]
5-ht1br	Serotonergic 1B receptor (presynaptic autoreceptor and postsynaptic)	Reduced response to SSRI in forced swim test, reduced serotonin level and increased serotonin release, increased SSRI-induced serotonin release, decreased serotonin-transporter expression[32]	Yes	Increased aggressiveness, reduced anxiety, increased exploration, increased use of cocaine[32]
p11 (protein)	Interacts with and enhances signaling efficiency of 5-HT1BR	Increased depressive behavior, increased serotonin turnover[20]	No	Not reported[20]
5-ht2ar	Serotonergic 2A receptor	No change[34]	No	Reduced inhibition in conflict-anxiety paradigms[34]
5-ht7	Serotonergic 7 receptor (possibly presynaptic autoreceptor and postsynaptic)	Reduced depressive behavior and REM sleep duration[35]	No	Normal locomotion[35]
α_{2a}*ar*	α_{2A}-Adrenergic receptors (presynaptic autoreceptor)	Reduced norepinephrine levels, presynaptic inhibition of release,[36] increased depressive behavior[37]	No	Altered sympathetic regulation,[36] impaired motor coordination
α_{2c}*ar*	α_{2C}-Adrenergic receptors (presynaptic autoreceptor restricted to central nervous system)	Reduced depressive behavior[38]	Yes	Increased aggressiveness,[32] increased locomotion response to amphetamines[36]
mao-a	Monoamine oxidase A	Increased brain serotonin and epinephrine levels[39]	No	Increased aggressiveness and response to stress,[30] decreased exploration[32]
ac VII (heterozygotes)	Adenylyl cyclase type 7	Reduced depressive behavior[40]	No	Unchanged anxiety[40]
impa1	Inositol monophosphatase 1	Reduced depressive behavior, unaltered brain inositol levels[41]	Yes	Increased hyperactivity and sensitivity to pilocarpine-induced seizures[41]
smit1	Sodium-*myo*-inositol transporter 1	Reduced depressive behavior and brain inositol levels[42]	Yes	Increased sensitivity to pilocarpine-induced seizures[42]
creb	Cyclic AMP–response element–binding protein	Reduced depressive behavior, normal antidepressant-induced behavior[43]	No	No increase in BDNF after long-term use of antidepressants[43]
bdnf				
Male mice	Brain-derived neurotrophic factor	No depressive behavior[44]	No	Increased aggressiveness, hyperphagia,[45] hyperactivity[44]
Female mice	Brain-derived neurotrophic factor	Increased depressive behavior[44]	Yes	Increased aggressiveness, hyperphagia[45]

* BDNF denotes brain-derived neurotrophic factor, 5-HT1AR 5-hydroxytryptamine 1A receptor, 5-HT1BR 5-hydroxytryptamine 1B receptor, REM rapid eye movement, and SSRI selective serotonin-reuptake inhibitor.

Hypothalamic - pituitary - cortisol hypothesis

postulates that abnormalities in the cortisol response to stress may underlie depression.

Stress is perceived by the cortex and the amygdala and transmitted to the hypothalamus. Corticotropin-releasing hormone (CRH) is released, inducing the anterior pituitary gland to secrete corticotropin into the bloodstream. Corticotropin stimulates the adrenal cortexes to secrete cortisol that induces feedback inhibition in the hypothalamus and the pituitary, suppressing the production of CRH and corticotropin,
Hippocampal size and the numbers of neurons and glia are decreased, possibly reflecting reduced neurogenesis due to elevated cortisol levels via reduced BDNF (brain-derived neurotrophic factor.

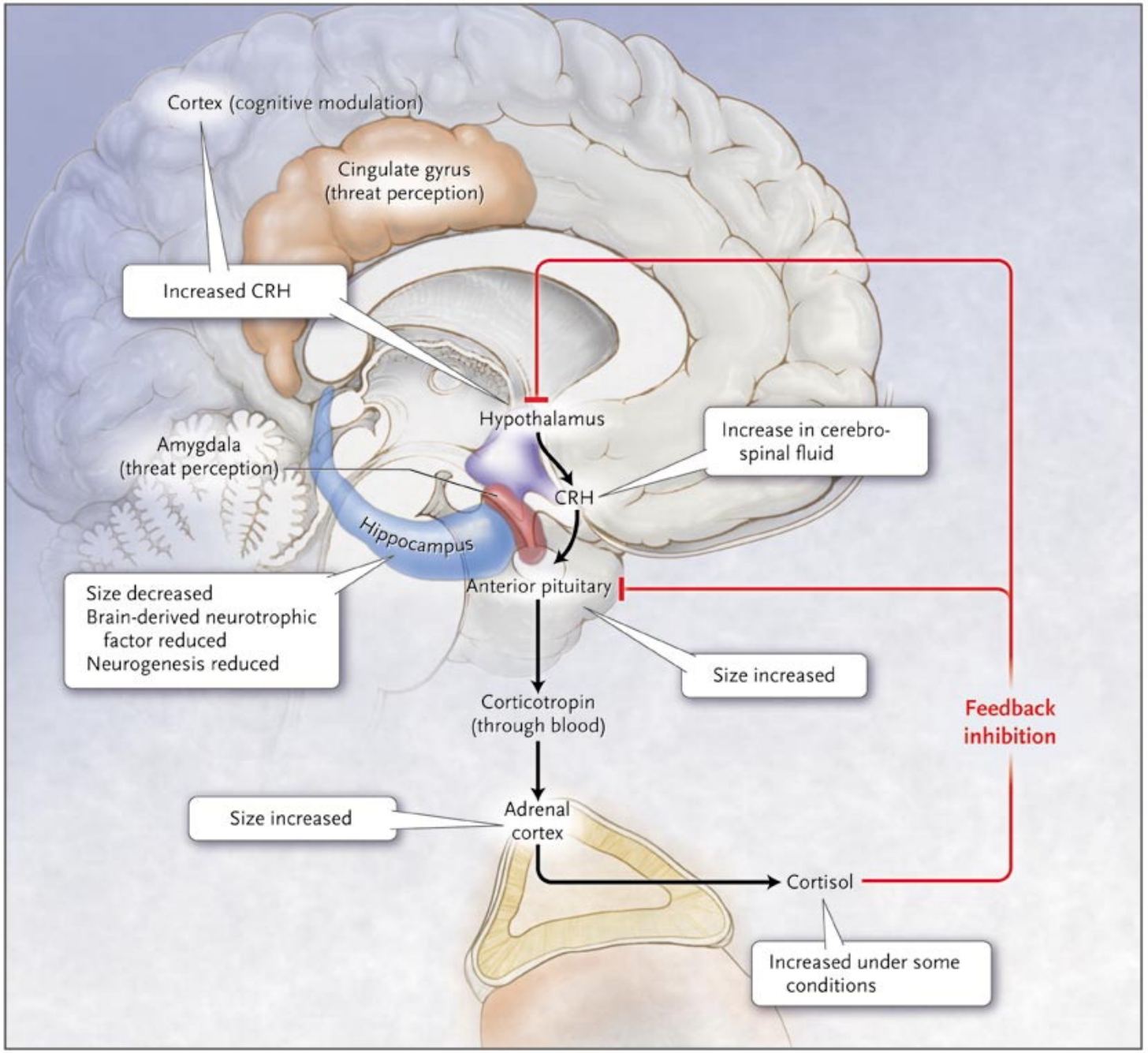
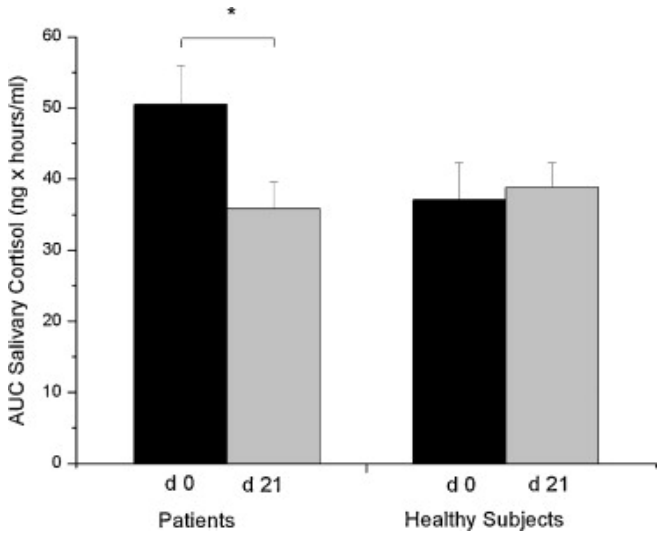


Figure 2. The Hypothalamic–Pituitary–Cortisol System in Depression.
The hypothalamic–pituitary–cortisol hypothesis of depression postulates that abnormalities in the cortisol response to stress may underlie depression. The black arrows show that in response to stress, which is perceived by the brain cortex and the amygdala and transmitted to the hypothalamus, corticotropin-releasing hormone (CRH) is released, inducing the anterior pituitary gland to secrete corticotropin into the bloodstream. Corticotropin stimulates the adrenal cortexes to secrete the glucocorticoid hormone cortisol. The red lines show that cortisol, in turn, induces feedback inhibition in the hypothalamus and the pituitary, suppressing the production of CRH and corticotropin, respectively. Findings in patients with depression that support the hypothalamic–pituitary–cortisol hypothesis include the following: cortisol levels are sometimes increased in severe depression, the size of the anterior pituitary and adrenal cortex is increased, and CRH levels in the cerebrospinal fluid and CRH expression in the limbic brain regions are increased. Hippocampal size and the numbers of neurons and glia are decreased, possibly reflecting reduced neurogenesis due to elevated cortisol levels or due to reduced brain-derived neurotrophic factor.

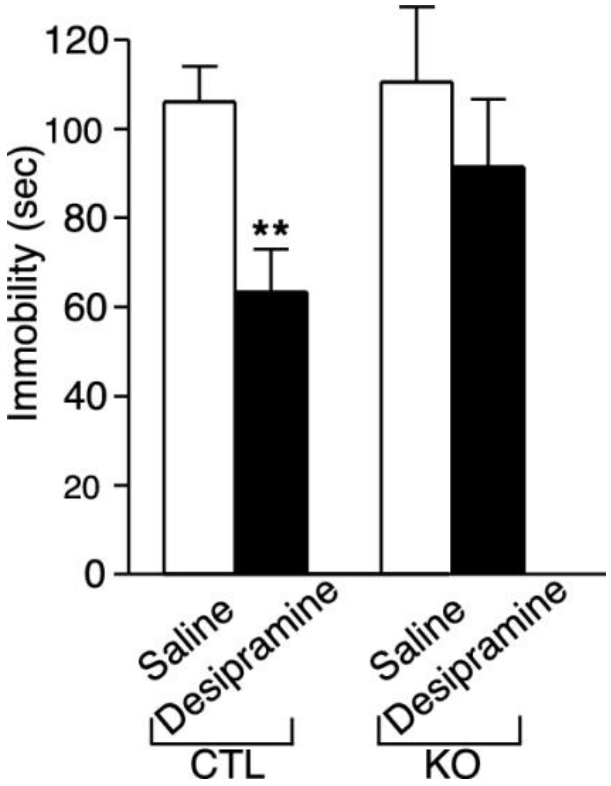


Salivary cortisol (area under the curve) of patients (*n* = 52) before and after a 3-weeks treatment with escitalopram compared to healthy subjects (*n* = 50). Bars represent mean area under the curve (AUC) cortisol values. Repeated-measures ANCOVA revealed a significant time × group interaction (*p* = .05). Post hoc tests revealed a significant reduction of cortisol in patients (*t*-test, *t* = 2.5, df = 51, *p* = 0.01)

Antidepressant-induced clinical remission is accompanied by reversal of some of these abnormalities.

It is possible that antidepressants relieve depression by reducing the secondary stress caused by a painfully dispirited mood rather than by directly elevating mood. An antistress mechanism could explain the general usefulness of antidepressants for a wide variety of psychiatric conditions, including panic disorder, post-traumatic stress disorder, bulimia, premenstrual syndrome, and obsessive–compulsive disorder.

Behavioral response of WILD-TYPE and BDNF-KO mice in the forced swim test to subchronic antidepressant treatment.



Animals were administered saline or desipramine 24, 4, and 1 h before the swim test (10 mg/kg i.p., 10 mg/kg i.p., and 20 mg/kg s.c., respectively). Saline-treated control (n = 10) and BDNF KO (n = 10) mice exhibited similar immobility times. Subchronic desipramine treatment significantly reduced immobility time in the control mice (n = 10) but not in the BDNF KO mice (n = 10). Results are presented as mean immobility (sec) ± SEM; ANOVA and post hoc Tukey's test revealed a significance of $P < 0.05$ (asterisks) for saline control versus desipramine control [$F_{(1, 57)} = 8.51$; $P < 0.01$].

Monteggia & al, Essential role of brain-derived neurotrophic factor in adult hippocampal function, Proc Natl Acad Sci U S A. 2004;101:10827.

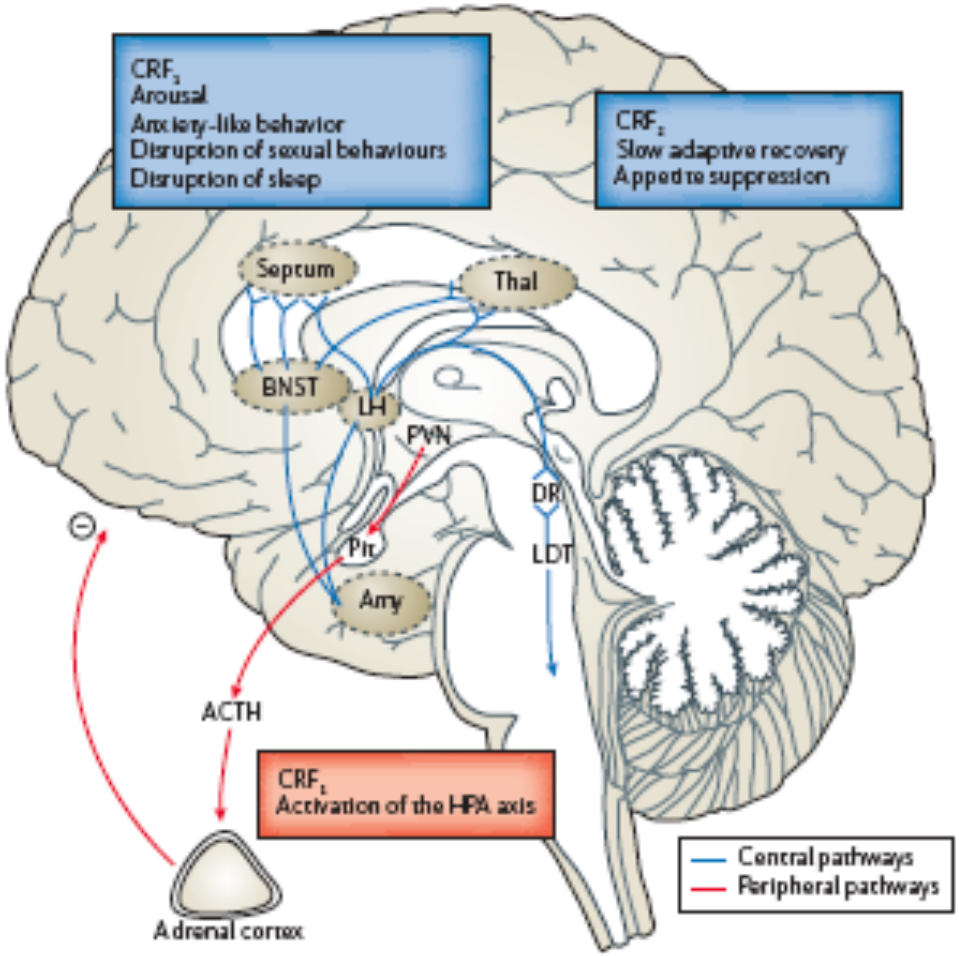
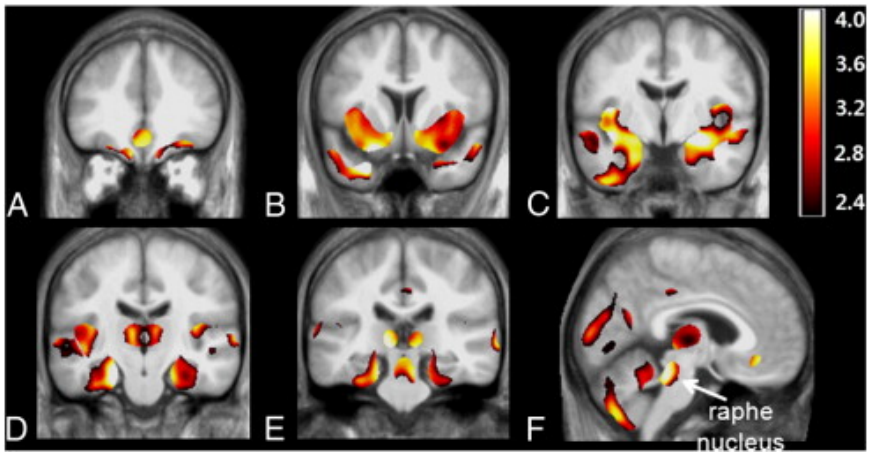


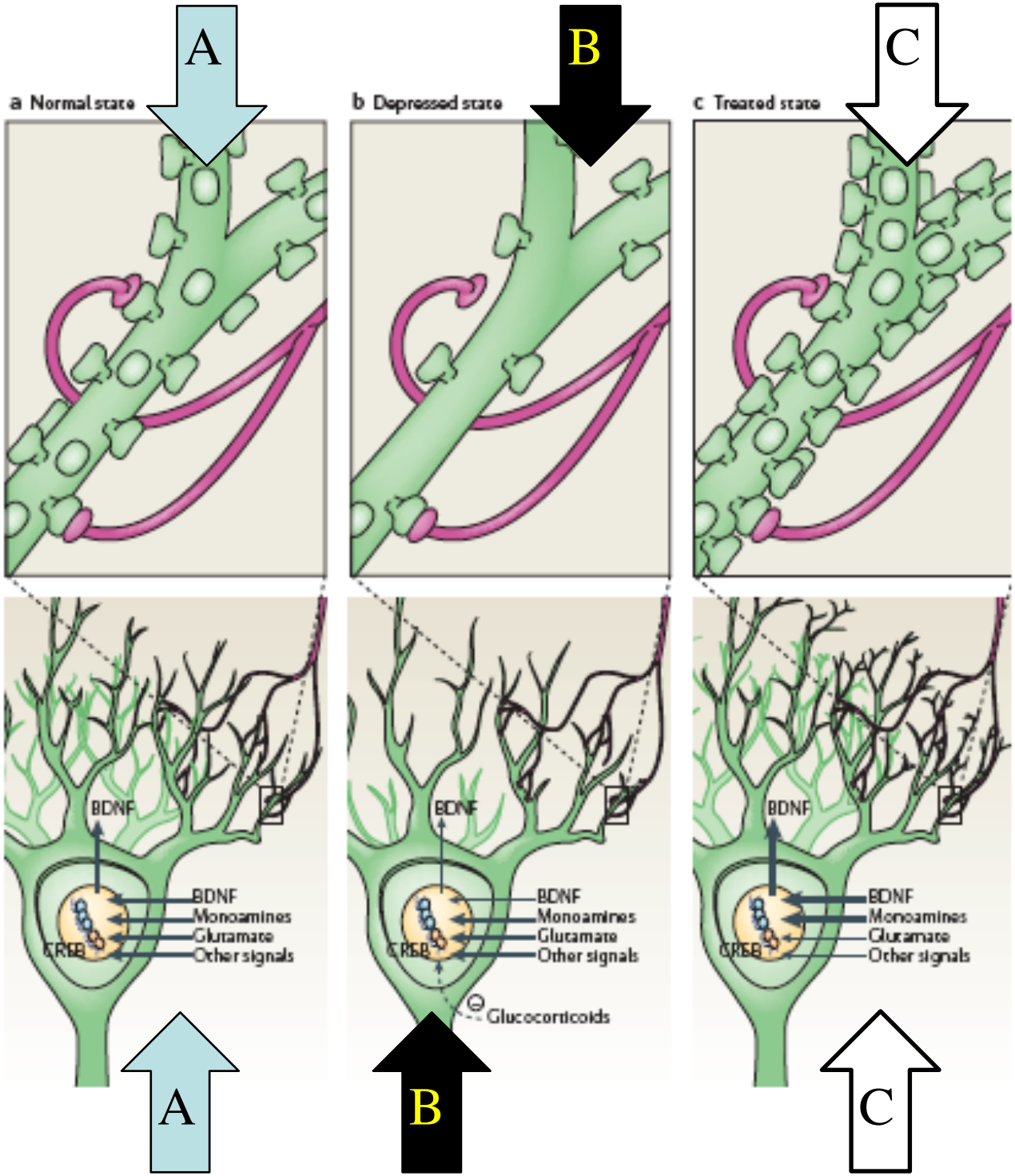
Figure 1 | The corticotropin-releasing factor system in depression. Corticotropin-releasing factor (CRF) from the paraventricular nucleus (PVN) of the hypothalamus is released into the hypophyseal portal system and triggers the release of corticotropin (ACTH) from the anterior pituitary via stimulation of CRF_1 receptors. ACTH, in turn, stimulates the secretion of glucocorticoid hormones (cortisol in humans or corticosterone in rodents) from the adrenal cortex. Increased glucocorticoid levels suppress hypothalamic CRF expression via negative feedback through hippocampal and hypothalamic glucocorticoid receptors. The neurotransmitter action of CRF on CRF_1 receptors throughout the limbic system mediates anxiogenic effects of stress. By contrast, its neurotransmitter action on CRF_2 receptors in more discrete regions of the brain might reduce anxiety-like behaviour in a delayed fashion. Amy, amygdala; BNST, bed nucleus of the stria terminalis; DR, dorsal raphe; HPA, hypothalamic–pituitary–adrenal; LDT, laterodorsal tegmental nucleus; LH, lateral hypothalamus; Pit, pituitary; Thal, thalamus.

