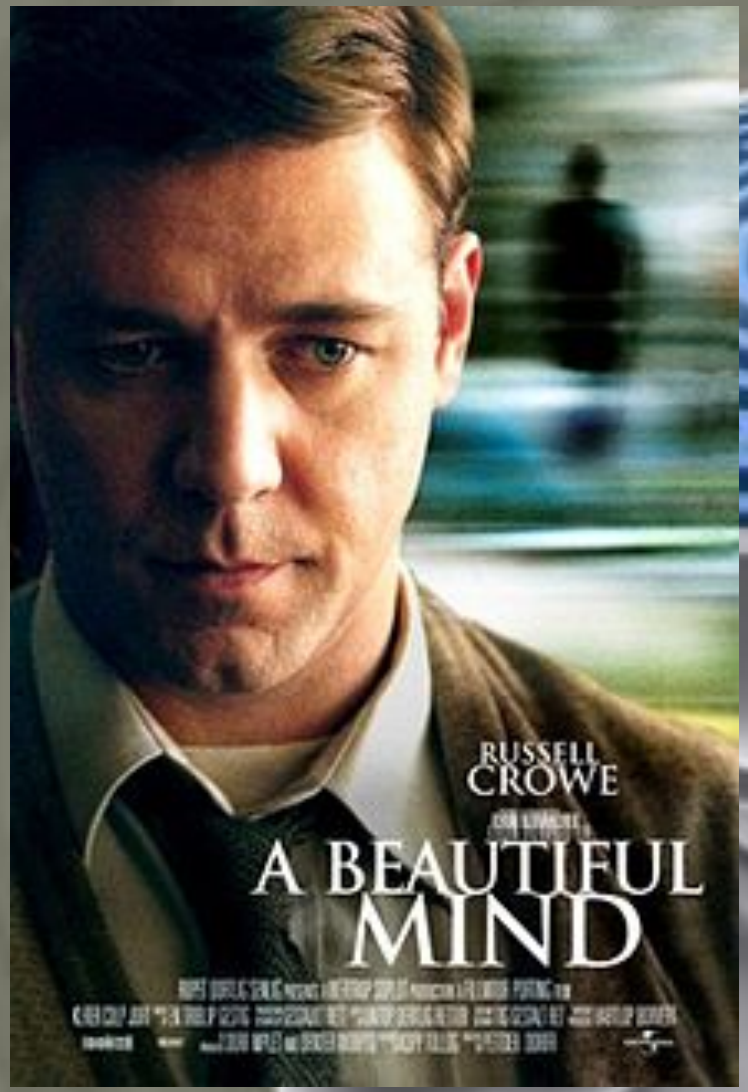


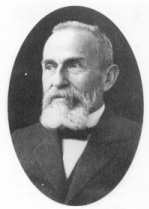
Treatment of the Psychotic Disorders: Schizophrenia

Psychosis

- Psychosis means abnormal condition of the mind characterized by a loss of contact with reality, usually including false beliefs about what is taking place or who one is (delusions) and seeing or hearing things that aren't there (hallucinations)

- A syndrome present in many illnesses, including intoxication
  - remove known cause or treat underlying illness
  - treat symptomatically with antipsychotic medications

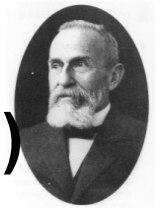
Emil Kraepelin (1856-1926)
Pioniere della psichiatria moderna preconizzó che le malattie psichiatriche fossero causate da alterazioni biologiche specifiche.
Introdusse una classificazione dei disturbi mentali basata sulla clinica che teneva conto non solo dei sintomi e dei segni, ma anche del loro decorso e dell'esito della malattia.
Propose quindi la distinzione fra disturbi del pensiero (dementia precox) e dell'umore (s. depressivo maniacale)



Eugene Bleuler (1857-1940)
Noto per avere coniato il termine schizophrenia, la malattia chiamata precedentemente *dementia praecox*. Bleuler realizzó che non compare sempre in individui giovani, e la nominó dal greco divisione (schizo) e mente (phrene).

SCHIZOPHRENIA OVERVIEW

- **It is the most common psychosis.**
- **Schizophrenia literally means 'split mind'. However, this makes it the most misused psychological term as schizophrenia does not really manifest as a split or multiple personality.**
- **The term was invented by Eugen Bleuler (1857-1940)**



to refer to patients who had a misplaced sense of reality.

- **Schizophrenia occurs in approximately 1% of the world's population.**
- **It is characterised by positive and negative symptoms.**

What is schizophrenia?

- A mental illness among the world's top ten causes of long-term disability
- Develops between the ages of 16 and 30
- Cause is unknown, but various theories have been proposed in regards to a biological cause
- In addition to biological causes, studies indicate a multitude of genetic and environmental factors

Clinical Features

- **Brain disorder - impairs ability to perceive, understand and interpret the environment.**

- **Impaired function - social and motivational**

- **Behavioral syndrome - positive and negative symptoms**

- **Genetically complex**

- Genetic & environmental factors

- Multiple genes with variable penetrance

Symptoms of Schizophrenia

- **Positive symptoms**: excesses of thoughts, emotions, and behavior (Delusions, hallucinations, disordered thoughts
- **Negative symptoms**: deficits of thoughts, emotions, and behavior
- **Psychomotor symptoms**: odd gestures, repeated grimaces, or awkward movements

Delusions (Positive Symptom)

- Fixed, false beliefs
- Types
  - Bizarre – something that the person's culture would view as implausible
  - Thought insertion – thoughts are being inserted into person's head
  - Thought withdrawal – thoughts are being taken out of person's head
  - Thought broadcast – thoughts are being broadcasted
  - Control – person is being controlled by something or someone else
  - Somatic – things happening to body
  - Nihilistic – person believes s/he is dead or does not exist
  - Grandiose – exaggeration of self
  - Religious – related to religious beliefs or themes
  - Persecutory – person is being chased, watched, or persecuted
  - Reference – neutral stimuli have special meaning to the person

Hallucinations (Positive Symptom)

- False sense perception
- Types
  - Auditory – hear something that is not there, most common hallucination
  - Tactile – feel something that is not there
  - Visual – see something that is not there, more commonly results from substance use or brain damage
  - Olfactory/Gustatory – smell or taste something that is not there

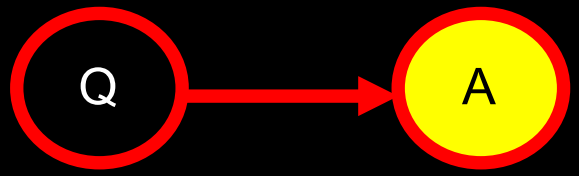
Hallucinations (Positive Symptom)

- Entra in chiesa e si strappa gli occhi ´Una voce mi ha detto di farlo
- l'uomo, un 44enne, Ë stato subito soccorso da un gruppo di fedeli
- IL PERSONAGGIO: Aldo, laureato in chimica, parla cinque lingue

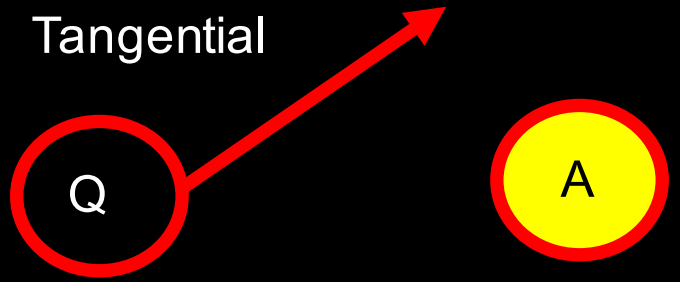
Disordered thoughts/speech (Positive Symptom)

