Pharmacokinetic and Pharmacodynamic Differences Among Antidepressants

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Financial Disclosures

- Medical Director, Brain Health
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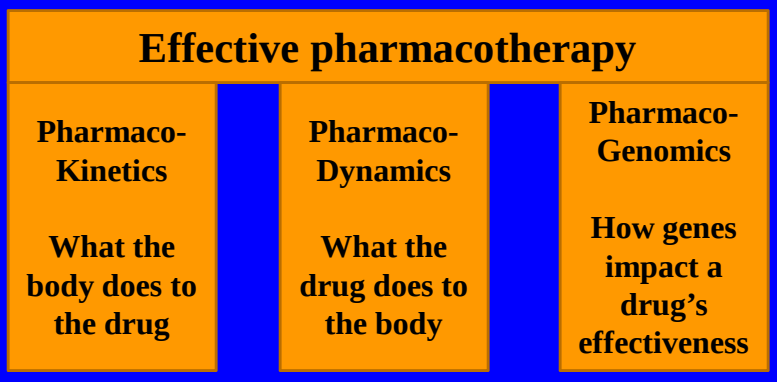
- Consulting Psychiatrist, Exeter Hospital, Exeter, NH
- Volunteer consultant to the Insight Meditation Society Barre, MA
- Speaker/consultant for Millennium Health
- Speaker/consultant for AstraZeneca
- Speaker/consultant for Sunovion
- Speaker for Forest (Actavis/Allergan)
- Speaker/consultant for Takeda/Lundbeck
- Speaker/consultant for Otsuka/Lundbeck

The handout for this presentation is available in full color, two slides per page for easy viewing, and downloadable at my website's homepage:

www.brain-health.co/

Three pillars of knowledge for rational medication prescribing



The Wiring of the Brain

- There are approximately 100 billion neurons in the human brain.
- There are on average 10,000 synapses/neuron
- Hence, there are approximately 1,000 trillion synapses. in the human brain = one quadrillion synapse/brain.

Carey, Nessa; The Epigenetics Revolution; New York; Columbia University Press; 2012

Part 1

The history of psychiatric drug discovery and our earliest psychiatric medications:

a case of serendipity

A long, long time ago
(about 14 billion years ago) . . .
In our very own universe . . .
An event occurred that lasted
one trillionth of one trillionth of one second . . .

And was named after a great TV show . . .

The Big Bang

Following the Big Bang, there were only three elements in the entire universe:

Hydrogen, Helium and Lithium

(over time, giant clouds of these 3 primordial elements accreted through gravitational forces to create stars and galaxies, and the additional 115 elements were created by strong forces within stars)

Mood Stabilizer - Lithium: our oldest psychiatric medication

- Reportedly used in spring water to treat mania in the Roman and Greek eras.
- 19th century used to treat gout.
- 1870s used to treat mania in USA and Denmark.
- 1900 lithium abandoned as a medication because pharmaceutical companies could not patent it.

Mood Stabilizer - Lithium: our oldest psychiatric medication

- 1949 Australian psychiatrist John Cade rediscovered the effectiveness of Li salts in the treatment of mania.
- 1970 FDA approved for mania.
- 1974 FDA approved for the prevention of manic-depressive disorder.

Clue about depression - Reserpine:
an antihypertensive that lowers blood pressure by depleting norepinephrine

- 1952 Indian snakeroot (Rauwolfia serpentina) was found to contain reserpine.
- 1954 reserpine was introduced in the USA.
- Norepinephrine depletion was associated with increased depression.
- Contributed significantly to the "monoamine depletion hypothesis of depression" (norepinephrine, dopamine and serotonin).

First Antidepressant - Iproniazid

- 1952 researchers observed that patients treated with isoniazid for tuberculosis became "inappropriately happy".
- Structure was modified, and in 1958 iproniazid was FDA approved as the first antidepressant.
- 1961 withdrawn from the US market due to liver toxicity.
- Mechanism of action is that of a monoamine oxidase inhibitor (MAOI). Raises levels of norepinephrine, dopamine and serotonin.
- Followed by the MAOIs Nardil and Parnate.

Monoamine Hypothesis of Depression

- All current FDA approved antidepressants work by modulating some aspect of the three monoamines serotonin, norepiniphrine and dopamine.

Monoamines are important neurotransmitters

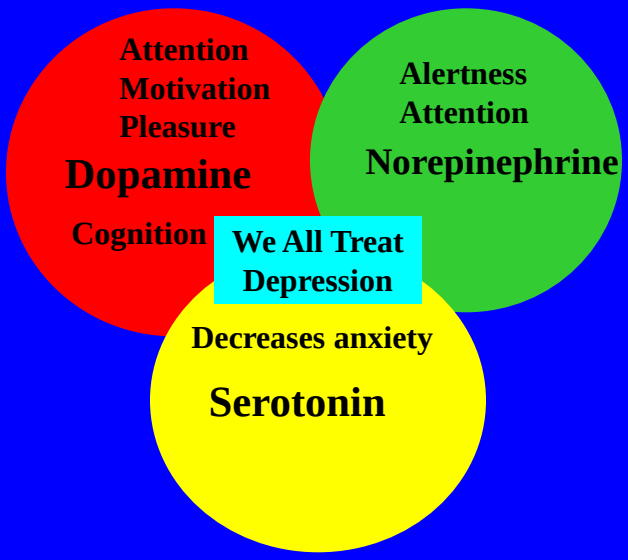
- Serotonin
- Dopamine
- Norepinephrine
- Epinephrine
- Melatonin
- Histamine

The fact that many psychiatric medications can bind to multiple structurally similar receptors helps us understand the etiology to the burden of side effects from psychiatric medications.

Current Medications FDA Approved to Treat Major Depression: Three important monoamine neurotramsmitters

- **Serotonin**
- **Dopamine**
- **Norepinephrine**

Three Important Neurotransmitters



Part 2

An overview of the mechanism of action of current psychiatric medications.

Neurotransmitters, medications, and how they communicate with neurons to create change in the way the brain functions.

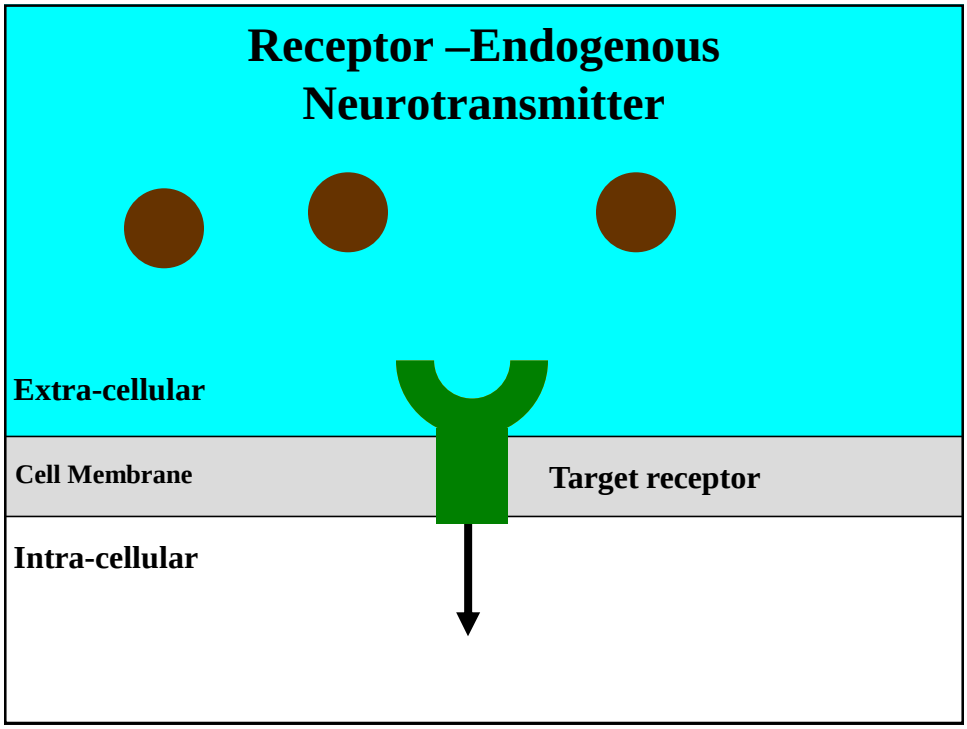
Our evolving understanding of how psychiatric medications work:

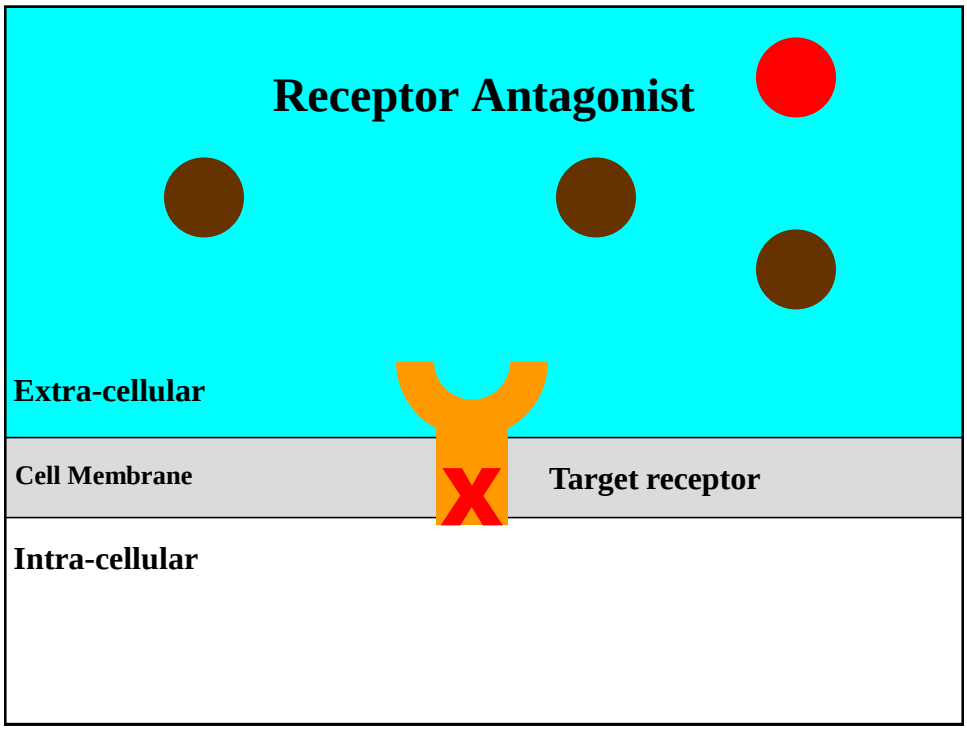
1) mechanism of action at the cellular level

