Clinician's Guide to Understanding Atypical Antipsychotic Drug Receptor Binding Properties

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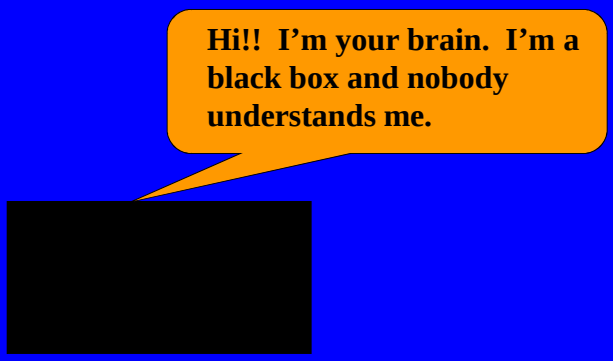
OBJECTIVES

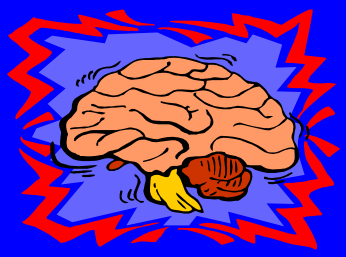
- Review the neurophysiology underlying the mechanisms of action of the various medications that are collectively called the Atypical Antipsychotics
- Describe the pharmacological receptor binding characteristics that differentiate the first, second and third generation antipsychotics.
- Appreciate the diversity of the serotonin and dopamine systems, especially in regards to their roles in divergent neurocircuits and target symptoms.
- Become familiar with the putative clinical consequences of modulating serotonergic, dopaminergic, adrenergic, histaminergic and cholinergic receptors by antipsychotic medications.

The "Black Box"



Circa 1980s

The Wiring of the Brain



- There are approximately 100 billion neurons in the human brain
- There are from 1,000 to 10,000 synapses/neuron
- Hence, there are up to 1,000 trillion synapses in the human brain – *an amazing quadrillion synapses!!*

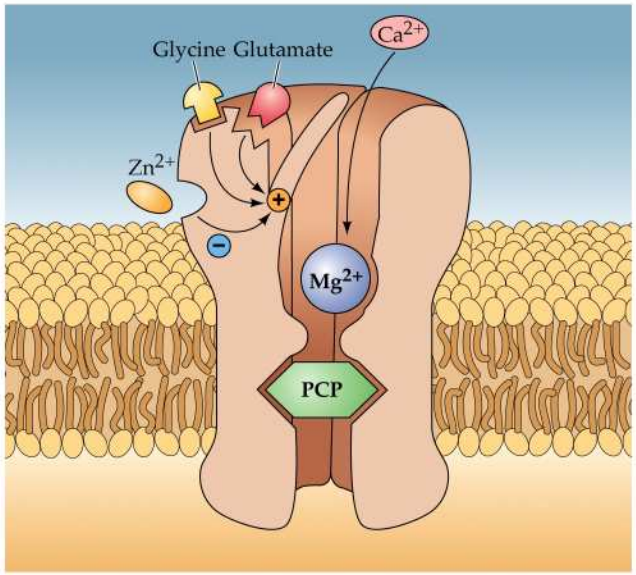
Putative etiologies of Schizophrenia

- Primary cortical dopamine deficiency
  - Secondary subcortical mesolimbic dopamine excess
- Primary subcortical dopamine excess
  - Overactivity of mesolimbic dopamine
- Primary cortical glutamate deficiency
  - Secondary cortical dopamine deficiency
  - Tertiary subcortical mesolimbic dopamine excess
- Primary excitation of serotonin 5HT-2A receptors

Animal models of schizophrenia

- NMDA-glutamate antagonists induce both positive and negative schizophrenia-like symptoms in animal models:
  - Ketamine
  - Phencyclidine (PCP)

(*b*) A model of PCP action on the NMDA receptor



Current pharmacological agents for the treatment of schizophrenia

- **All FDA approved medications that treat the postitive symptoms of schizophrenia share the property of antagonizing the dopamine D-2 receptor either by pure antagonism (first and second generation agents) or by antagonism/partial agonism (third generation agents)**

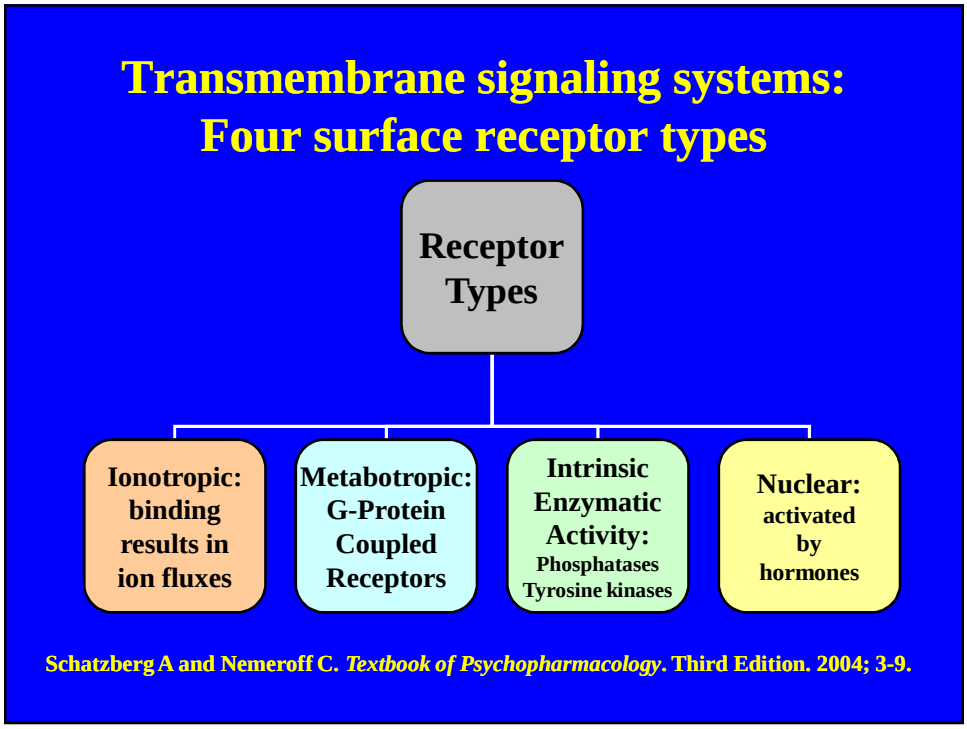
Glutamate Signaling

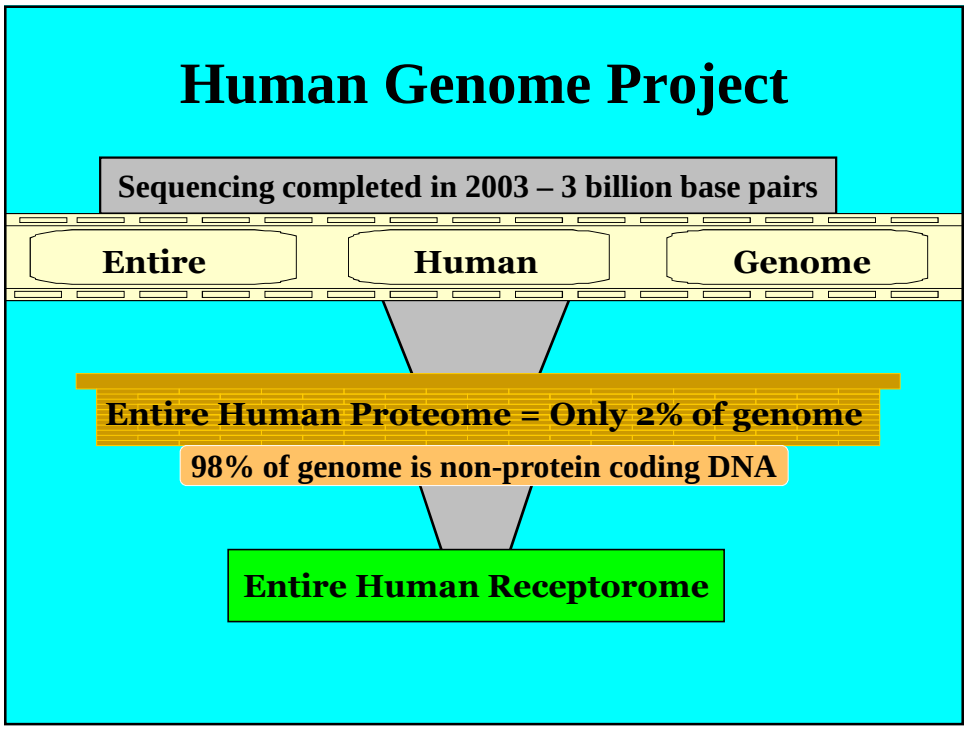
- Glutamate synthesis
  - Glutamine synthetase
  - glutaminase
- Glutamate transporters
  - Excitatory amino acid transporters
    - 5 subtypes
  - Vesicular Glu transporters
    - 3 subtypes
- Ionotropic Glutamate Receptors
  - NMDA (N-methyl-D-aspartate)
    - 7 subtypes
  - AMPA (DL-alpha-amino-3-hydroxy-5-methylisoxasole-4-propionate)
    - 4 subtypes
  - KA (kainate)
    - 5 subtypes
- Metabotropic Glutamate Receptors
  - mGluR1 through mGluR8
  - Divided into 3 subtypes (Type 1 = 2; Type 2 = 2; Type 3 = 4)

Hinoi E, et. al.; Glutamate Transporters as Drug Targets; Current Drug Targets – CNS & Neurological Disorders; 2005; 4; 211-220.

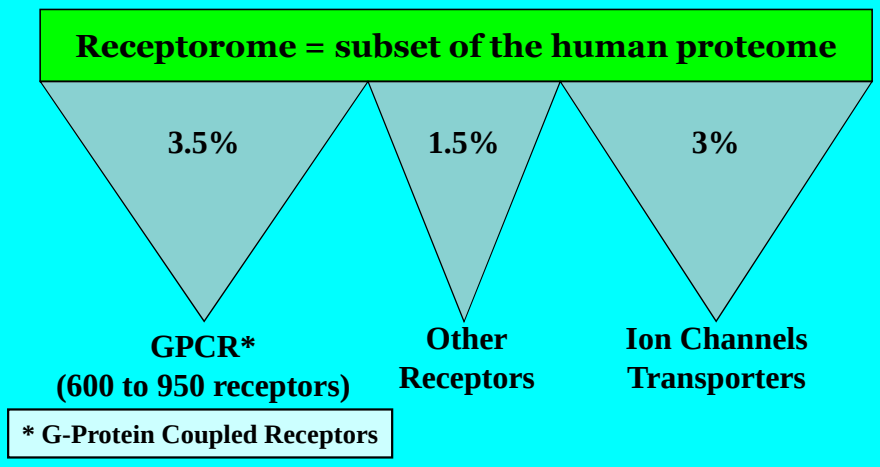
Glutamatergic agents currently in various stages of drug development

- Metabotropic glutamate agonists (mGlu 2/3)
- Glutamate transporter modulators
- Glycine transporter inhibitors (sarcosine)
- Glycine analogues


Transmembrane signaling systems:
Four surface receptor types
Receptor Types
Ionotropic: binding results in ion fluxes
Metabotropic: G-Protein Coupled Receptors
Intrinsic Enzymatic Activity: Phosphatases Tyrosine kinases
Nuclear: activated by hormones
Schatzberg A and Nemeroff C. *Textbook of Psychopharmacology*. Third Edition. 2004; 3-9.