Decreased gray matter concentration in the brain in major depressive disorder: voxel-based morphometry study



Decreased gray matter concentration (GMC) in patients with depression. Compared to the GMC in normal controls, the GMC in patients with depression was decreased in the subgenual anterior cingulate cortex (A), short insular cortex (B), amygdala (C), mediodorsal thalamic nucleus, hippocampus, perirhinal gyrus (D), fusiform gyrus (E), and midbrain encompassing dorsal raphe nucleus (F).

- **The classic teaching is that neurons do not divide in the adult mammalian brain, but studies have shown that neurogenesis occurs in several areas of the brain, especially the hippocampus.**
- **Elevated levels of glucocorticoids can reduce neurogenesis, and this has been suggested as a mechanism for the decreased size of the hippocampus in many patients with depression**
- **Brain-derived neurotrophic factor (BDNF) is critical for axonal growth, neuronal survival, and synaptic plasticity, and its levels are affected by stress and cortisol**
- **Evidence suggests that BDNF is the link among stress, neurogenesis, and hippocampal atrophy in depression.**



A) normal hippocampal pyramidal neuron and its innervation by glu, monoaminergic and its regulation by BDNF.

B) Severe stress causes a reduction in their dendritic arborization, and a reduction in BDNF expression. The reduction in BDNF is mediateby excessive glucocorticoids

C) Antidepressants produce the opposite effects to those seen in b: they increase dendritic arborization and BDNF expression of these hippocampal neurons.

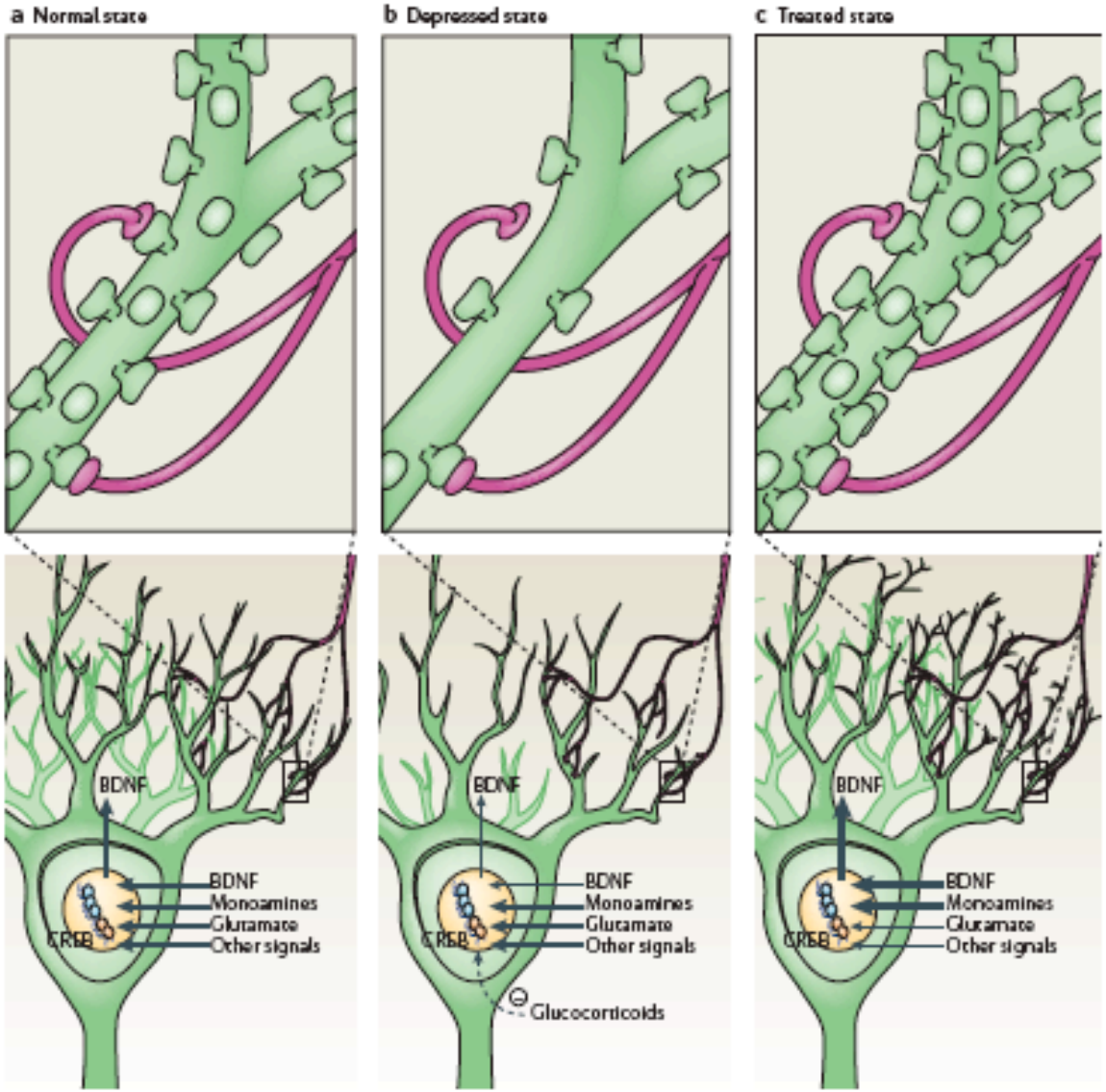
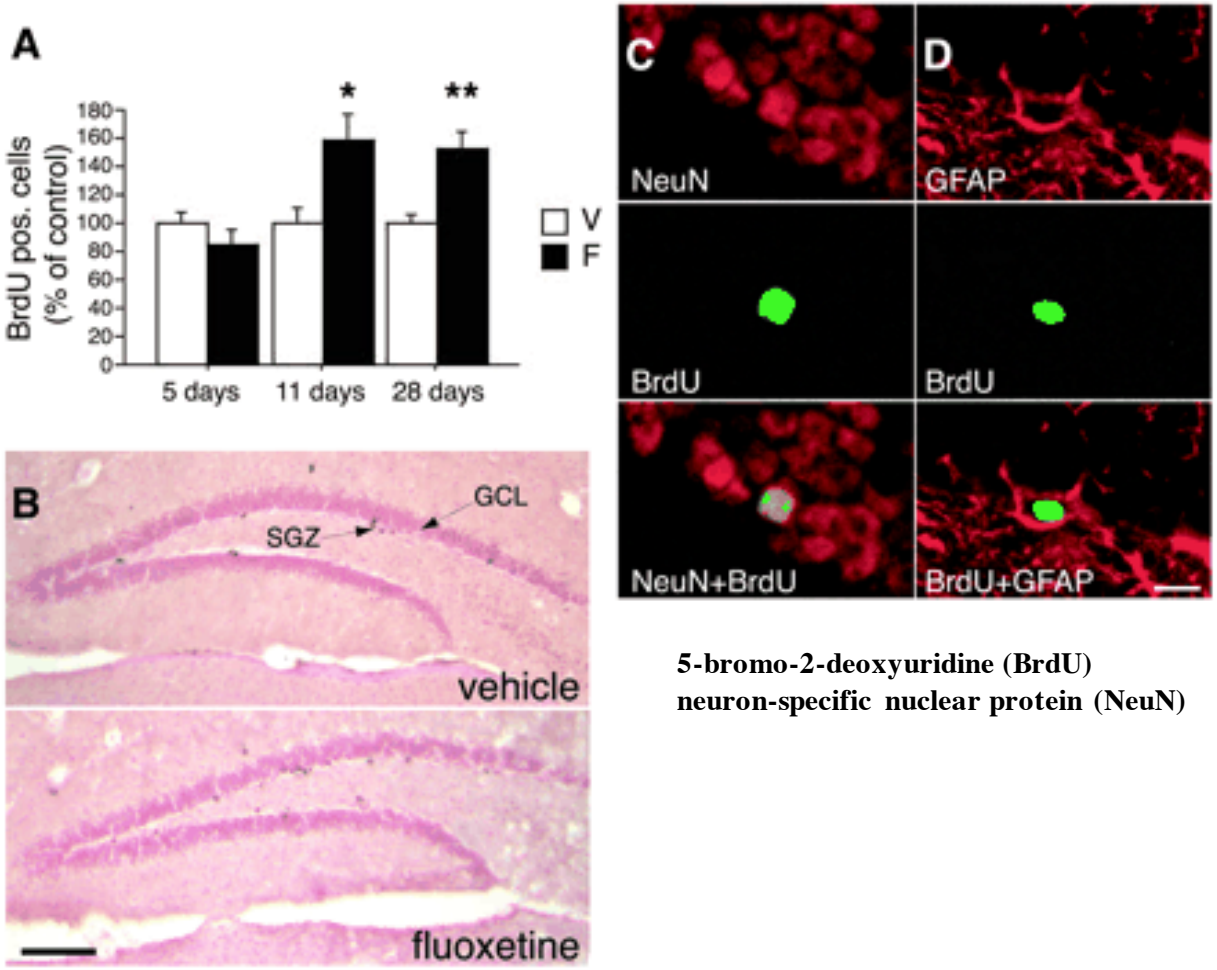


Figure 3 | Neurotrophic mechanisms in depression and antidepressant action. a | Shows a normal hippocampal pyramidal neuron and its innervation by glutamatergic, monoaminergic and other types of neuron. Its regulation by brain-derived neurotrophic factor (BDNF), which is derived from the hippocampus or other brain areas, is also shown. b | Severe stress causes several changes in these neurons, including a reduction in their dendritic arborization, and a reduction in BDNF expression (which could be one of the factors mediating the dendritic effects). The reduction in BDNF is mediated partly by excessive glucocorticoids, which could interfere with the normal transcriptional mechanisms (for example, through cyclic AMP-responsive-element-binding protein, CREB) that control BDNF expression. c | Antidepressants produce the opposite effects to those seen in b: they increase dendritic arborization and BDNF expression of these hippocampal neurons. The latter effect appears to be mediated at least in part by activation of CREB. By these actions, antidepressants might reverse and prevent the effects of stress on the hippocampus, and ameliorate some symptoms of depression. Modified, with permission, from REF. 2 © (2002) Cell Press.

Santarelli & al, **Requirement of Hippocampal Neurogenesis for the Behavioral Effects of Antidepressants,** *Science 2003:301:805*



5-bromo-2-deoxyuridine (BrdU)
neuron-specific nuclear protein (NeuN)

Chronic fluoxetine treatment increases BrdU uptake and neurogenesis in the dentate gyrus. (A) The number of BrdU-positive cells was significantly increased after 11 and 28 days of treatment with fluoxetine (F) relative to vehicle (V) (mean percentage of BrdU-positive cells in vehicle mice ± SEM; Fisher post hoc analysis; *n* = 7 to 10). (B) BrdU immunoreactivity in the dentate gyrus after a 28-day treatment. Cell counts were made in the granule cell layer (GCL) and in the SGZ. Scale bar, 200 µm. (C and D) Confocal micrographs of cells double-labeled for BrdU (green) and NeuN or GFAP (red). Scale bar, 10 µm

Table 2. Additional Biologic Theories of the Pathophysiology of Depression.*

Theory	Supporting Evidence	Contradictory Evidence
Altered glutamatergic neurotransmission	Glutamate and glutamine levels in the prefrontal cortex are reduced[91]	Glutamate levels in the occipital cortex are increased[92,93]
	Intravenous ketamine, an NMDA antagonist, induces rapid, sustained antidepressant effect [94]	Ketamine binds to high-affinity-state D2 dopamine receptors[95]
	Cortical messenger RNA levels of glutamate transporters and of the enzyme that converts glutamate to glutamine are reduced[96]	It is not clear whether antidepressants affect AMPA receptors in the brain[97]
Reduced GABAergic neurotransmission	Levels of GABA in plasma, cerebrospinal fluid, the dorsolateral prefrontal cortex, and the occipital cortex are reduced[91-93]	GABA occurs in more than 30% of brain synapses, suggesting nonspecificity
	GABA-modulating agents have effects in animal models of depression[98]	There is a lack of difference in prefrontal cortex GABA levels on MRS in depression[99]
	Antidepressants affect GABAergic function[98]	GABA neurotransmission may be related to symptoms of anxiety in depression
	GABA neuron immunoreactivity is reduced in the prefrontal cortex[100]	
Abnormal circadian rhythms	Sleep deprivation and light therapy have antidepressant effects[101,102]	The association between clock-related genes and depression is inconsistent[103]
	Some patients with depression have circadian abnormalities of mood, sleep, temperature, and neuroendocrine secretion[104]	
	Rodents active during the day become depressed when daylight is shortened[105]	
Deficient neurosteroid synthesis	Cholesterol levels are low in plasma and the brain during depression[106]	The findings in schizophrenia are similar[107]
	DHEA has antidepressant effects in patients with depression[108]	Neurosteroids (neuroactive steroids in the brain that modulate neurotransmitter receptors) mostly affect memory and sleep
Impaired endogenous opioid function	δ-Opioid–receptor agonists have antidepressant-like effects in rodents and up-regulate levels of BDNF in the brain[109]	Although early reports suggested that opiates may be effective in treating depression,[110] data from large, controlled, randomized trials are lacking
	Capacity for cortical μ-opioid–receptor binding is decreased in response to sustained sadness[111]	
Monoamine–acetylcholine imbalance	Depressed mood can be induced in humans by administration of physostigmine, an acetylcholinesterase inhibitor[112]	Mecamylamine, a nicotinic acetylcholine receptor antagonist, reduced symptoms of depression[113]
	Nicotinic acetylcholine receptor antagonists potentiate antidepressants[114]	Many antidepressants are not anticholinergic
Cytokine-mediated cross-talk between the immune system and the brain	Depression is common in infectious and autoimmune diseases[115]	Most studies are correlative[116]
	Exposure to cytokines induces depressive symptoms, and cytokine secretion is increased in major depression[115]	Cytokine-induced depressive symptoms are temporary and not replicated in all studies[117]
	Antidepressants have antiinflammatory effects[115]	Substance P antagonists are not therapeutic in depression
	Cytokines affect the hypothalamic–pituitary–adrenal axis and monoamines[115]	
Thyroxine abnormalities	Levels of transthyretin are reduced in the cerebrospinal fluid in patients with depression[118]	
	Thyroid hormones modulate the serotonergic system in the brain[119]	Thyroxine monotherapy is ineffective
	Brain neurogenesis is decreased after the administration of thyroxine in adult rats with hypothyroidism[120]	Hypothyroidism is not manifested in most patients with depression
	Rate of response to triiodothyronine is increased during depression[121]	
Dysfunction of specific brain structures and circuits	Transcranial magnetic stimulation of the prefrontal cortex[122] and deep-brain stimulation of the anterior cingulate affect mood[123]	Implicated brain areas differ from study to study
	Glucose use is reduced in the prefrontal cortex[124] and subgenual prefrontal cortex[125]	Inconsistent findings with respect to blood flow, volumetric, glucose utilization, and postmortem methodologies[63,124,126]
	Circuit dynamics in the hippocampus are altered in a rat model of depression[127]	

* AMPA denotes alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, BDNF brain-derived neurotrophic factor, DHEA dehydroepiandrosterone, GABA γ-aminobutyric acid, MRS magnetic resonance spectroscopy, and NMDA *N*-methyl-D-aspartic acid.

DRUGS

The modern era in the treatment of depressive illness began with the introduction of a monoamine oxidase inhibitor.

The observation that IPRONIAZIDE had an antidepressant effect was serendipitous. IPRONIAZIDE was being investigated for anti-TB effects when it was noted that the patients who received the IPRONIAZIDE had a clear improvement in mood independent to the progression of their disease.

Subsequent investigation showed that iproniazide inhibited monoamine oxidase, and increased NA levels in neurons.

This suggested that specific pharmacologic tools could be used to treat depressive illness.

IPRONIAZIDE

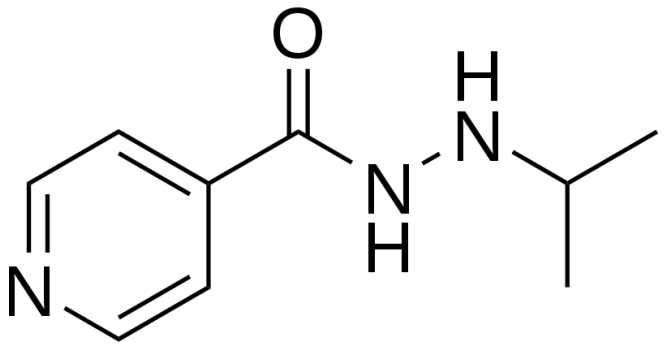


Table 1 | Currently available antidepressant treatments

Type of treatment	Mode of action	Examples
*Medication**		
Tricyclics	Inhibition of mixed noradrenaline and serotonin reuptake	Imipramine, desipramine
Selective serotonin reuptake inhibitors (SSRIs)	Inhibition of serotonin-selective reuptake	Fluoxetine, citalopram
Noradrenaline reuptake inhibitors (NRIs)	Inhibition of noradrenaline-selective reuptake	Atomoxetine, reboxetine
Serotonin and noradrenaline reuptake inhibitors (SNRIs)	Inhibition of mixed noradrenaline and serotonin reuptake	Venlafaxine, duloxetine
Monoamine oxidase inhibitors (MAOIs)	Inhibition of monoamine oxidase A (MAO_A). Inhibition of MAO_B does not have antidepressant effects	Tranylcypromine, phenelzine
Lithium	Lithium has many molecular actions (for example, inhibition of phosphatidylinositol phosphatases, adenylyl cyclases, glycogen synthase kinase 3β and G proteins) but which of its actions is responsible for its antimanic and antidepressant effects is unknown	
Atypical antidepressants	Unknown. Although these drugs have purported monoamine-based mechanisms (for example, bupropion inhibits dopamine reuptake, mirtazapine is an α_2-adrenergic receptor antagonist and tianeptine an activator of monoamine reuptake), these actions are not necessarily the mechanisms that underlie the drugs' therapeutic benefit	Bupropion, mirtazapine, tianeptine
Non-medication		
Electroconvulsive therapy (ECT)	General brain stimulation	
Magnetic stimulation	General brain stimulation? A magnetic field is thought to affect the brain by inducing electric currents and neuronal depolarization	
Vagal nerve stimulation (VNS)	Unknown	
Psychotherapies	Exact mechanism is uncertain, but is thought to involve learning new ways of coping with problems	Cognitive-behavioural therapy, interpersonal therapy
Deep brain stimulation	In severely ill patients, stimulation of a region of the cingulate cortex found to function abnormally in brain imaging scans reportedly has antidepressant effects[64]	

*Many patients respond to several types of treatment, although it is not yet possible to predict which patient will respond optimally to a particular treatment. Although they elevate mood in patients with depression, antidepressants do not elevate mood in healthy individuals and are non-addictive.