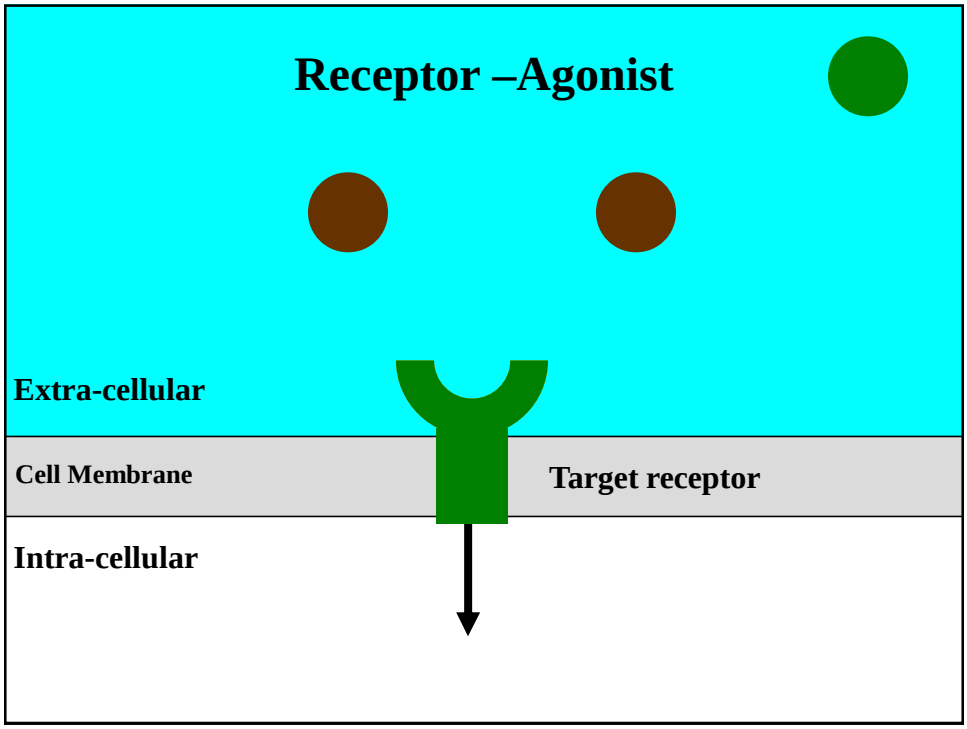
2) mechanism of action at the level of circuits

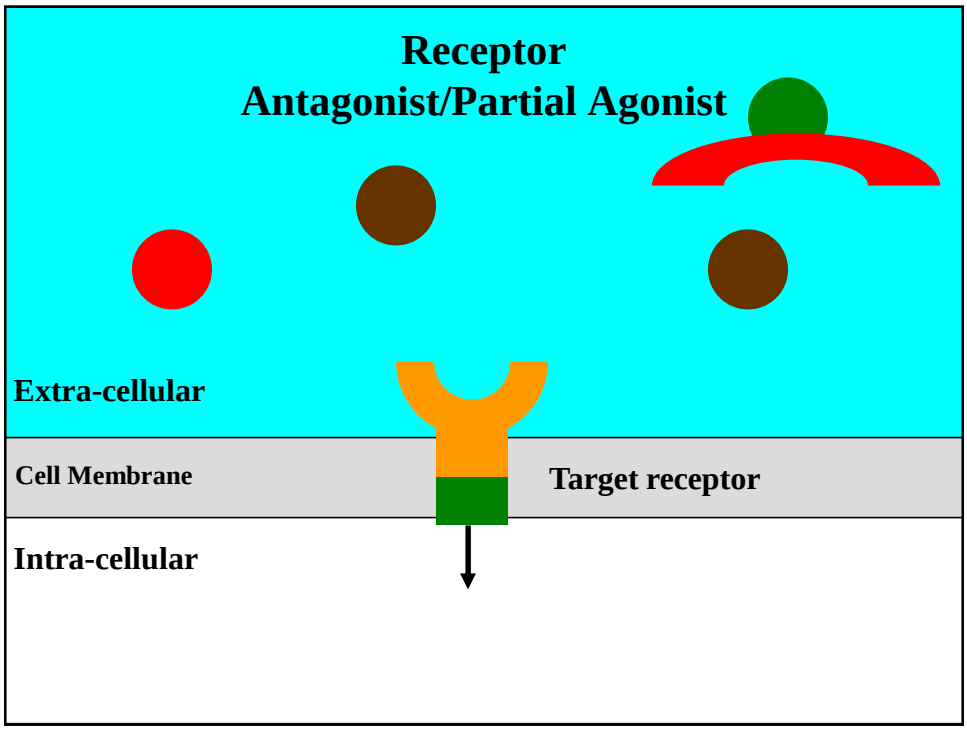
Basic mechanism of action of some psychiatric medications.

- Mechanism of action at the cellular level.
- Research paradigm shift after the completion of the sequencing of the human genome in 2003.
- Effects on receptors at the neuronal surface.
- Effects in the intracellular environment.
- Effects on the information flow through circuits of different types of neurons


Receptor –Endogenous Neurotransmitter
Extra-cellular
Cell Membrane
Target receptor
Intra-cellular


Receptor Antagonist
Extra-cellular
Cell Membrane
Target receptor
Intra-cellular


Receptor –Agonist
Extra-cellular
Cell Membrane
Target receptor
Intra-cellular

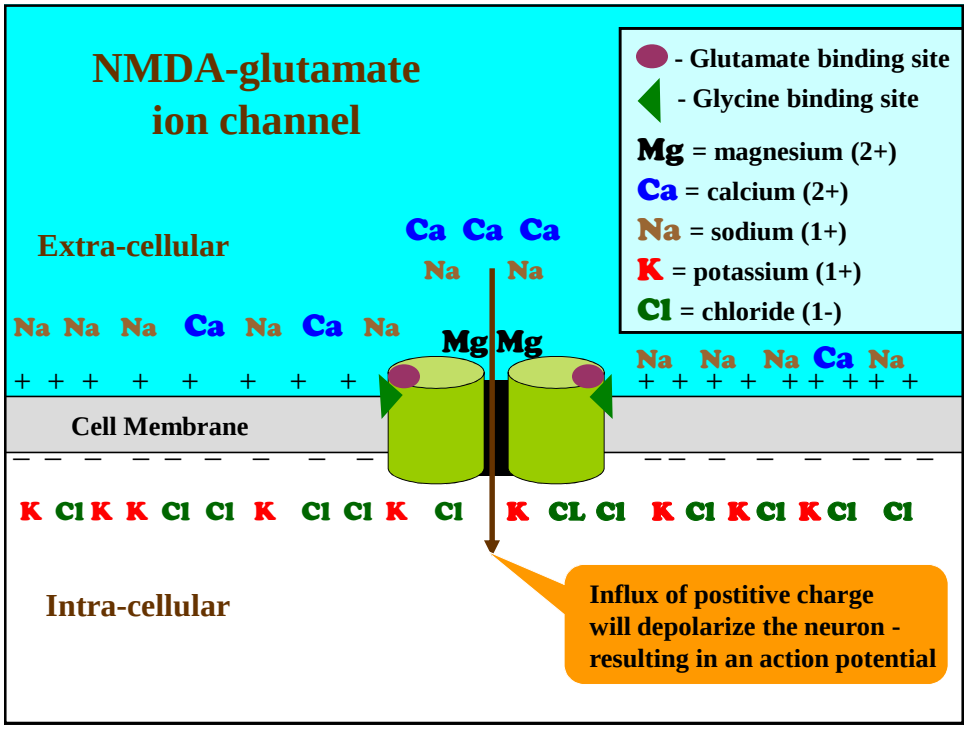

Receptor
Antagonist/Partial Agonist
Extra-cellular
Cell Membrane
Target receptor
Intra-cellular