Speech that is hard to understand or follow, impairs communication

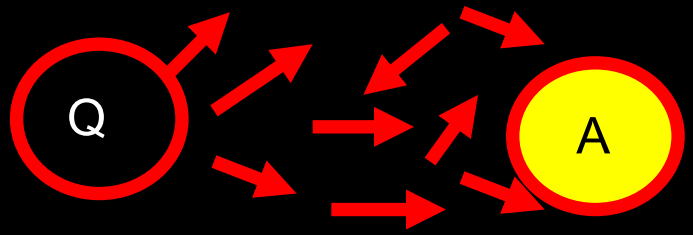
Normal: goal directed and linear



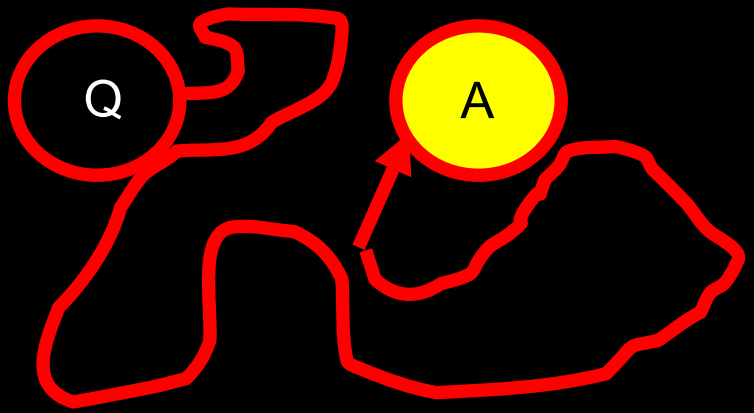
Tangential



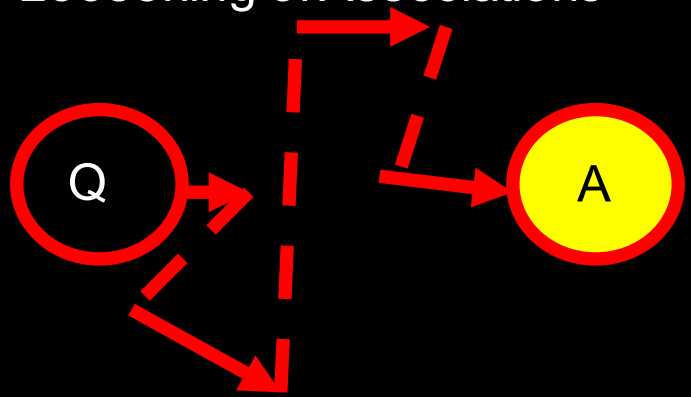
Incoherence



Circumlocution



Loosening of Associations

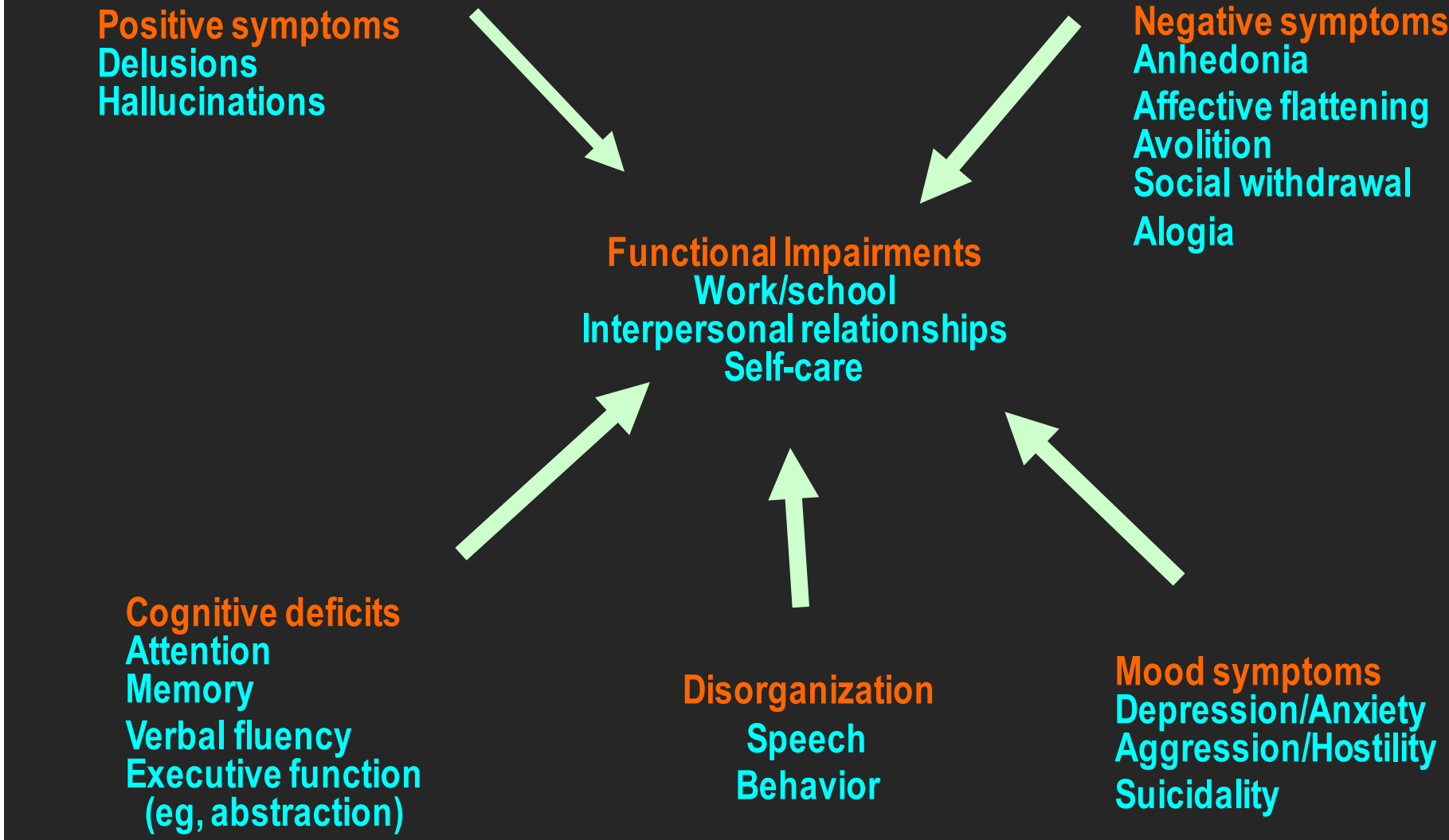


Negative Affect (Negative Symptom)

Absence or insufficiency of normal behavior

- Spectrum of Negative Symptoms
  - Avolition (or apathy) – Lack of initiation and persistence
  - Alogia – Relative absence of speech
  - Anhedonia – Lack of pleasure, or indifference
  - Affective flattening – Little expressed emotion

Features of Schizophrenia



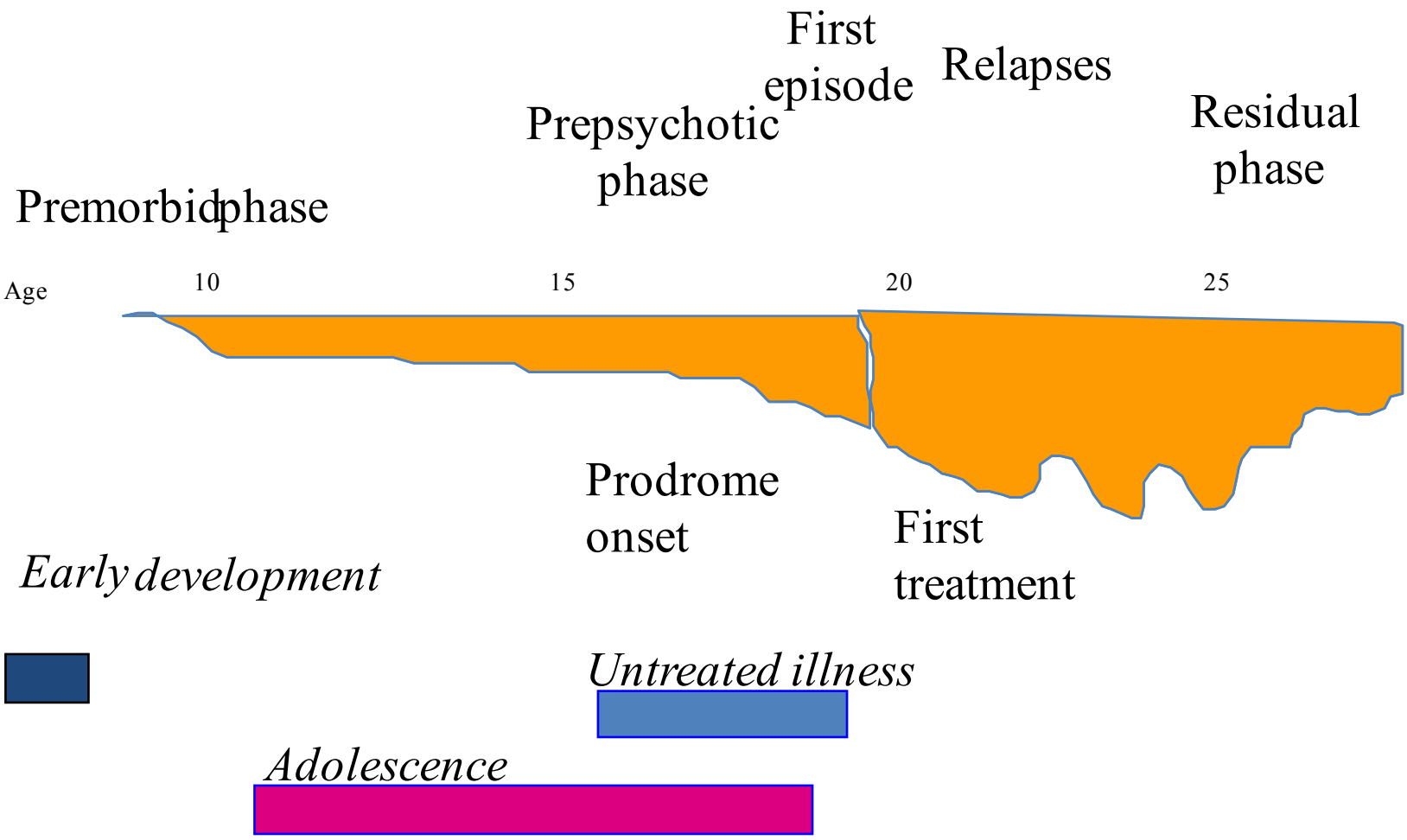
DSM-IV Schizophrenia

- 2 or more of the following for most of 1 month:
  - Delusions
  - Hallucinations
  - Disorganized speech
  - Grossly disorganized or catatonic behavior
  - Negative symptoms
- Social/occupational dysfunction
- Duration of at least 6 months
- Not due to substance abuse or a general medical disorder

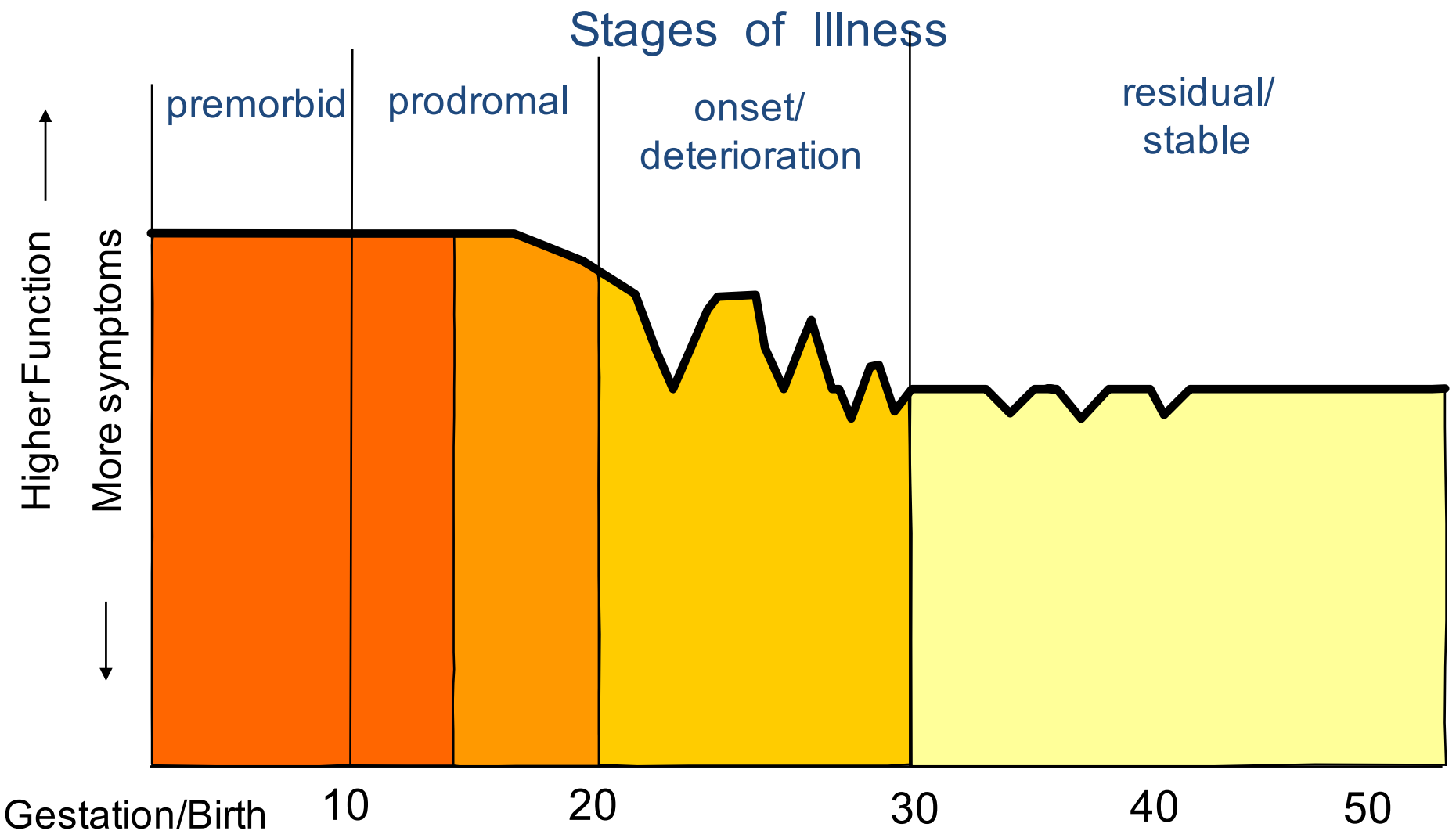
Onset, Course, and Prognosis

- Onset of schizophrenia: age 16-30 (usually earlier in men than in women)
- Onset lasts 5 years
  - Prodrome
  - Cognitive impairment
  - Psychosis/hospitalization
- Psychosis is episodic over time; negative symptoms are more stable
- No cure; less than average life-expectancy