Monoamine Oxidase Inhibitors

Abbreviated as MAOI

1952- First MAOI found with antidepressant properties in process of looking for an antituberculosis drug

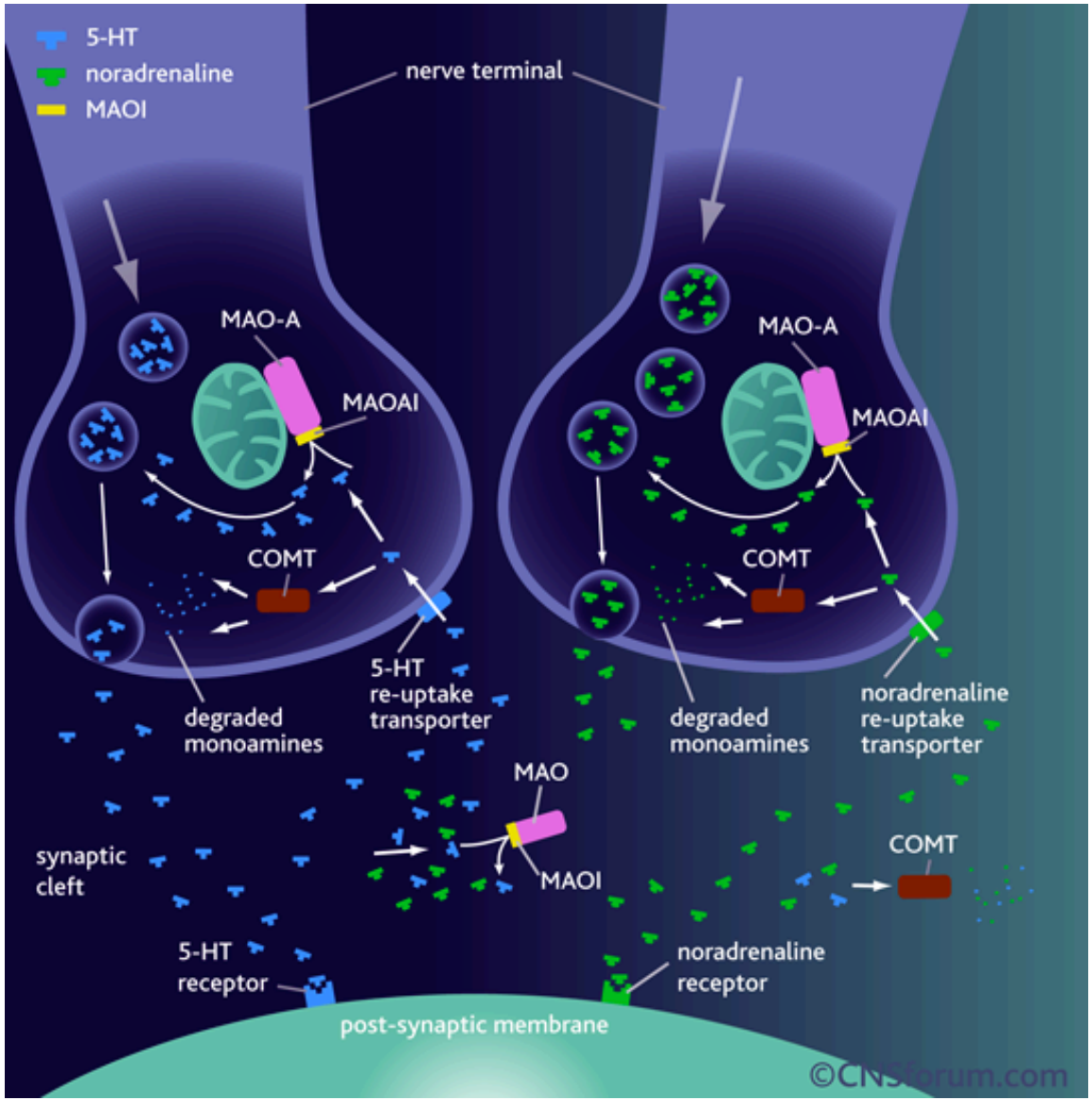
1962- Investigation of a death from hypertensive crisis by someone ingesting tyramine rich food while taking an MAOI

1960's- Institution of strict dietary restriction of tyramine containing foods and other interacting substances.

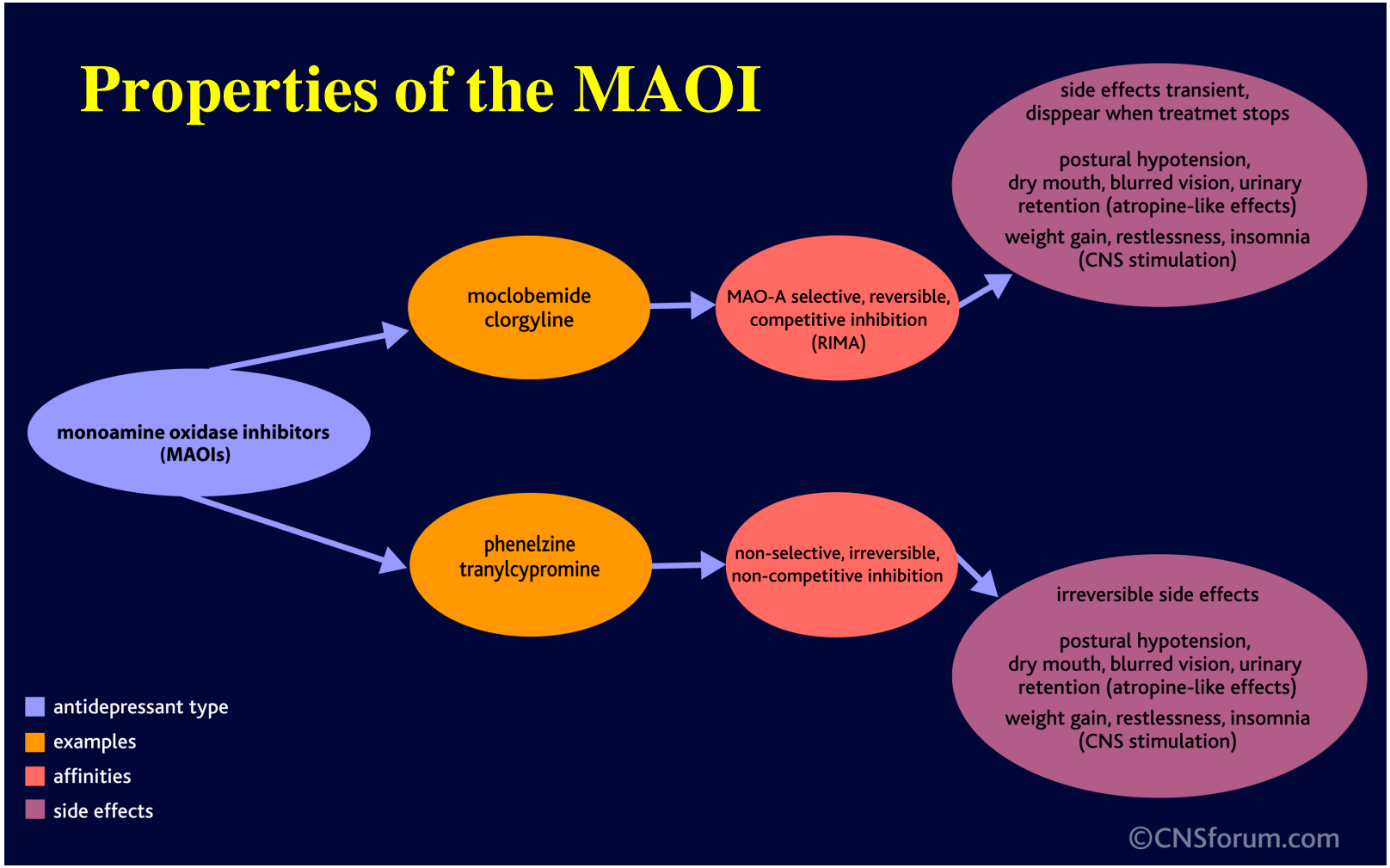
1960's- Significant reduction in use due to introduction of TCAs which do not have the severe restrictions of MAOIs.

2006- Transdermal selegiline patch (Emsam) approved to treat depression

The mechanism of action of MAOI



- **MAOA is an enzyme involved in the metabolism of the monoamines, eg 5HT & NA. It converts the monoamines into their corresponding carboxylic acid via an aldehyde intermediate.**
- **MAOA regulates both the free intraneuronal concentration and the releasable stores of 5-HT and NA.**
- **Preventing monoamine degradation. This results in greater stores of monoamines available for release.**



•MAOI were the first antidepressants to be introduced clinically. Phenelzine and tranylcypromine cause a non-competitive, irreversible inhibition and do not distinguish between MAO-A, MAO-B.

•Antidepressant effect of MAOIs is associated with MAO-A inhibition.

•The unwanted side effects of MAOIs include hypotension; atropine-like side effects (sympathomimetic effect); weight gain; and excessive CNS stimulation. The side effects associated with moclobemide are much milder than those reported with other MAOIs

Monoamine Oxidase Inhibitors

- Available formulations
  - phenylzine (**NARDIL®**);
  - isocarboxazid (**MARPLAN®**);
  - tranylcypromine (**PARNATE®**)

- Similar medications
  - selegiline (Eldepryl)
    - used to treat Parkinson's symptoms
    - selective "B" inhibitor at low doses so restrictions not critical
    - at higher doses acts like typical MAOI and so need restrictions
    - recently available as transdermal patch (Emsam) to tx depression and not needing food restrictions at low dose

Monoamine Oxidase Inhibitors

- Features

  - Very long duration requiring caution when mixing with restricted substances or medications

Tyramine containing foods:
many cheeses (aged), soybeans, hot dogs, dry sausage, caffeine, beer, wine, olives etc.

HYPERTENSIVE CRISIS
MAOIs blocks the breakdown of tyramine, that increases blood pressure. Eating foods high in tyramine can lead to a build-up in the body and dangerously high blood pressure

Monoamine Oxidase Inhibitors

- **The following is a list of interactions between MAOI and other common medications/drugs.**

- Other Antidepressants
- Asthma Medicines
- Cold, Cough, Allergy, Sinus, Decongestant and Hay Fever Medications
- Diabetes Medications
- Medications to Treat Low Blood Pressure
- Medications for High Blood Pressure
- Mood Stabilizers
- Painkillers and Anesthetics
- Sedatives and Tranquilizers
- Stimulants (Pep Pills) and Street Drugs
- Weight Loss and Appetite-Suppression Medications

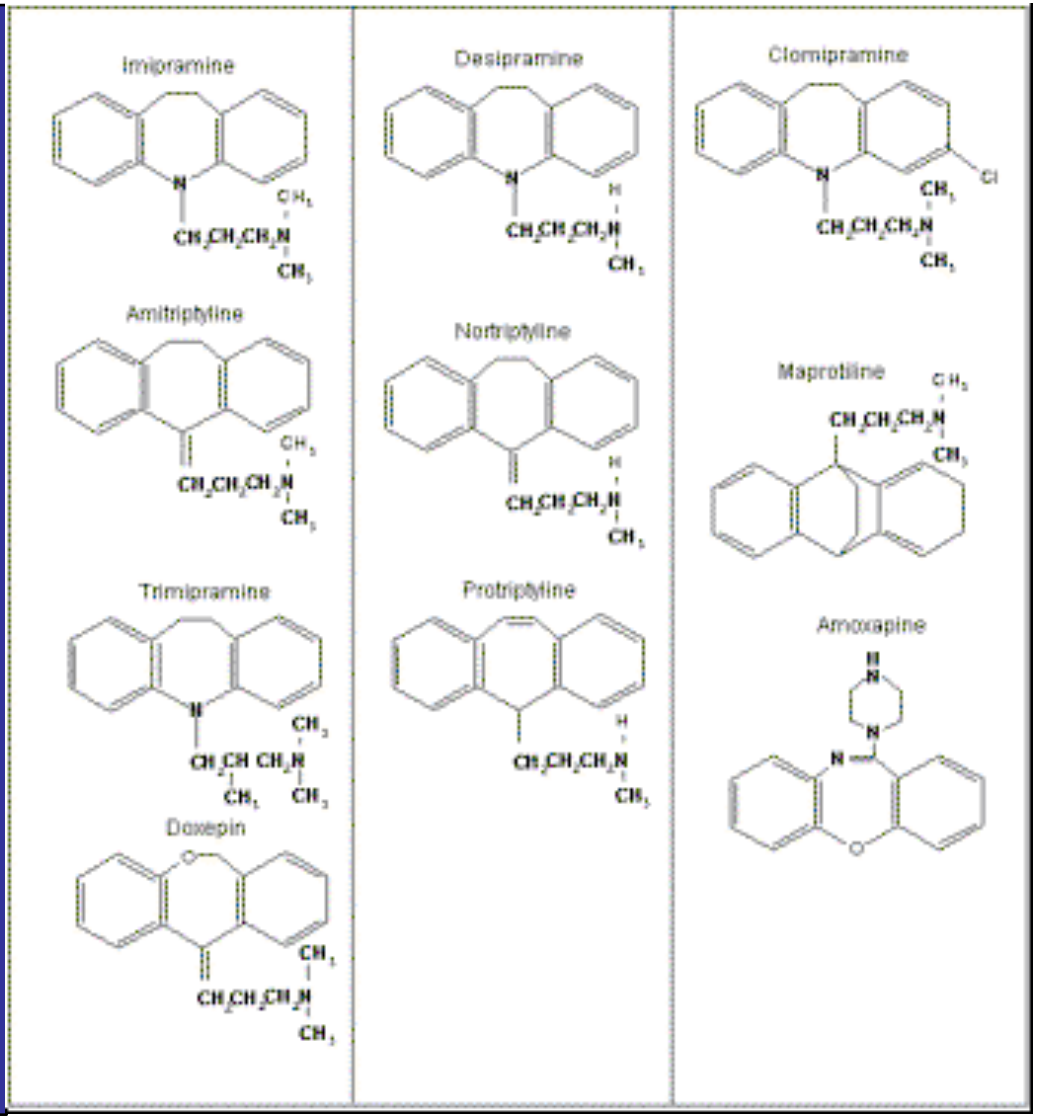
Tricyclic antidepressants

Describes a group of drugs with similar structure and function (abbreviated as TCA)

1958- Kuhn (1958) assessed imipramine effectiveness as an antipsychotic and failed to show chlorpromazine like effects. However a subgroup of psychotic patients with depressive symptoms showed remarkable improvement. He then evaluated nonpsychotic depressed patients and established a specific antidepressant effect of imipramine.

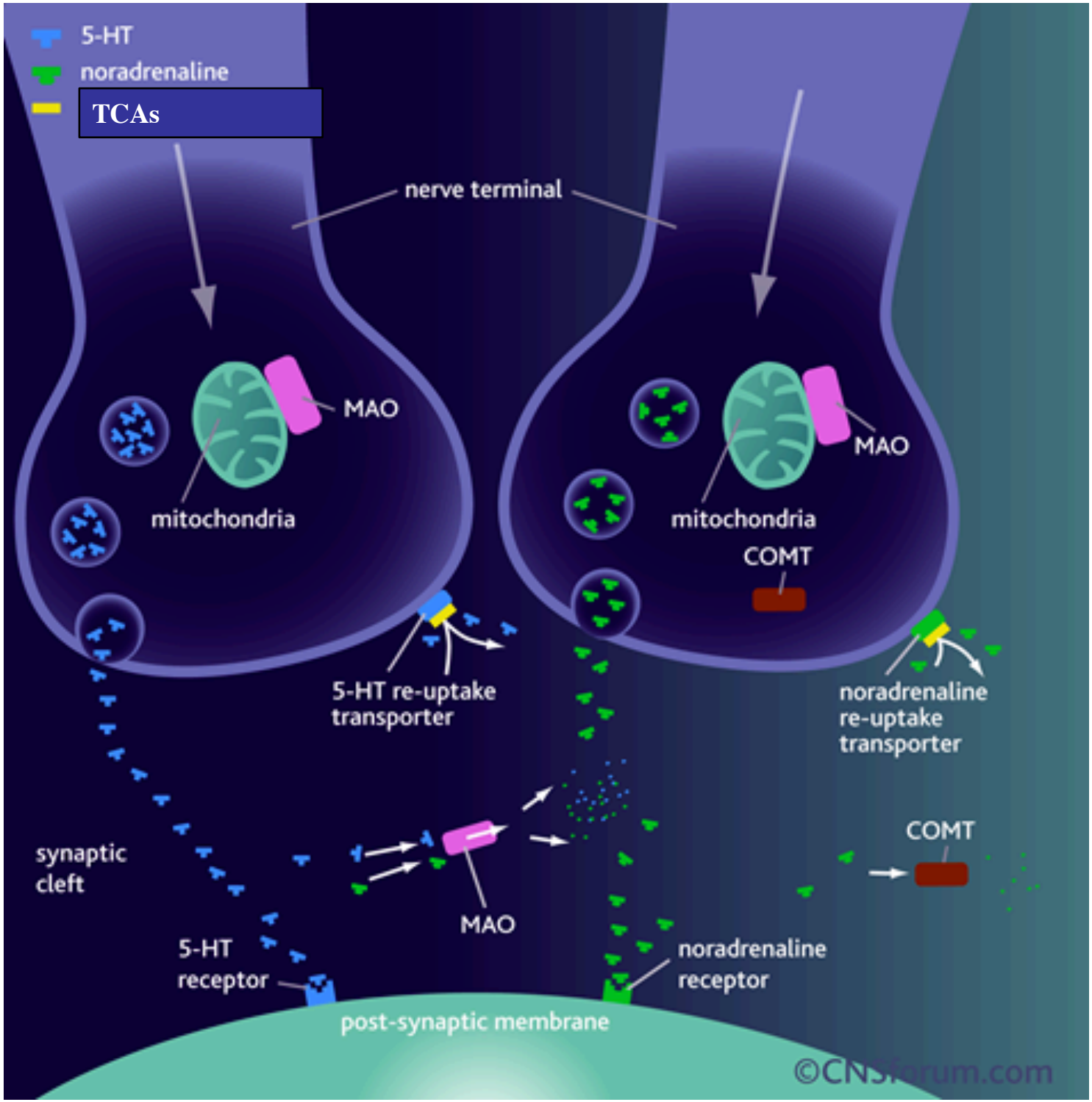
1960's- multiple other TCA's developed and placed into use

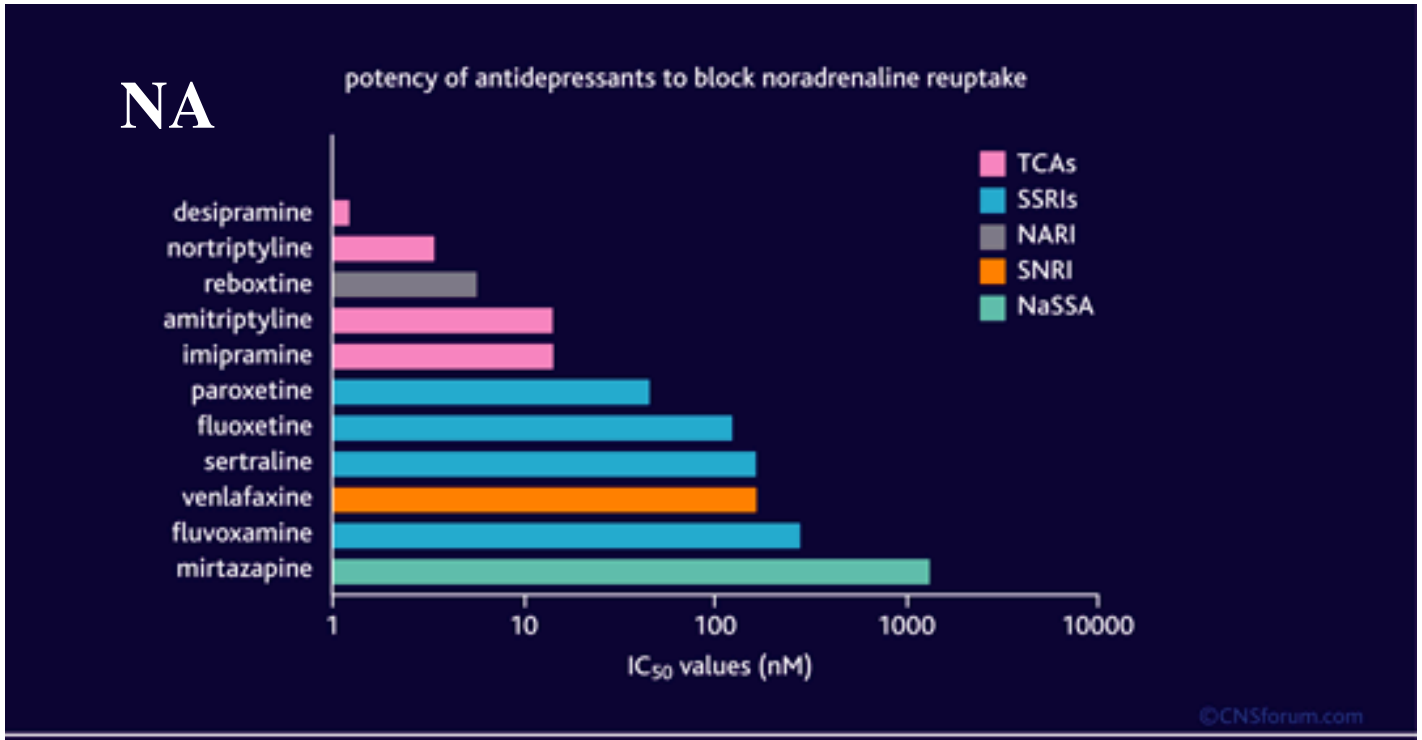
1990's- significant reduction in use due to introduction of SSRIs which have fewer side effects