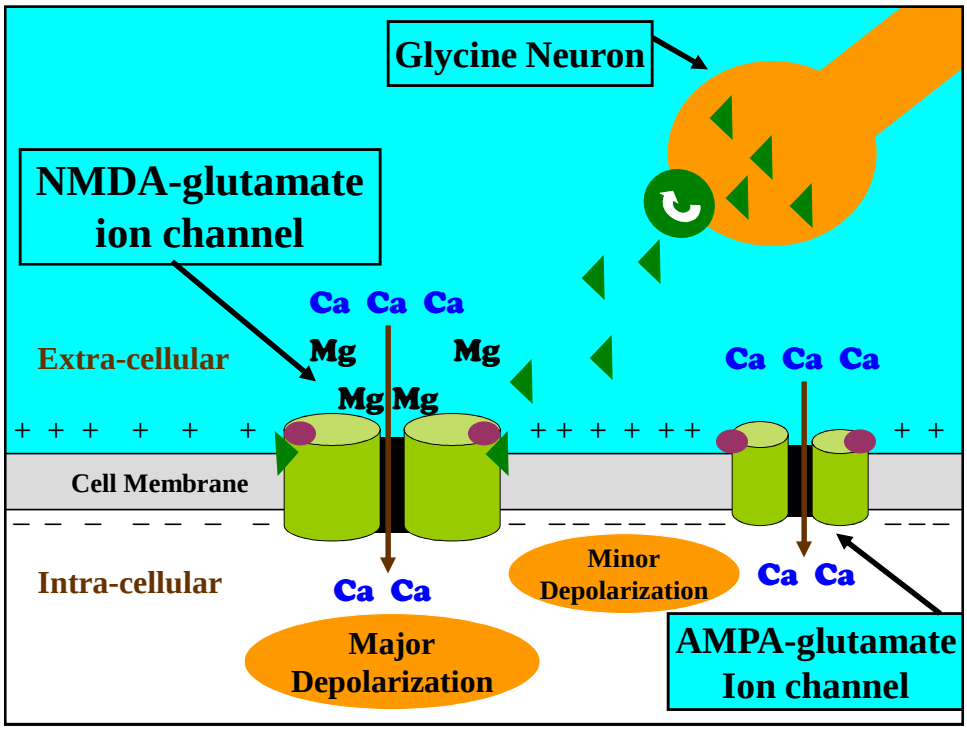
Ionotropic Receptors

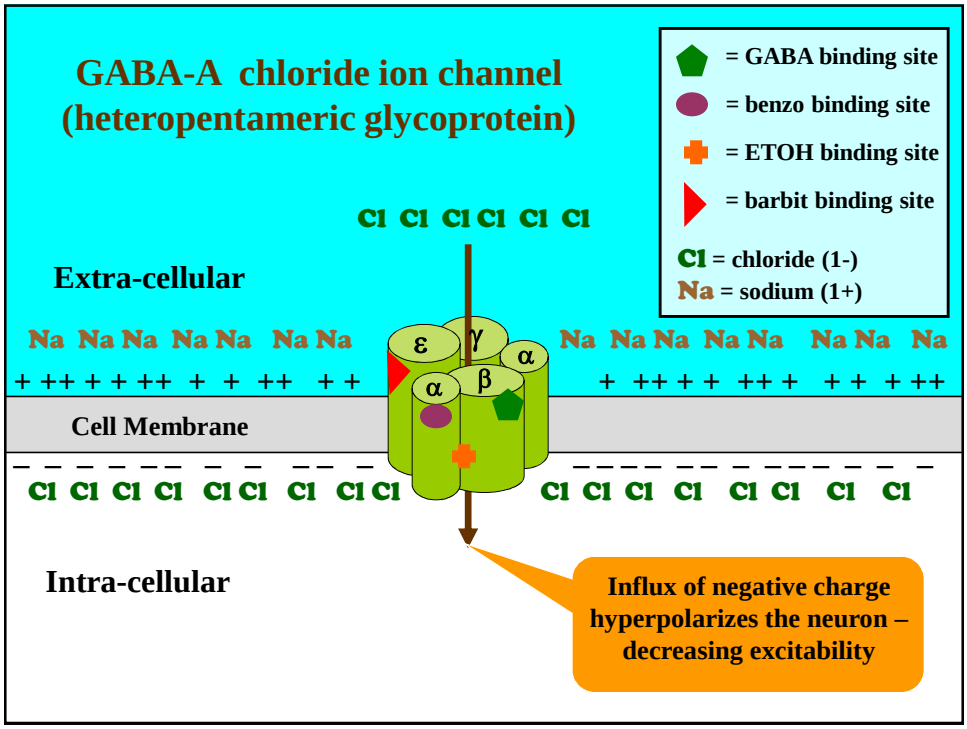
- Receptors that open or close ion channels, altering the influx or efflux of charged ions.
- Response occurs in milliseconds.
- Result is a change in the polarization of a cell: depolarization or hyperpolarization.

Two significant ionotropic receptor systems

- Glutamate
  - The primary excitatory neurotransmitter
  - NMDA-glutamate receptors manage influx of positive charge into neurons (Ca++, Na+) – this is the receptor that ketamine antagonizes
- GABA (gamma-amino butyric acid)
  - The primary inhibitory neurotransmitter
  - GABA-A receptors manage the influx of negative charge into neurons (Cl-)

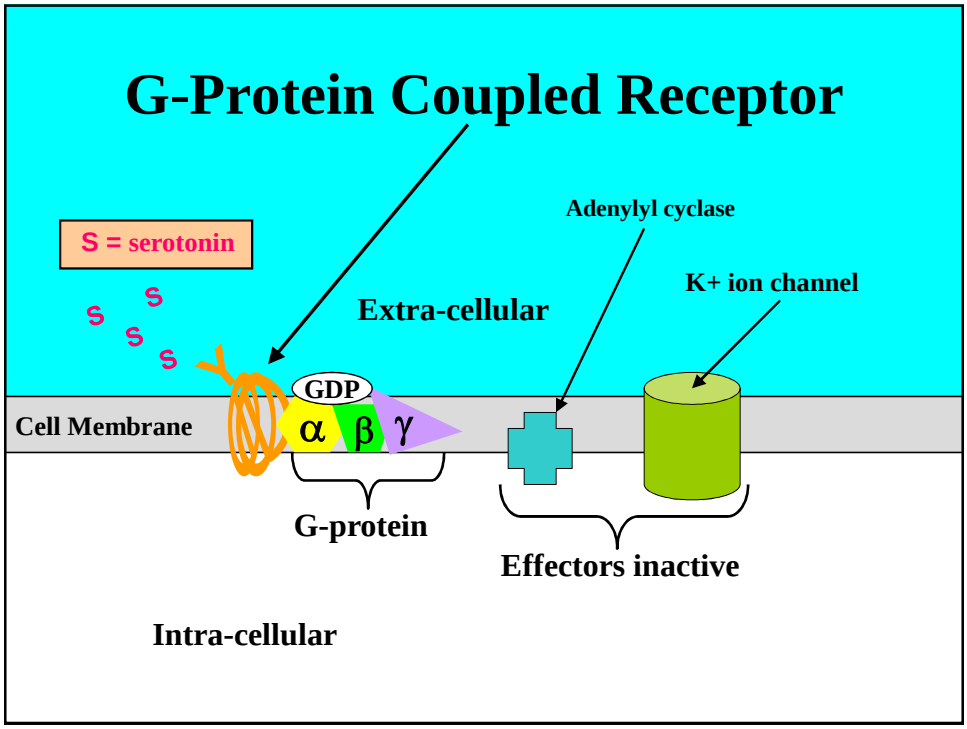

NMDA-glutamate
ion channel
- Glutamate binding site
- Glycine binding site
Mg = magnesium (2+)
Ca = calcium (2+)
Na = sodium (1+)
K = potassium (1+)
Cl = chloride (1-)
Extra-cellular
Ca Ca Ca
Na Na
Na Na Na Ca Na Ca Na
Mg Mg
Na Na Na Ca Na
Cell Membrane
K Cl K K Cl Cl K Cl Cl K Cl
K Cl Cl K Cl K Cl K Cl Cl
Intra-cellular
Influx of postitive charge
will depolarize the neuron -
resulting in an action potential

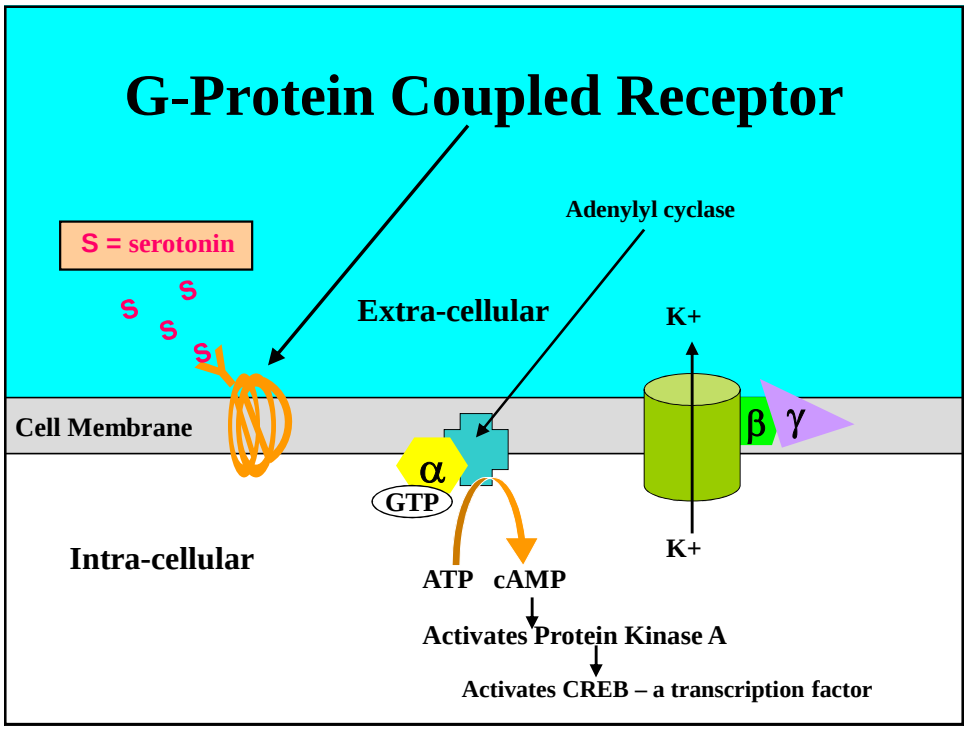

Glycine Neuron
NMDA-glutamate
ion channel
Ca Ca Ca
Extra-cellular
Mg
Mg
Mg Mg
Ca Ca Ca
Cell Membrane
Intra-cellular
Ca Ca
Minor
Depolarization
Ca Ca
Major
Depolarization
AMPA-glutamate
Ion channel

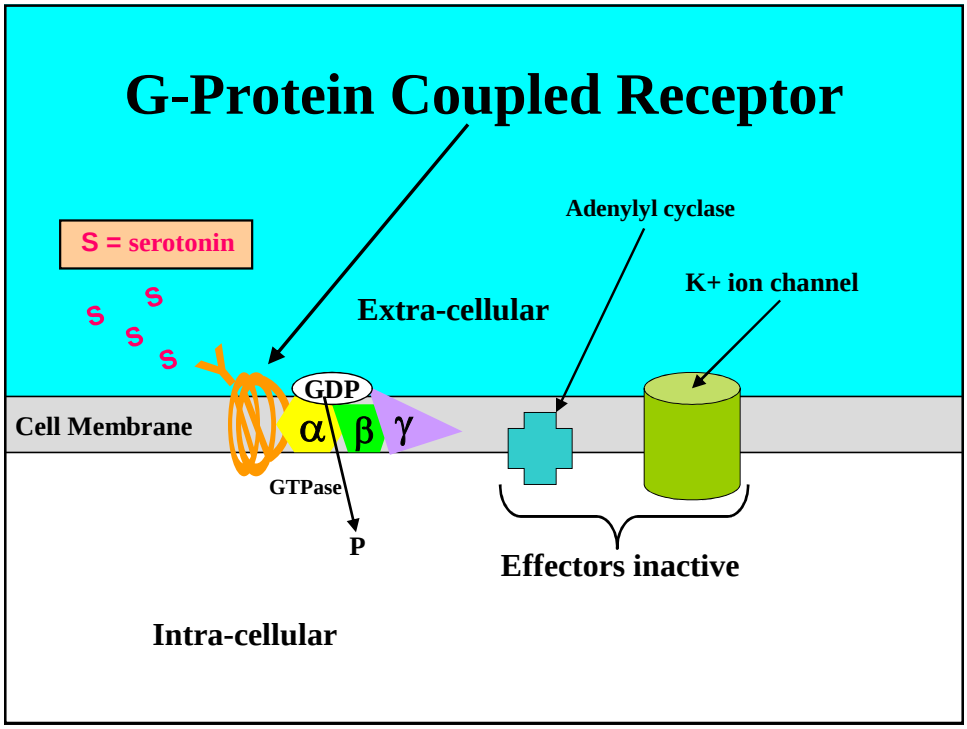


Metabotropic Receptors

- Receptors that mediate their response through secondary messenger systems.
- These receptors include the large population of "G-Protein Coupled Receptors", which may constitute 80% of all human receptors.
- Initial response takes seconds, but the final result may take days, weeks or even months.
- G-Protein Coupled Receptors allow for an amplification of the original signal up to 10,000 fold.