Human Genome Project
Sequencing completed in 2003 – 3 billion base pairs
Entire
Human
Genome
Entire Human Proteome = Only 2% of genome
98% of genome is non-protein coding DNA
Entire Human Receptorome

Human Genome Project



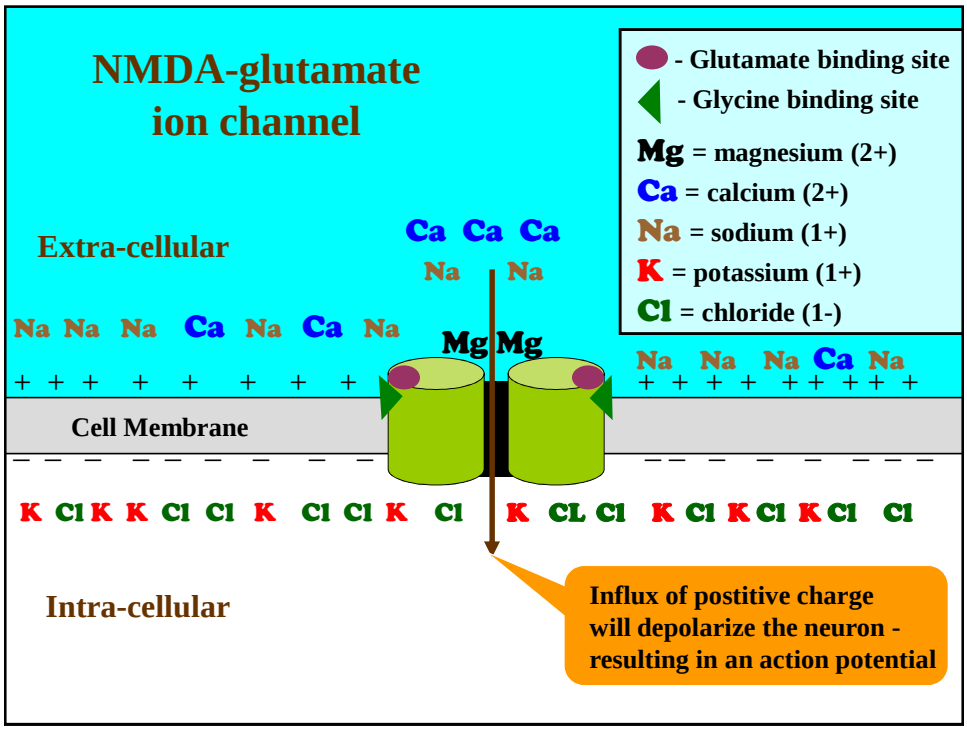
Roth BL et al. Pharmacology & Therapeutics 102 (2004) 99-110.

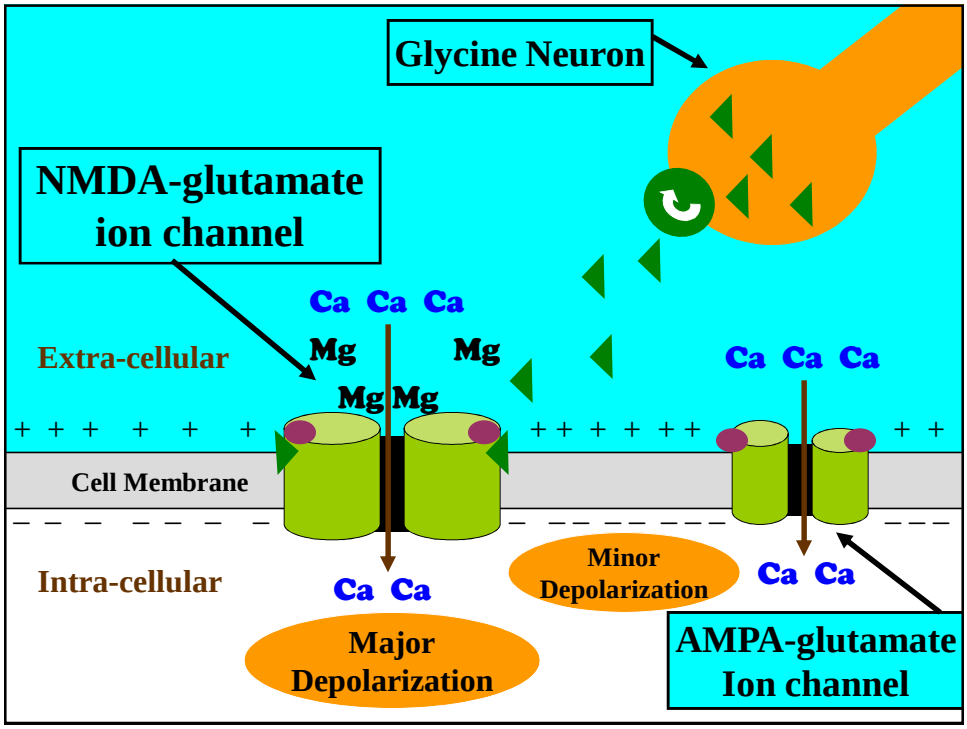
Ionotropic Receptors

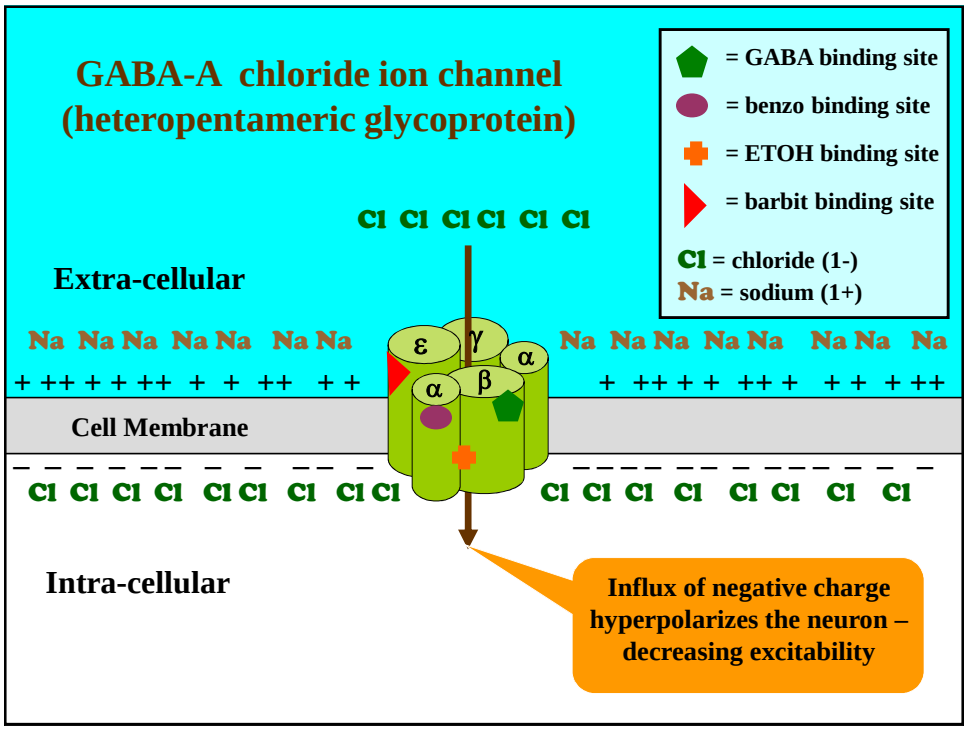
- Receptors that open or close ion channels, altering the influx or efflux of charged ions
- Response occurs in milliseconds
- Result is a change in the polarization of a cell: depolarization or hyperpolarization

Two significant ionotropic receptor systems

- Glutamate
  - The primary excitatory neurotransmitter
  - NMDA-glutamate receptors manage influx of positive charge into neurons (Ca++, Na+)
- GABA (gamma-aminobutyric acid)
  - The primary inhibitory neurotransmitter
  - GABA-A receptors manage the influx of negative charge into neurons (Cl-)

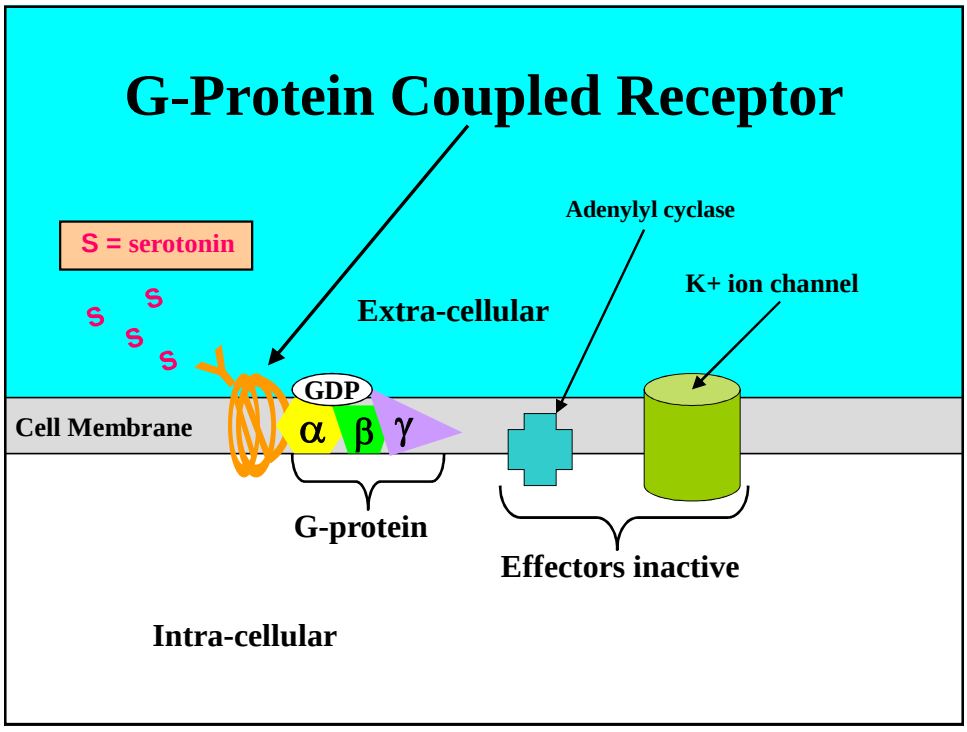


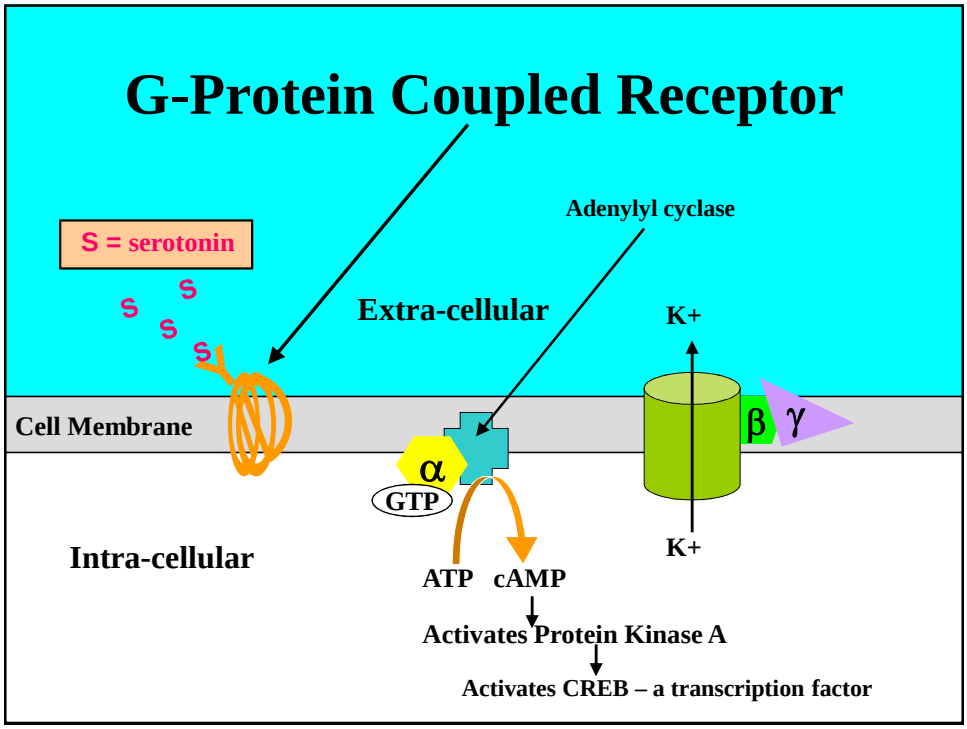

Glycine Neuron
NMDA-glutamate ion channel
Ca Ca Ca
Mg
Mg
Mg Mg
Extra-cellular
Ca Ca Ca
Cell Membrane
Intra-cellular
Ca Ca
Minor Depolarization
Ca Ca
Major Depolarization
AMPA-glutamate Ion channel