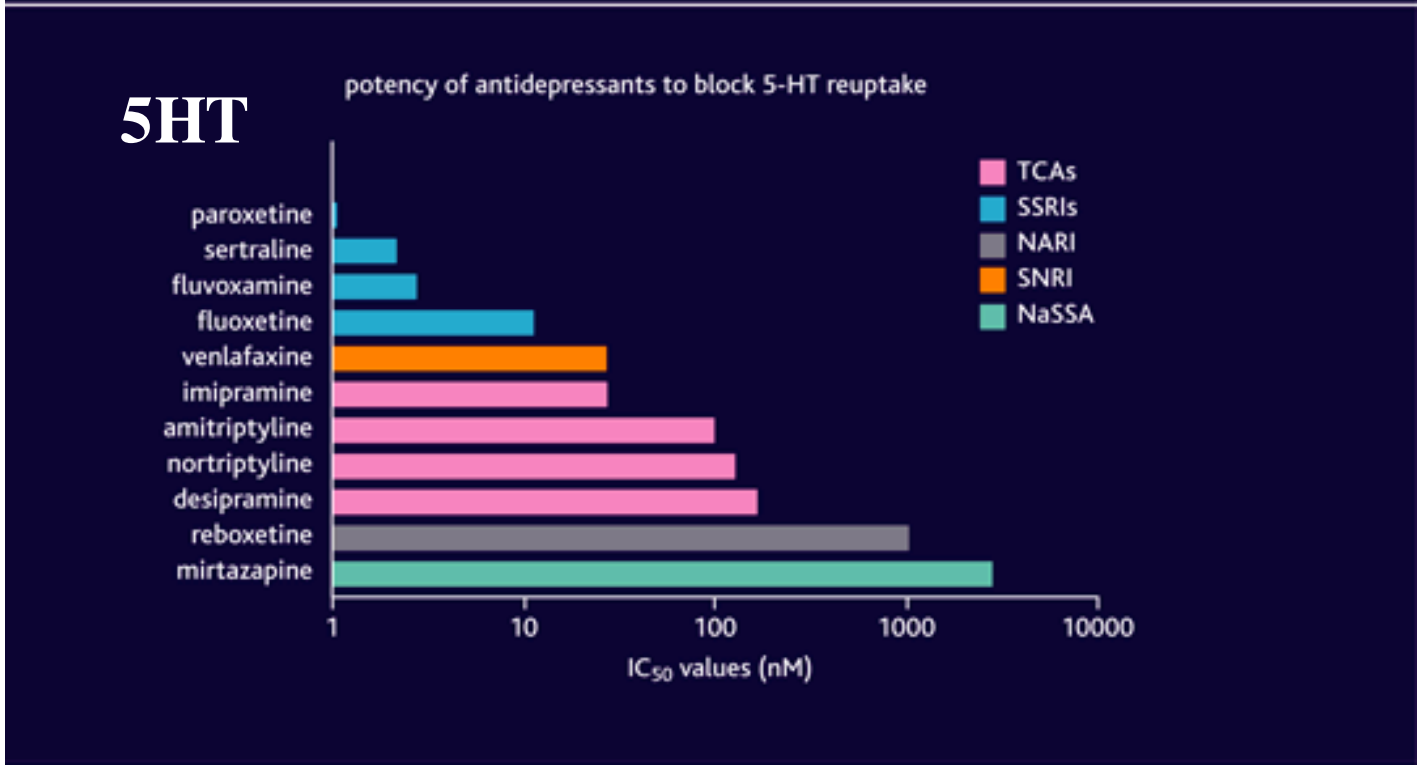


TCA main pharmacological effect is, the blockade of the NA & 5HT reuptake transporter in the presynaptic 5HT and NA nerve terminal.

TCAs have very little effect on DA reuptake.

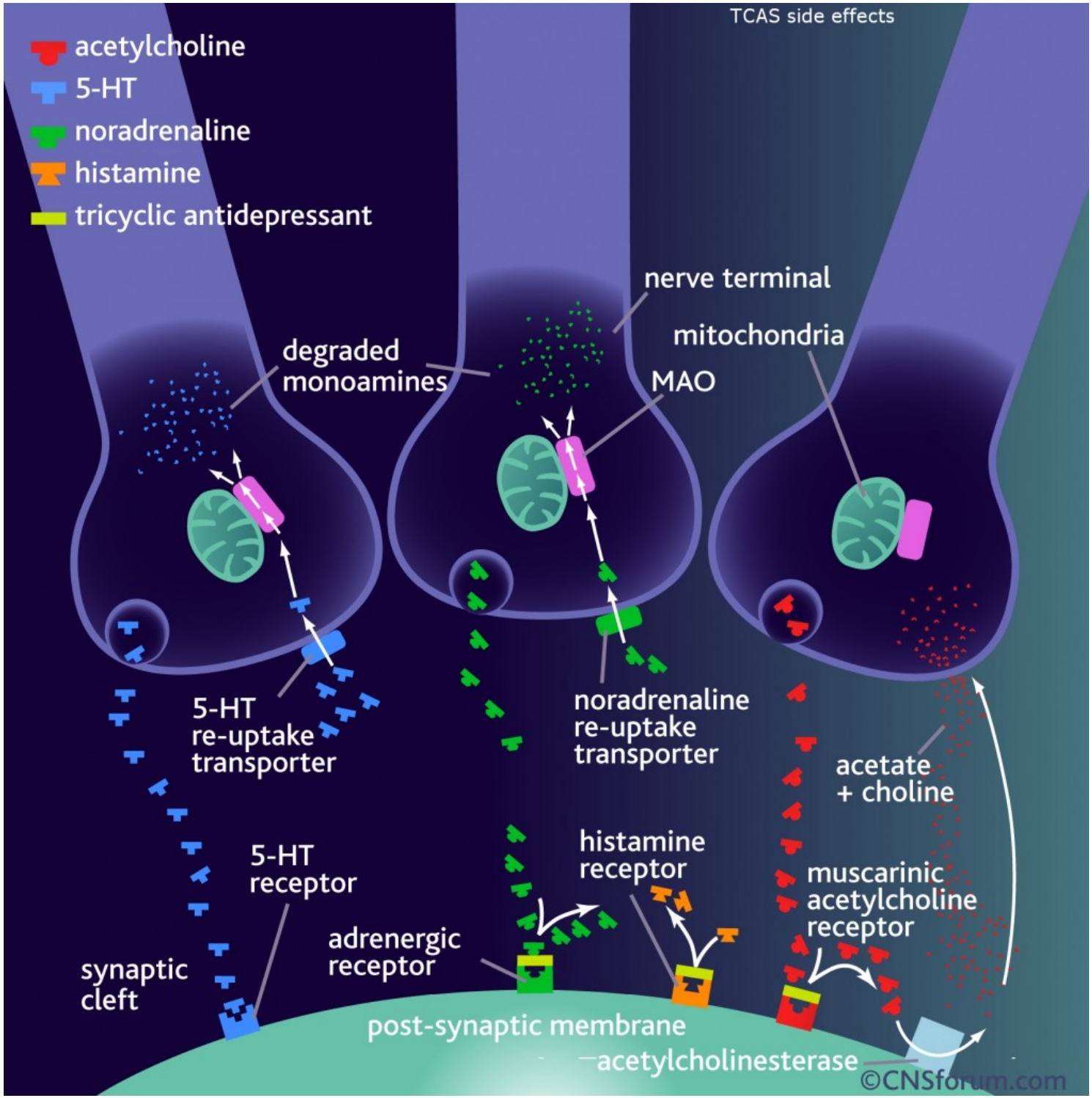






Differences in specificity

- **Secondary amine TCAs, such as desipramine and nortriptyline, are relatively selective inhibitors of noradrenaline re-uptake.**
- **Tertiary amine TCAs, such as amitriptyline and imipramine, are slightly more potent inhibitors of noradrenaline re-uptake than 5-HT re-uptake.**
- **NARIs and SSRIs are selective inhibitors of noradrenaline and 5-HT re-uptake, respectively.**
- **'Nonselective' re-uptake inhibitor, in vitro venlafaxine is a more potent blocker of 5-HT re-uptake than noradrenaline reuptake.**
- **Mirtazapine is a very weak inhibitor at both noradrenaline and 5-HT re-uptake sites. It exerts its effects by antagonising α2-adrenoceptors.**



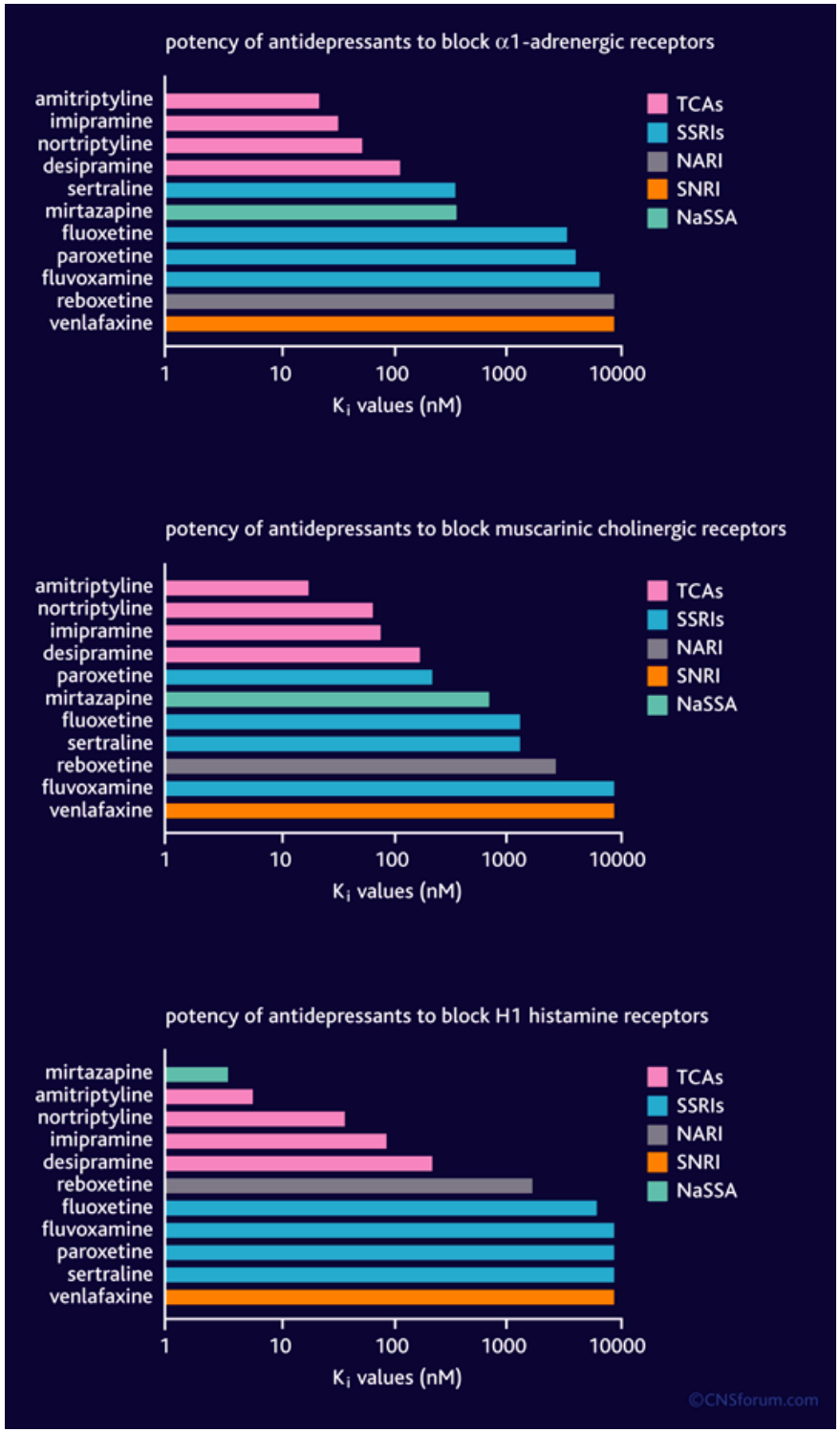
TCAs adverse effects

Drowsiness
Dry mouth
Blurred vision
Constipation
Urinary retention

Dizziness
Delayed orgasm and low sex drive, particularly in men
Increased heart rate
Disorientation or confusion
Low blood pressure, which can cause lightheadedness

Increased appetite
Weight gain
Sedation

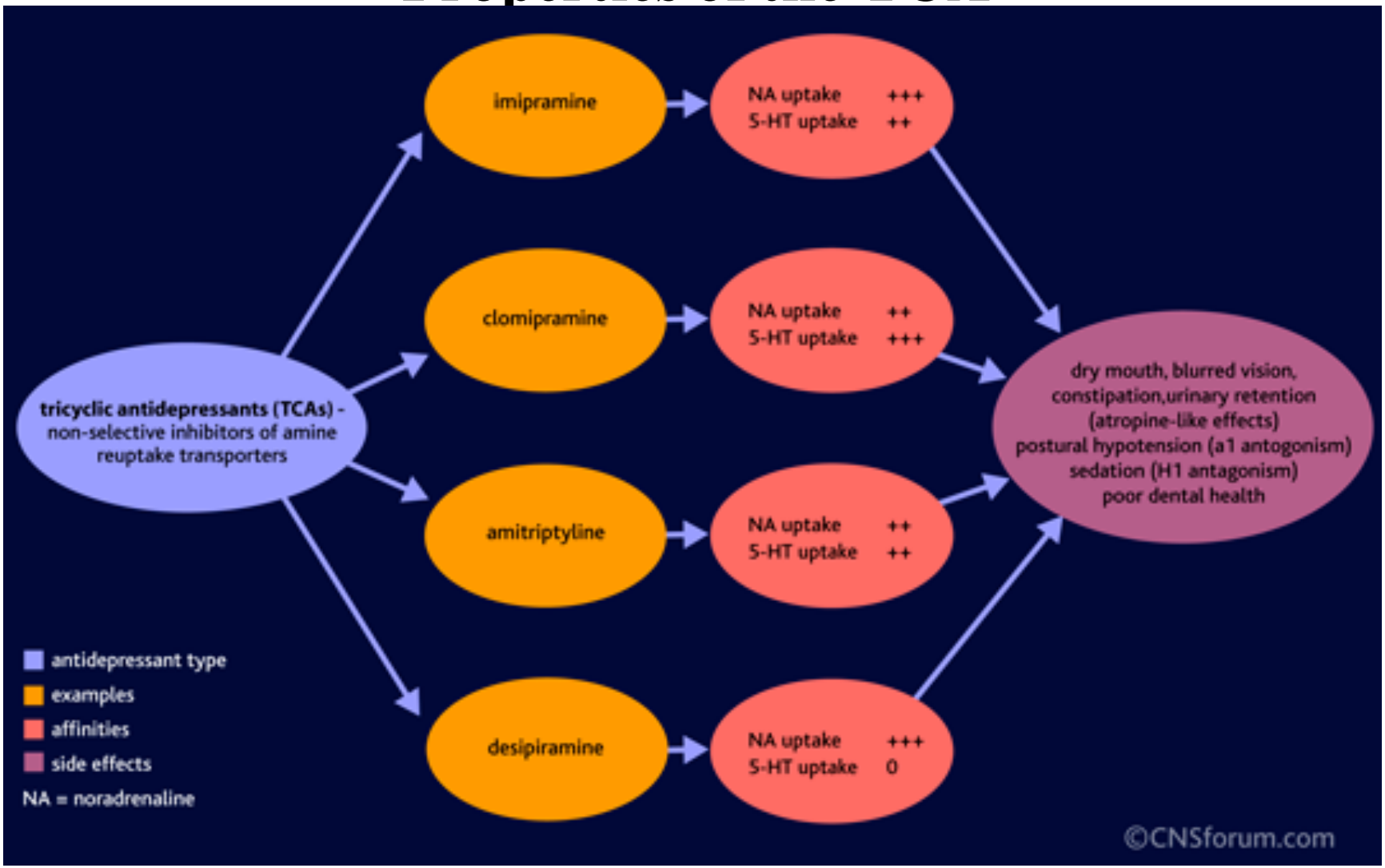
Fatigue
Headache
Sensitivity to sunlight
Nausea
Seizures (particularly with maprotiline)



The differences in specificity between ANTIDEPRESSANTS

- The side effects produced by many of the antidepressant drugs arise from their ability to block muscarinic cholinergic receptors, H1 histamine receptors and α1-adrenergic receptors. The affinity (K_i) of a drug for a specific receptor is defined as the concentration of drug needed to occupy 50% of the available receptors; the lower the K_i value, the more potently the receptor is blocked.
- Many antidepressants block muscarinic cholinergic receptors causing side effects such as; dry mouth, blurred vision, constipation and urinary retention.
- TCA block these receptors more potently than other types of antidepressant, and they are all associated with these side effects.
- Postural hypotension is associated with blockade of α1-adrenoceptors and this side effect is often seen with TCAs due to their relatively high affinity at these receptors.
- Histamine H1 receptor blockade causes sedation and drowsiness. Given the high affinity of mirtazapine for H1 receptors it is not surprising that many patients taking this medication report drowsiness and sedation.
- These side effects are not frequently observed with selective 5-HT re-uptake transporters, reboxetine or venlafaxine due to low affinity at H1 receptors.

Properties of the TCA



- **TCA include imipramine, clomipramine, amitriptyline and desipramine.**
- **Most TCAs are non-selective and inhibit noradrenaline and 5-HT uptake to a similar degree, but have much less effect on dopamine uptake.**
- **TCAs produce a number of side effects, mainly due to interference with autonomic control, including atropine-like effects (Mr block), postural hypotension (α1-r block) and sedation (H1r block)**

TCA Contraindications and Precautions

AV block , bundle-branch block , QT prolongation, cardiac arrhythmias

closed-angle glaucoma

prostatic hypertrophy, urinary retention

seizure disorder

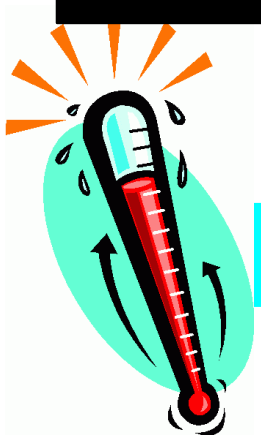
Tricyclic antidepressants

- Drug-drug interactions (DDI)
  - Multiple significant interactions in each direction with potentially serious consequences
- Cautions
  - Overdose is frequently fatal
  - Pts with bipolar d/o may be pushed into mania or rapid cycling
- Indications & off-label uses
  - Depression and similar spectrum of disorders as SSRIs
  - Especially helpful with **chronic pain** and depression secondary to medical conditions such as AIDS
  - enuresis, narcolepsy, premature ejaculation, insomnia, migraine prophylaxis
- Blood levels: May be obtained to monitor dose effectiveness

TCA OVERDOSE

- Mild to moderate poisoning with 10 mg/kg of tricyclic ingested. Such patients may present with dilated pupils, dry mouth, drowsiness, sinus tachycardia, urinary retention, increased tendon reflexes, and extensor plantar responses.