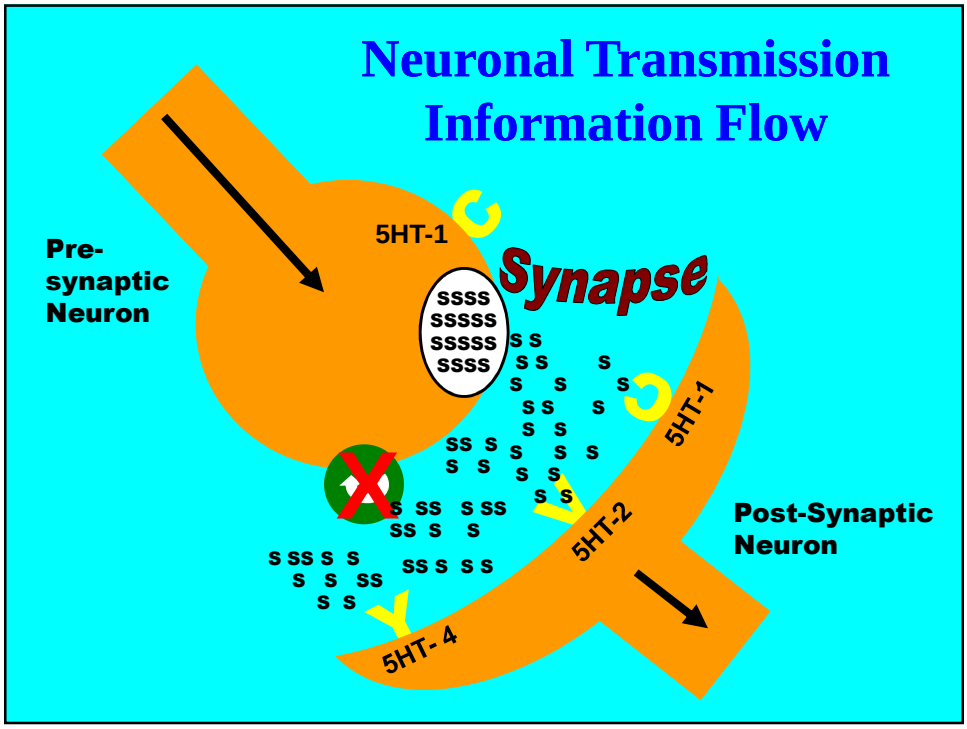

G-Protein Coupled Receptor
S = serotonin
S
S
S
S
Extra-cellular
Adenylyl cyclase
K+ ion channel
GDP
Cell Membrane
α
β
γ
G-protein
Effectors inactive
Intra-cellular

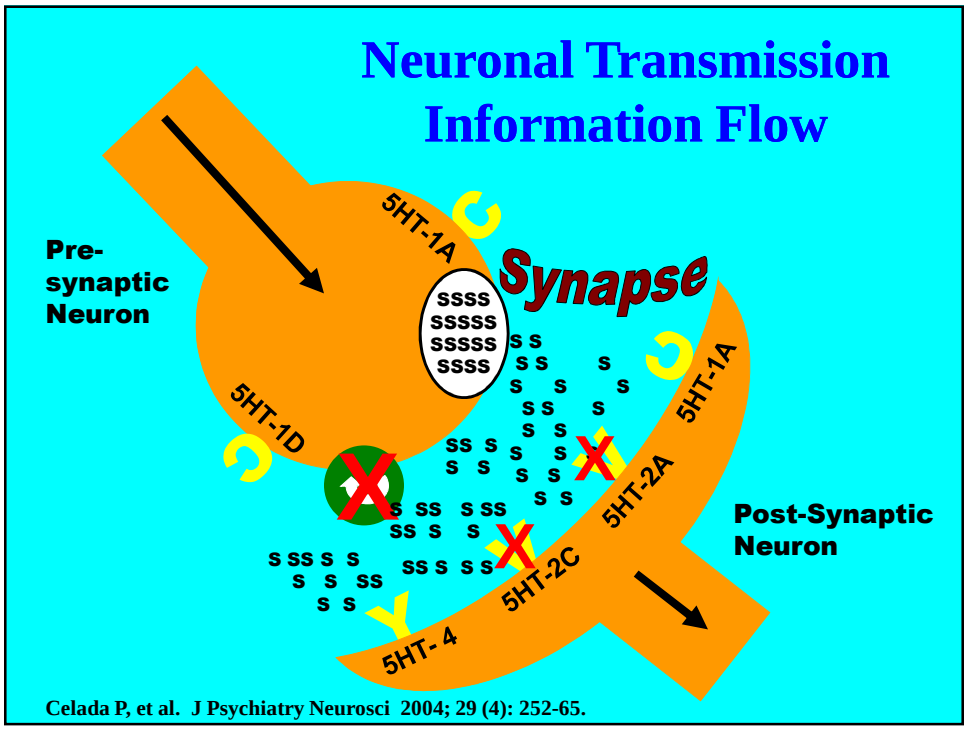

G-Protein Coupled Receptor
S = serotonin
S
S
S
S
Extra-cellular
Adenylyl cyclase
K+
Cell Membrane
β
γ
α
GTP
K+
Intra-cellular
ATP
cAMP
Activates Protein Kinase A
Activates CREB – a transcription factor

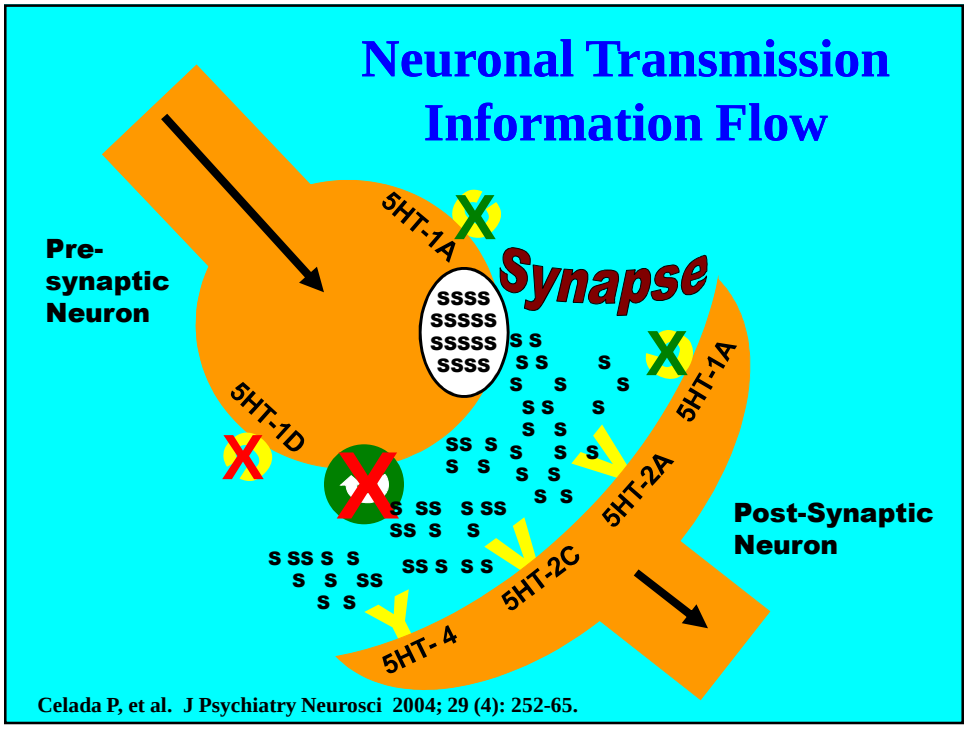


A close up view of a

synapse


Neuronal Transmission
Information Flow
Pre-
synaptic
Neuron
5HT-1
Synapse
5HT-1
5HT-2
5HT- 4
Post-Synaptic
Neuron


Neuronal Transmission
Information Flow
Pre-
synaptic
Neuron
5HT-1A
Synapse
5HT-1D
5HT-1A
5HT-2A
5HT-2C
5HT- 4
Post-Synaptic
Neuron
Celada P, et al. J Psychiatry Neurosci 2004; 29 (4): 252-65.



The Serotonin System

- **Serotonin = 5-HT – needs to be synthesized**
  - **Folic acid does not cross the blood-brain-barrier**
  - **Folic acid is metabolized by a multi-step process, with the critical point involving the final methylation by Methylene TetraHydroFolate Reductase (MTHFR) to form L-methyl-folate**
  - **L-methyl-folate is a carbon donor that contributes to the synthesis of serotonin (and dopamine/norepinephrine)**
- **Serotonin transporter = 5-HTT**
  - **Two promoter sequences: short & long**
  - **Two 5-HTT genes = 4 genotypes**
  - **s,s; l,l; s,l; l,s**
- **Serotonin receptors**
  - **Seven families = 5-HT-1, 2, 3, 4, 5, 6 and 7**

Serotonin Receptor Families

- 5-HT 1A, B, D, E, F – these are inhibitory
- 5-HT 2A, B, C
- 5-HT 3A, B
- 5-HT 4A, B, C, D, E, F, H
- 5-HT 5A, B – these are inhibitory
- 5-HT 6
- 5-HT 7

Adayev T et al. *Biosci Rep*. 2005 Oct-Dec;25(5-6):363-85
Pytliak M. 2011. *Physiol Res.* 60: 15-25.
Stahl SM. Stahl's Essential Psychopharmacology. 2008.
Khan A. *Expert Opin Investig Drugs*. 2009; 18: 1753-1764.
Barnes NM and Sharp T. *Neuropharmacology*. 1999: 38: 1083-1152.