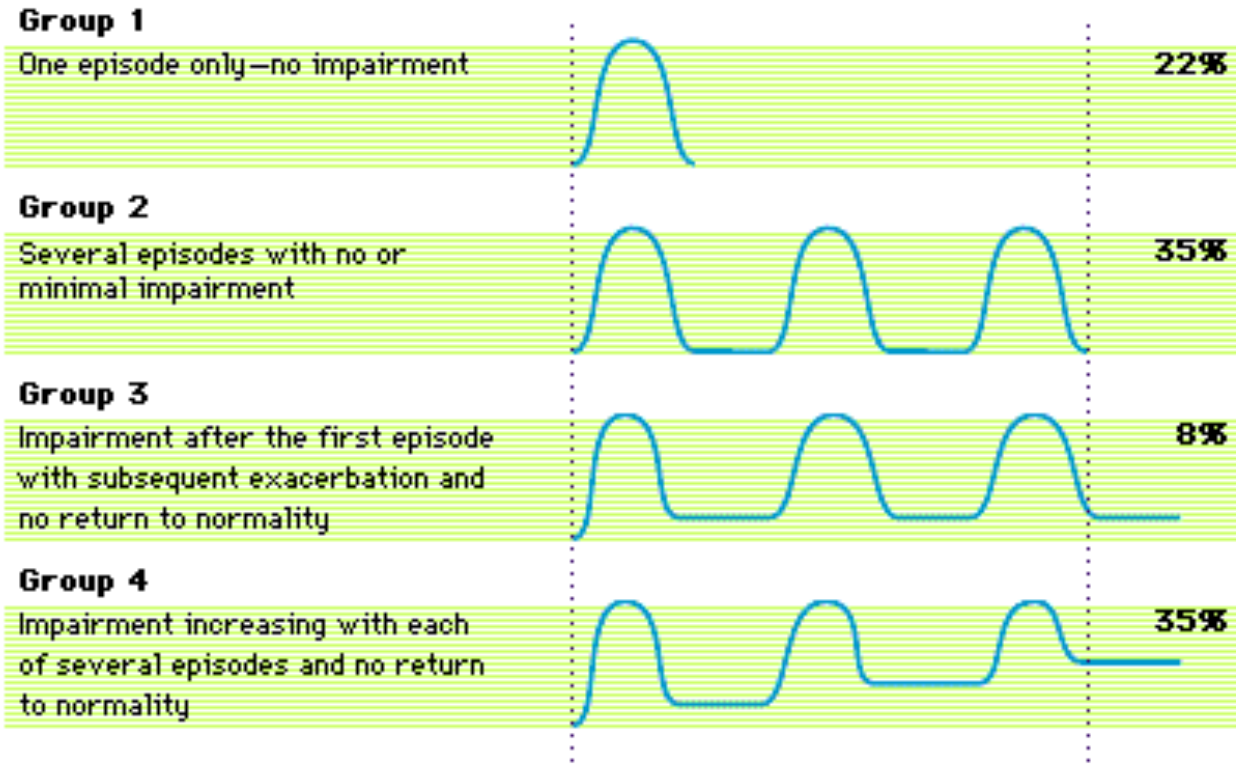
Clinical Course



Clinical Course



Clinical Course



After 30 years, of the people diagnosed with schizophrenia and regularly treated:

25% Completely Recover

35% Much Improved, relatively independent

15% Improved, but require extensive support network

10% Hospitalized, unimproved

15% Dead (Mostly Suicide

What about Suicide Risk?

- People with schizophrenia have a 50 times higher risk of attempting suicide than the general population.
- Suicide is the number one cause of premature death among people with schizophrenia, with an estimated 10% to 13% killing themselves and approximately 40% attempting suicide at least once (and as much as 60% of males attempting suicide).
- The extreme depression and psychoses that can result due to lack of treatment are the usual causes.
- These suicides rates can be compared to the general population, which is somewhere around 0.01%.

Schizophrenia and Violence

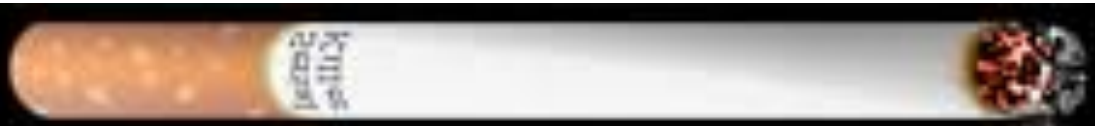
- People with schizophrenia are far more likely to harm themselves than be violent toward the public.

- Violence is not a symptom of schizophrenia.

- News and entertainment media tend to link mental illnesses including schizophrenia to criminal violence. Most people with schizophrenia, however, are not violent toward others but are withdrawn and prefer to be left alone.

Schizophrenia and Substance Abuse

- Substance abuse doesn't cause schizophrenia
- People who have schizophrenia tend to abuse alcohol and/or drugs more often than the general population.
- Substance abuse can reduce the effectiveness of treatment for schizophrenia. Amphetamines, cocaine, PCP and marijuana may worsen schizophrenia symptoms.
- Substance abuse also makes it more likely that patients will not follow their treatment plan.



Smoking and Schizophrenia

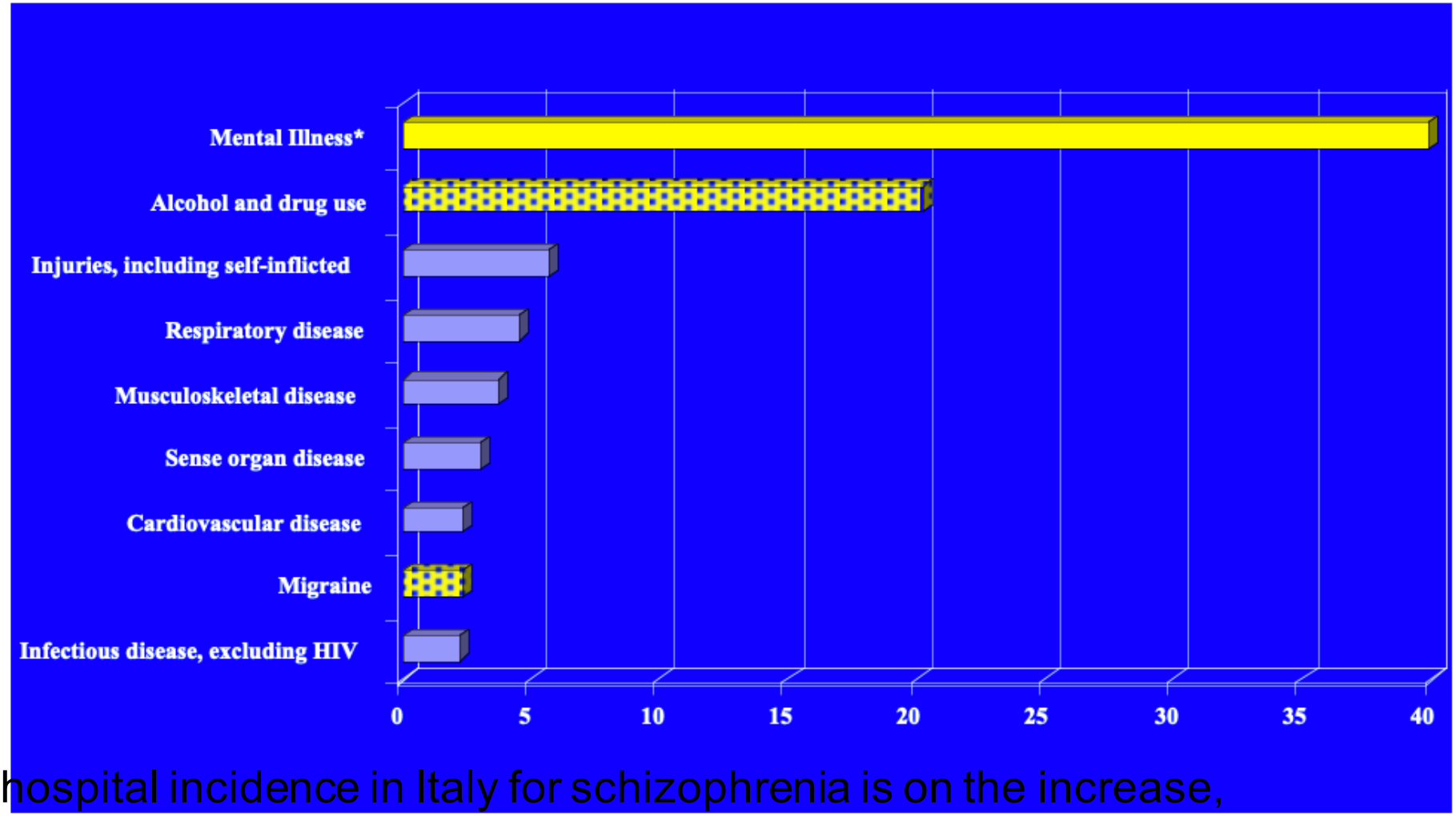
Nicotine is an especially addictive substance for people with schizophrenia.

- **~ 85% of people who have schizophrenia are also heavy cigarette smokers**
- **In patients with schizophrenia, cigarette smoking is probably the single most important risk factor for developing pulmonary disease, including asthma... and lung cancer." stated Clinical Psychiatry journal (April, 2005). Experts estimate that smoking kills 200,000 mentally ill people per year.**
- **People with schizophrenia may smoke at a high rate because nicotine reduces some of the disease symptoms**

Epidemiology and Prevalence

- 1% of population world wide
- Males and females equally affected but females have later onset and better functional outcome
- Onset in late adolescence, early adulthood
- Very high cost for the society as direct care costs and lost productivity

Causes of Disability by Illness Category
United States and Canada
15-44 years old