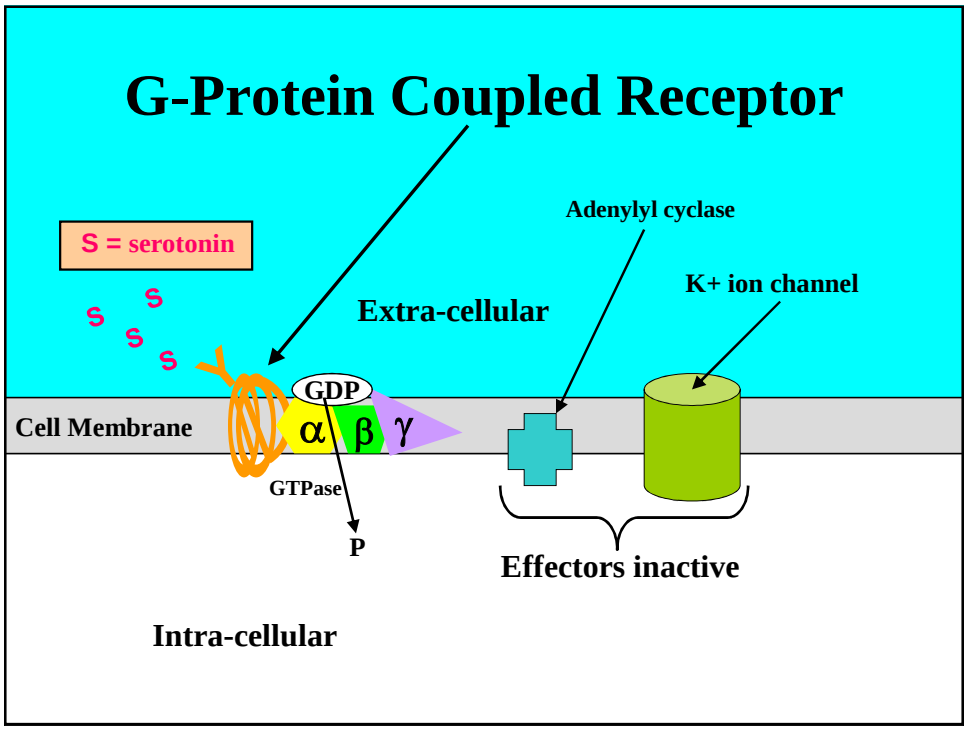

GABA-A chloride ion channel
(heteropentameric glycoprotein)
= GABA binding site
= benzo binding site
= ETOH binding site
= barbit binding site
Cl = chloride (1-)
Na = sodium (1+)
Cl Cl Cl Cl Cl Cl
Extra-cellular
Na Na Na Na Na Na Na
Na Na Na Na Na Na Na Na
ε
γ
α
α
β
Cell Membrane
Cl Cl Cl Cl Cl Cl Cl Cl Cl
Cl Cl Cl Cl Cl Cl Cl Cl
Intra-cellular
Influx of negative charge hyperpolarizes the neuron – decreasing excitability

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


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

Receptor binding properties of antipsychotic medications

Complexity of the brain requires complex pharmacology

- "Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia"*
- Treatment of schizophrenia began with "dirty drugs" = Thorazine and Mellaril
- Evolved to clean "magic bullets" = Haldol
- Current paradigm supports "magic shotguns", drugs with activity at multiple receptors

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

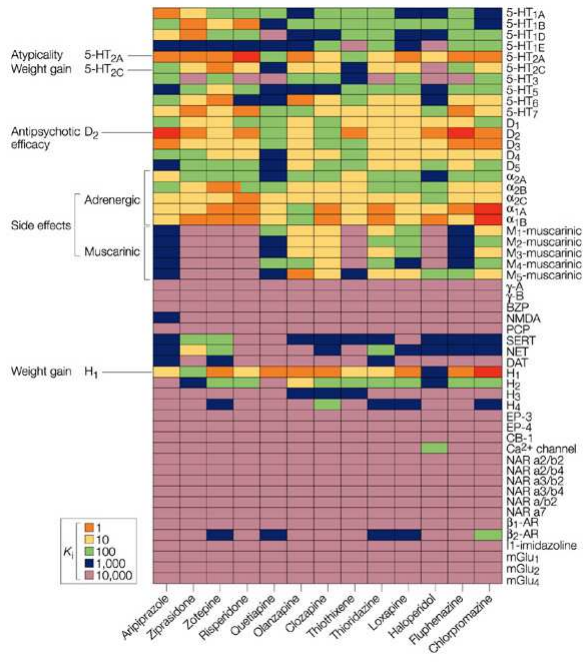
Complexity of the brain requires complex pharmacology

From Serendipity:

Chlorpromazine (Thorazine) – FDA approved 1954

Antipsychotic efficacy discovered by a French physician in 1952 who observed that psychotic patients with nausea had both their nausea and psychosis improve with chlorpromazine.

To Molecular "fingerprinting":

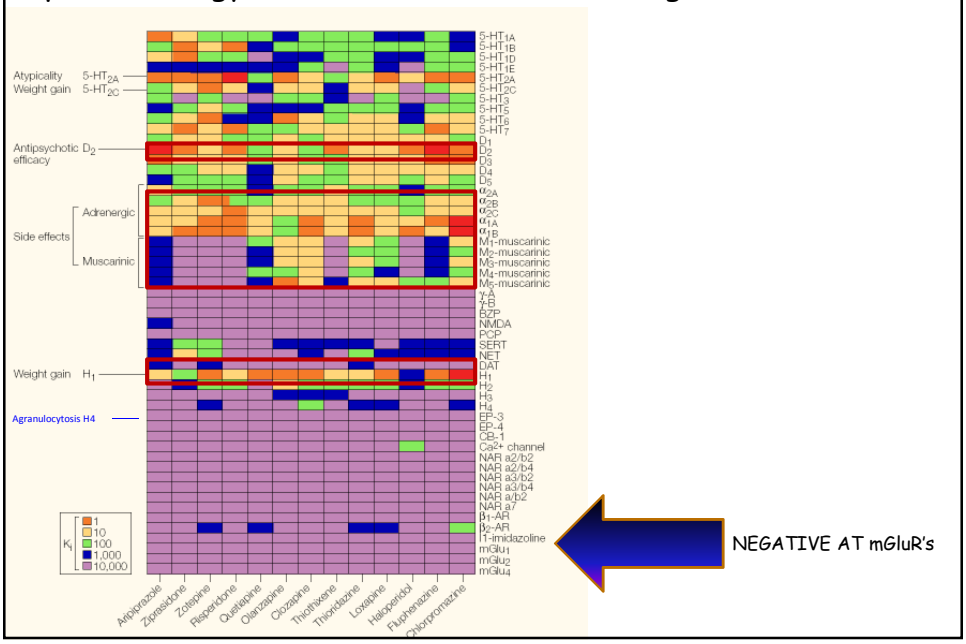


53 receptors

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

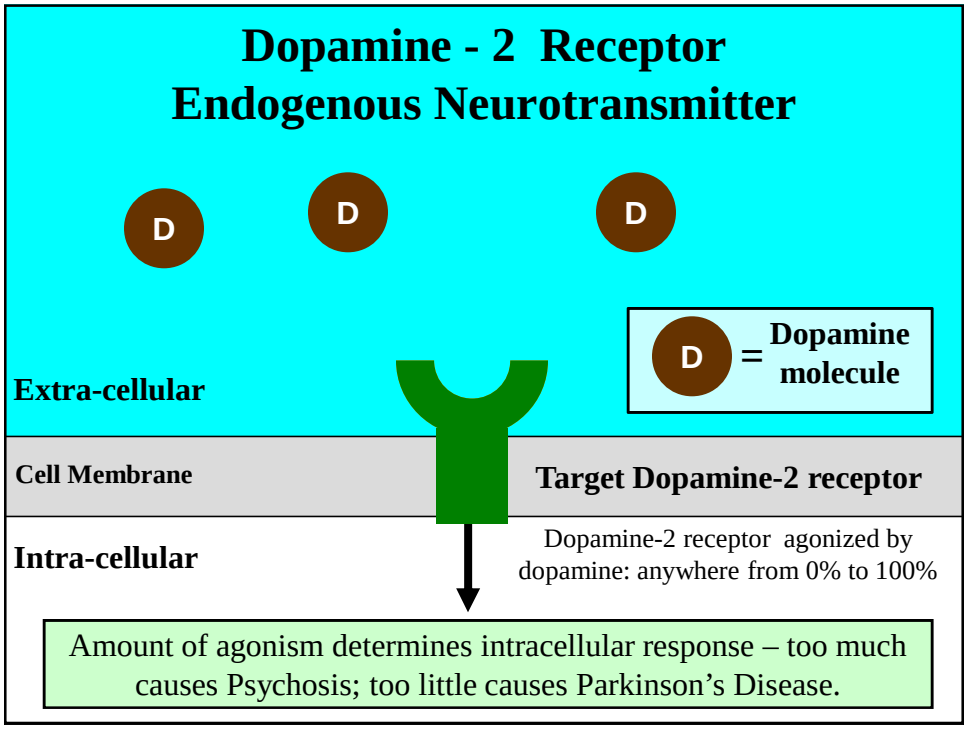
Nature Reviews | Drug Discovery

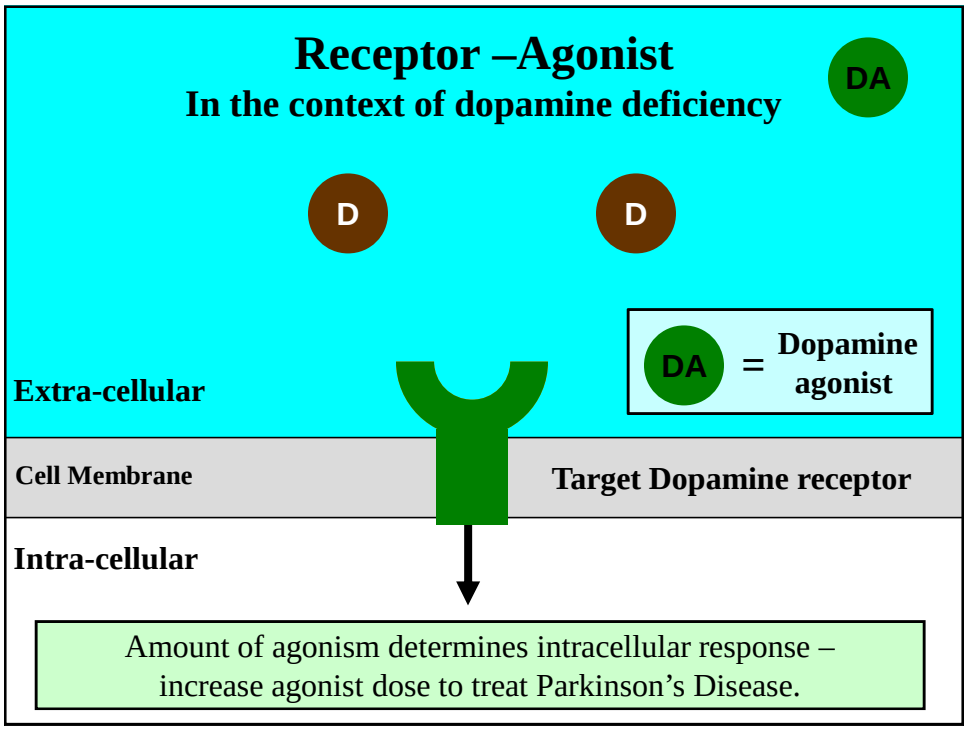
All clinically effective antipsychotic drugs have a complex pharmacology (Roth et al, Nature Rev Drug Discov, 2004)