Serotonin Receptor Classes

- Metabotropic = GPCR
  (G-Protein Coupled Receptors)
  - All except 5-HT 3
- Ionotropic = 5-HT-Gated Ion-Channel
  - Only 5-HT 3
  - Permeable to monovalent cations
  - Includes Na+, K+, Li+ and NH4+

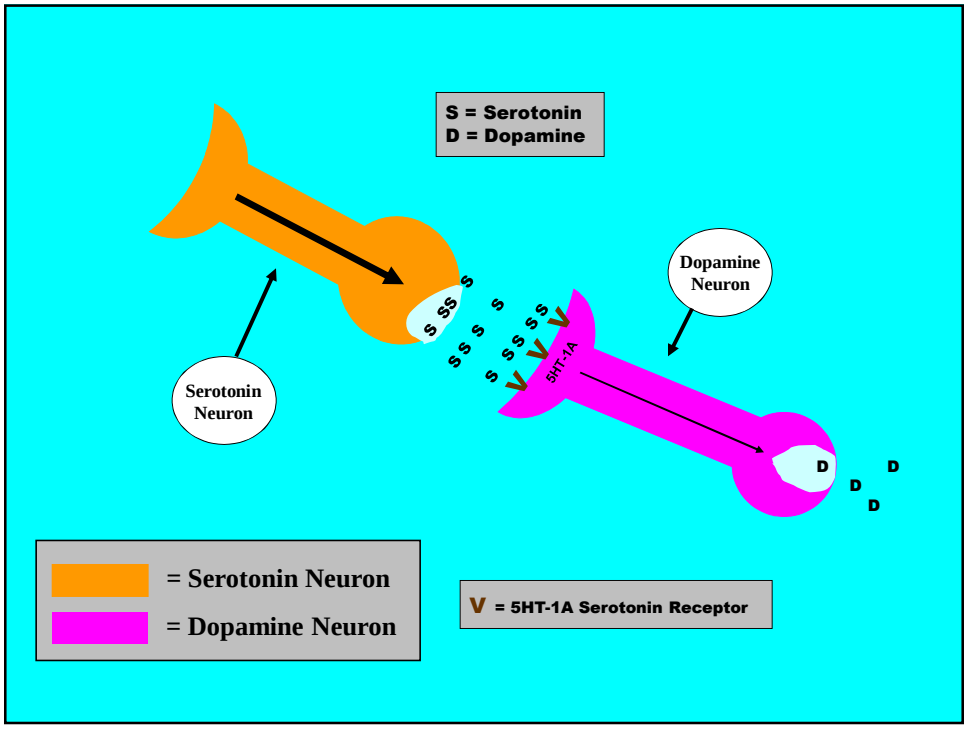
Adayev T et al. Biosci Rep. 2005 Oct-Dec;25(5-6):363-85

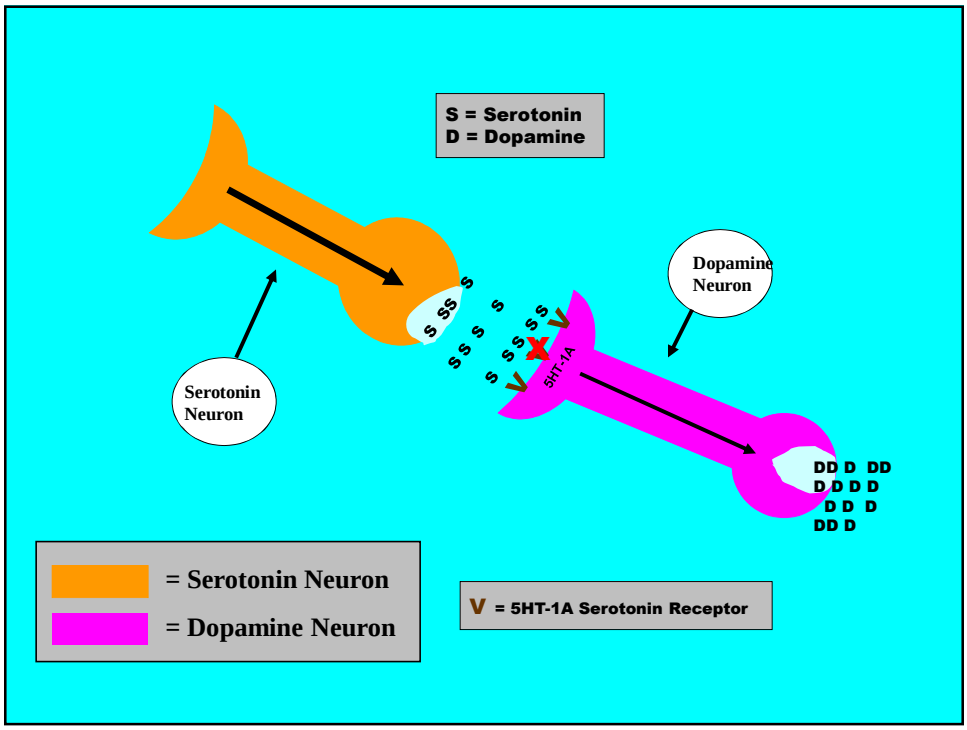
From receptors . . .

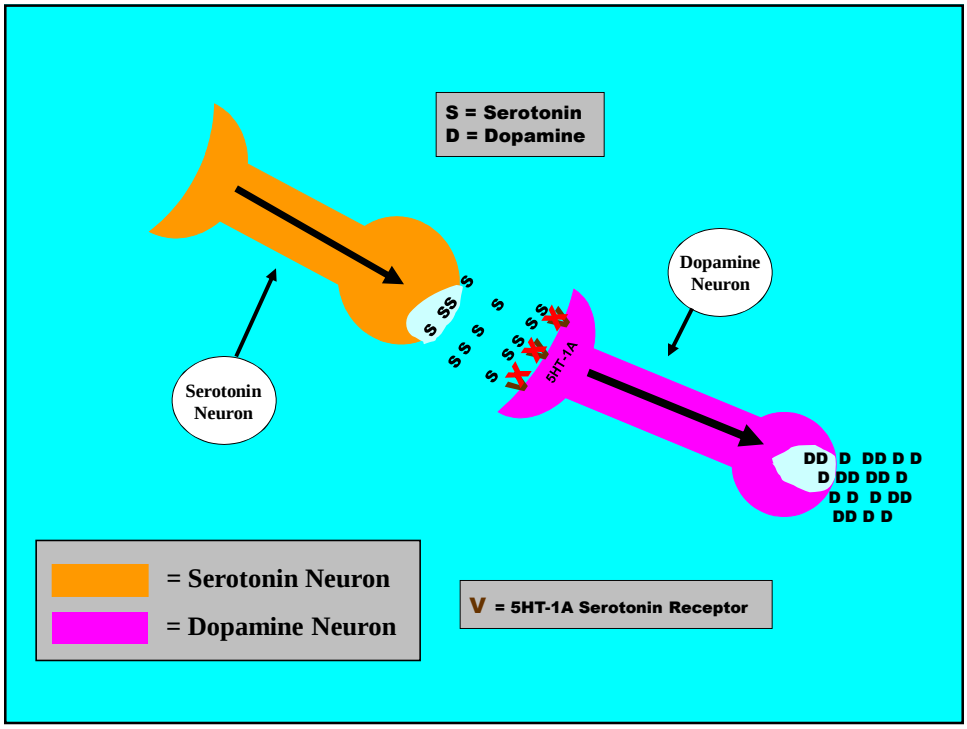
To . . .

Circuits

A serotonin neuron modulating a dopamine neuron

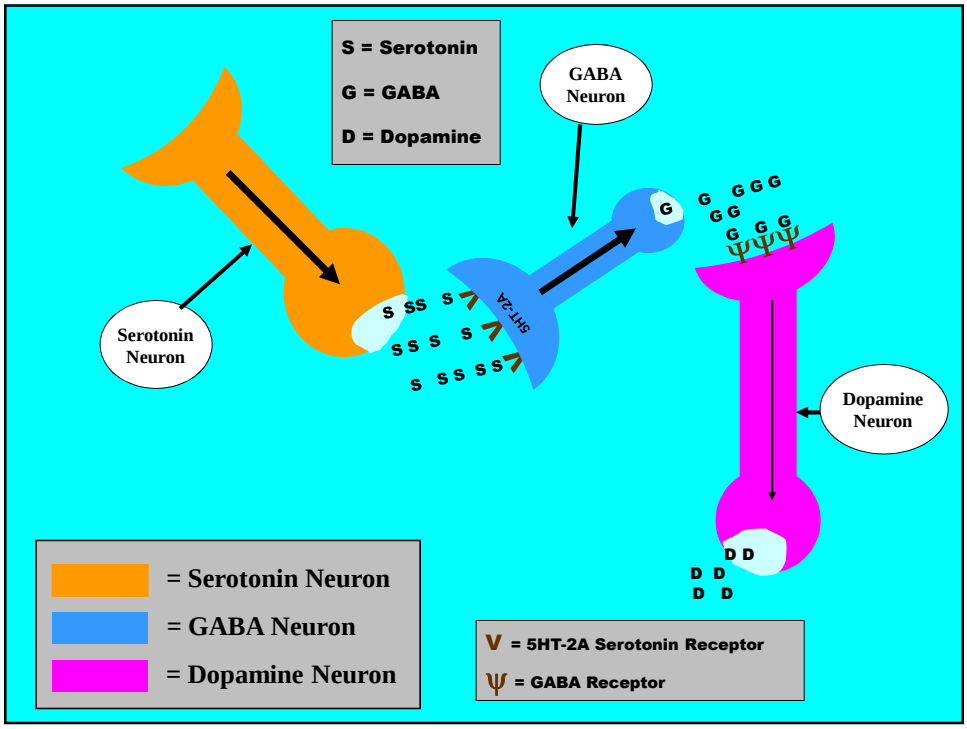

S = Serotonin
D = Dopamine
Dopamine Neuron
Serotonin Neuron
5HT-1A
= Serotonin Neuron
= Dopamine Neuron
V = 5HT-1A Serotonin Receptor

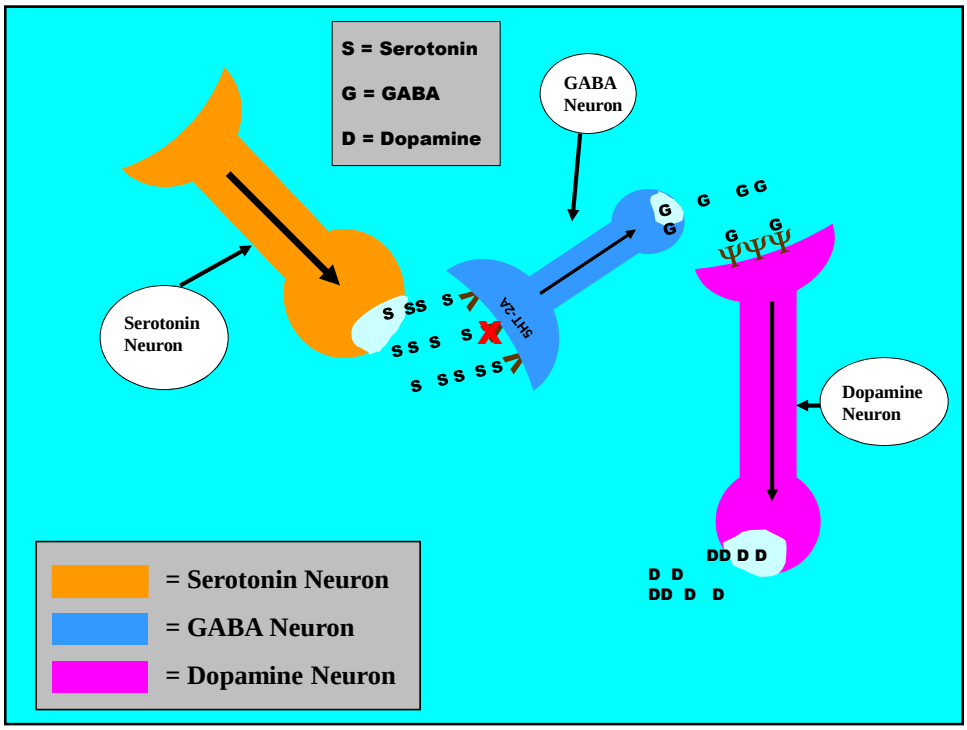

S = Serotonin
D = Dopamine
Dopamine Neuron
Serotonin Neuron
5HT-1A
= Serotonin Neuron
= Dopamine Neuron
V = 5HT-1A Serotonin Receptor