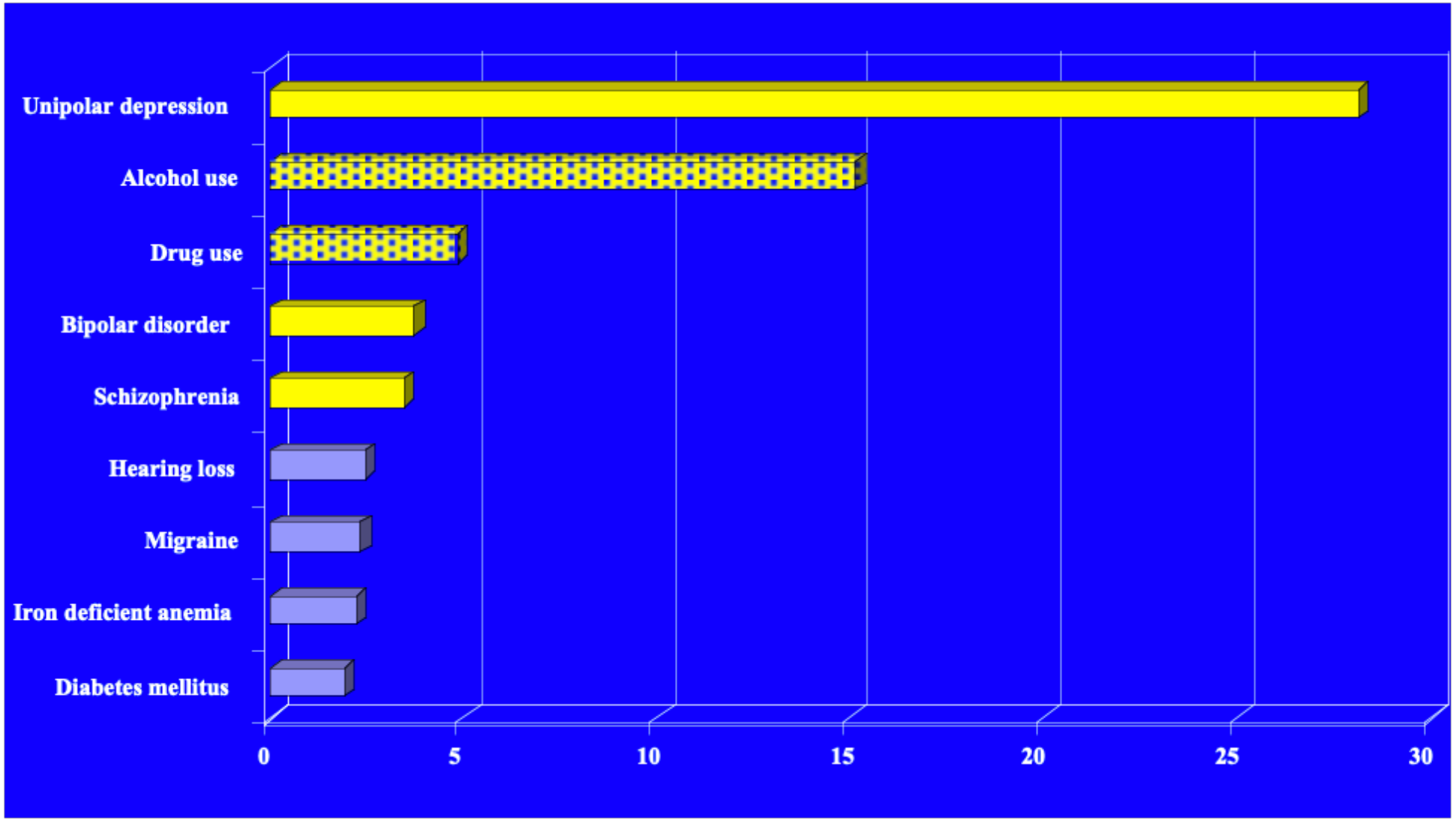


hospital incidence in Italy for schizophrenia is on the increase,

WHO World Health Report 2002

Causes of Disability by Specific Illness
United States and Canada

15-44 years old



WHO World Health Report 2002

Etiology and Risk factors

Genetic factors

- Higher rates of illness among relatives of a patient than in general population

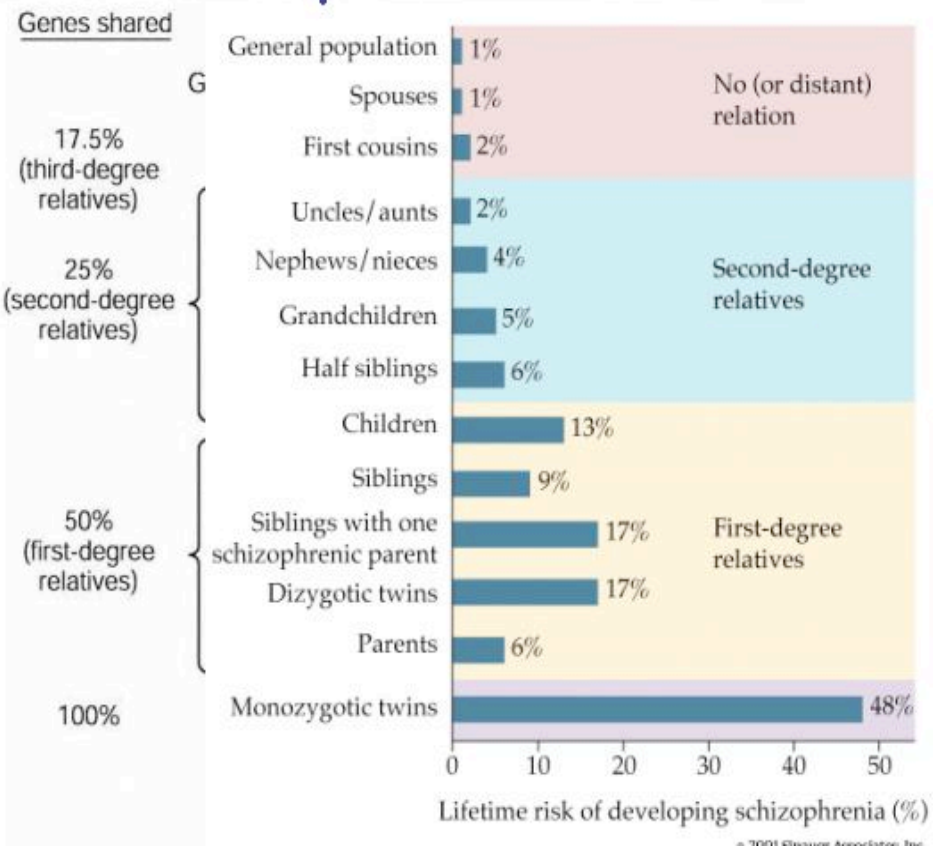
Environmental factors

- Prenatal/obstetric complications
- Brain abnormalities
- Poverty and low social class (two reasons)
- Urban residents, migrants, and minorities

Strong genetic component to schizophrenia

Note that even identical twins are not 100% concordant

i.e. genetics are not the whole story



Biological factors - Genetic

Table 1 Diagnoses in the relatives of chronic schizophrenic index probands and controls in the national sample of adoptees

Relatives	Schizoid personality	Latent schizophrenia	Chronic schizophrenia	Total relatives
Biological, of 46 chronic schizophrenic adoptees	12 4.4%	27 9.8% 0.00003*	14 5.1% 0.0008*	275
Biological, of 49 control adoptees	13 5.1%	4 1.6%	1 0.4%	253
Adoptive, of 46 chronic schizophrenic adoptees	0	2 1.8%	0	111
Adoptive, of 49 control adoptees	0	2 1.6%	0	124

*Fisher exact 1-tailed *P* for biological index and control relatives.
Reprinted from the Journal of Psychiatric Research[12].

Kety, *Nature Medicine* **5**, 1113 - 1116 (1999)

Table 1. Candidate Schizophrenia Susceptibility Genes and the Strength of Evidence in Four Domains

		Strength of evidence (0 to 5+)			
		Association with schizophrenia	Linkage to gene locus	Biological plausibility	Altered expression in schizophrenia
COMT	22q11	++	++++	+++	yes, +
DTNBP1	6p22	+++++	++++	++	yes, ++
NRG1	8p12-21	+++++	++++	+++	yes, +
RGS4	1q21-22	+++	+++	++	yes, ++
GRM3	7q21-22	+++	+	++	no, ++
DISC1	1q42	++++	++	++++	not known
DAOA (G72/G30)	13q32-34	+++	++	++	not known
DAAO	12q24	++	+	++++	not known
PPP3CC	8p21	+	++++	++++	yes, +
CHRNA7	15q13-14	+	++	+++	yes, +++
PRODH2	22q11	+	++++	++	no, +
AKT1	14q22-32	+	+	++	yes, ++
GAD1	2q31.1	++		++	yes, +++
ERBB4	2q34	++			yes, ++
FEZ1	11q24.2	++		+++	yes, ++
MUTED	6p24.3	++++	++++	+++	yes
MRDS1 (OFCC1)	6p24.3	++	++++	+	not known
NPAS3	9q34	++		++	not known
GRIK4	11q23	++	+	++	not known

Adapted from Straub and Weinberger (2006).

Biological factors - Genetic

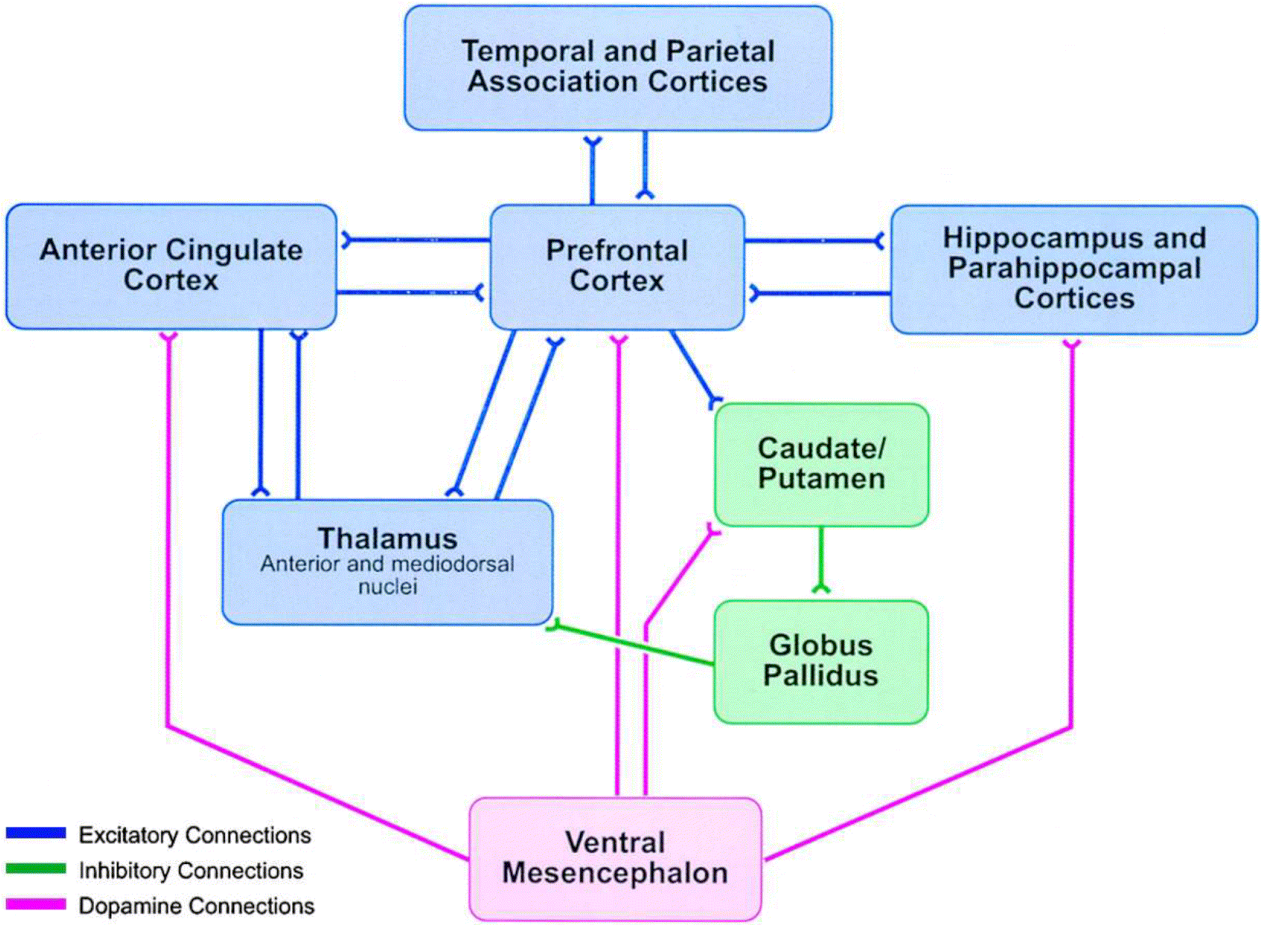
- Schizophrenia appears to be heritable which is good evidence for it being a biological disorder.
- However, it does not appear to be caused by a single gene as less than 50% of the children whose parents are both schizophrenic have the disorder.
- Thus, schizophrenia is either caused by several genes or the genetic involvement produces a propensity for the disorder.