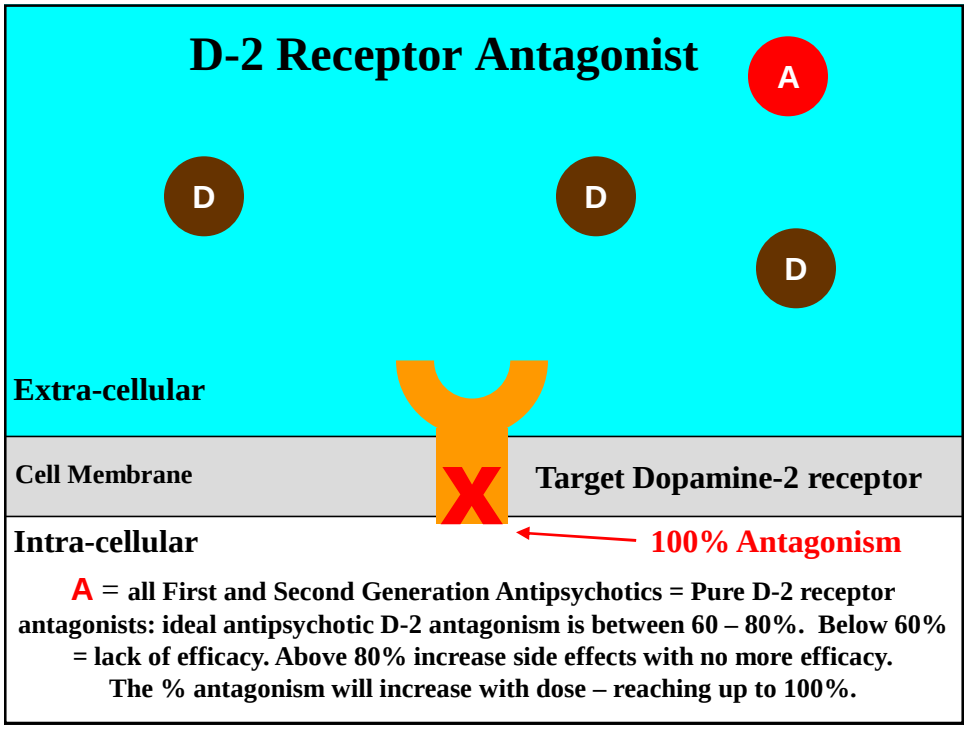


Pharmacology of antipsychotics

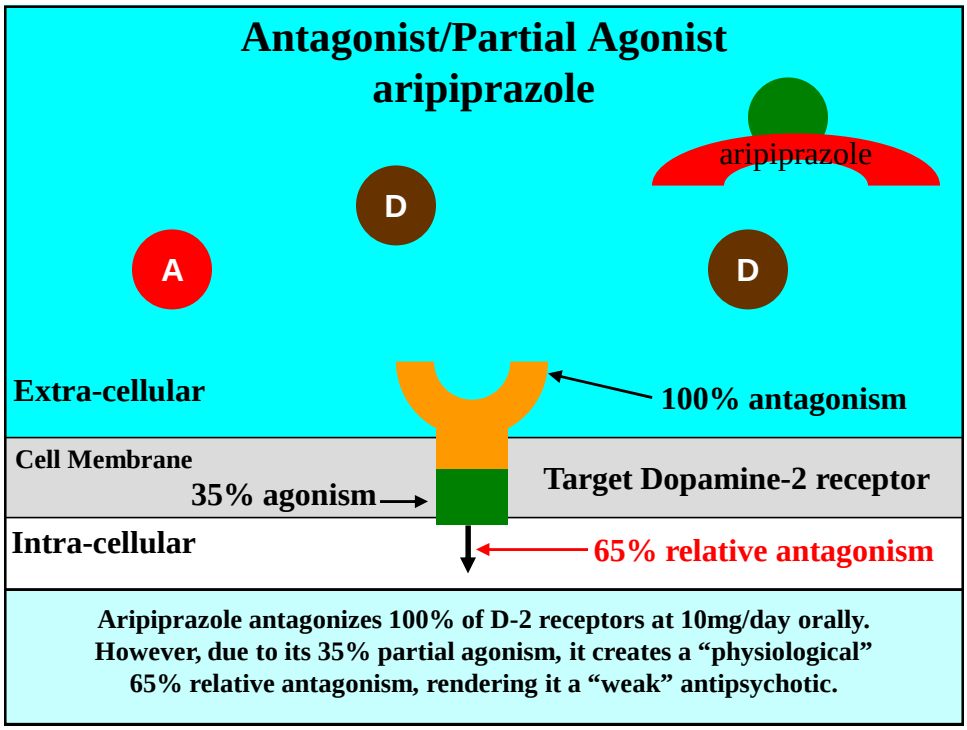
- **First Generation = "typical"**
  - **MOA = D-2 receptor antagonists**
  - **Thorazine, Mellaril, Stelazine, Trilafon, Navane, Haldol, Prolixin, Orap and others**
- **Second Generation = "atypical"**
  - **MOA = serotonin/dopamine receptor modulators**
  - **1958 clozapine developed; FDA approved 1989**
  - **risperidone, olanzapine, quetiapine, ziprasidone, paliperidone, iloperidone, asenapine and lurasidone**
- **Third Generation = "atypical"**
  - **MOA = dopamine receptor antagonist/partial agonist**
  - **aripiprazole, brexpiprazole, cariprazine**


Dopamine - 2 Receptor
Endogenous Neurotransmitter
D
D
D
D = Dopamine molecule
Extra-cellular
Cell Membrane
Target Dopamine-2 receptor
Intra-cellular
Dopamine-2 receptor agonized by dopamine: anywhere from 0% to 100%
Amount of agonism determines intracellular response – too much causes Psychosis; too little causes Parkinson's Disease.

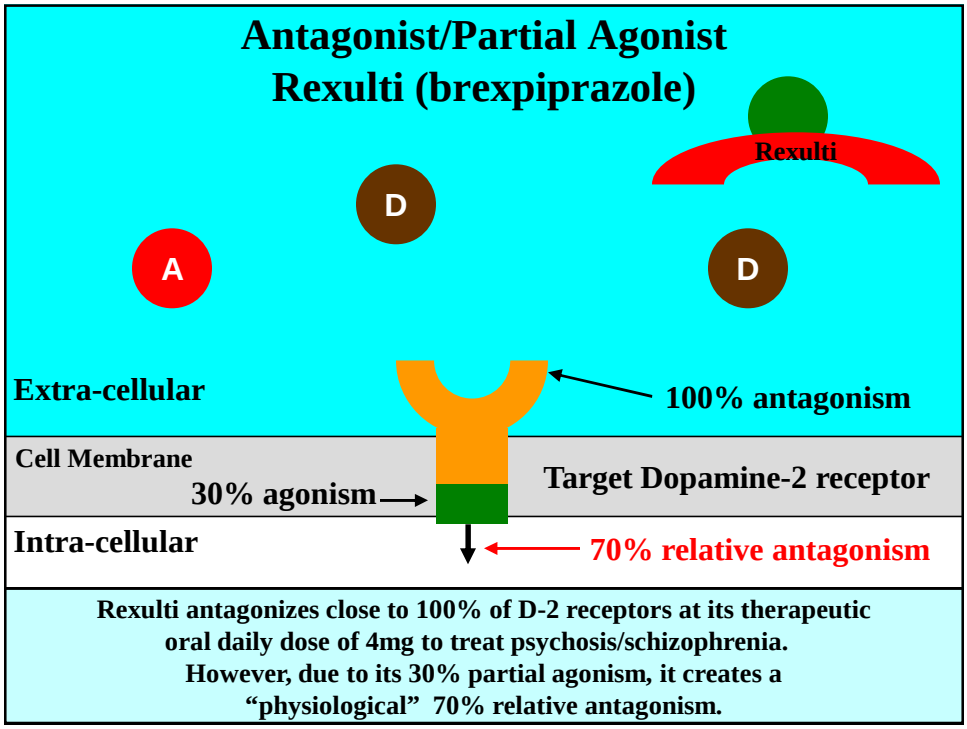

Receptor –Agonist
In the context of dopamine deficiency
DA
D
D
DA = Dopamine agonist
Extra-cellular
Cell Membrane
Target Dopamine receptor
Intra-cellular
Amount of agonism determines intracellular response – increase agonist dose to treat Parkinson's Disease.



A = all First and Second Generation Antipsychotics = Pure D-2 receptor antagonists: ideal antipsychotic D-2 antagonism is between 60 – 80%. Below 60% = lack of efficacy. Above 80% increase side effects with no more efficacy. The % antagonism will increase with dose – reaching up to 100%.



Aripiprazole antagonizes 100% of D-2 receptors at 10mg/day orally. However, due to its 35% partial agonism, it creates a "physiological" 65% relative antagonism, rendering it a "weak" antipsychotic.



Mechansims of antipsychotic drugs

Note: may bind only D-2 receptor, or additional dopamine receptors = D-1, D-3, D-4 and D-5

First Generation	Second Generation	Third Generation
D-2 Antagonism as primary mechanism of action	5HT-2A antagonism is more potent than D-2 antagonism with varying activity at other 5HT receptors	Potent D-2 antagonism/ partial agonism with 5HT-2A antagonism and 5HT-1A partial agonism

Grunder G, et al. Arch Gen Psychiatry. 2003 Oct; 60(10):974-7.

Monoamines are important neurotransmitters

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

Affective and Psychotic Disorders: Three important monoamine neurotramsmitters

- Serotonin
- Dopamine
- Norepinephrine

The Dopamine System

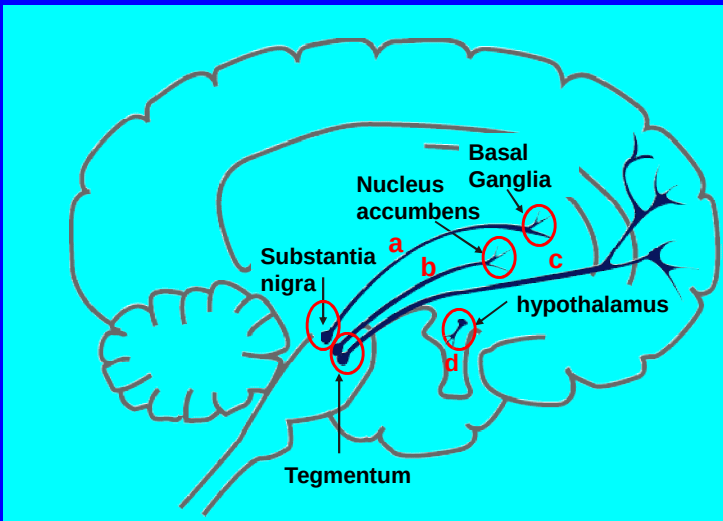
- Dopamine = D
- Dopamine transporter = DAT
- Dopamine receptors
  - Five families = D-1, 2, 3, 4 and 5

Dopamine Receptor Families

- All 5 are Metabotropic = GPCR (G-Protein Coupled Receptors)
- D-1 and D-5 are structurally similar
  - Turn on adenylyl cyclase = increase cAMP
- D-2, 3 and 4 are structurally similar
  - Turn off adenylyl cyclase = decrease cAMP

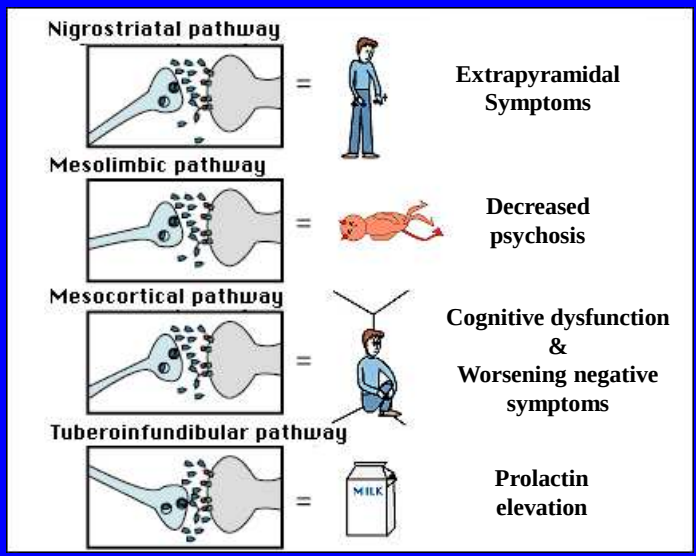
The Pharmacological Basis of Therapeutics; Goodman & Gilman; 10th Edition; 2001

DOPAMINE PATHWAYS



Stahl S. *Essential Psychopharmacology*. Second Edition. 2000; 375.