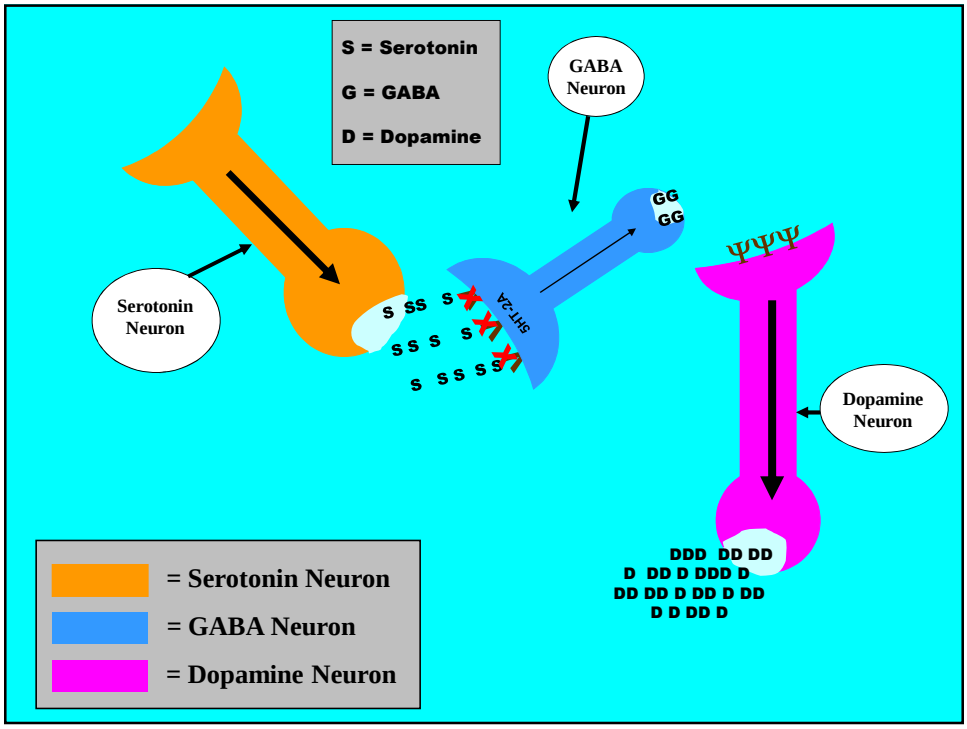


A serotonin neuron modulating a domapine neuron

through **a GABA (gamma-amino butyric acid) inter-neuron**

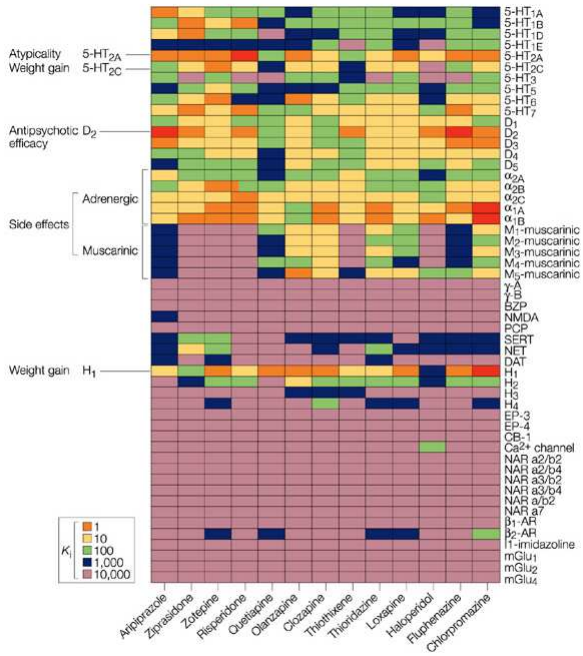

S = Serotonin
G = GABA
D = Dopamine
GABA Neuron
Serotonin Neuron
Dopamine Neuron
5HT-2A
= Serotonin Neuron
= GABA Neuron
= Dopamine Neuron
V = 5HT-2A Serotonin Receptor
Ψ = GABA Receptor


S = Serotonin
G = GABA
D = Dopamine
GABA Neuron
Serotonin Neuron
Dopamine Neuron
5HT-2A
= Serotonin Neuron
= GABA Neuron
= Dopamine Neuron



Psychiatric Medications Today

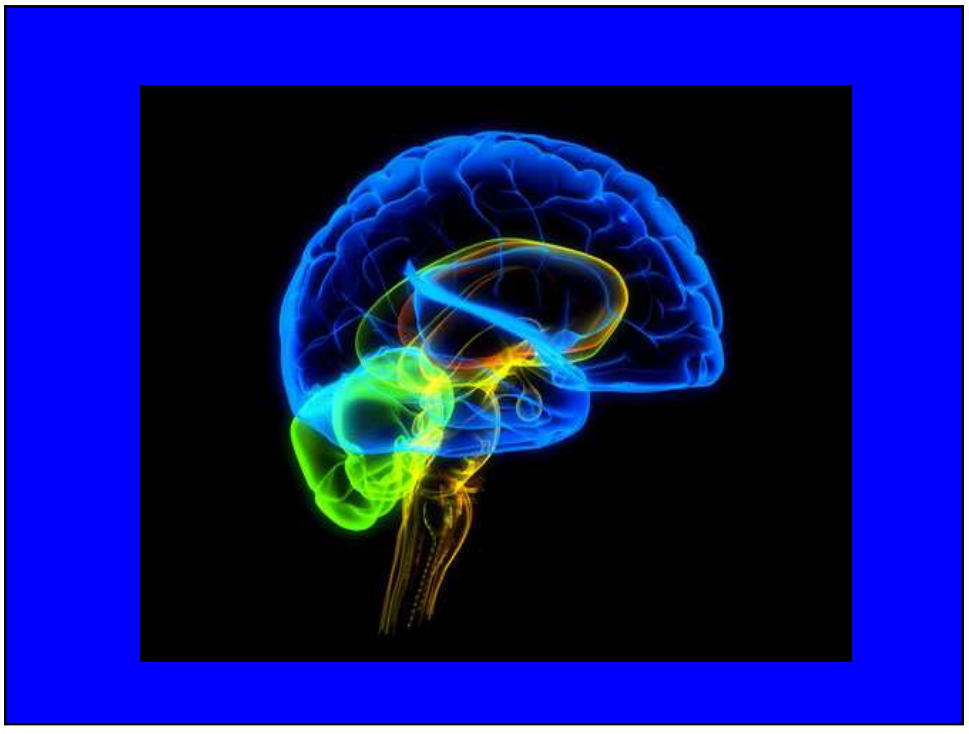
From Serendipity:
To Molecular "fingerprinting"



53 receptors

***Roth BL, Sheffler DJ and Kroeze WK. Nat Rev Drug Discov. 2004 Apr;3(4):353-9**

Nature Reviews | Drug Discovery



Part 3

Our current medication portfolio for the pharmacological treatment of Major Depressive Disorder:

Pharmacodynamics of Antidepressants

Targeting "symptoms" or treating a "diagnosis".

- Patient with "Major Depressive Episode" could present with:
  - Insomnia OR hypersomnia
  - No appetite/weight loss OR hyperphagia
  - Psychomotor retardation OR activation
  - Severe worry/anxiety OR extreme apathy
  - Choose treatment based on symptoms, not diagnosis.

Antidepressants

- Classes:
  - Monoamine oxidase inhibitors (5)
  - Tricyclic Antidepressants (10)
  - Selective Serotonin Reuptake Inhibitors (6)
  - Serotonin Norepinephrine Reuptake Inhibitors (4)
  - Other (6)

Antidepressants

- Classes:
  - Monoamine oxidase inhibitors
    - Iproniazid = 1958 FDA approved as the first antidepressant; 1961 removed due to hepatotoxicity
    - Phenelzine (Nardil)
    - Isocarboxazid (Marplan)
    - Tranylcypromine (Parnate)
    - Selegiline (EMSAM [transdermal patch])

Monoamine oxidase inhibitors

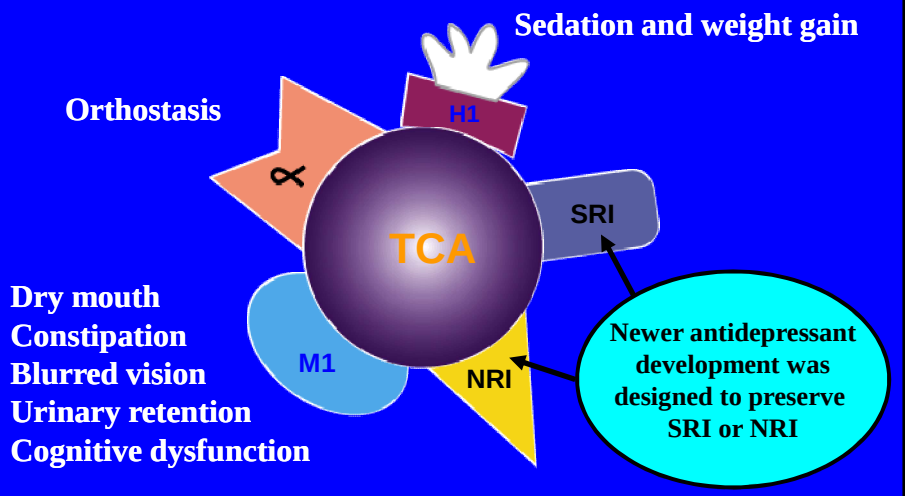
- Oldest class of antidepressants
- Development related to the "monoamine hypothesis" of depression.
- Still occasionally used – underutilized.
- Raises brain levels of serotonin, dopamine and norepinephrine.
- "Tyramine crisis" – caused by certain foods/drinks
- "Hypertensive crisis" – caused by many common prescription and OTC drugs.

Schatzberg AF, Nemeroff CB, Eds. *Essentials of Clinical Psychopharmacology*, 3rd ed. Washington, DC: American Psychiatric Publishing; 2013.