Biological factors- NEUROLOGICAL

- Most schizophrenics show symptoms which would suggest that they are suffering from brain damage.

- Generally, evidence from CT scans suggests that there can be damage to the frontal lobes, temporal lobes and hypothalamus. Frontal lobe damage may account for some of the negative symptoms.

- Evidence suggests that the hippocampus and corpus callosum may develop abnormally in some schizophrenics.



Affected Brain Regions in Schizophrenia

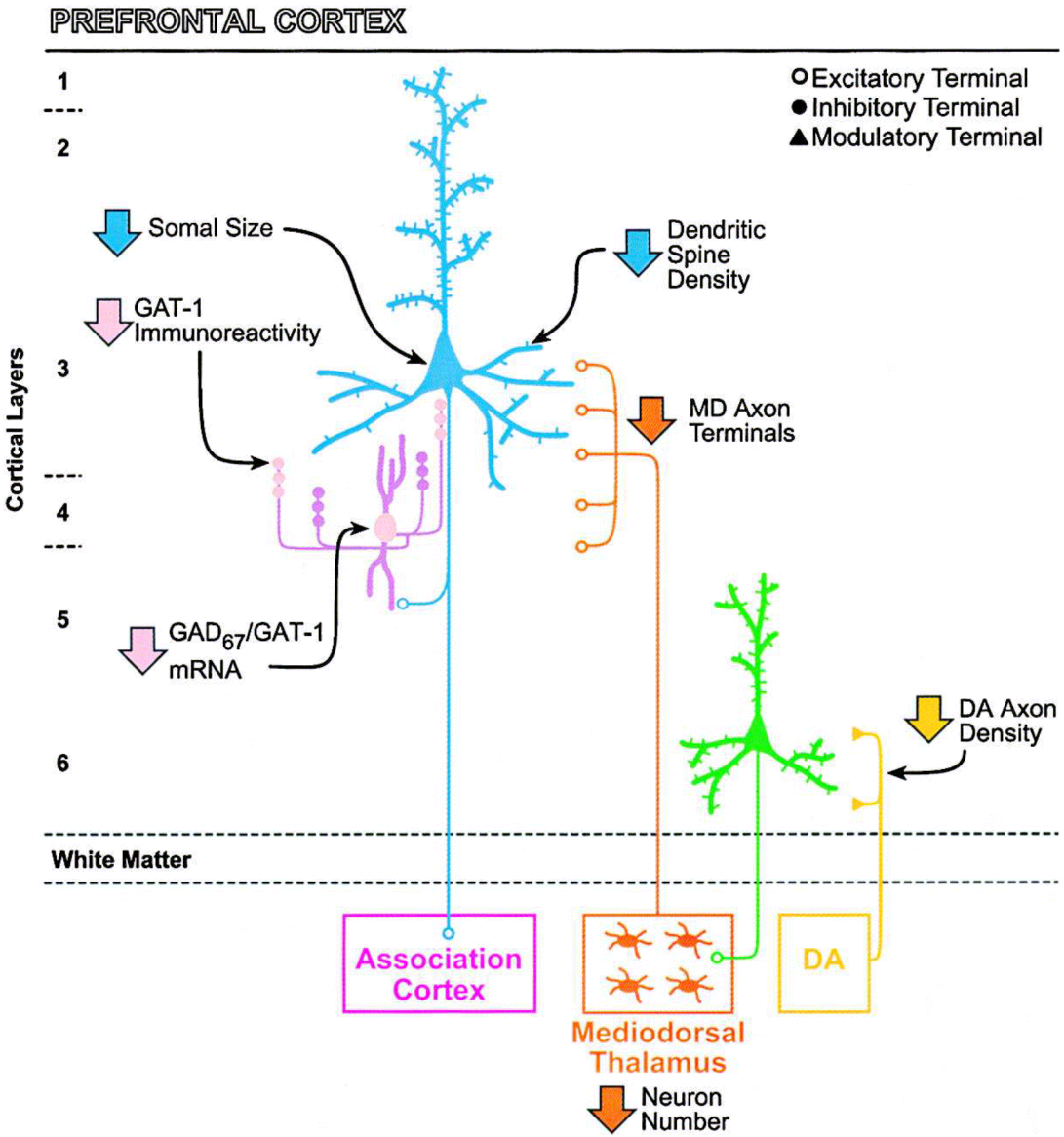
diagram of the brain regions that have been implicated in the pathophysiology of schizophrenia.

The nature of the pathophysiological changes appears to differ across regions with

a reduction in neuronal number reported in some nuclei of the thalamus,

decreases in markers of synaptic connectivity in the prefrontal cortex and hippocampal for mation,

evidence of either a functional excess or deficit of dopamine neurotransmission in the striatum and prefrontal cortex.



Cortical Circuitry in Schizophrenia

Disturbances between the mediodorsal (MD) thalamic nucleus and the dorsal prefrontal cortex (PFC). Postmortem studies reported that schizophrenics have (1) decreased number of neurons in the MD thalamic nucleus;

(2) diminished density of thalamic axon terminals, selectively in deep layers 3–4, the termination zone of MD projections to the PFC;

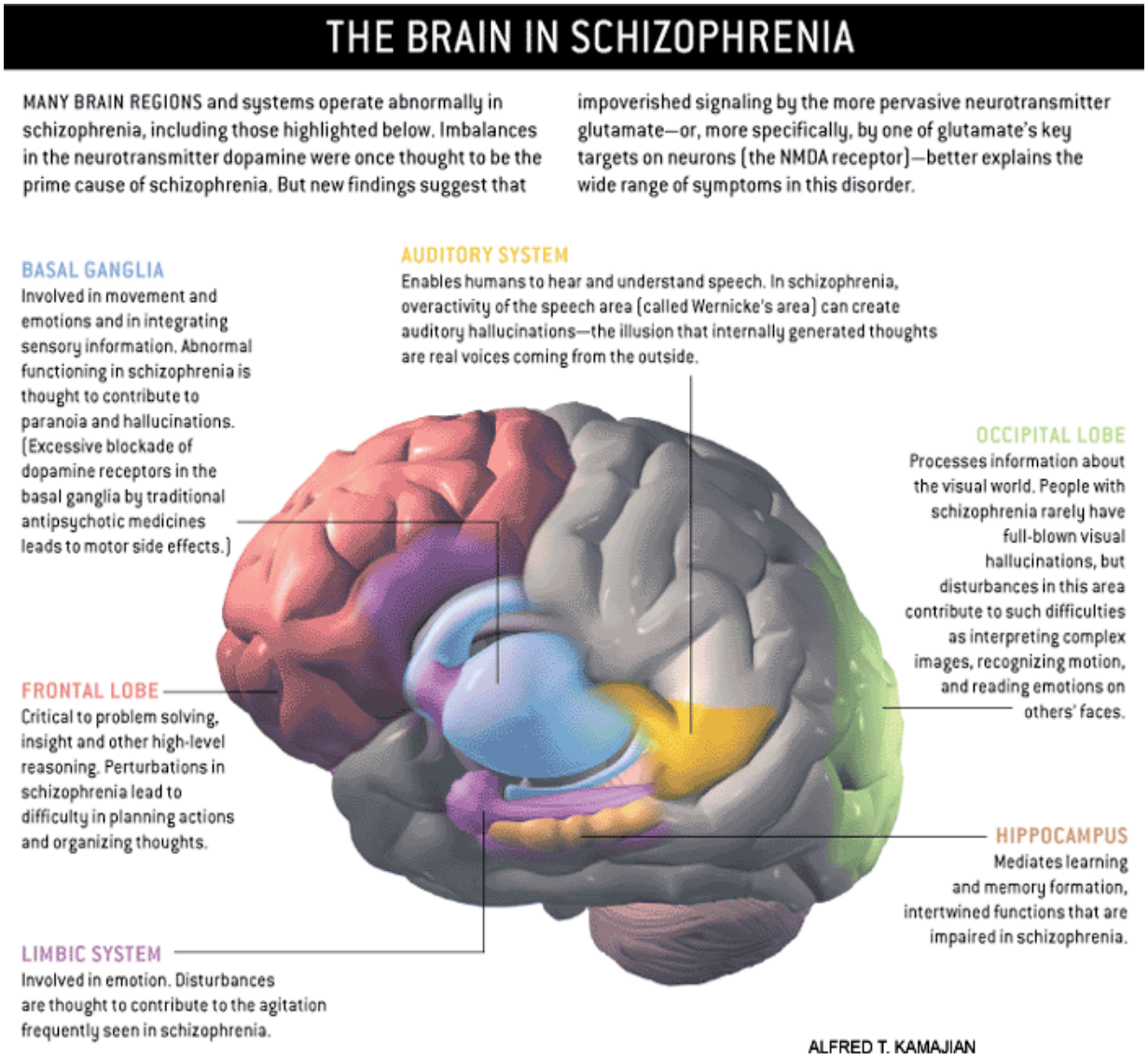
(3) reduction in spine density on the basilar dendrites of deep layer 3 pyramidal neurons, a principal synaptic target of the excitatory projections from the MD;

(4) reduced expression for GAD, the synthesizing enzyme for GABA, in a subset of PFC GABA neurons;

(5) decreased density of vertically arrayed axon terminals of GABAergic chandelier neurons, which synapse exclusively on the axon initial segment of pyramidal neurons; and

(6) decreased DA innervation of layer 6, the principal location of pyramidal neurons that provide corticothalamic feedback projections.