Consequences of D-2 antagonism at the 4 dopamine circuits



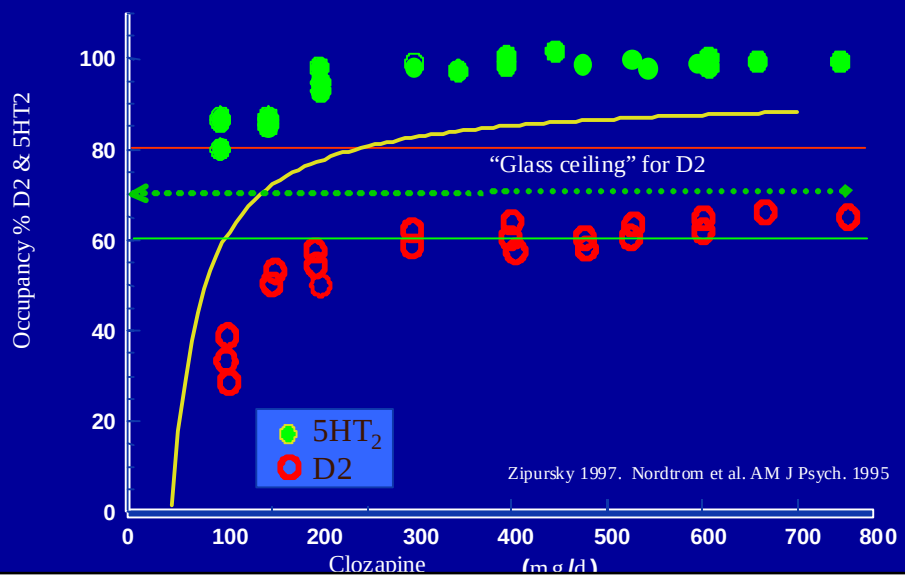
Adapted from: Stahl S. *Essential Psychopharmacology*. Second Edition. 2000; 403-407.

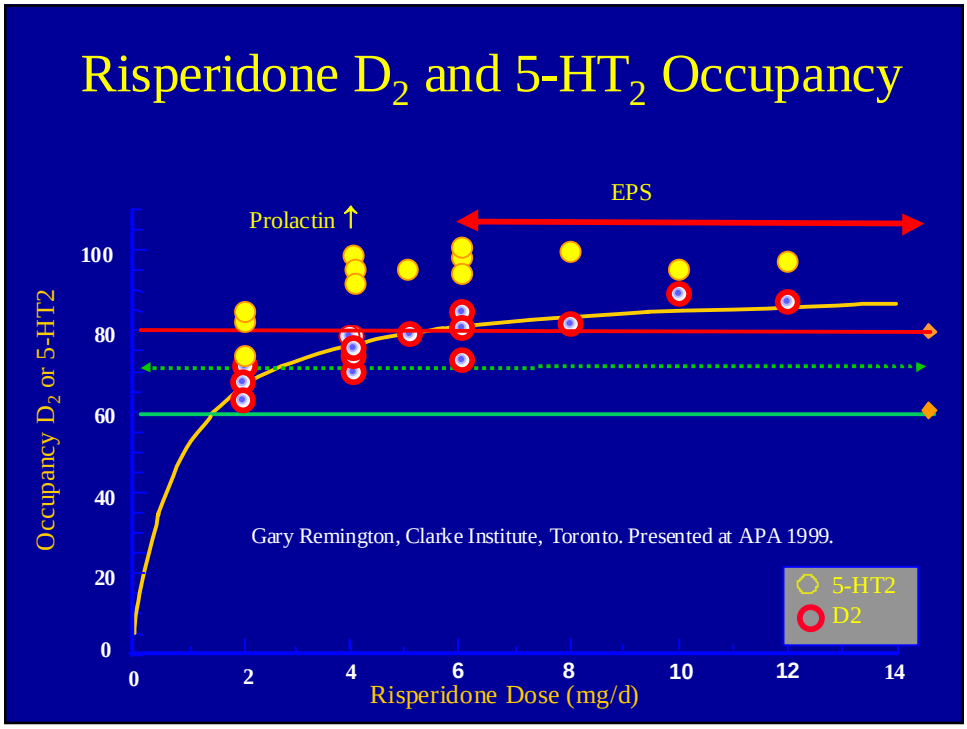
Consequences of increasing occupancy of D-2 receptors

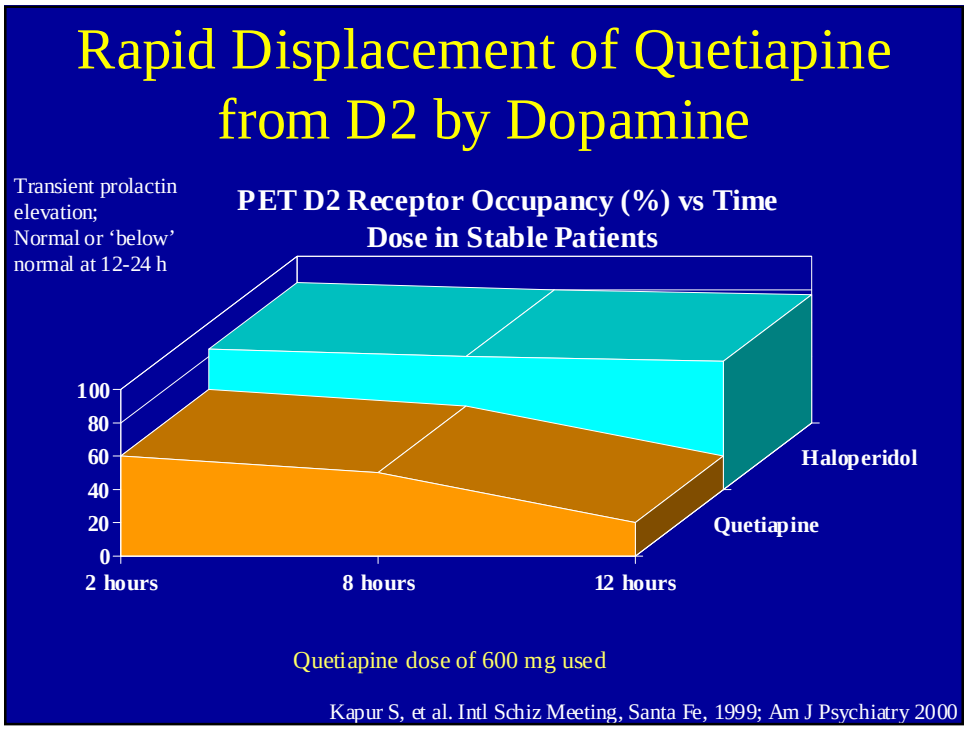
% Occupancy of D-2 receptors	Clinical Consequences
< 60%	minimal
60 – 80%	Antipsychotic/antimanic
> 70%	Elevation of prolactin
> 80%	Increasing EPS

Kapur S. Mol Psychiatry. 1998 Mar; 3(2):135-40.
Tauscher J, et al. Psychopharmacology. 2002 Jun; 162(1):42-9.
Grunder G, et al. Arch Gen Psychiatry. 2003 Oct; 60(10):974-7.
Seeman P. Can J Psychiatry. 2002 Feb; 47(1):27-38.

Clozapine D_2 and 5-HT_2 Occupancy

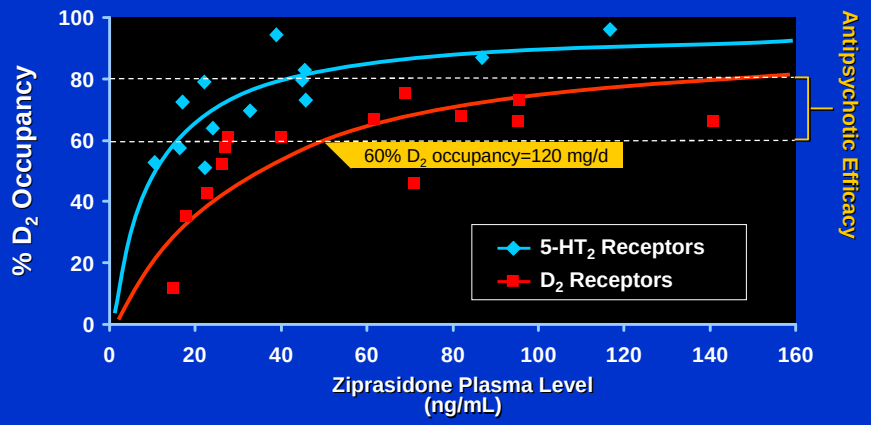



Risperidone D_2 and 5-HT_2 Occupancy
EPS
Prolactin ↑
Occupancy D_2 or 5-HT2
100
80
60
40
20
0
0
2
4
6
8
10
12
14
Risperidone Dose (mg/d)
Gary Remington, Clarke Institute, Toronto. Presented at APA 1999.
5-HT2
D2


Rapid Displacement of Quetiapine from D2 by Dopamine
Transient prolactin elevation; Normal or 'below' normal at 12-24 h
PET D2 Receptor Occupancy (%) vs Time
Dose in Stable Patients
100
80
60
40
20
0
2 hours
8 hours
12 hours
Haloperidol
Quetiapine
Quetiapine dose of 600 mg used
Kapur S, et al. Intl Schiz Meeting, Santa Fe, 1999; Am J Psychiatry 2000

Pharmacokinetics

Plasma Level vs % D_2 Occupancy at 12 Hours Postdose



- Clinical response to atypical antipsychotics occurs at approximately 60%-80% D_2 receptor occupancy
- Estimated oral dose of ziprasidone associated with 60% D_2 occupancy is 120 mg/d

Adapted from Mamo D et al. *Am J Psychiatry* 2004;161:818-825.

The Serotonin System

- Serotonin = 5-HT
- 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
- 5-HT 2A, B, C
- 5-HT 3A, B
- 5-HT 4A, B, C, D, E, F, H
- 5-HT 5A, B
- 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

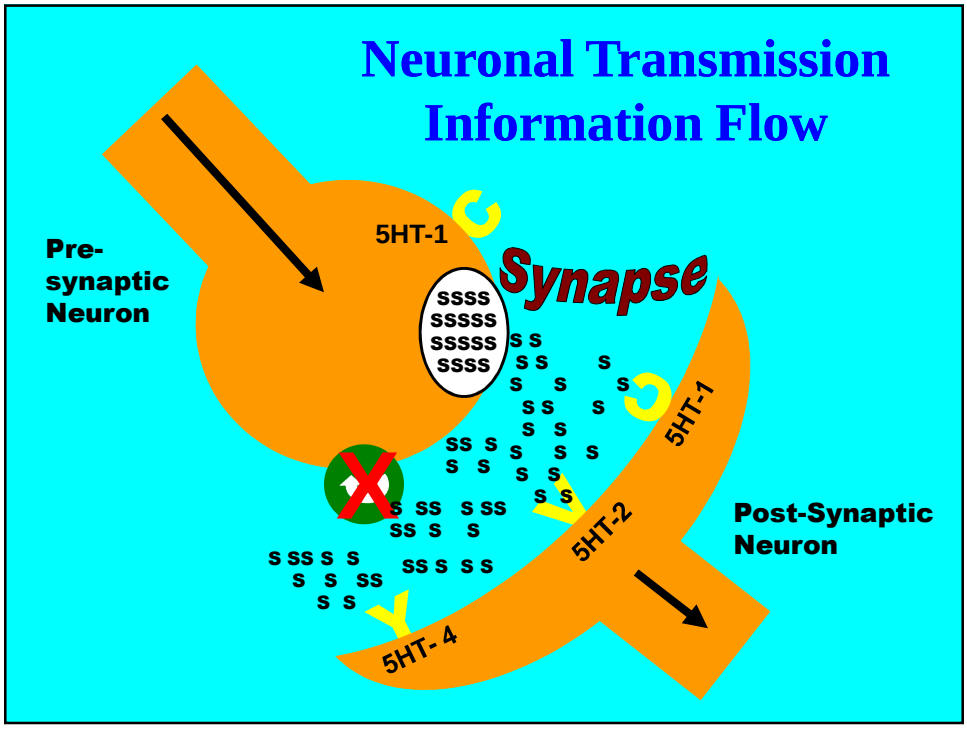
Pharmacological Agents Targeting Specific Serotonin Sub-receptors