Antidepressants

- **Classes:**
  - **Tricyclic Antidepressants**
    - **Amitriptyline**
    - **Imipramine**
    - **Nortriptyline**
    - **Desipramine**
    - **Clomipramine**
    - **Doxepin**
    - **Amoxapine**
    - **Trimipramine**
    - **Protriptyline**
    - **Maprotiline**
      - ***tetracyclic***

Tricyclic Antidepressants: Many side effects

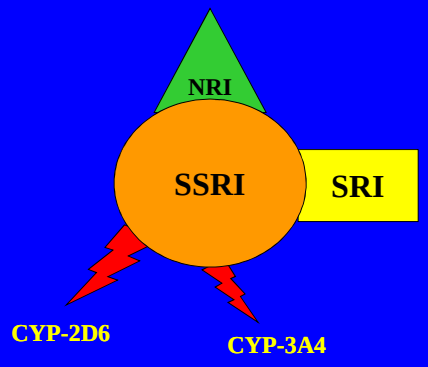


Adapted from: Stahl SM. *Stahl's Essential Psychopharmacology, 3rd Edition;* New York , NY; Cambridge University Press; 2008.

Antidepressants

- **Classes:**
  - **Selective Serotonin Reuptake Inhibitors**
    - **Prozac (fluoxetine)**
    - **Zoloft (sertraline)**
    - **Paxil (paroxetine)**
    - **Luvox (fluvoxamine)**
    - **Celexa (citalopram)**
    - **Lexapro (es-citalopram)**

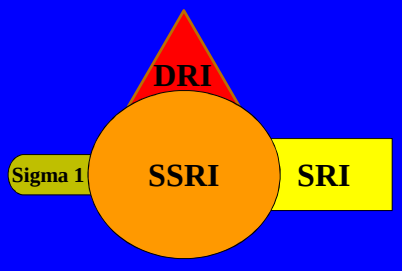
Fluoxetine (Prozac, Sarafem)



SSRI = serotonin selective re-uptake inhibitor; SRI = serotonin re-uptake inhibitor; NRI = norepinephrine re-uptake inhibitor; CYP = cytochrome P-450 isoenzyme

Adapted from: Stahl SM. *Stahl's Essential Psychopharmacology, 3rd Edition*; New York , NY; Cambridge University Press; 2008.

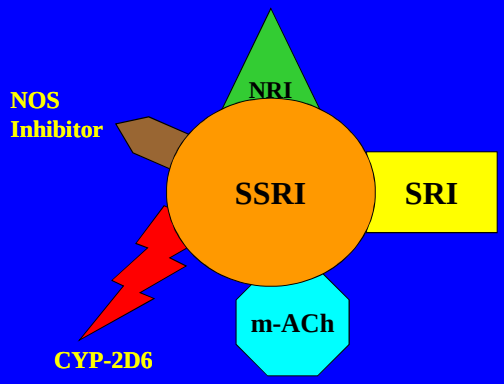
Sertraline (Zoloft)



SSRI = serotonin selective re-uptake inhibitor; SRI = serotonin re-uptake inhibitor; DRI = dopamine re-uptake inhibitor

Adapted from: Stahl SM. *Stahl's Essential Psychopharmacology, 3rd Edition*; New York , NY; Cambridge University Press; 2008.

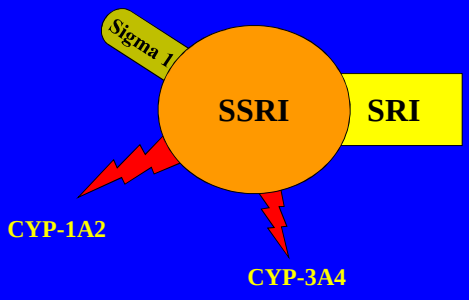
Paroxetine (Paxil)



SSRI = serotonin selective re-uptake inhibitor; SRI = serotonin re-uptake inhibitor; NRI = norepinephrine re-uptake inhibitor; m-ACh = muscarinic AntiCholinergic; CYP = cytochrome P-450 isoenzyme; NOS = nitric oxide synthase

Adapted from: Stahl SM. *Stahl's Essential Psychopharmacology, 3rd Edition;* New York , NY; Cambridge University Press; 2008.

Fluvoxamine (Luvox)



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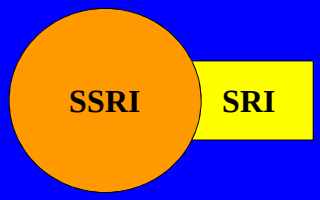
Adapted from: Stahl SM. *Stahl's Essential Psychopharmacology, 3rd Edition;* New York , NY; Cambridge University Press; 2008.

Citalopram (Celexa)
es-Citalopram (Lexapro)



SSRI = serotonin selective re-uptake inhibitor; SRI = serotonin re-uptake inhibitor

Adapted from: Stahl SM. *Stahl's Essential Psychopharmacology, 3rd Edition*; New York , NY; Cambridge University Press; 2008.

Inhibition of binding to human monoamine uptake transporters (Ki in nm) *in vitro*

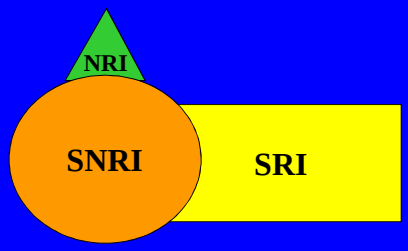
SRI	NE	5-HT	NE/5-HT
Duloxetine	7.5	0.8	9
Venlafaxine	2480	82	30
Clomipramine	38	0.28	136
Fluoxetine	240	0.81	296
Paroxetine	40	0.13	308
Fluvoxamine	1300	2.2	591
Sertraline	420	0.29	1448
Citalopram	4070	1.2	3392

Wong DT, Bymaster FP.; In: Jucker E, ed. *Progress in Drug Research; 2002.*

Antidepressants

- Classes:
  - Serotonin Norepinephrine Reuptake Inhibitors
    - Effexor (venlafaxine)
    - Cymbalta (duloxetine)
    - Pristiq (desvenlafaxine)
    - Fetzima (levomilnacipran)

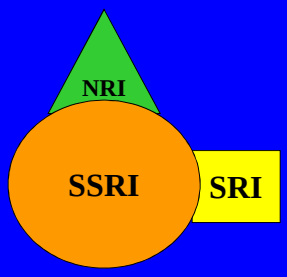
Venlafaxine (Effexor), duloxetine (Cymbalta) and desvenlafaxine (Pristiq)



SNRI = serotonin norepinephrine re-uptake inhibitor;
SRI = serotonin re-uptake inhibitor;
NRI = norepinephrine re-uptake inhibitor.

Adapted from: Stahl SM. *Stahl's Essential Psychopharmacology, 3rd Edition;* New York , NY; Cambridge University Press; 2008.

levomilnacipran (Fetzima)

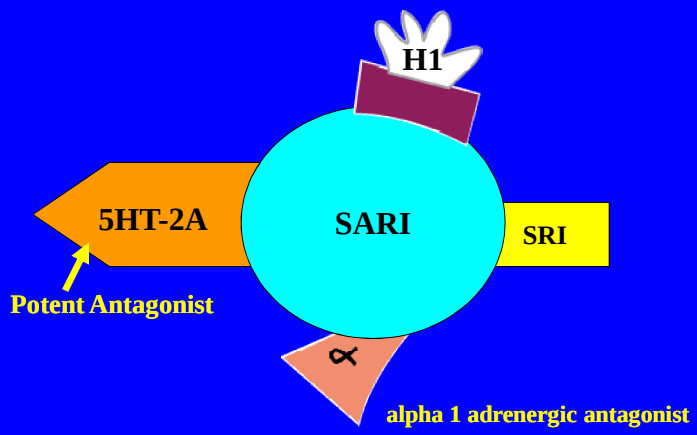


NSRI = norepinephrine serotonin re-uptake inhibitor;
NRI = norepinephrine re-uptake inhibitor;
SRI = serotonin re-uptake inhibitor.

Antidepressants

- Classes:
  - Other
    - Desyrel (trazodone)
    - Serzone (nefazodone)
    - Remeron (mirtazapine)
    - Wellbutrin (bupropion)
    - Viibryd (vilazodone)
    - Brintellix (vortioxetine)

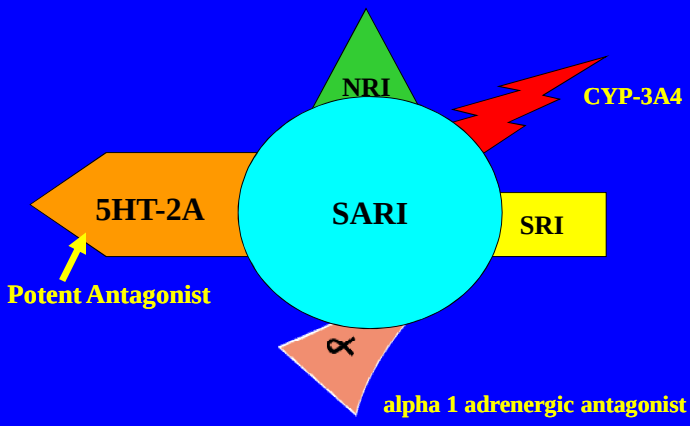
Trazodone (Desyrel)



SARI = serotonin 2A antagonist/reuptake inhibitor; SRI = serotonin re-uptake inhibitor; H1 = anti-histamine.

Adapted from: Stahl SM. *Stahl's Essential Psychopharmacology, 3rd Edition;* New York , NY; Cambridge University Press; 2008.

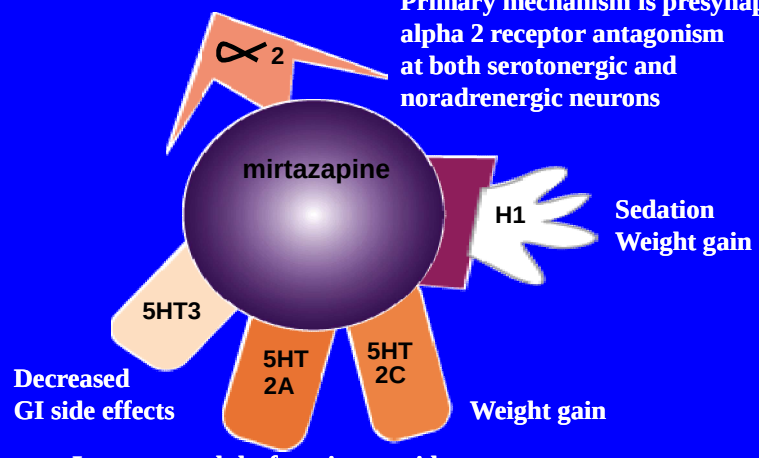
Nefazodone (Serzone)



SARI = serotonin 2A antagonist/reuptake inhibitor; SRI = serotonin re-uptake inhibitor; NRI = norepinephrine re-uptake inhibitor; CYP = cytochrome P-450 isoenzyme

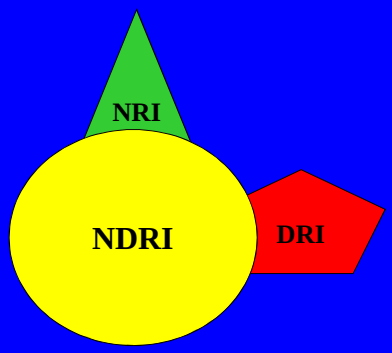
Adapted from: Stahl SM. *Stahl's Essential Psychopharmacology, 3rd Edition;* New York , NY; Cambridge University Press; 2008.