Severe poisoning with >15 - 20 mg/kg ingested. These patients often present with fits, coma, and cardiac arrhythmias. Death from cardiac arrest may also occur



Patients may develop malignant hyperpyrexia >43° C

- Symptoms usually appear within 30 to 60 minutes of ingestion.
- About 7% of all suicides are antidepressant related.

Tricyclic antidepressants

	NE	5HT	Ach	Sed	Comments
amitriptyline (Elavil)……	low	high	high	high	pain, MgrHA
amoxapine (Asendin)……	high	low	mod	low	tetracyclic
clomipramine (Anafranil).	low	high	high	high	tx OCD; SSRI-like
desipramine (Norpramin)	high	low	low	low	activating
doxepin (Sinequan)…….	low	low	mod	high	used for insomnia
imipramine (Tofranil)…….	low	low	mod	mod	pain; enuresis
maprotiline (Ludiomil)……	high	low	low	mod	tetracyclic
nortriptyline (Pamelor)…..	mod	low	mod	mod	chronic pain
protriptyline (Vivactil)……	high	low	mod	low	most activating
trimipramine (Surmontil)..	low	low	high	high	

NE- noropinephrine activity; 5HT- serotonin activity (5-hydroxy-tryptamine); OCD:Obsessive-compulsive d/o
Ach- anticholinergic effects; Sed- sedation; mod-moderate; MgrHA- migraine headache prophylaxis

THE DISCOVERY OF FLUOXETINE HYDROCHLORIDE (PROZAC)

In the early 1970s, evidence of the role of 5HT in depression began to emerge and the hypothesis that enhancing 5-HT neurotransmission would be a viable mechanism to mediate antidepressant response was put forward. On the basis of this hypothesis, efforts to develop agents that inhibit the uptake of 5-HT from the synaptic cleft were initiated. These studies led to the discovery and development of the selective serotonin reuptake inhibitor fluoxetine hydrochloride (Prozac; Eli Lilly), which was approved for the treatment of depression by the US FDA in 1987.

Commonly prescribed SSRIs include the following:

* Fluoxetine (Prozac)

* Sertraline (Zoloft)

* Paroxetine (Paxil)

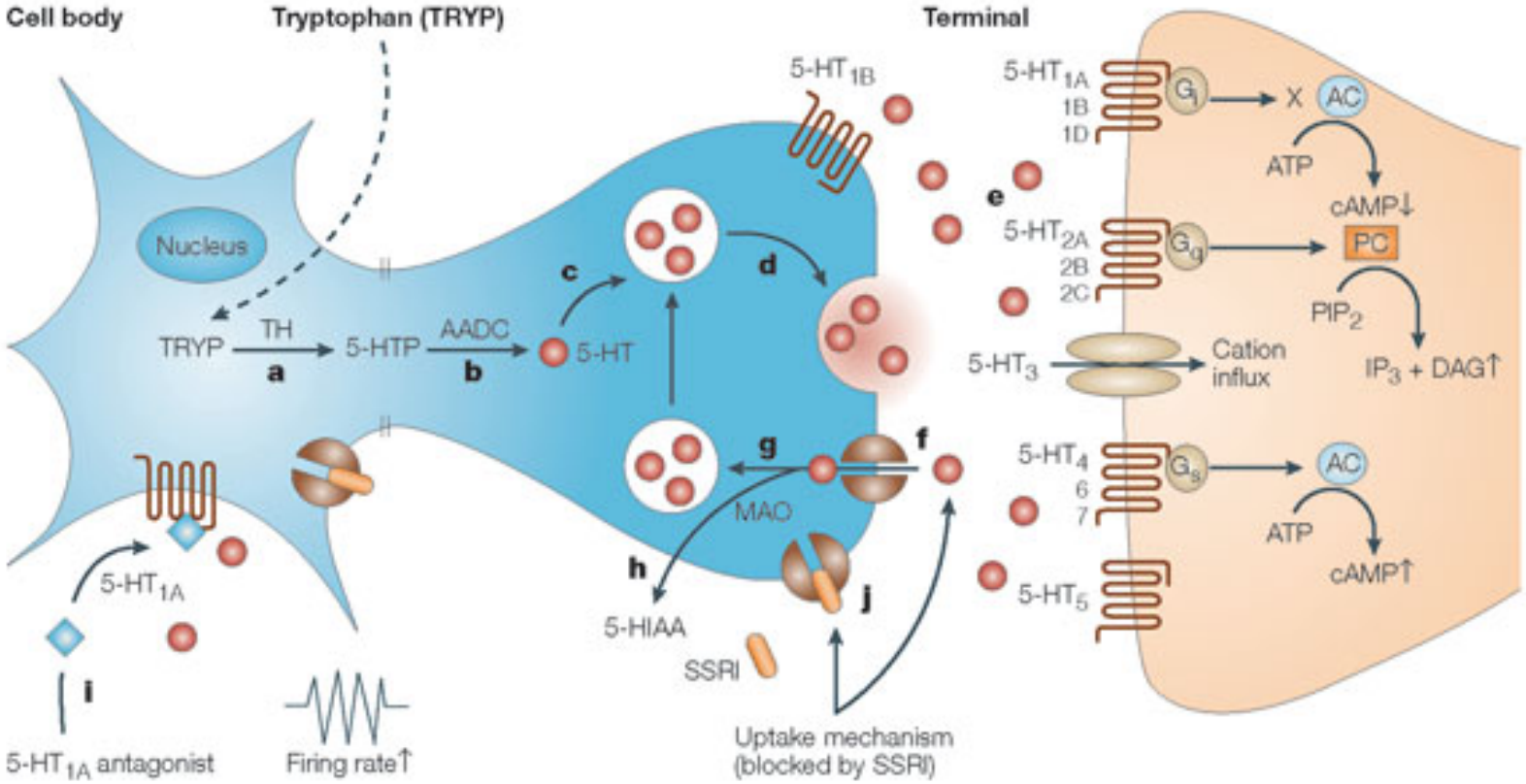
* Escitalopram (Lexapro)

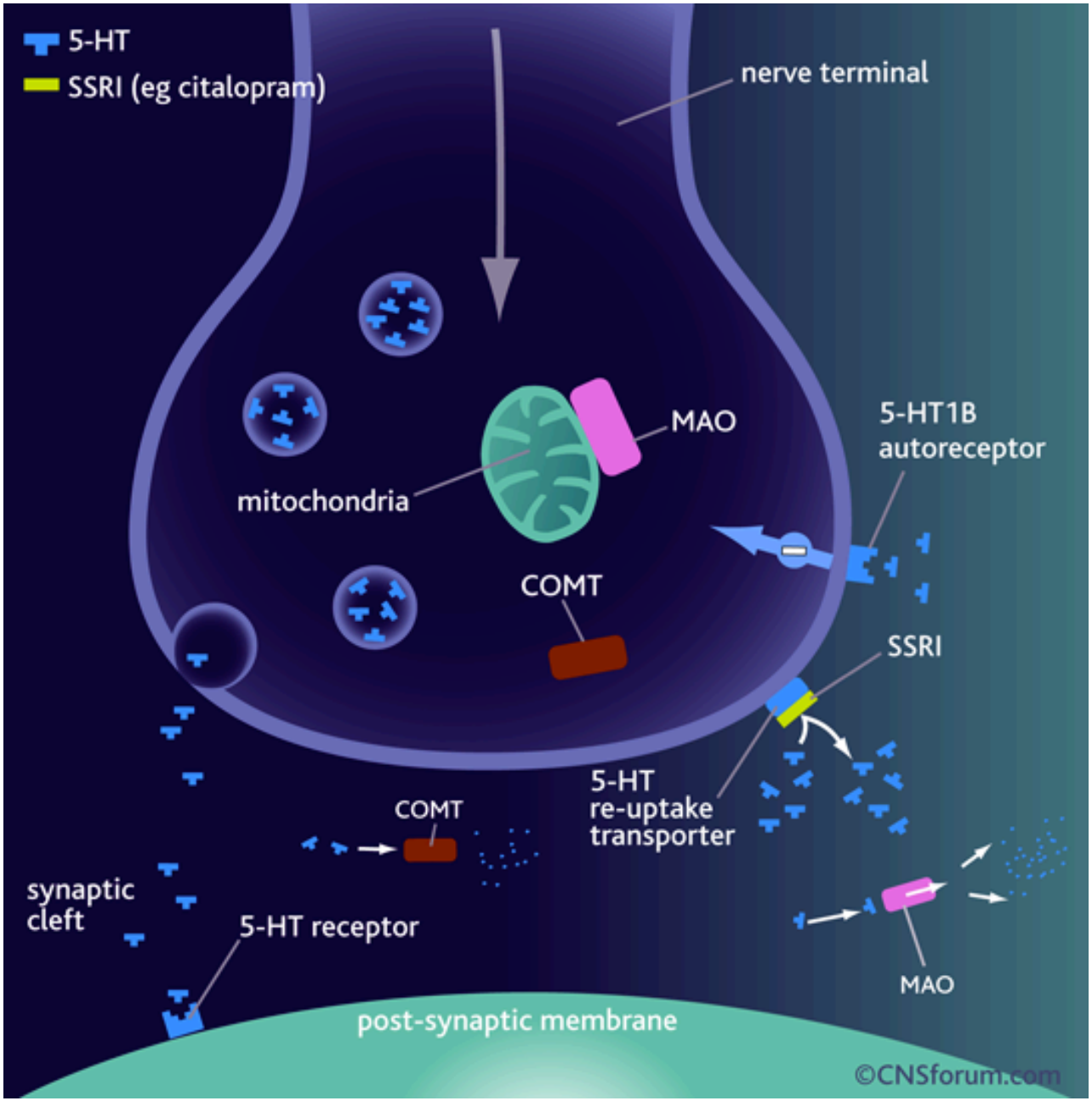
* Fluvoxamine (Luvox)

* Citalopram (Celexa)

SSRIs are available as tablets, capsules, or oral solution.

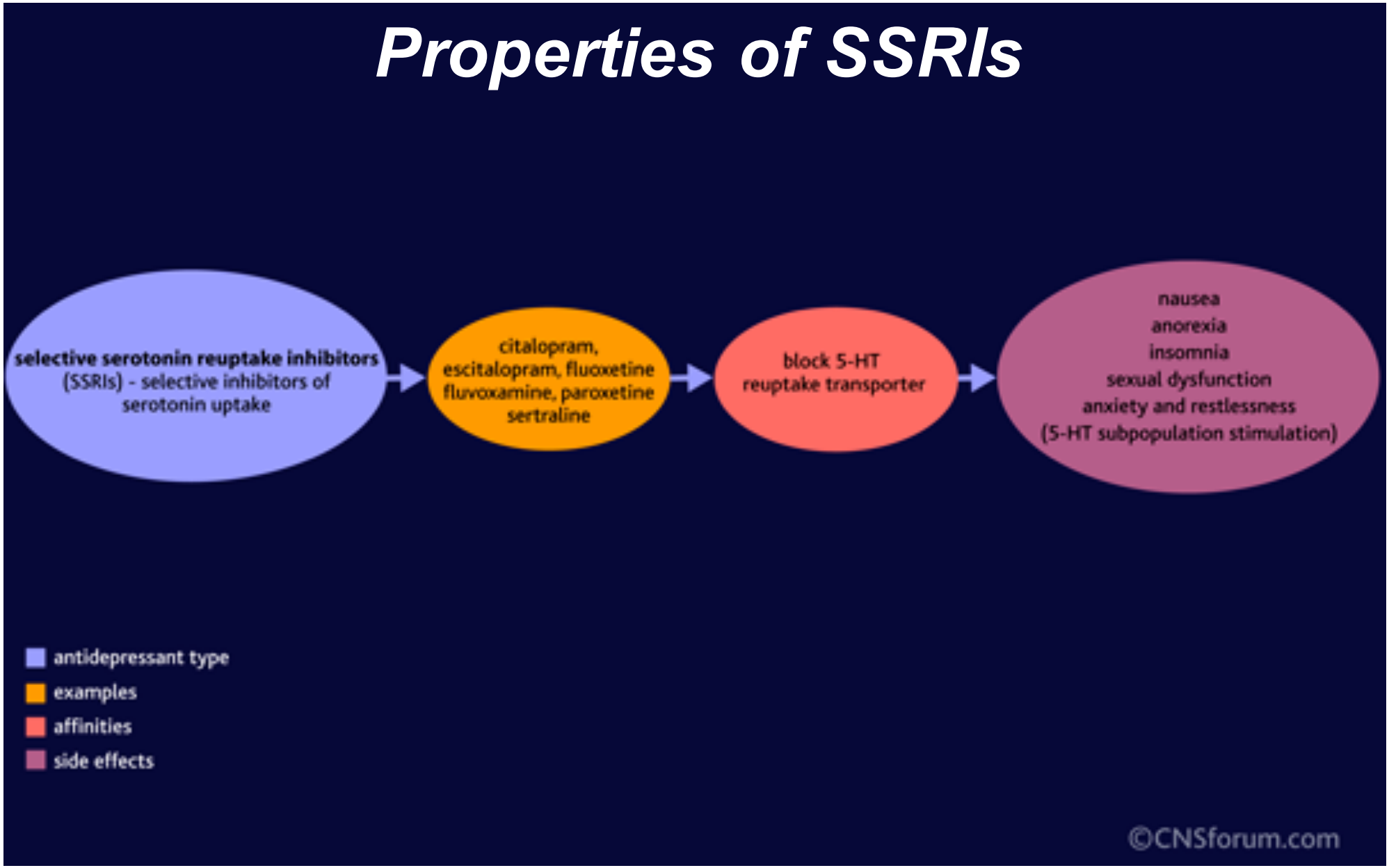
Schematic of processes associated with serotonergic neurotransmission





The mechanism of action of specific 5HT re-uptake inhibitors

- The selective 5-HT re-uptake inhibitors (SSRIs) are thought to restore the levels of 5-HT in the synaptic cleft by binding at the 5-HT re-uptake transporter preventing the re-uptake and subsequent degradation of 5-HT.
- This re-uptake blockade leads to the accumulation of 5-HT in the synaptic cleft and the concentration of 5-HT returns to within the normal range.



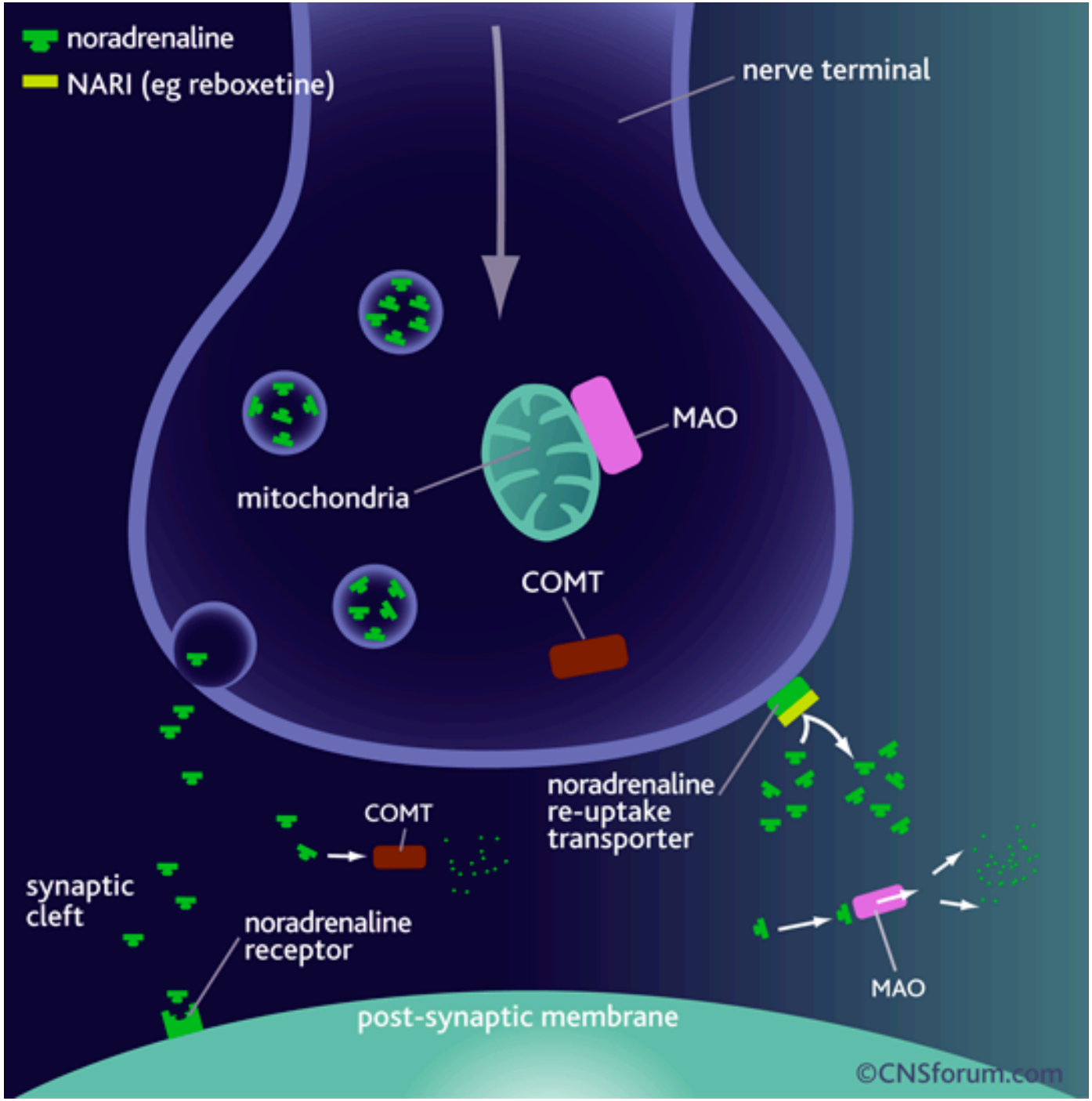
- **SSRIs include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, currently the most commonly prescribed antidepressants.**
- **SSRI show selectivity with respect to 5-HT over noradrenaline uptake inhibition, but without the anticholinergic side-effects.**
- **Unwanted effects (nausea, anorexia, insomnia and sexual dysfunction)**

SSRI safety in overdose

SSRI antidepressants are very rarely fatal in overdose when taken alone. Moderate overdoses (up to 30 times the common daily dose) are associated with minor or no symptoms, while ingestions of greater amounts typically result in drowsiness, tremor, nausea, and vomiting.

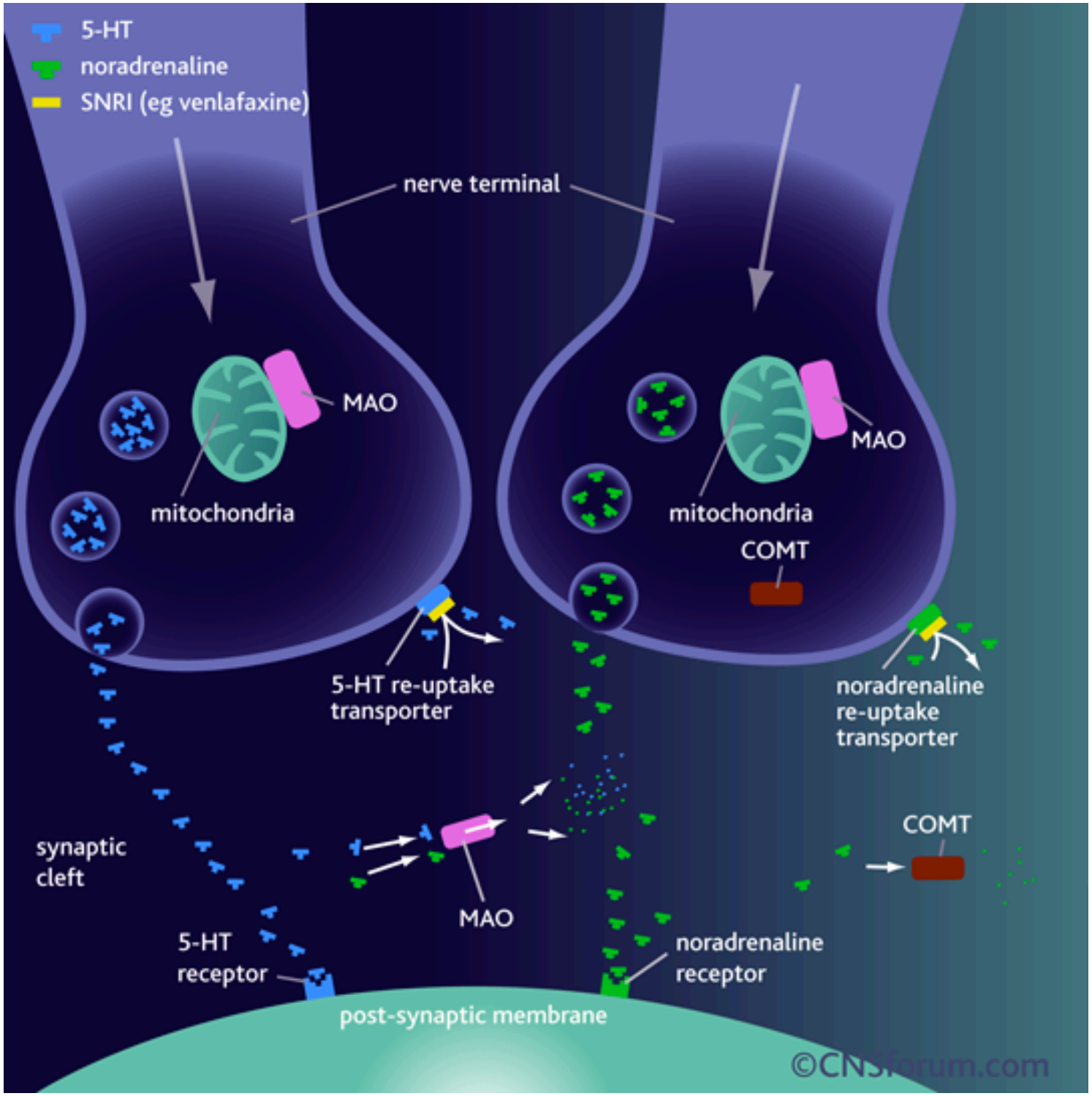
At very high doses (> 75 times the common daily dose), more serious adverse events, including seizures, electrocardiogram (ECG) changes, and decreased consciousness may occur. SSRI overdoses in combination with alcohol or other drugs are associated with increased toxicity, and almost all fatalities involving SSRIs have involved coingestion of other substances.