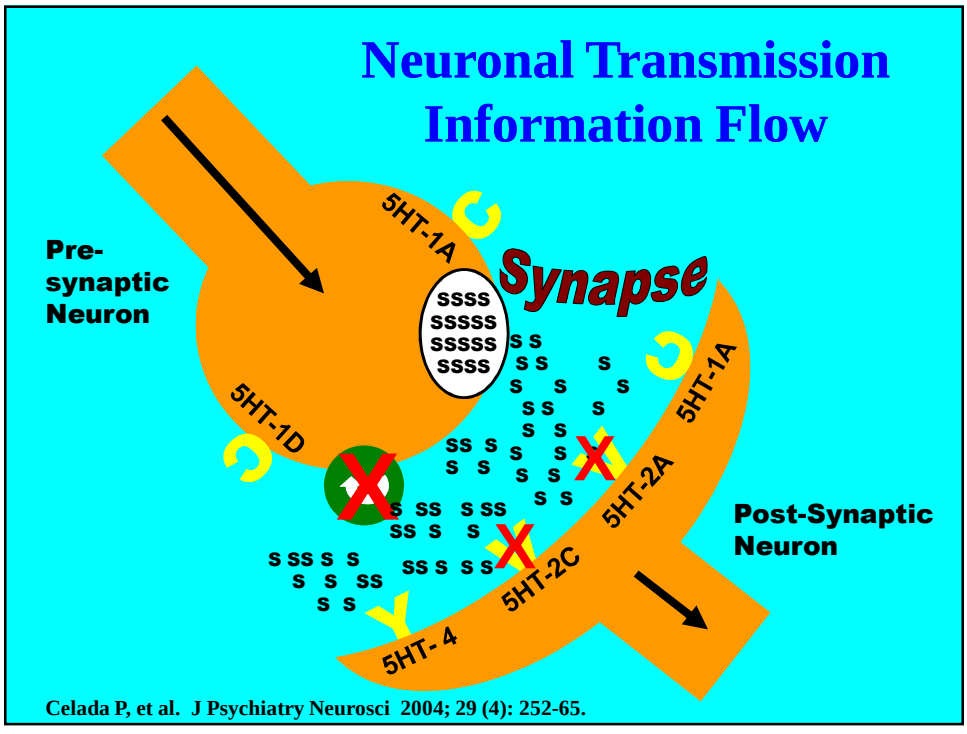
Receptor	Drug	Putative Activity
5HT-1A	agonists = buspirone, gepirone, tandospirone	Anti-depressant, Anti-anxiety, Cognitive improvement
5HT-1B	agonist = triptans	Anti-migraine
5HT-1D	agonist = triptans	Anti-migraine
5HT-2A	antagonist = nefazodone, atypical antipsychotics	Anti-depressant, Anti-anxiety, Cognitive improvement
5HT-2B	agonist = fenfluramine	Causes cardiac valve disease
5HT-2C	agonist = mCPP	Anxiogenic
	antagonist = agomelatine	Novel Antidepressant
5HT-3	antagonist = ondansetron	Rx nausea/vomitting
5HT-4	agonist = tegaserod	Rx constipation

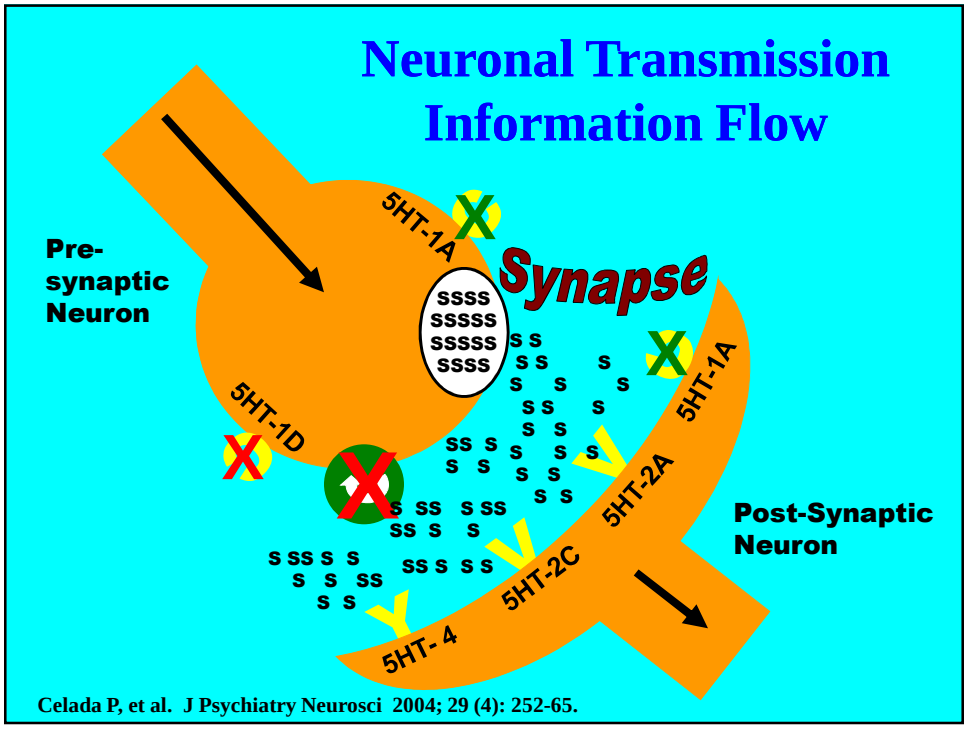
Putative clinical effects of various serotonin (5-HT) sub-receptors

- **5-HT 2A antagonism**
  - **Increases dopamine release**
  - **Likely antidepressant effect**
  - **Decreases EPS**
  - **Improves negative symptoms**
- **5-HT 2C antagonism**
  - **May increase dopamine/norepinephrine in cortex**
  - **Improves cognitive symptoms**
  - **Improves affective symptoms**
- **5-HT 1A agonism**
  - **Improves cognition, anxiety and depression**
- **5-HT 1D antagonism**
  - **Disinhibits presynaptic serotonin release**
  - **Antidepressant and antianxiety effects**

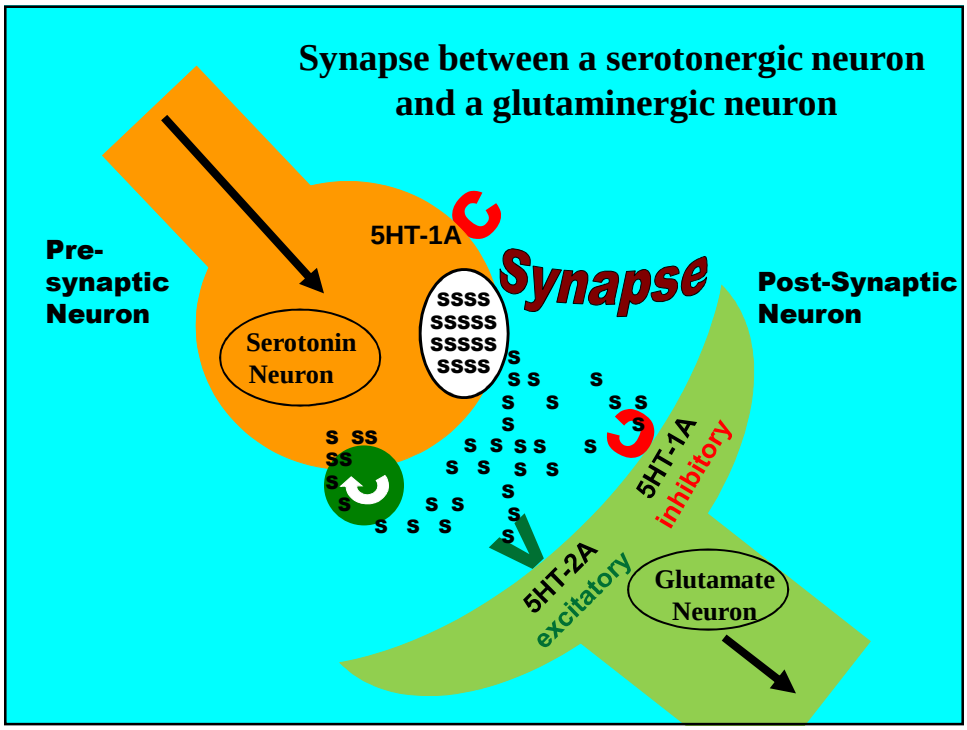
Stahl, S. & Shayegan, D.; J Clin Psych; 2003; 64 [suppl 19]: 6-12

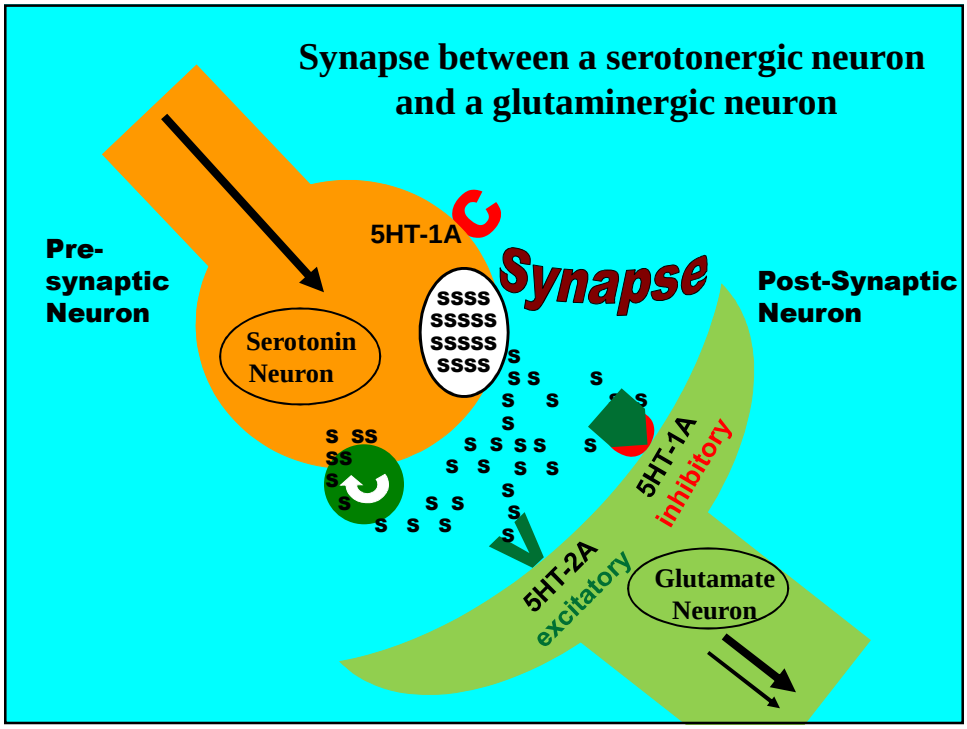

Neuronal Transmission
Information Flow
Pre-
synaptic
Neuron
5HT-1
Synapse
5HT-1
5HT-2
5HT- 4
Post-Synaptic
Neuron

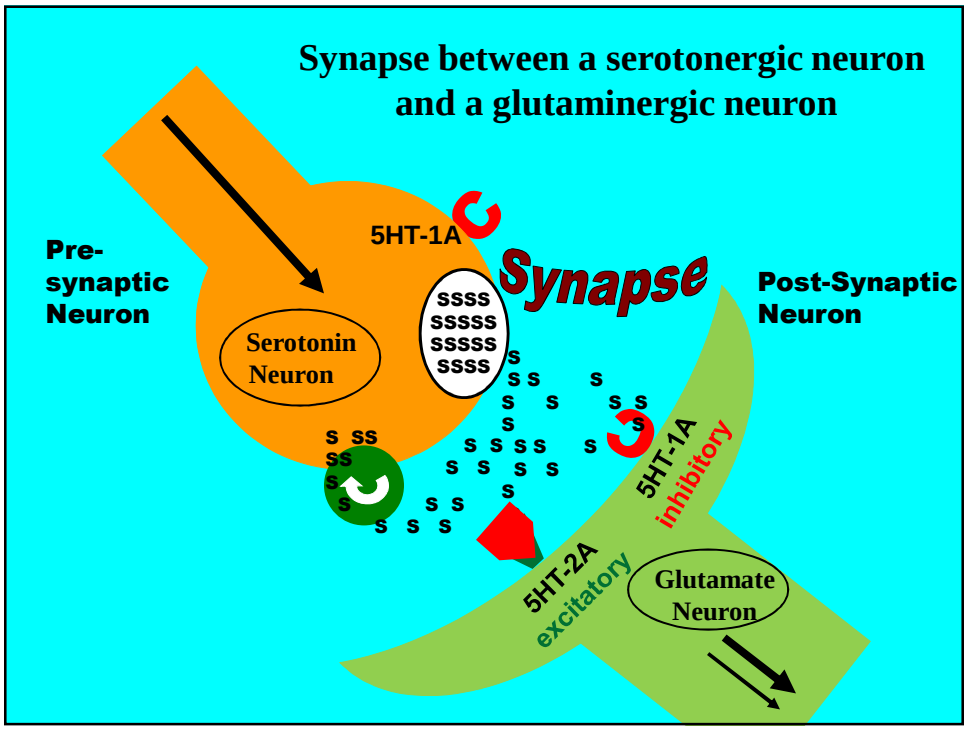

Neuronal Transmission
Information Flow
Pre-
synaptic
Neuron
5HT-1A
Synapse
5HT-1D
5HT-1A
5HT-2A
5HT-2C
5HT- 4
Post-Synaptic
Neuron
Celada P, et al. J Psychiatry Neurosci 2004; 29 (4): 252-65.