Biological factors- NEUROLOGICAL



Biological factors- NEUROLOGICAL

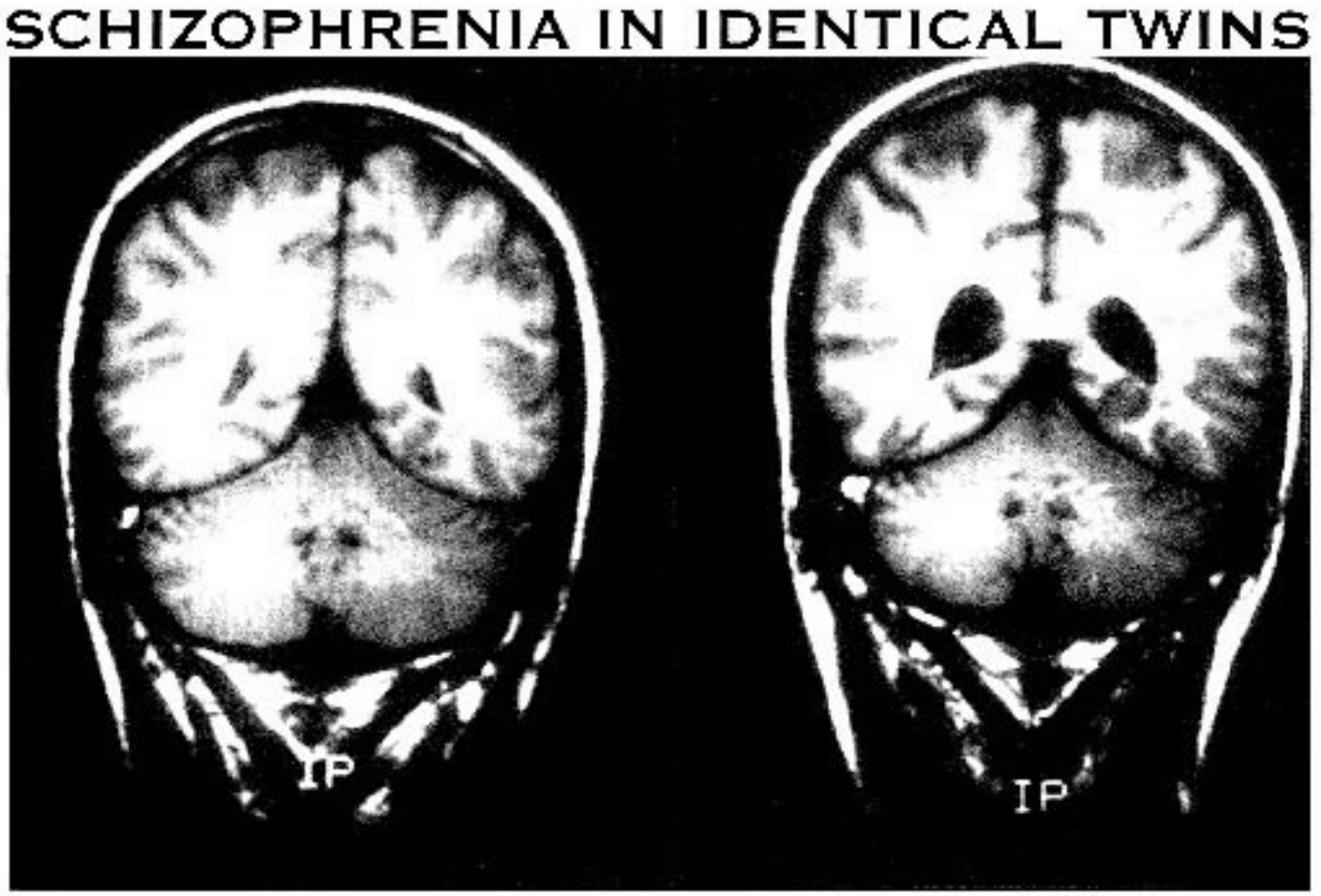
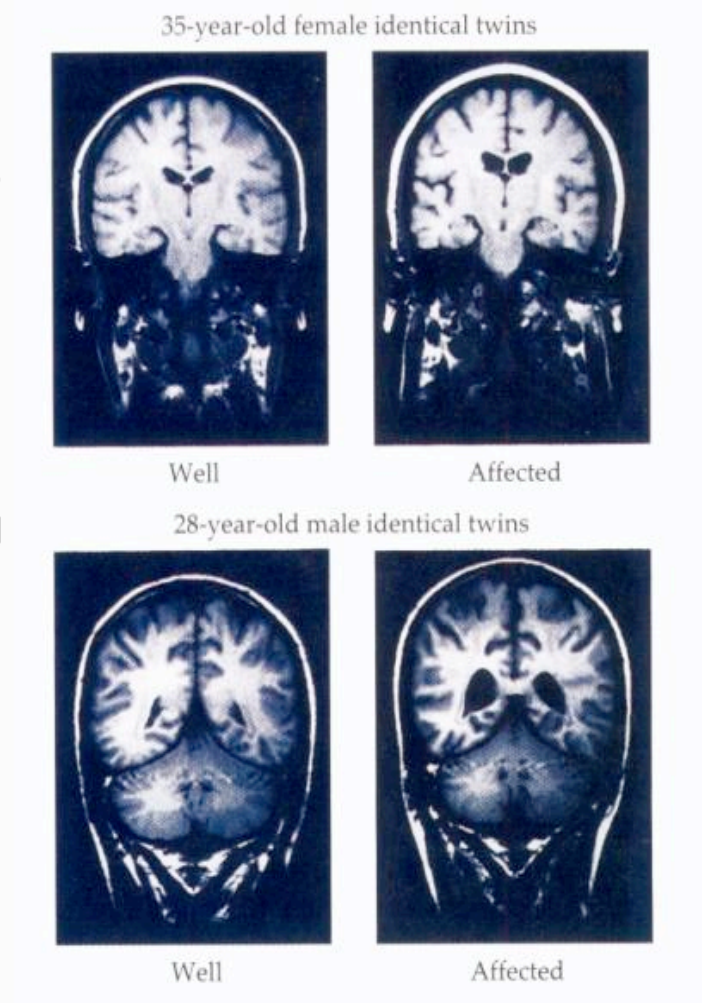


Photo courtesy of Drs. E. Fuller Torrey and Daniel Weinberger.

MRI scans of 28-year-old male identical twins showing the enlarged brain ventricles in the twin with schizophrenia (right) compared to his well brother (left).

Biological factors- NEUROLOGICAL

- MRI images of monozygotic twins discordant for schizophrenia
  - Ventricles are enlarged in schizophrenia



Biological factors- NEUROLOGICAL

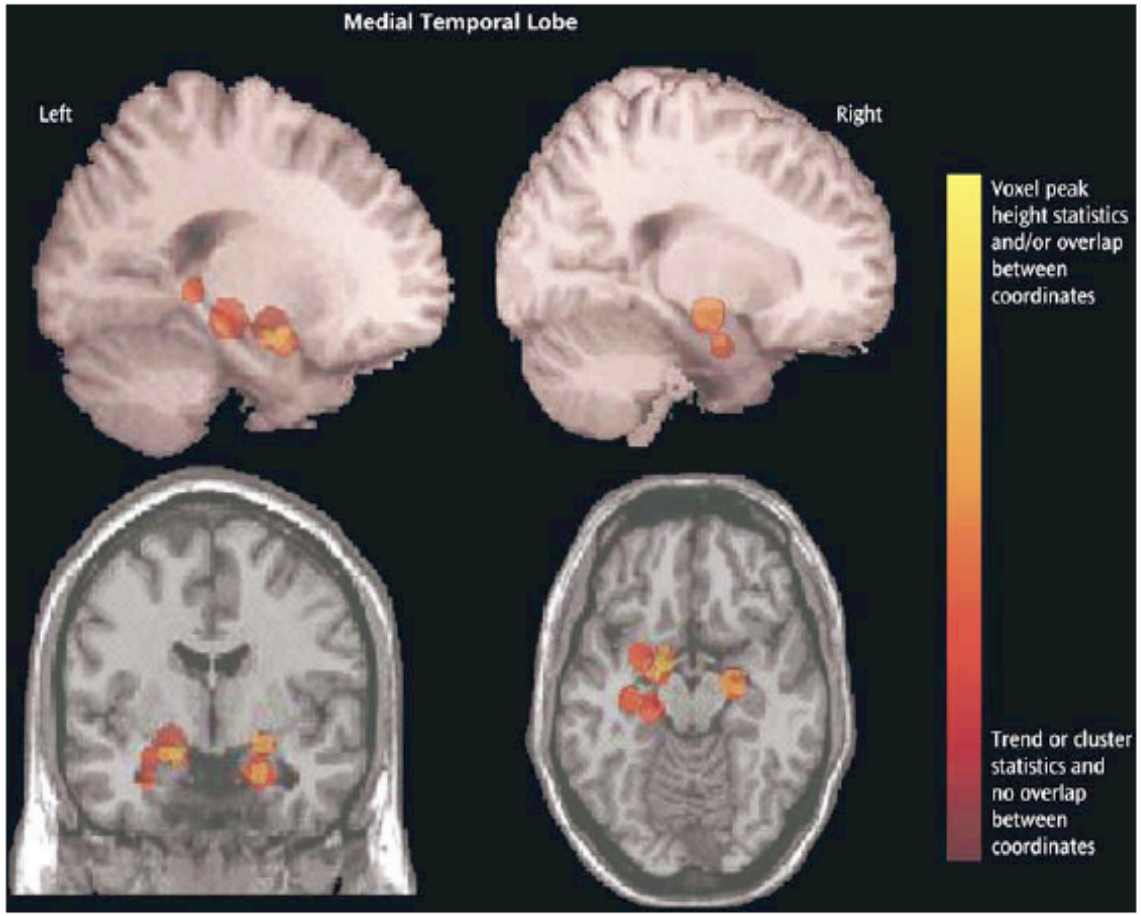
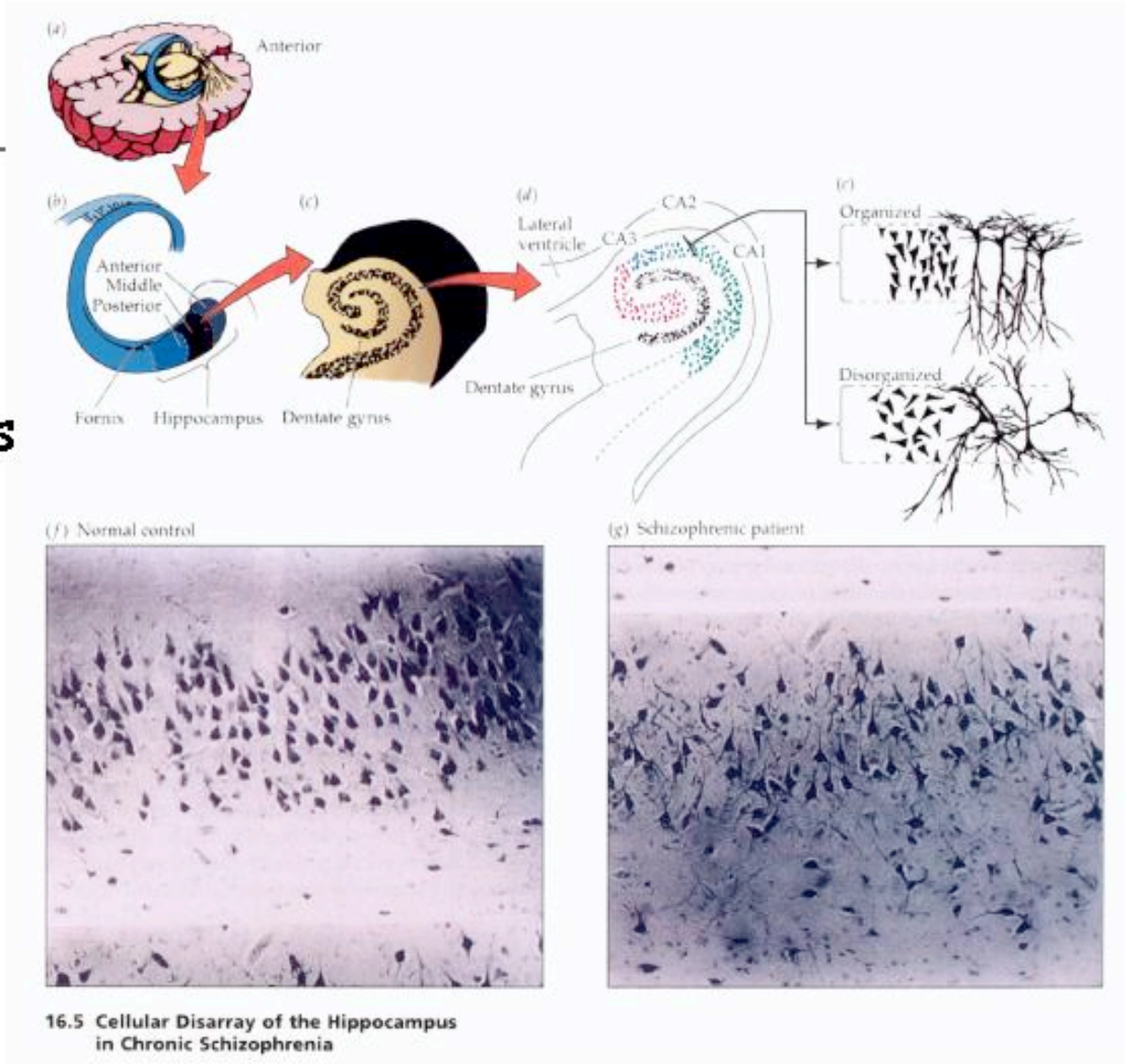


Figure 1. Structural Abnormalities Identified by MRI Scan in Schizophrenia

Location of voxel-based morphometry findings of significant volume deficits in the medial temporal lobe (including the amygdala and hippocampus) in patients with schizophrenia. The top images are left and right 3D images, respectively; the bottom left image is a coronal view, and the bottom right image is an axial view. The color scale depicts the stringency of the statistics used in the studies. From Honea et al. (2005), with permission of the publisher.