There is no apparent difference among SSRIs with respect to overdose safety.



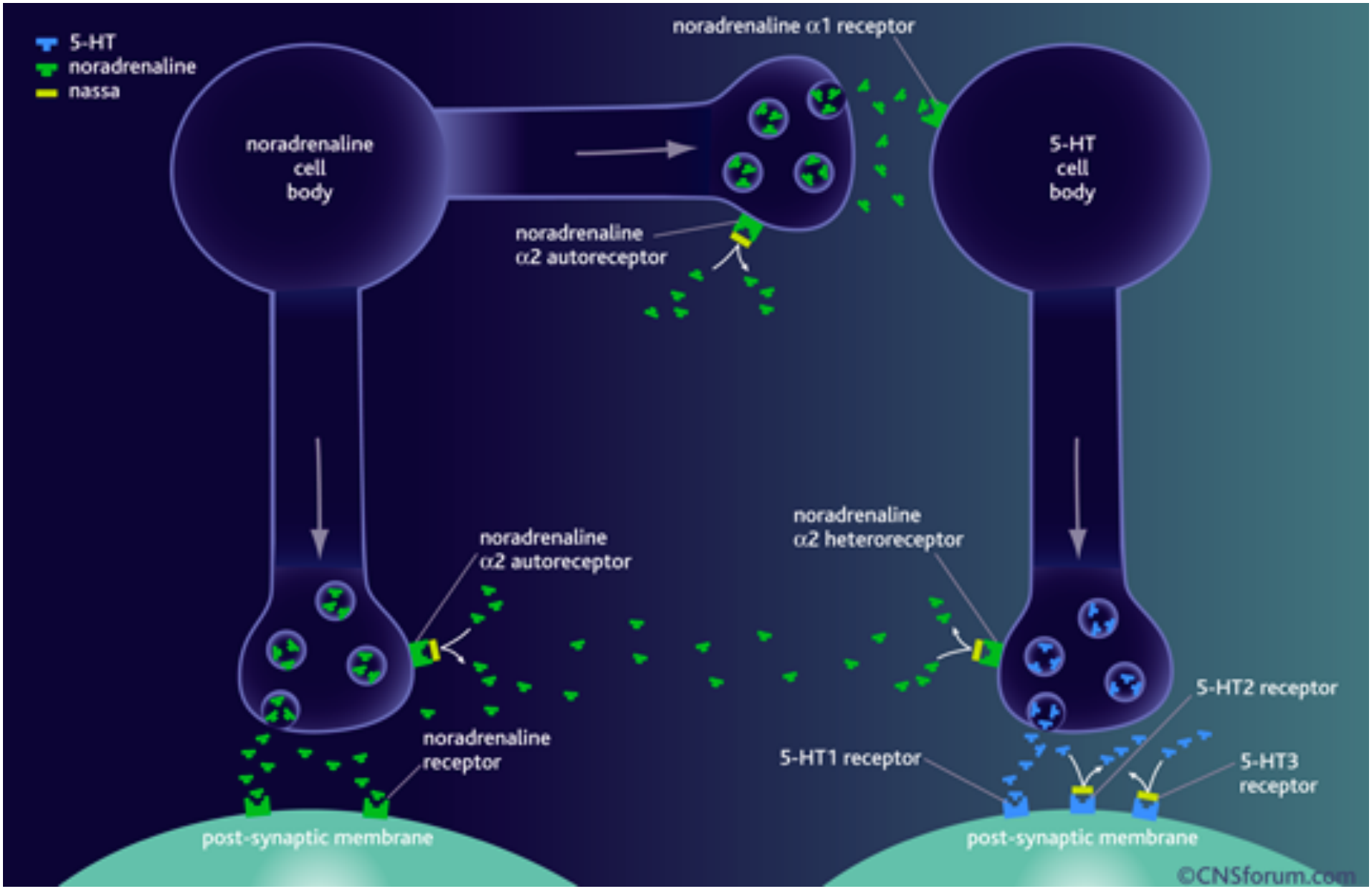
The mechanism of action of specific NA re-uptake inhibitors (NARI)

- (NARIs) are thought to restore the levels of noradrenaline in the synaptic cleft by binding at the NA re-uptake transporter preventing the re-uptake and subsequent degradation of NA.
- This re-uptake blockade leads to the accumulation of NA and its concentration returns to within the normal range.
- This action of NARIs is though to contribute to the alleviation of the symptoms of depression. In the presence of the NARI, small amounts of noradrenaline continue to be degraded in the synaptic cleft.



The mechanism of action of specific 5HT & NA re-uptake inhibitors (SNRI)

- **SNRIs restore the levels of 5HT and NA in the synaptic cleft by binding at 5HT and NA re-uptake transporters.**
- **This re-uptake blockade leads to the accumulation of 5HT and NA and its concentration returns to within the normal range.**
- **This action of SNRIs is though to contribute to the alleviation of the symptoms of depression.**

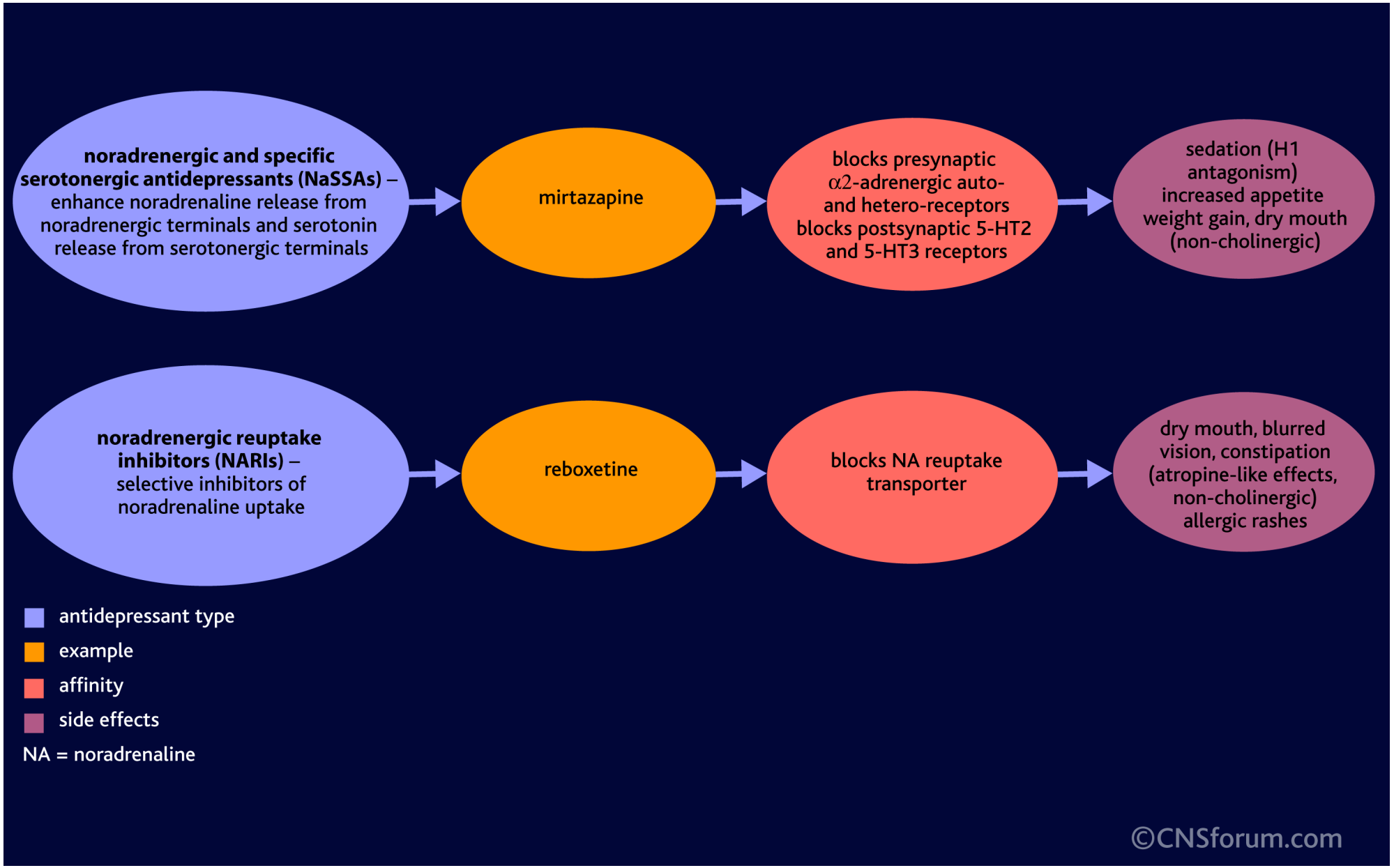


The mechanism of action of NA and specific 5HT antidepressants (NaSSAs)

•NaSSAs, such as mirtazapine, increase the concentration of 5-HT and NA in the synaptic cleft.

•NaSSAs inhibit a2-r, and prevent the negative feedback effect.

•NaSSAs also block 5-HT2 and 5-HT3 receptors on the post-synaptic membrane, which causes enhanced 5-HT1 mediated neurotransmission.



Mirtazapine exerts its effects by blocking α2R, 5-HT2 and 5-HT3R. The increase in 5-HT transmission is specifically mediated via 5-HTR

Reboxetine exhibits specificity for inhibiting the NA re-uptake transporter

The consequences of long term antidepressant treatment

Although the acute action of antidepressant treatment is associated with monoamine re-uptake inhibition, the molecular adaptations underlying the therapeutic action of these agents have still to be determined.

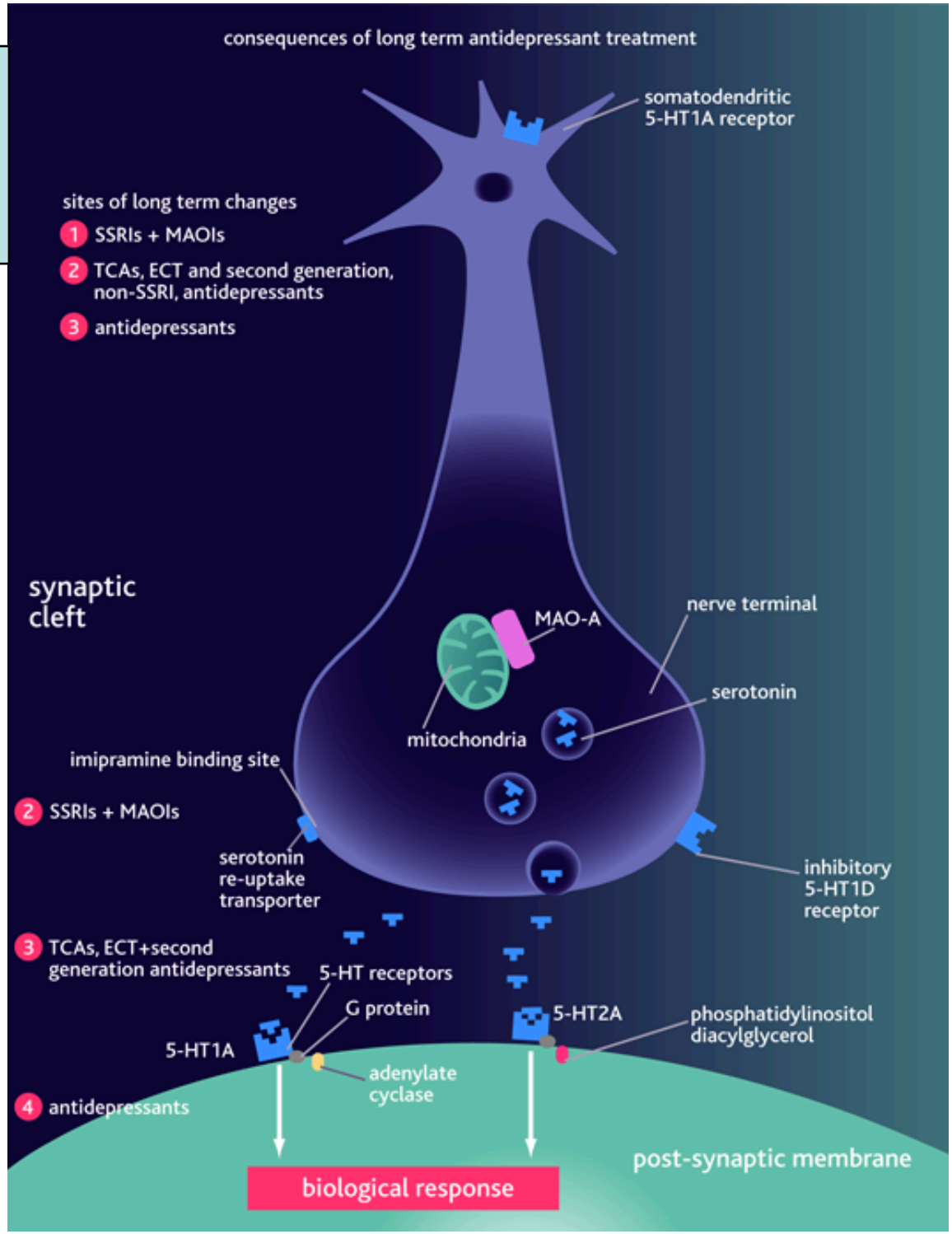
The consequences of long term antidepressant treatment

Chronic administration of antidepressants can cause a number of changes in the brain, depending on the particular drug type:

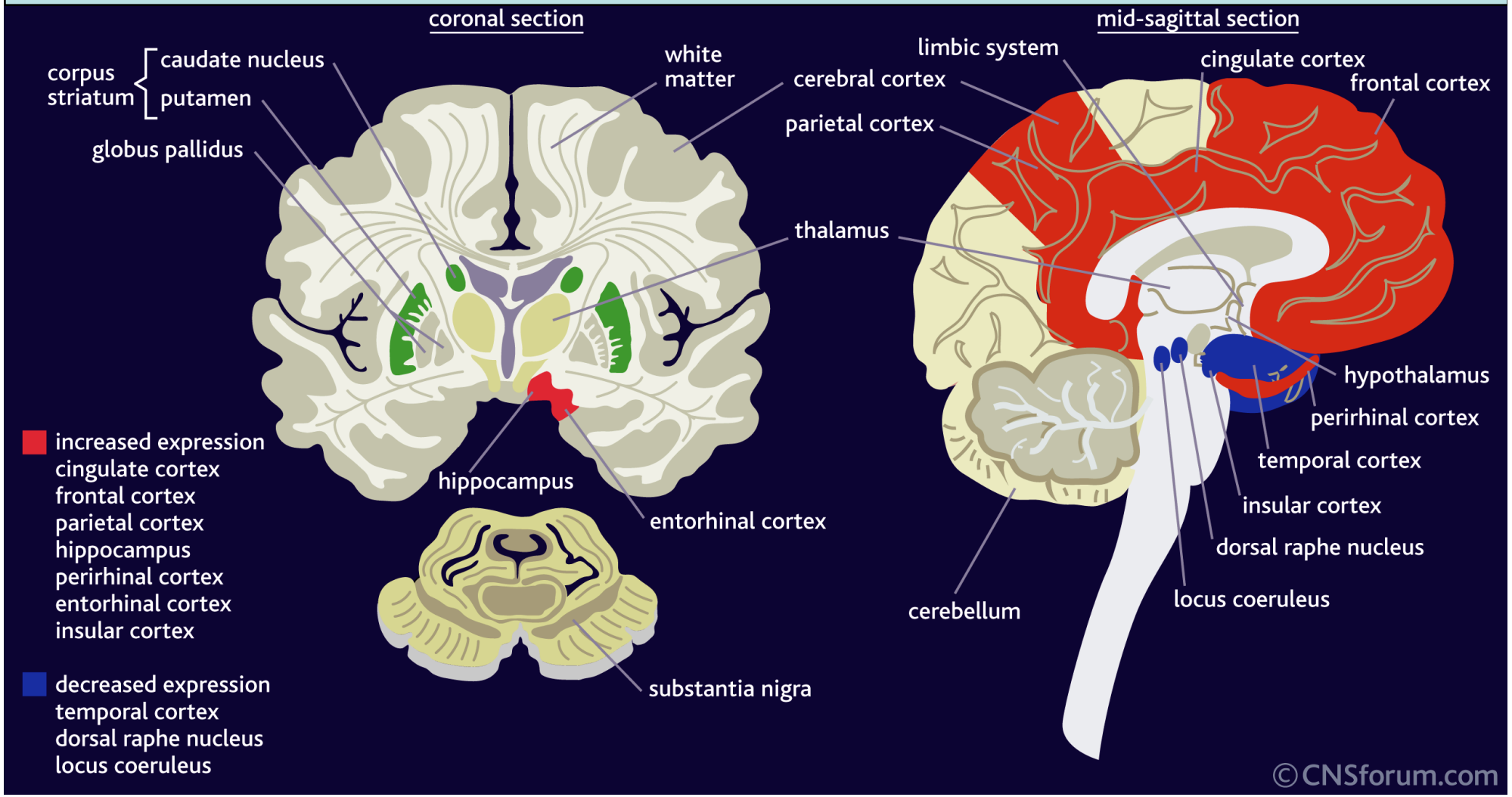
SSRIs and MAOIs desensitize inhibitory 5-HT1A somatodendritic receptors and inhibitory pre-synaptic 5-HT1D autoreceptors. They can also prevent the uptake of 5-HT into the nerve terminal by binding to the imipramine binding site

TCA, electroconvulsive therapy (ECT) and other non-SSRI antidepressants can sensitize inhibitory post-synaptic 5-HT1A receptors and can reduce the expression of stimulatory 5-HT2A receptors.

Experimental evidence suggests that chronic antidepressant treatment can also affect post-receptor signalling mechanisms, such as G-proteins.