Celada P, et al. J Psychiatry Neurosci 2004; 29 (4): 252-65.




Synapse between a serotonergic neuron and a glutaminergic neuron
Pre-synaptic Neuron
5HT-1A
Synapse
Post-Synaptic Neuron
Serotonin Neuron
5HT-1A inhibitory
5HT-2A excitatory
Glutamate Neuron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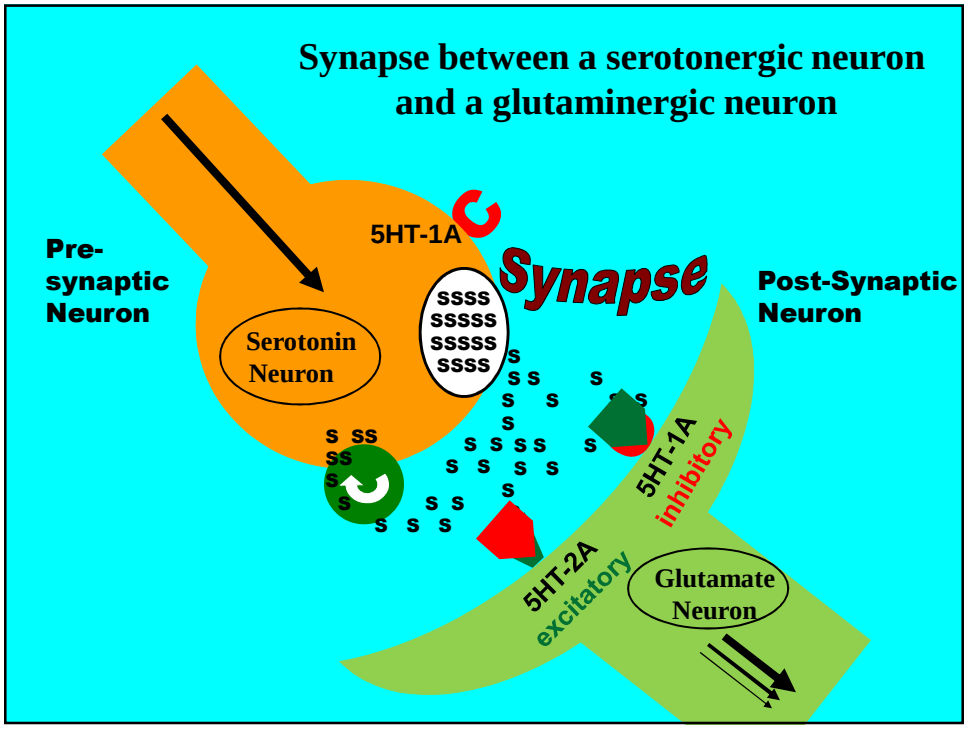
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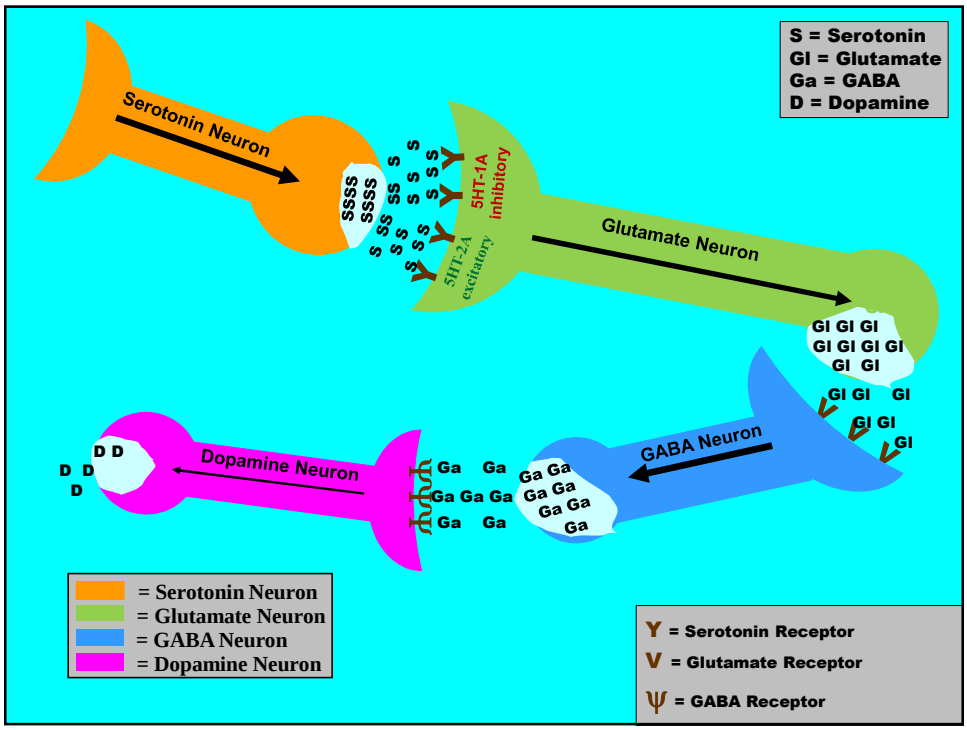
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Gl = Glutamate
Ga = GABA
D = Dopamine
Serotonin Neuron
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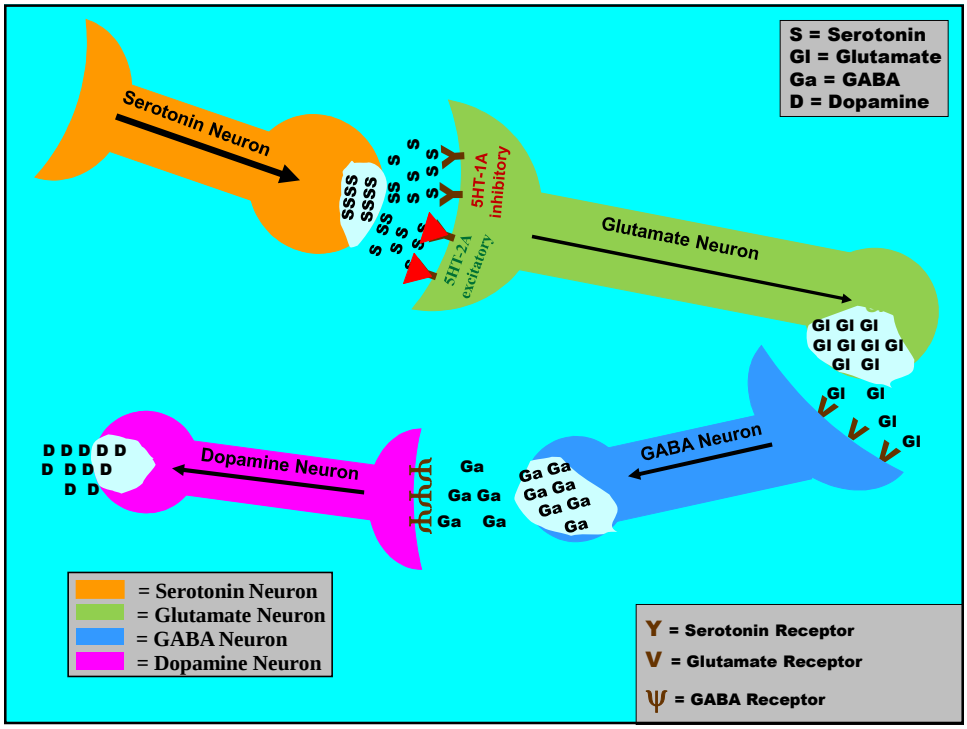
= Dopamine Neuron
Y = Serotonin Receptor
V = Glutamate Receptor
Ψ = GABA Receptor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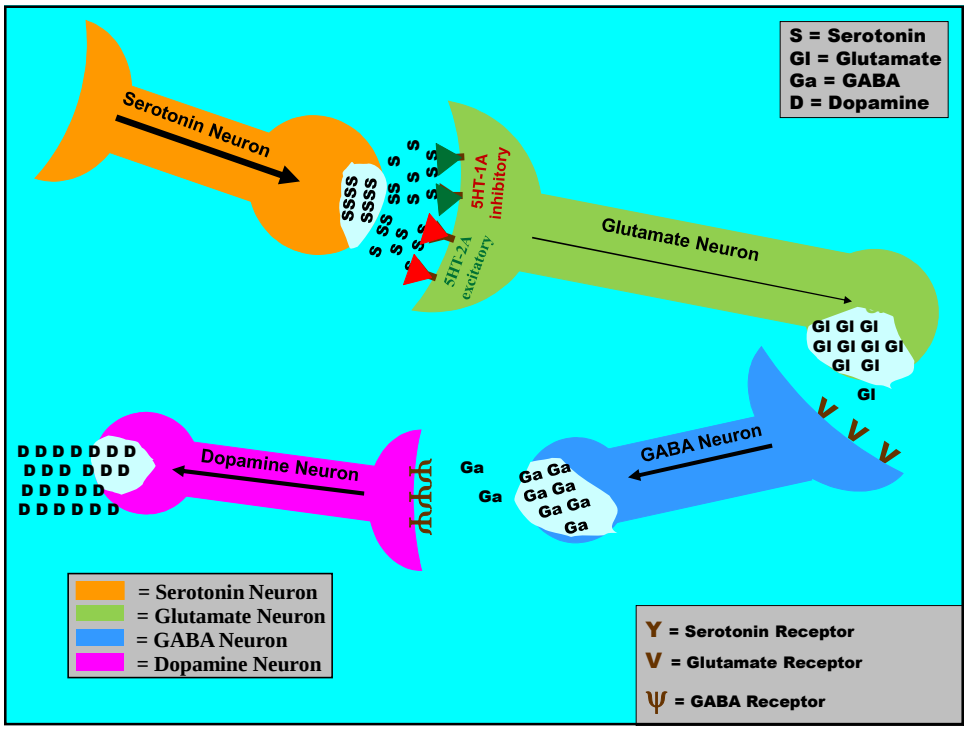
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The Adrenergic System

- Epinephrine = E
- Norepinephrine = NE
- Noradrenergic transporter = NET
- Adrenergic receptors
  - Three families = α1, α2, β

Adrenergic Receptor Families

- Alpha 1 = α1A, α1B, and α1D
- Alpha 2 = α2A, α2B, and α2C
- Beta = β1, β2 and β3
- All are metabotropic = GPCR (G-Protein Coupled Receptors)

The Pharmacological Basis of Therapeutics; Goodman & Gilman; 10th Edition; 2001

Alpha Adrenergic Receptor Antagonism Effects

- Alpha 1 antagonism (prazosin)
  - Side effects include transient:
    - Sedation
    - Orthostasis
    - Syncope
- Alpha 2 antagonism (mirtazapine)
  - Benefits include:
    - Elevation of synaptic norepinephrine
    - Elevation of synaptic serotonin