Biological factors- NEUROLOGICAL

Cellular disarray in hippocampus of schizo-phrenic

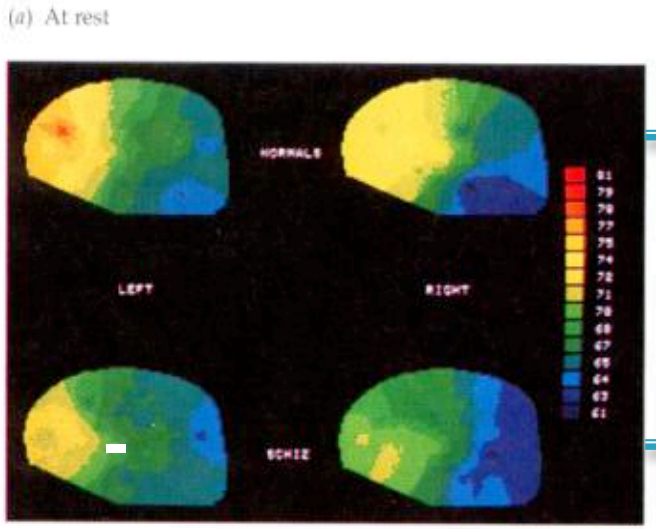


16.5 Cellular Disarray of the Hippocampus in Chronic Schizophrenia

Biological factors- NEUROLOGICAL

Hypofrontality in schizophrenia

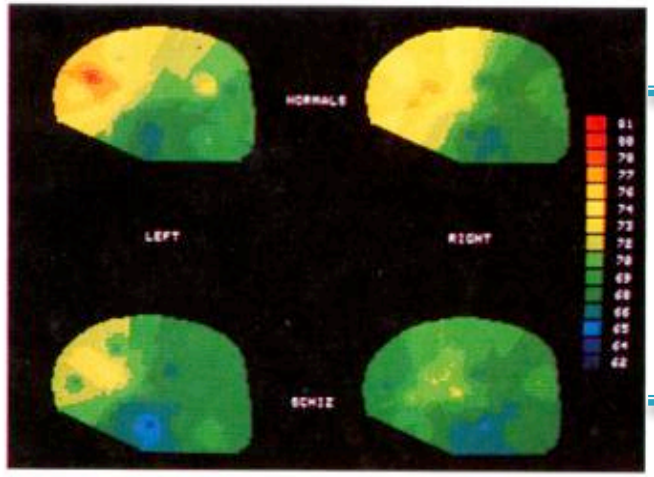
- At rest



NORMAL

SCHIZO.

- During Wisconsin Card Sorting task

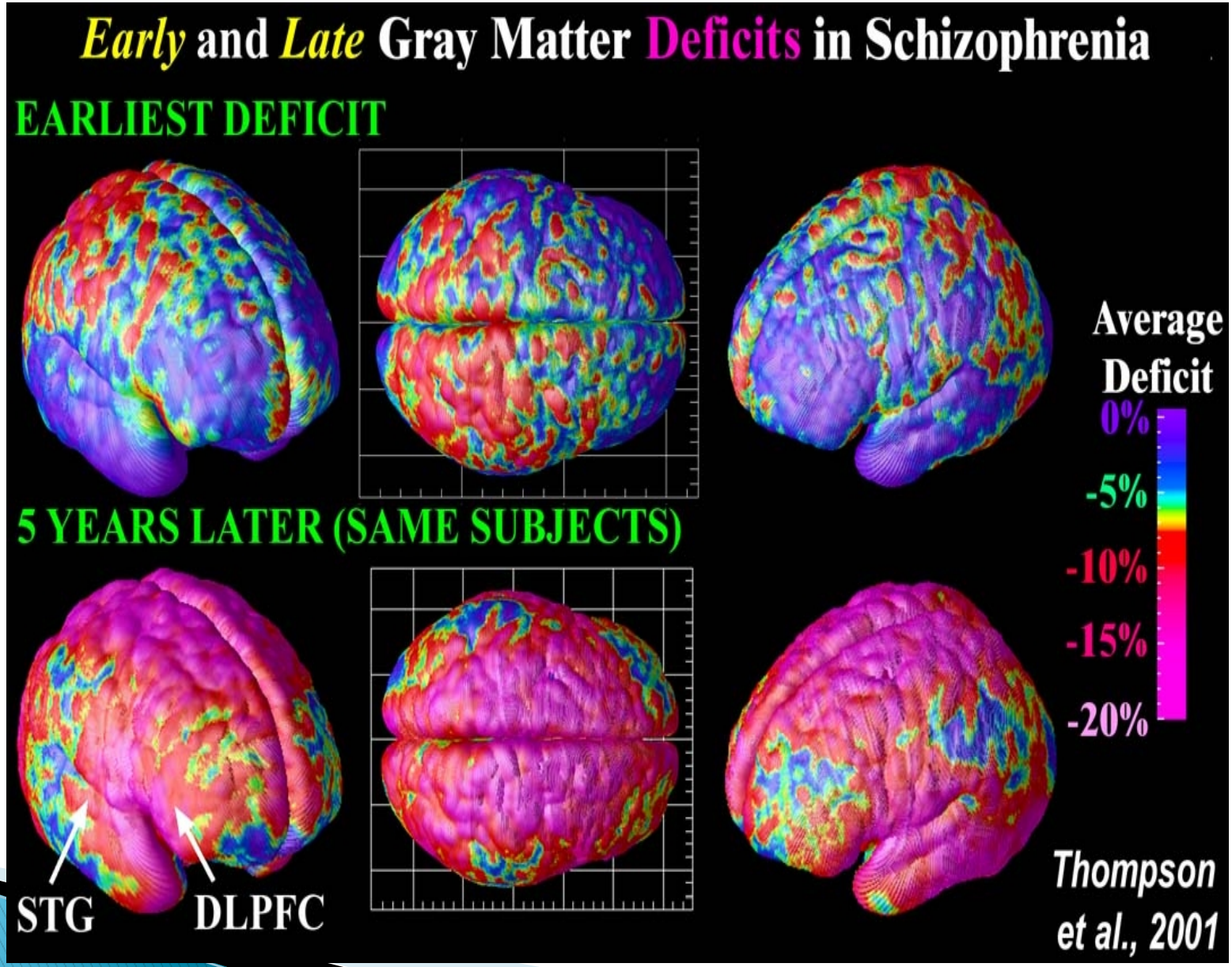


NORMAL

SCHIZO.

Mental disorders are brain disorders: Loss of gray matter in childhood schizophrenia

Biological factors - NEUROLOGICAL



Biological factors – NEUROLOGICAL

CAUSES OF BRAIN ABNORMALITIES

- **Birth trauma (obstetrical issues)**
- **Viral infections that impair neural development during the second and third trimester.**
- **Nutritional issue (Pellagra & other avitaminosis)**
- **Others (toxic agents - lead)**

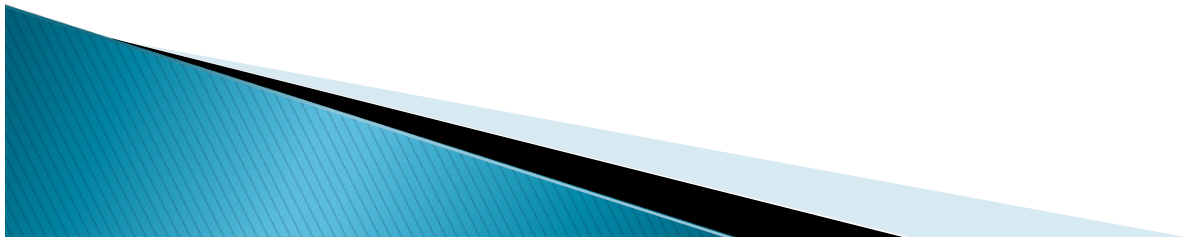
Social factors

- The effect of social class

General life stresses might cause schizophrenia

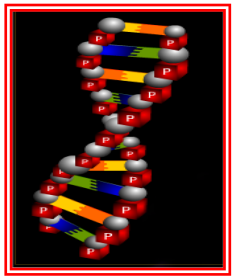
Sociogenic hypothesis – stress from a low level of education, with poor rewards and opportunities, can lead to schizophrenia.

Social selection theory – suggest its not class that cause schizophrenia but those with the illness drift downwards in terms of social class.

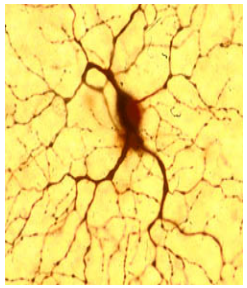


CONCLUSIONS

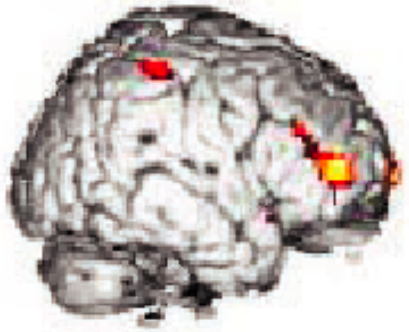
- Not purely a genetic problem
- Not purely a abnormality problem
- Is probably a combination problem triggered by an environmental event
- E.g., Infants exposed to influenza during second and third trimesters.