Mirtazapine (Remeron)



Adapted from: Stahl SM. *Stahl's Essential Psychopharmacology, 3rd Edition*; New York , NY; Cambridge University Press; 2008.

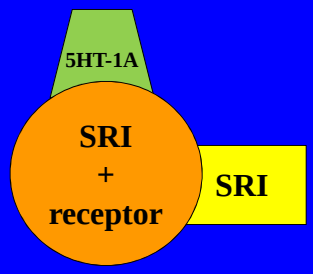
Bupropion (Wellbutrin) IR, SR and XL



NDRI = norepinephrine and dopamine re-uptake inhibitor;
NRI = norepinephrine re-uptake inhibitor; DRI = dopamine re-uptake inhibitor

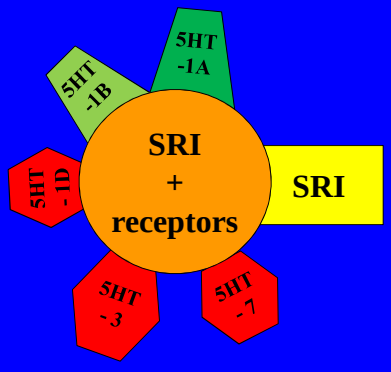
Adapted from: Stahl SM. *Stahl's Essential Psychopharmacology, 3rd Edition*; New York , NY; Cambridge University Press; 2008.

Vilazodone (Viibryd)



SRI = serotonin re-uptake inhibitor; serotonin 5HT-1A receptor partial agonist

Vortioxetine (Brintellix)



SRI = serotonin re-uptake inhibitor; serotonin 5HT-1A receptor full agonist; 5HT-1B partial agonist; 5HT-1D antagonist; 5HT-3 antagonist; 5HT-7 antagonist.

Part 4

The incredible journey: From the pill box to the toilet

Pharmacokinetics of Antidepressants

Factors that impact how a drug enters and leaves the body

- Absorption (gut, skin, sub-lingual, IM, IV)
- Bioavailibility
- Protein Binding
- P- Glycoproteins
- Phase I Metabolism = CYP450 Enzyme System
- Phase II Metabolism = Conjugation
  - Glucuronidation, Sulfation and Methylation
- Half-life (T ½) of the medication
- Drug-Drug Interactions
- Excretion (urine, bile and gut)

From the medicine bottle to the toilet: the long and complex journey.

Getting the medication into the body:

- oral administration
- sublingual administration
- transdermal administration
- nasal spray
- nebulizer inhaler
- subcutaneous injection
- intramuscular injection
- intravenous injection

From the medicine bottle to the toilet: the long and complex journey.

Absorption from the gastro-intestinal tract:

- gastric
- small intestine
- large intestine
- P-glycoprotein metabolism
- Cytochrome P-450 metabolism
- effects of irritable bowel syndrome
- effects of gastric stapling/lap band

Protein Binding

Not as clinically relevant as previously believed.

Properties of a drug that predict clinically relevant displacement by protein binding:

- low clearance drugs
- low therapeutic index
- small volume of distribution

Examples: warfarin, tolbutamide, phenytoin

Protein Binding and Urinary Excretion of SRIs

Drug	% Protein Bound	% Urinary Excretion	Half-Life
fluoxetine	94	<2.5	14 days
S-sertraline	98	<1	26 hours
R-paroxetine	95	<2	21 hours
fluvoxamine	77	<5	15 hours
venlafaxine	27	4.6	5 hours
D-M-venlafaxine	30	29	11 hours
citalopram	80	10.5	35 hours
S-citalopram	56	18*	29 hours

The Pharmacological Basis of Therapeutics; Goodman & Gilman; 10th Edition; 2001
*From Physician's Desk Reference; 2004; page 1302.

Differing Metabolic Pathways

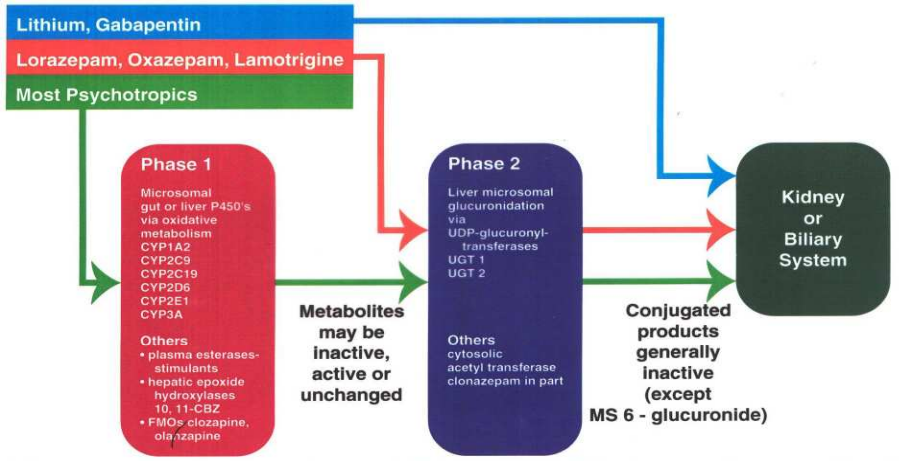
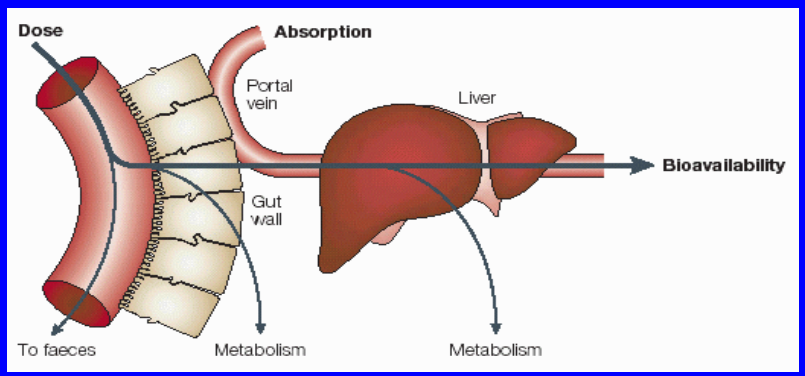


Figure 2. Phase 1 and Phase 2 Biotransformation

Uptake of an orally administered drug proceeds after the stomach passage via the small intestine. In the gut and liver, a series of metabolic transformation occurs.



From the medicine bottle to the toilet: the long and complex journey.

Hepatic metabolism ("first pass"):

- Cytochrome P-450 enzymes
  - substrate
  - inhibitor
  - inducer
- Conjugation
  - Glucuronidation
  - Sulfonation
  - Methylation

In Vivo inhibitory effects of SSRIs on the Major Human Cytochrome P450 enzymes*

SSRI	1A2	2D6	2C9/10	2C19	3A3/4
Citalopram (40mg)	-	++	-	-	-
Escitalopram (20mg)	-	++	-	-	-
Fluoxetine (20mg)	-	+++	+++	++	+
Fluvoxamine (150mg)	+++	-	+++	+++	++
Paroxetine (20mg)	-	+++	-	-	-
Sertraline (100-200mg)	-	+	-	-	-

* (- = <20%; + = 20%-50%; ++ = 50%-150%; +++ = >150%)

Preskorn, S; *J Psych Practice*; Vol. 9, No. 3; page 229; May 2003

From the medicine bottle to the toilet: the long and complex journey.

- Crossing the blood brain barrier
  - lipophilicity
  - P-glycoproteins
- Polymorphisms of brain receptors
  - gene variants
  - single nucleotide polymorphisms (SNPs)
  - promoter sequence variants
  - processing introns/exons

From the medicine bottle to the toilet: the long and complex journey.

- Getting out of the body:
  - renal excretion
  - biliary excretion
  - sweating it out
  - breathing it out
  - hemodialysis

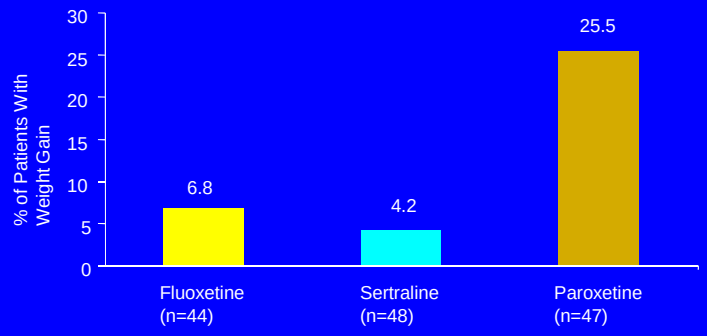
Reasons for treatment failure.

- Dose too low
- Time too short
- Absorption issues
- Non-compliance
- Drug-Drug interaction
- Wrong diagnosis
- Substance abuse
- Ongoing psychosocial stressors
- Need to add/change psychotherapy
- Need to augment/combine medication

Reasons for treatment failure.

- Unacceptable side effects leading to discontinuation:
  - Sedation
  - Orthostasis
  - Constipation
  - Dry mouth
  - Bizarre dreams
  - Activation
  - Sexual dysfunction
  - Weight gain/loss
  - Rash
  - Cognitive effects
  - Hyperprolactinemia

Long-term Changes in Weight – Fluoxetine, Sertraline, and Paroxetine



Fava, M; Weight Gain and Antidepressants; J Clin Psychiatry 2000;61 (suppl 11):37-41

Adapted from Table 2: "Incidence of Sexual Dysfunction With Antidepressants Assessed by the Psychotropic-Related Sexual Dysfunction Questionnaire" (N=1022)

Drug	N	Mg mean dose	# with SD	% with SD
Citalopram	66	28.7	48	72.7
Paroxetine	208	23.4	147	70.7
Venlafaxine	55	159.5	37	67.3
Sertraline	159	90.4	100	62.9
Fluvoxamine	77	115.7	48	62.3
Fluoxetine	279	24.5	161	57.7

Montejo, A., et. al.; J Clin Psychiatry; 62 (suppl 3), pages 10-21 (2001)

Polypharmacy.

- Avoid if possible
- After adequate dose/time on a medication, consider cross titration to a different medication.
- After failure of several monotherapy trials, consider “rational” polypharmacy.
- Polypharmacy includes combination therapy (using two agents, each FDA approved as monotherapy) as well as augmentation therapy (the second agent is not FDA approved as monotherapy).

Thank you for your attention!

Questions??

Additional References

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