The Pharmacological Basis of Therapeutics; Goodman & Gilman; 10th Edition; 2001

The Histamine System

- Histamine receptors = H1, H2, H3 and H4
- G-Protein Coupled Receptors
- Side effects from CNS H1 antagonism:
  - Sedation
  - Weight gain
  - Increased appetite
  - Paradoxical excitation
    - restlessness, nervousness and insomnia
- H2 antagonist currently in development
  - Histamine pre-synaptic auto-receptor
  - Increases attention and wakefulness

The Acetylcholine System

- Nicotinic Cholinergic = Ionotropic
  - Pentamer ion channels with diverse subunits
  - 17 genes code for:
    - 10 alpha subunits
    - 4 beta subunits
    - 1 gamma subunit
    - 1 delta subunit
    - 1 epsilon subunit
- Varenicline (Chantix)
  - Alpha 4 (two subunits)/beta 2 (three subunits) antoginst/partial agonist
  - At 1mg BID antagonizes 100% of this ionotropic receptor
  - Simultaneously agonizes 45% of this receptor resulting in dopamine release in the nucleus accumbens

The Acetylcholine System

- Muscarinic Cholinergic = Metabotropic
  - All are G Protein Coupled Receptors
  - M1, M2, M3 , M4 and M5
  - Side effects from M1 Anticholinergic activity
    - Dry mouth, constipation, urinary retention, blurred vision, orthostasis and cognitive impairment
  - N-des-methyl clozapine agonizes M1 receptor
    - May explain clozapine's improvement of negative symptoms

CYP450 Metabolic Pathways of the Atypical Antipsychotics

Atypical	Primary	Secondary
Aripiprazole	2D6, 3A4	-
Asenapine	UGT1A4, 1A2	3A4, 2D6
Clozapine	1A2	3A4, 2D6, 2C9, 2C19
Iloperidone	2D6, 3A4	-
Lurasidone	3A4	-
Olanzapine	1A2	2D6
Paliperidone	3A4	-
Quetiapine	3A4	-
Risperidone	2D6, 3A4	-
Ziprasidone	Aldehyde oxidase	3A4
Brexpiprazole	2D6, 3A4	-
Cariprazine	3A4	2D6

FDA approved product inserts for each antipsychotic

Half-lives of the Atypical Antipsychotics

Atypical	T 1/2	Oral Tmax	Protein Binding
Aripiprazole	75 hours	3-5 hours	99%
Asenapine	24 hours	1 hour	95%
Clozapine	12 hours	2.5 hours	97%
Iloperidone	18-33 hours	2-4 hours	95%
Lurasidone	18 hours	1-3 hours	99%
Olanzapine	30 hours	6 hours	93%
Quetiapine	6 hours	1.5 hours	83%
Paliperidone	23 hours	24 hours	74%
Risperidone*	20-30 hours	1 hour	90%
Ziprasidone	7 hours	6-8 hours	99%
Brexpiprazole	91 hours	4 hours	99%
Cariprazine	1-3 weeks	3-6 hours	91-97%

2010 FDA approved product inserts; *2007 FDA approved product insert.

Active Metabolites of Atypical Antipsychotics

Atypical Antipsychotic	Metabolite
Clozapine (Clozaril)	N-desmethylclozapine
Risperidone (Risperdal)	9-hydroxyrisperidone (paliperidone)
Olanzapine (Zyprexa)	no active metabolites
Quetiapine (Seroquel)	N-desalkylquetiapine (norquetiapine)
Ziprasidone (Geodon)	no active metabolites
Aripiprazole (Abilify)	dehydro-aripiprazole
Paliperidone (Invega)	no active metabolites
Iloperidone (Fanapt)	P88, P95
Asenapine (Saphris)	"primarily due to the parent drug"
Lurasidone (Latuda)	"primarily due to the parent drug"
Brexpiprazole (Rexulti)	"DM-3411 is considered not to contribute"
Cariprazine (Vraylar)	desmethyl and didesmethyl cariprazine

Equilibrium dissociation constants for antipsychotic drugs at human brain receptors

	Aripipraz*	Haloperidol	Ziprasidone	9-OH-ris	Risperidone	Olanzapine	Clozapine	Quetiapine
D-2	0.34	2.6	2.6	2.8	3.77	20	210	770
5HT-2A	3.4	61	0.12	1.21	0.15	1.48	2.59	31
2HT-2C	15	4,700	0.9	48	32	4.1	4.8	3,500
5HT-1A	1.7	1,800	1.9	480	190	610	160	300
5HT-1D	-	40	2.4	19	3.9	150	130	560
Alpha-1	57	17	2.6	10.1	2.7	44	6.8	8.1
Alpha-2	-	600	154	80	8	280	15	80
histamine	61	260	4.6	3.4	5.2	0.087	3.1	19
M-cholin	>1000	>10,000	2,440	8,800	34,000	36	9	1,400

Richelson E, Souder T: Binding of antipsychotic drugs to human brain receptors: Focus on newer generation compounds. Life Sci 68: 29-39, 2000 [Kd (nM)]
*From FDA approved product insert - 2007 [Ki (nM)]

Receptor binding affinities of haloperidol

Receptor	Kd (nM)
Dopamine D-2	2.6
Alpha-adrenergic-1	17
Serotonin 5-HT 1D	40
Serotonin 5-HT 2A	61
Histaminergic	260
Alpha-adrenergic-2	600
Serotonin 5-HT 1A	1,800
Serotonin 5-HT 2C	4,700
Cholinergic- Muscarinic	>10,000

Based on data from:
Richelson E, Souder T: Binding of antipsychotic drugs to human brain receptors: Focus on newer generation compounds. Life Sci 68: 29-39, 2000

Receptor binding affinities of clozapine

Receptor	Ki (nM)
Histaminergic 1	1.1
Alpha-adrenergic 1A	1.6
Serotonin 5HT 6	4.0
Serotonin 5-HT 2A	5.4
Cholinergic- Muscarinic 1	6.2
Serotonin 5-HT 7	6.3
Serotonin 5-HT 2C	9.4
Alpha-adrenergic-2A	90
Serotonin 5-HT 3	95
Serotonin 5-HT 1A	120
Dopamine D-2	160

FDA approved 2013 product insert

Receptor binding affinities of olanzapine

Receptor	Ki (nM)
Serotonin 5-HT 2A	4
Serotonin 5-HT 6	5
Histaminergic 1	7
Serotonin 5-HT 2C	11
Alpha-adrenergic 1	19
Dopamine D-2	20
Serotonin 5-HT 3	57
Cholinergic- Muscarinic	73
Alpha-adrenergic-2	280

FDA approved 2013 product insert

Receptor binding affinities of quetiapine and its active metabolite N-desalkyl quetiapine (norquetiapine)

Receptor	Ki (nM) quetiapine	Ki (nM) norquetiapine
Histamine 1	4.41	1.15
Alpha-adrenergic 1B	14.6	46.4
Serotonin 5-HT 2A	38	2.9
Norepinephrine transporter	>1000	34.8
Serotonin 5-HT 1A	1040	191
Dopamine D-2	626	489
Cholinergic- Muscarinic	1,086	38.3
Alpha-adrenergic 2	617	1290

FDA approved 2013 product insert

Receptor binding affinities of:

risperidone

Receptor	Kd (nM)
Serotonin 5-HT 2A	0.15
Alpha-adrenergic-1	2.7
Dopamine D-2	3.77
Serotonin 5-HT 1D	3.9
Histaminergic	5.2
Alpha-adrenergic-2	8
Serotonin 5-HT 2C	32
Serotonin 5-HT 1A	190
Cholinergic-Muscarinic	34,000

9-OH-risperidone

Receptor	Kd (nM)
Serotonin 5-HT 2A	1.21
Dopamine D-2	2.8
Histaminergic	3.4
Alpha-adrenergic-1	10.1
Serotonin 5-HT 1D	19
Serotonin 5-HT 2C	48
Alpha-adrenergic-2	80
Serotonin 5-HT 1A	480
Cholinergic- Muscarinic	8,800

Richelson E, Souder T: Binding of antipsychotic drugs to human brain receptors: Focus on newer generation compounds. Life Sci 68: 29-39, 2000

Receptor binding affinities of ziprasidone

Receptor	Ki (nM)
Serotonin 5-HT 2A	0.4
Serotonin 5-HT 2C	1.3
Serotonin 5-HT 1D	2.0
Serotonin 5-HT 1A	3.4
Dopamine D-2	4.8
Alpha-adrenergic 1	10
Histaminergic 1	47
Cholinergic- Muscarinic	>1,000

FDA approved 2014 product insert

Receptor binding affinities of aripiprazole

Receptor	Ki (nM)	Activity
Dopamine D-2	0.34	Ant/Part Agon
Serotonin 5-HT 1A	1.7	Ant/Part Agon
Serotonin 5-HT 2A	3.4	Antagonist
Serotonin 5-HT 2C	15	Antagonist
Serotonin 5-HT 7	39	Antagonist
Alpha-adrenergic-1	57	Antagonist
Histaminergic	61	Antagonist
Cholinergic-Muscarinic	>1000	Antagonist

FDA approved 2014 product insert

Receptor binding affinities of iloperidone

Receptor	Ki (nM)
Alpha-adrenergic-1	0.36
Serotonin 5-HT 2A	5.6
Dopamine D-2	6.3
Serotonin 5-HT 7	22
Serotonin 5-HT 1A	168
Histaminergic	473
Cholinergic-Muscarinic	>1000

FDA approved 2014 product insert

Receptor binding affinities of asenapine
(limited receptors – see next slide for additional receptor Ki's)

Receptor	Ki (nM)
Serotonin 5-HT 2C	0.03
Serotonin 5-HT 2A	0.06
Serotonin 5-HT 7	0.13
Histaminergic	1.0
Alpha-adrenergic-1,2	1.2
Dopamine D-2	1.3
Serotonin 5-HT 1A	2.5
Cholinergic-Muscarinic	8128

FDA approved 2014 product insert

Receptor binding affinities of asenapine

FDA approved 2014 product insert

Receptor	Ki (nM)
Serotonin 5-HT 2C	0.03
Serotonin 5-HT 2A	0.06
Serotonin 5-HT 7	0.13
Serotonin 5-HT 2B	0.16
Serotonin 5-HT 6	0.25
Dopamine D-3	0.42
Histaminergic	1.0
Dopamine D-4	1.1
Alpha-adrenergic-1,2	1.2
Dopamine D-2	1.3
Dopamine D-1	1.4
Serotonin 5-HT 5	1.6
Serotonin 5-HT 1A	2.5
Serotonin 5-HT 1B	4.0
Cholinergic-Muscarinic	8128

Receptor binding affinities of lurasidone

Receptor	Ki (nM)
Serotonin 5-HT 2A	0.5
Serotonin 5-HT 7	0.5
Dopamine D-2	1.0
Serotonin 5-HT 1A	6.4
Alpha-adrenergic-2c	11
Alpha-adrenergic-2a	41
Histamine-H-1	>1,000
Cholinergic- Muscarinic-1	>1,000

FDA approved 2013 product insert

Receptor binding affinities of brexpiprazole

Receptor	Ki (nM)	Activity
Serotonin 5-HT 1A	0.12	Ant/Part Agon
Alpha-adrenergic 1B	0.17	Antagonist
Dopamine D 2	0.3	Ant/Part Agon
Serotonin 5-HT 2A	0.47	Antagonist
Alpha-adrenergic 2C	0.59	Antagonist
Alpha-adrenergic 1D	2.6	Antagonist
Serotonin 5-HT 7	3.7	Antagonist
Alpha-adrenergic 1A	3.8	Antagonist
Histaminergic 1	19	Antagonist

FDA approved 2015 product insert

Receptor binding affinities of cariprazine

Receptor	Ki (nM)	Activity
Dopamine D-3	0.085	Ant/Part Agon
Dopamine D-2L	0.49	Ant/Part Agon
Serotonin 5-HT 2B	0.58	Antagonist
Dopamine D-2S	0.69	Ant/Part Agon
Serotonin 5-HT 1A	2.6	Ant/Part Agon
Serotonin 5-HT 2A	18.8	Antagonist
Histaminergic – 1	23.2	Antagonist
Serotonin 5-HT 2C	134	Antagonist
Noradrenergic alpha 1A	155	Antagonist
Cholinergic-Muscarinic	>1000	Antagonist

FDA approved 2016 product insert

Questions??