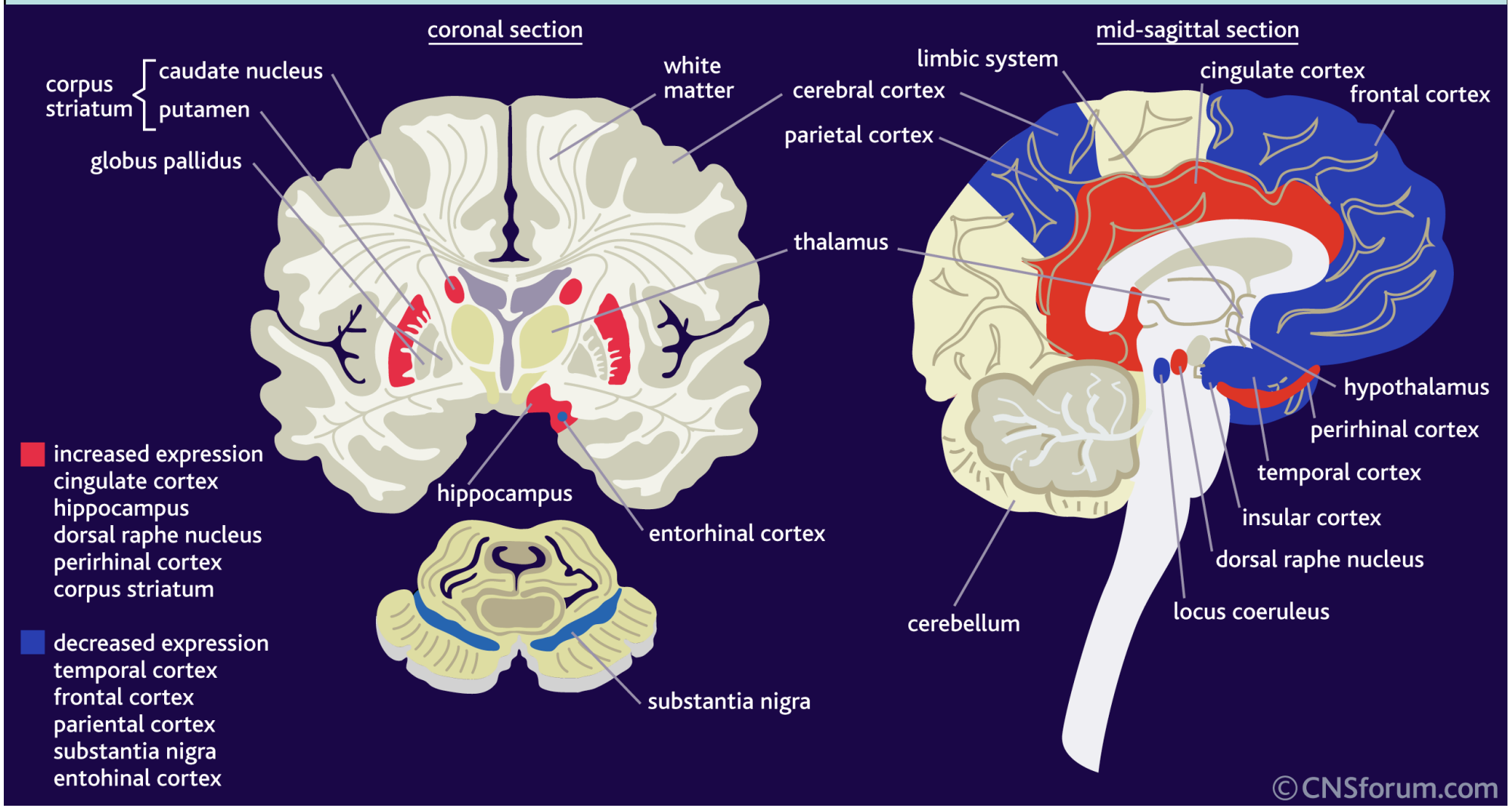


Changes in gene expression of NA re-uptake transporter



- TCA and SNRI rapidly bind to and block the action of NA re-uptake transporters (NART). Chronic administration of these ADs leads to changes in NART gene expression.
- A significant increase in NART expression is seen in the hippocampus and the in cingulate, frontal, parietal, perirhinal, entorhinal and insular cortices in response to chronic antidepressant treatment.
- A decrease in NART expression is seen in the temporal cortex

Changes in gene expression of SERT



TCAs and SSRIs bind to and block the action of SERTs.

A significant increase in SERT expression is seen in the hippocampus and the cingulate, insular, perirhinal and parietal cortices in response to chronic antidepressant treatment

The consequences on gene expression

- up-regulate the cAMP signal transduction cascade
- increased expression and function of CREB, in various regions of the brain, particularly the cerebral cortex and hippocampus
- Increased BDNF expression is increased in the hippocampus.
- Increased expression of NGF1-A, mineralocorticoid receptor (MR), glucocorticoid receptor (GR)
- Decreases in mRNA of corticotrophin-releasing factor (CRF) and its receptor CRF-R1

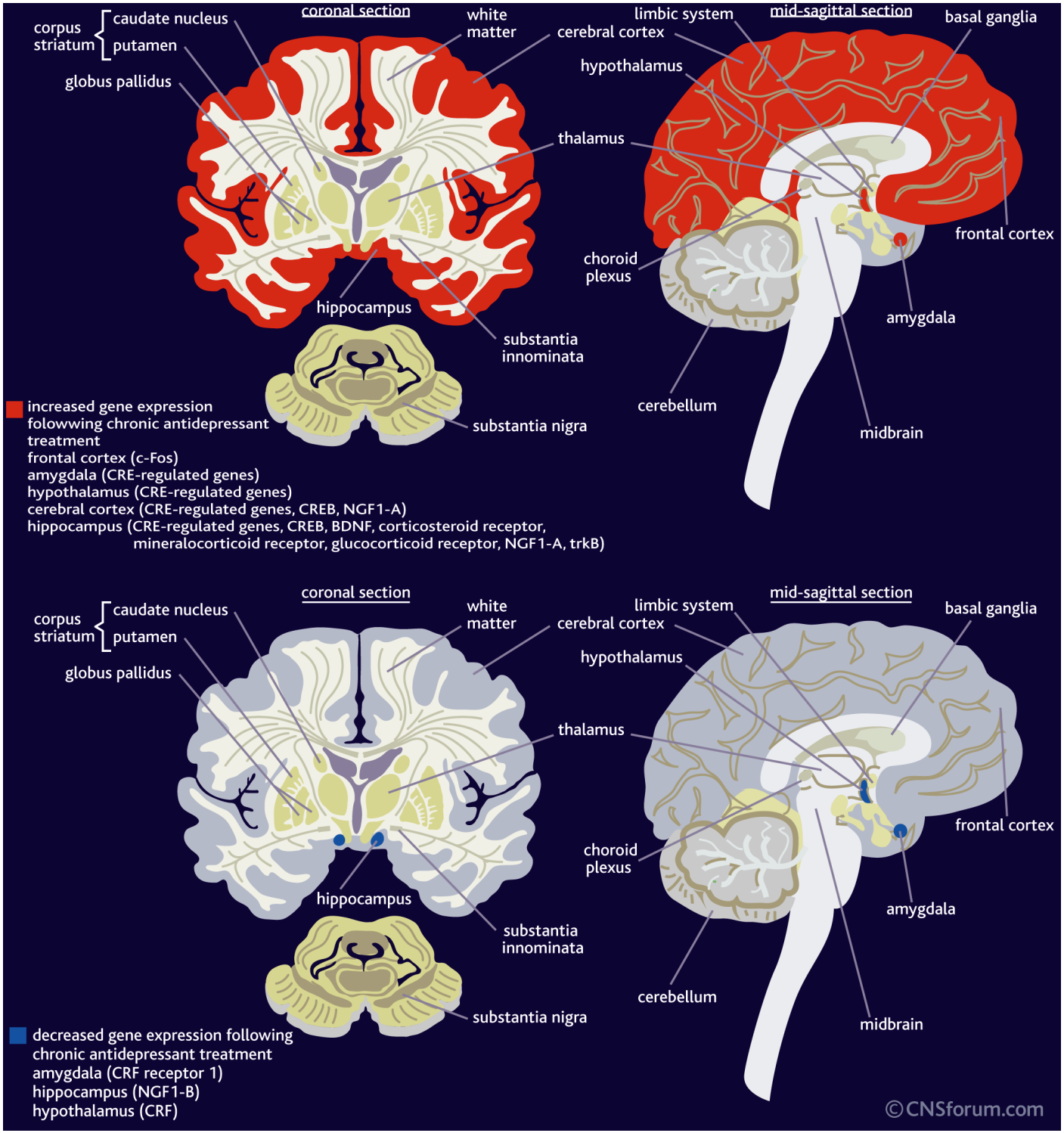


Table 1. Classification, Doses, Safety, and Side Effects of Antidepressants.*

Mechanism of Action and Functional Classification	Starting Dose	Standard Dose	Lethality in Overdose	Side Effects						
				Insomnia and Agitation	Sedation	Hypotension	Anticholinergic Effects†	Nausea or Gastrointestinal Effects	Sexual Dysfunction	Weight Gain
	mg/day									
Reuptake inhibitors										
Selective serotonin-reuptake inhibitors (SSRIs)										
Fluoxetine (Prozac)	20	20–40	Low	Moderate	None or mild	None or mild	None or mild	Moderate	Moderate	Mild
Paroxetine (Paxil)	20	20–40	Low	Moderate	None or mild	None or mild	Mild	Moderate	Moderate	Mild
Sertraline (Zoloft)	50	50–150	Low	Moderate	None or mild	None or mild	None or mild	Moderate	Moderate	Mild
Fluvoxamine (Luvox)	50	100–250	Low	Moderate	Mild	None or mild	None or mild	Moderate	Moderate	Mild
Citalopram (Celexa)	20	20–40	Low	Moderate	None or mild	None or mild	None or mild	Moderate	Moderate	Mild
Escitalopram (Lexapro)	10	10–20	Low	Moderate	None or mild	None or mild	None or mild	Moderate	Moderate	Mild
Selective norepinephrine-reuptake inhibitors (NRIs)										
Reboxetine (Edronax)‡	4–8	8–12	Low	Mild	None or mild	None or mild	None or mild	Mild	Mild	None or mild
Nonselective norepinephrine-reuptake inhibitors										
Desipramine (Norpramine)	25–50	100–300	High	Mild	None or mild	Moderate	Mild	None or mild	Mild	Mild
Nortriptyline (Pamelor)	25–50	75–200	High	Mild	Mild	Mild	Mild	None or mild	Mild	Mild
Maprotiline (Ludiomil)	75	75–200	High	Mild	None or mild	Mild	Mild	None or mild	Mild	Moderate
Mixed or dual-action reuptake inhibitors										
Older agents (TCAs)										
Amitriptyline (Elavil)	25–50	100–300	High	None or mild	Moderate	Moderate	Severe	None or mild	Mild	Moderate
Dothiepin (Dothep)‡	25–50	100–300	High	None or mild	Moderate	Moderate	Moderate	None or mild	Mild	Moderate
Clomipramine (Anafranil)	25–50	100–250	High	Mild	Moderate	Moderate	Moderate	Mild	Mild	Moderate
Imipramine (Tofranil)	25–50	100–300	High	Moderate	Mild	Moderate	Moderate	None or mild	Mild	Moderate

Newer agents (non-TCAs)										
Venlafaxine (Effexor) (NRI plus SRI)	37–75	75–225	Moderate	Moderate	None or mild	None or mild	None or mild	Moderate	Moderate	None or mild
Milnacipran (Ixel) (NRI plus SRI)‡	50–100	100–200	Low	Moderate	None or mild	None or mild	None or mild	Moderate	Moderate	None or mild
Bupropion (Wellbutrin) (NRI plus DRI)	150	150–300	Low	Moderate	None or mild	None or mild	Mild	Mild	None or mild	None or mild
Duloxetine (Cymbalta) (NRI plus SRI)	30	30–90	Low	None or mild	Mild	None or mild	Mild	Mild	None or mild	None or mild
MAOIs										
Irreversible agents										
Phenelzine (Nardil)	15	30–90	High	Moderate	Mild	Moderate	Mild	Mild	Moderate	Mild
Tranylcypromine (Parnate)	10	20–60	High	Moderate	Mild	Moderate	Mild	Mild	Moderate	Mild
Isocarboxazid (Marplan)	20	20–60	High	Moderate	None or mild	Moderate	Mild	Mild	Moderate	Moderate
Selegiline (Eldepryl)	10	20–40	Moderate	Mild	None or mild	Mild	Mild	Mild	Mild	Mild
Reversible agents										
Modobemide (Manerix)‡	150	300–600	Low	Mild	None or mild	None or mild	Mild	Mild	None or mild	None or mild
Mixed-action newer agents										
Mirtazapine (Remeron) (5-HT_2 plus 5-HT_3 plus α_2-adrenergic receptors)	30	30–60	Low	None or mild	Severe	Mild	None or mild	None or mild	None or mild	Severe
Mianserin (Bolvidon) (5-HT_2 plus α_1- and α_2-adrenergic receptors)‡	30	60–120	Low	None or mild	Moderate	Mild	Mild	None or mild	None or mild	Mild
Nefazodone (Serzone) (5-HT_2 receptors)	100	300–600	Low	None or mild	Moderate	Mild	Mild	Mild	None or mild	Mild
Trazodone (Desyrel) (5-HT_2 plus α_1-adrenergic receptors)	50–100	200–600	Low	None or mild	Severe	Mild	None or mild	Mild	Moderate	Mild

* These doses are standard in psychiatric practice but may not always conform to doses recommended in the *Physician's Desk Reference* or drug package insert. More detailed reviews of side effects for all classes of antidepressants may be found in the Guidelines of the American Psychiatric Association 2000 and the Agency for Health Care Policy and Research 1999. NRI denotes norepinephrine-reuptake inhibitor, TCA tricyclic antidepressant, SRI serotonin-reuptake inhibitor, MAOI monoamine oxidase inhibitor, and DRI dopamine-reuptake inhibitor.
† Symptoms include dry mouth, constipation, sweating, blurred vision, and urinary retention.
‡ This drug is not available in the United States.

Table 2. Augmenting or Adjunctive Drugs.*

Drug	Starting Dose	Standard Dose	Main Side Effects					
			Weight Gain	Lethargy	Ataxia	Nausea	Tremor	Other
	mg/day							
Mood stabilizers								
Lithium	600–900	450–1500	Severe	Mild	None or mild	Moderate	Severe	Polyuria, fatigue, hypothyroidism, cognitive deficits, acne, headache, worsens psoriasis
Lamotrigine (Lamictal)	25	50–300	Mild	Moderate	Moderate	Moderate	None or mild	Dizziness, headache, insomnia, severe skin reactions (e.g., Stevens–Johnson syndrome)
Valproic acid (Depakene) or divalproex (Depakote)	15 per kg of body weight	Up to 60 per kg of body weight	Moderate	Moderate	Moderate	Moderate	Severe	Headache, ovarian cysts
			Weight Gain	Sedation	Diabetes or Lipid Increase	Tardive Dyskinesia	Hypotension	
Antipsychotic agents								
Typical								
Chlorpromazine (Thorazine)	25	75–200	Moderate	Severe	None or mild	Severe	Mild	EPS, sinus tachycardia
Haloperidol (Haldol)	2–6	10–20	None or mild	None or mild	None or mild	Severe	Mild	EPS, akathisia, sinus tachycardia
Atypical								
Clozapine (Clozaril)	25	300–400	Severe	Severe	Moderate	None or mild	Severe	Low white-cell count
Olanzapine (Zyprexa)	5	10–20	Severe	Mild	Moderate	Mild	Mild	EPS, hepatic effects, dizziness
Risperidone (Risperdal)	1–2	4–6	Mild	Mild	None or mild	Mild	Mild	EPS, insomnia, agitation, CVA in dementia
Quetiapine (Seroquel)	50	300–600	Mild	Mild	Mild	Mild	Moderate	Somnolence, dizziness, dyspepsia
Aripiprazole (Abilify)	10–15	15–30	None or mild	Mild	None or mild	Mild	Mild	EPS, insomnia, agitation, anxiety
Ziprasidone (Geodon)	40–80	80–160	None or mild	Mild	None or mild	Mild	Mild	EPS, constipation, fatigue, insomnia, QT prolongation
Thyroid supplement								
Thyroxin (Synthroid)	0.05	0.05–0.1	NA	NA	NA	NA	NA	None if thyroid function is monitored

* These doses are standard in psychiatric practice but may not always conform to doses recommended in the *Physicians' Desk Reference* or in drug package inserts. EPS denotes extrapyramidal syndrome, CVA cardiovascular accident, and NA not applicable.

Antidepressants Reduce the Risk of Suicide among Elderly Depressed Patients

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Abarbanel Mental Health Center and Geha Mental Health Center, Affiliated with the Sackler Faculty of Medicine, Tel-Aviv University, Bat-Yam, Israel

Treatment with selective serotonin reuptake inhibitors (SSRIs) may increase the risk of impulsive acts including suicide, while data from epidemiological studies suggest that the effect of SSRIs in the elderly may be beneficial. We aimed to evaluate the association between exposure to antidepressants and suicidality in a cohort of elderly patients suffering from major depressive disorder (MDD). This was a retrospective matched case-controlled evaluation over a 10-year period. All records of admissions of patients with MDD (ICD-10) were assessed. The index group comprised all patients who had attempted suicide in the month prior to admission. The case-controlled group was the next admission of a patient suffering from MDD, matched for sex and age who had not attempted suicide in the month prior to admission. The index group during the 10-year period (1995–2004) consisted of 101 patients suffering from MDD who were hospitalized following a suicide attempt. Mean age for the group was 76.576.6 years; there were 42 men and 59 women. The control group patients (N 101) were matched for age (mean 76.676.9 years) and sex. The proportion of patients exposed to an antidepressant was significantly greater in the control group, than in the group of patients who had attempted suicide (58 vs 42%, odds ratio 1.94 (95% CI: 1.1–3.4), p 0.019). SSRIs were prescribed in 29% of patients in the control group vs 21% of patients in the index group (p 0.03). It is of interest to note that concomitant prescription of benzodiazepines also conferred a protective effect. In conclusion, elderly depressed patients treated with antidepressants may be at reduced risk of attempting suicide. These findings need support from prospective randomized trials.

Neuropsychopharmacology (2006) 31, 178–181

Down-regulation of beta receptors in the cortex.

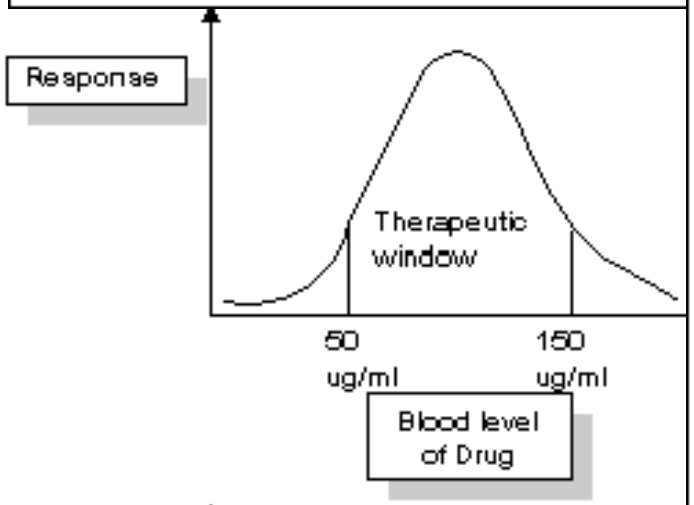
Almost all known treatments of depression, including ECT, result in down-regulation of beta receptors within a few weeks of treatment. This suggest that the down-regulation is a homeostatic response to restore an appropriate response to an altered noradrenergic system.
Other effects of chronic antidepressants in these animal models include effects on the alpha - 2 receptors. It is possible that it is the relative effect on the beta and alpha-2 autoreceptors which is most important in determining an antidepressant effect.

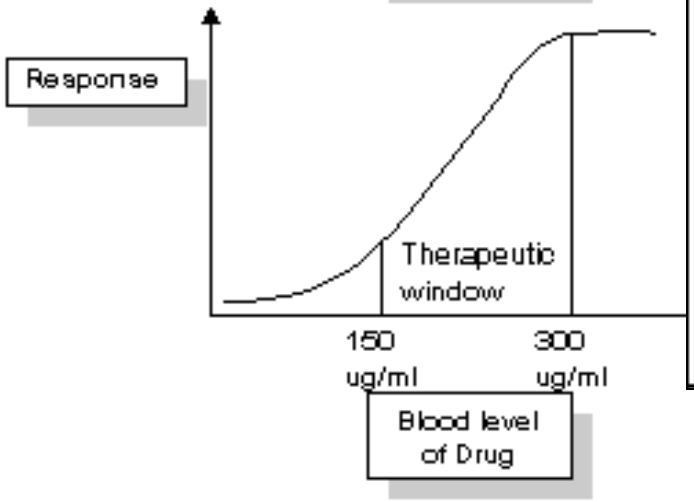
Effects on the serotonergic system are also important in determining antidepressant activity. Most types of antidepressants ultimately reduce 5TH-2 receptor binding. A notable exception is ECT, which upregulates 5HT-2 receptors.

Receptor affinity and side effects

Agent	Alpha 1	Alpha 2	Histamine 1	anticholinergic/muscarinic site	Dopamine 2
Imipramine	++	**0**	+	++	**0**
Desipramine	+	**0**	**0**	+	**0**
Amitriptyline	+++	±	++++	++++	**0**
Nortriptyline	+	**0**	+	++	**0**
Clomipramine	++	**0**	+	++	**0**
Trimipramine	++	±	+++	++	+
Doxepin	++	**0**	+++	+++	**0**

enlarged prostate
narrow angle glaucoma
patients with unsteady gaits
paralytic ileus
arrhythmias with AV node blocks
poorly controlled seizures





Psychiatric side effects	sedation, induction of mania in bipolar patients, confusion, decreased memory, anticholinergic delirium
Neurologic side effects	sedation, blurred vision due to dilation of the pupil(avoid in patients with narrow angle glaucoma), myoclonic twitches, tremors, rare plasies, paresthcesias, ataxia, extrapyramidal symptoms (especially with Amoxapine due to DA blockade see chart above) seizures (maprotiline is especially known for this at doses above 225mg/day)
Cardiac effects	Orthostatic hypotension, tachycardia (reflex to the orthostasis), prolonged QT intervals (quinidine like effect), avoid in patients with preexisting blocks, flattened T waves
Allergic and	erythematous rashes, rare jaundice,

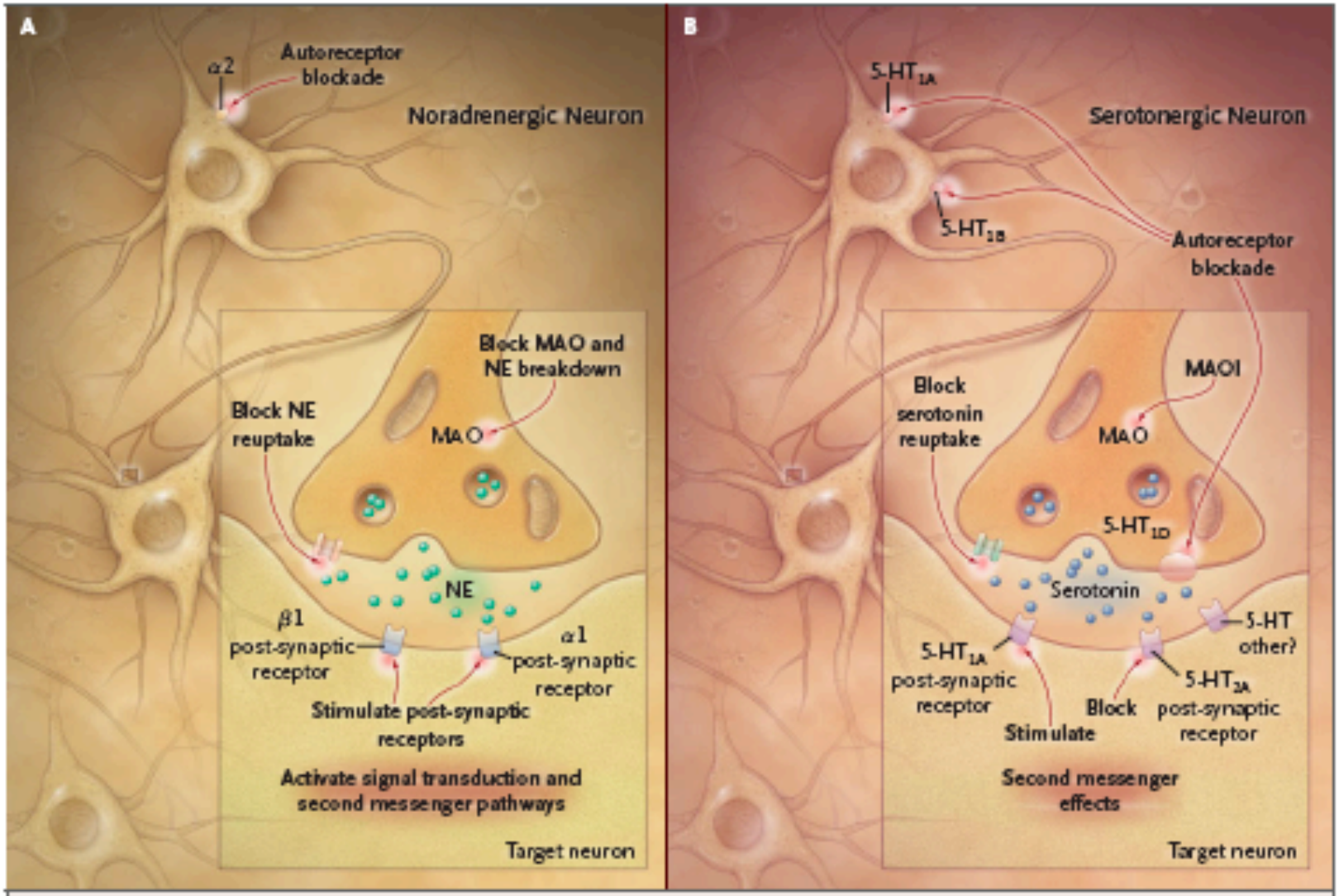
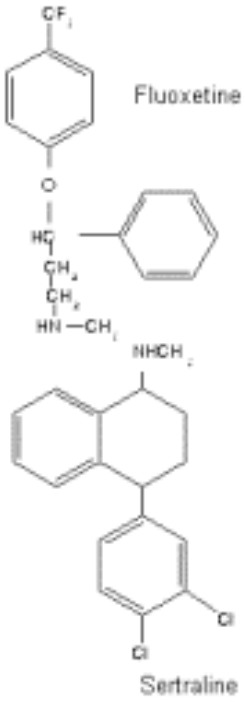
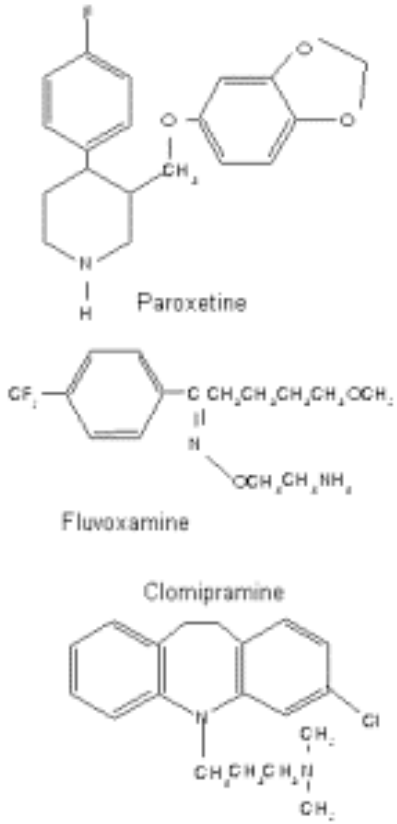


Figure 1. Targets of Antidepressant Action on Noradrenergic and Serotonergic Neurons.

In Panel A, targets of action for antidepressants in the noradrenergic system can enhance activity by blockade of the α_2-adrenergic autoreceptor, blockade of norepinephrine (NE) reuptake at the synaptic cleft, stimulation of α_1-adrenergic and β_1-adrenergic postsynaptic receptors, activation of signal transduction and second-messenger pathways, and blockade of monoamine oxidase (MAO), the enzyme involved in NE breakdown. In Panel B, targets of action for antidepressants in the serotonergic system can enhance activity by blockade of 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} autoreceptors; blockade of serotonin reuptake at the synaptic cleft; activation of the 5-HT_{1A} postsynaptic receptor; activation of signal transduction and second-messenger pathways; and blockade of the 5-HT_{2A} postsynaptic receptor. Monoamine oxidase inhibitors (MAOIs) function by blockade of MAO, the enzyme involved in serotonin breakdown.





CNS	Gastrointestinal	Sexual
Headache mild stimulation (occasionally aggitation)* Dattime drowsiness and insomnia* fatigue* anxiety* tremor myolonus anorexia	Diarrhea Nausea vomitting	Anorgasmia reduced libido* Abnormmal ejaculation or orgasm

Box 3 | **Animal models of depression and antidepressant action**

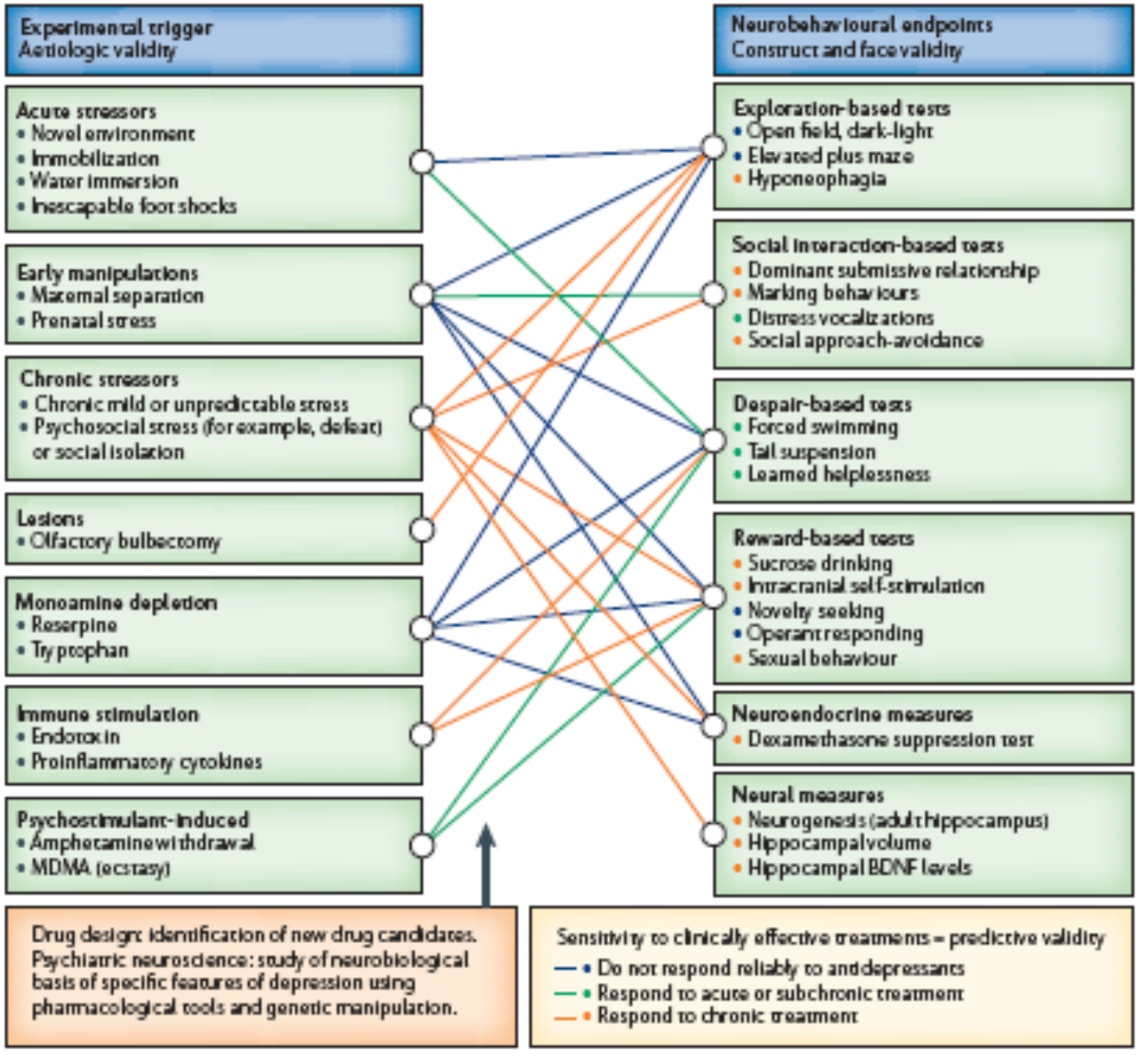
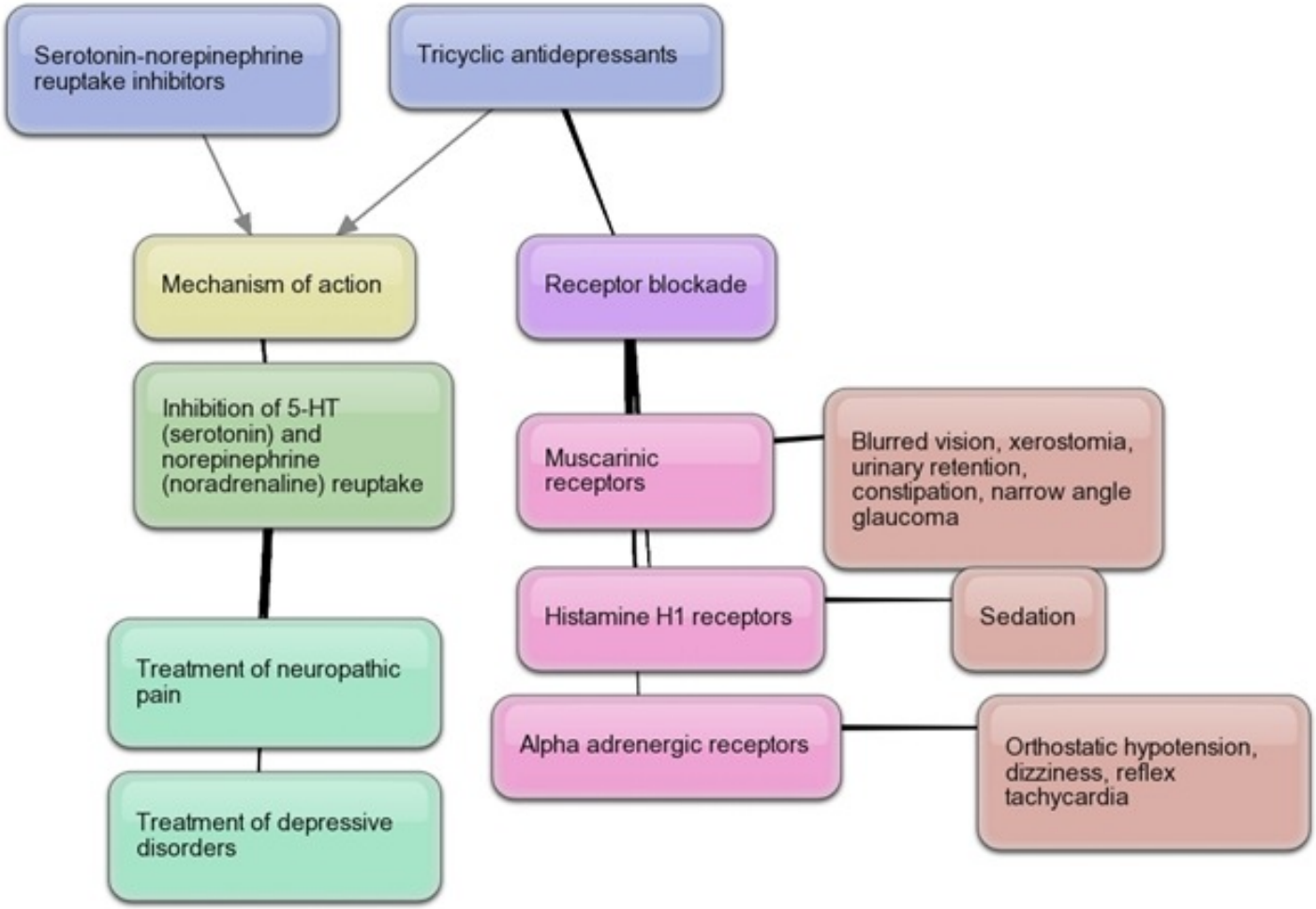


Table 3. Treatments for Bipolar Disorder.*

Drug Class and Agent	Dose	Research or Approval				Side Effects and Warnings
		Depression	Mania	Mixed Symptoms	Maintenance Therapy	
Atypical antipsychotic agent						Warnings for increased risk of death among elderly patients with dementia-related psychosis, neuroleptic malignant syndrome, tardive dyskinesia, hyperglycemia or diabetes, and seizures
Aripiprazole†	For acute mania or maintenance therapy, 15–30 mg/day	Controlled studies do not support use as monotherapy	FDA-approved	FDA-approved	FDA-approved	Extrapyramidal side effects, somnolence, and tremor
Asenapine†	For acute mania, 10 mg twice daily sublingually		FDA-approved	FDA-approved		Extrapyramidal side effects, weight gain, somnolence, and dizziness
Olanzapine†	For acute mania, 10–20 mg/day; for maintenance therapy, 5–20 mg/day	Controlled study supports use as monotherapy	FDA-approved	FDA-approved	FDA-approved	Extrapyramidal side effects, weight gain, dry mouth, dizziness, tremor, and gastrointestinal side effects; additional warnings for hyperlipidemia and hyperprolactinemia
Quetiapine and quetiapine, extended release†‡	For acute mania or maintenance therapy, 400–800 mg/day; for depression, 300–600 mg/day	FDA-approved	FDA-approved	FDA-approved	FDA-approved	Extrapyramidal side effects, weight gain, dry mouth, fatigue, and gastrointestinal side effects; additional warning for hyperlipidemia
Risperidone						
Oral†	For acute mania, 1–6 mg/day		FDA-approved	FDA-approved		Extrapyramidal side effects, somnolence, and gastrointestinal side effects; additional warning for hyperprolactinemia
Intramuscular§	25 mg every 2 wk				FDA-approved	
Ziprasidone‡	For acute mania or maintenance therapy, 80–120 mg/day	Controlled studies do not support use as adjunct or monotherapy	FDA-approved	FDA-approved	FDA-approved	Extrapyramidal side effects, somnolence, dizziness, asthenia, abnormal vision, and vomiting; additional warnings for QT prolongation and rash
Olanzapine–fluoxetine combination	6–12 mg and 25–50 mg once a day	FDA-approved				Fluoxetine associated with increased risk of suicidal thoughts and actions among some children, teenagers, and young adults
Antiepileptic drug						
Carbamazepine, extended release	For acute mania, 400–1600 mg in divided doses twice daily		FDA-approved	FDA-approved		Dizziness, somnolence, and coordination problems; warnings for serious rash, including Stevens–Johnson syndrome and toxic epidermal necrolysis (the risk of these two conditions is higher among patients with the HLA-B*1502 allele), agranulocytosis, suicidal ideation, teratogenicity, and aplastic anemia
Divalproex sodium, delayed or extended release	For acute mania, 25 mg/kg/day, with dose adjusted to obtain clinical response (85–125 μg/ml)	Meta-analysis supports use as monotherapy	FDA-approved	FDA-approved		Somnolence, gastrointestinal side effects, and dizziness; warnings for hepatotoxicity, pancreatitis, teratogenicity, thrombocytopenia, suicidal ideation, hyperammonemia, and hyperammonemic encephalopathy
Lamotrigine	Maintenance dose, 200–400 mg once a day	Meta-analysis supports use as monotherapy			FDA-approved	Headache, somnolence, nausea, fatigue, and insomnia; warnings for serious rash (including Stevens–Johnson syndrome and toxic epidermal necrolysis), hypersensitivity reaction, suicidal ideation, and aseptic meningitis
Lithium	For acute mania, gradually increase dose to obtain clinical response (0.8–1.2 mmol/liter)		FDA-approved		FDA-approved	Renal and thyroid dysfunction (baseline and periodic monitoring of renal and thyroid function recommended); lithium toxicity closely related to serum lithium levels

* FDA denotes Food and Drug Administration.
† This agent is indicated as both monotherapy and an adjunct to lithium or divalproex sodium for manic or mixed symptoms.
‡ This agent is indicated only as an adjunct to lithium or divalproex sodium for maintenance (i.e., prevention of manic, mixed, hypomanic, or depressive episodes).
§ This agent is indicated as both monotherapy and an adjunct to lithium or divalproex sodium for maintenance therapy (i.e., prevention of manic, mixed, hypomanic, or depressive episodes).


Serotonin-norepinephrine reuptake inhibitors
Tricyclic antidepressants
Mechanism of action
Receptor blockade
Inhibition of 5-HT (serotonin) and norepinephrine (noradrenaline) reuptake
Muscarinic receptors
Blurred vision, xerostomia, urinary retention, constipation, narrow angle glaucoma
Histamine H1 receptors
Sedation
Treatment of neuropathic pain
Alpha adrenergic receptors
Orthostatic hypotension, dizziness, reflex tachycardia
Treatment of depressive disorders