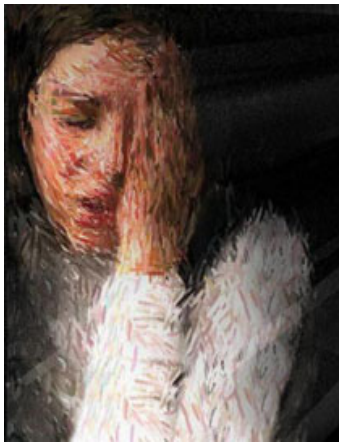
Genes x Environment



Development



Behavior
Emotion
Cognition
Perception

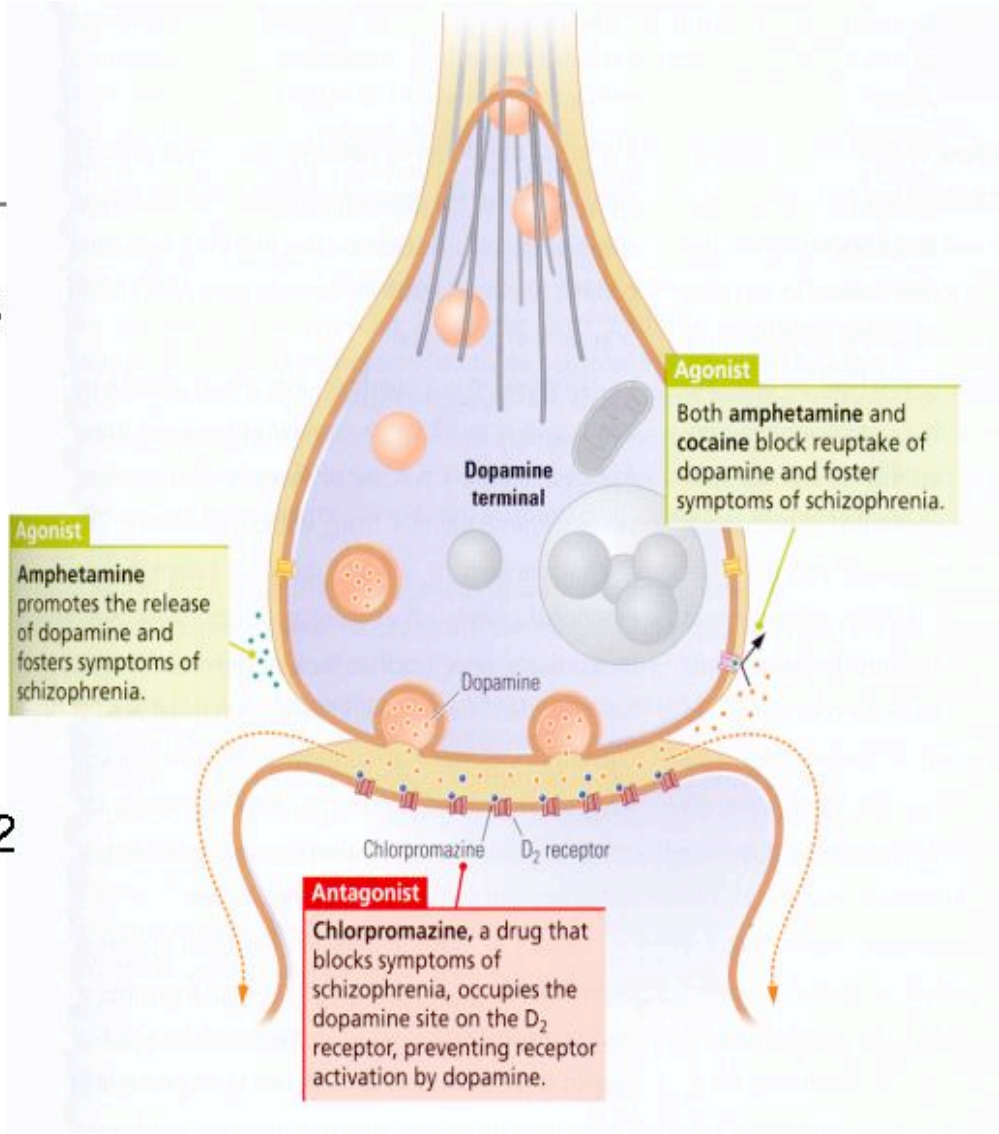


Dopamine hypothesis

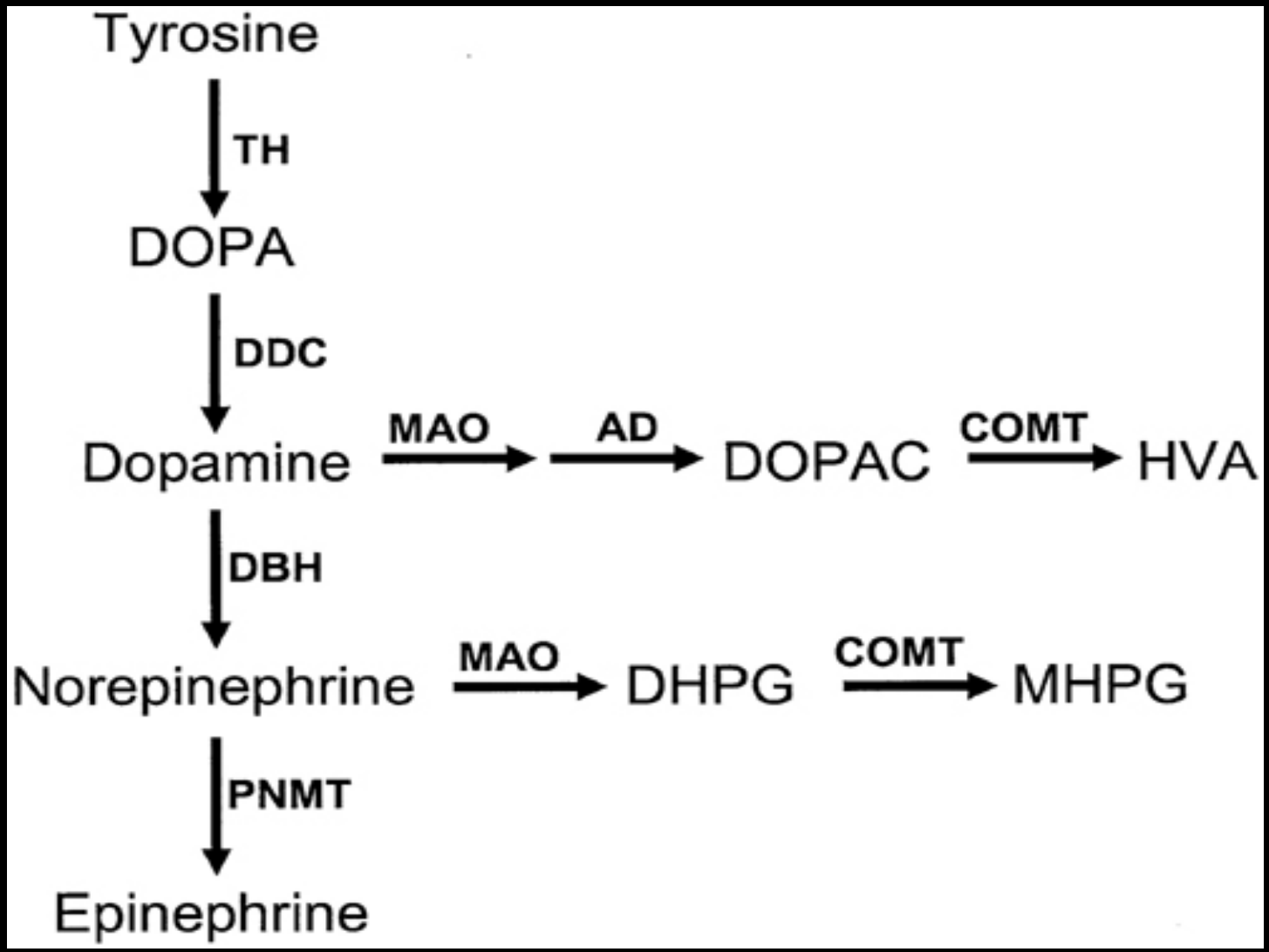
- Antipsychotic drugs like chlorpromazine block DA receptors
  - Long term usage of phenothiazines often develops parkinsonian-like symptoms (tardive dyskinesia)
- Amphetamine psychosis resembles schizophrenia
  - Amphetamine blocks DA transporters, thereby raising DA levels
  - Amphetamine exacerbates schizophrenia

Chlorpromazine was the first effective neuroleptic drug

Phenothiazines block dopamine D2 receptor



Biosynthetic pathway for catecholamines



Dopamine Projection Pathways

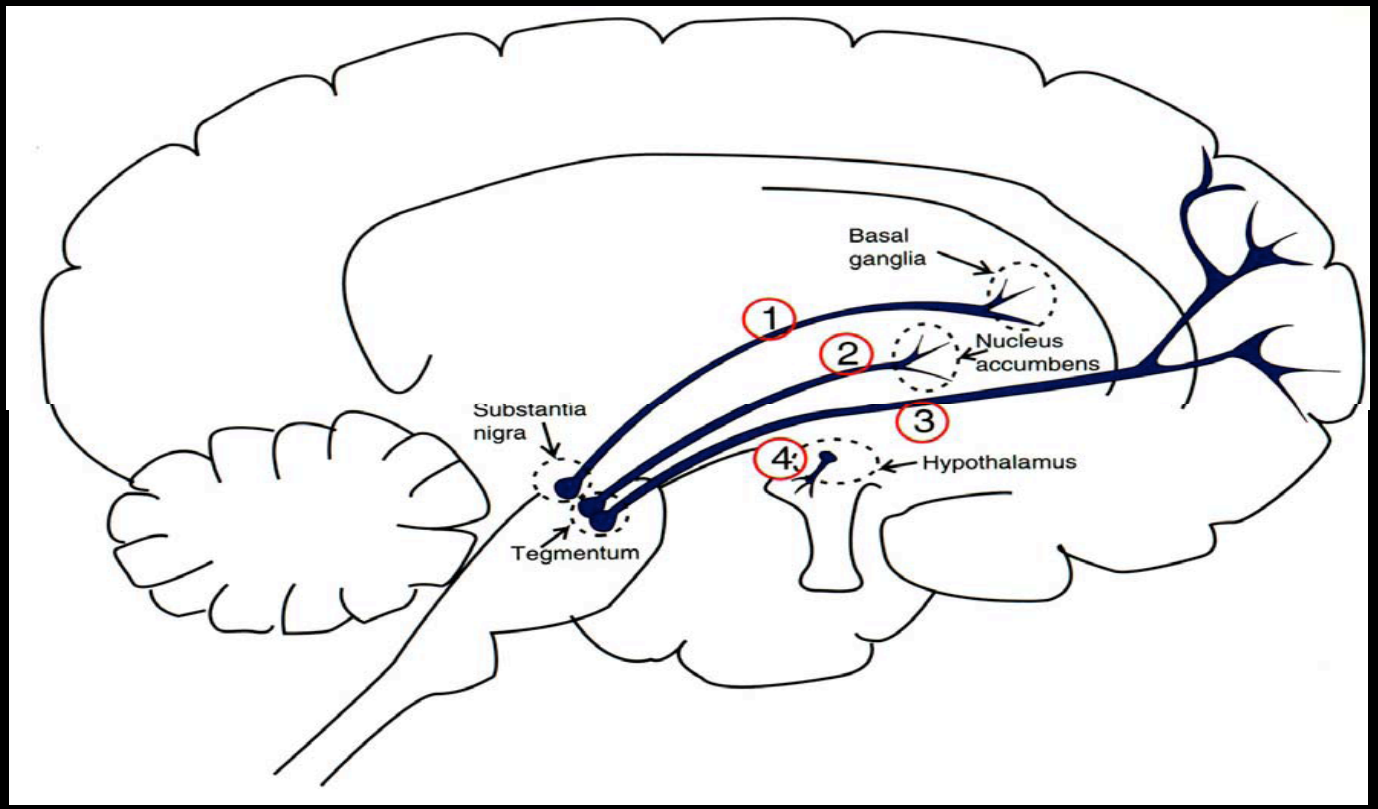
1. Neostriatal – Caudate/Putamen – Regulates Motor Function
2. Mesolimbic – Nucleus Accumbens and Amygdala – Regulates emotions

Carlsson hypothesizes the positive symptoms result from overactivity of this system

3. Mesocortical – Limbic Cortex – Regulates Attention/Cognition/Motivation/Planning/Social Behavior

Hypothesized to be involved with negative symptoms of schizophrenia

4. Tuberohypophysial – Arcuate Nucleus – Regulates Prolactin Release

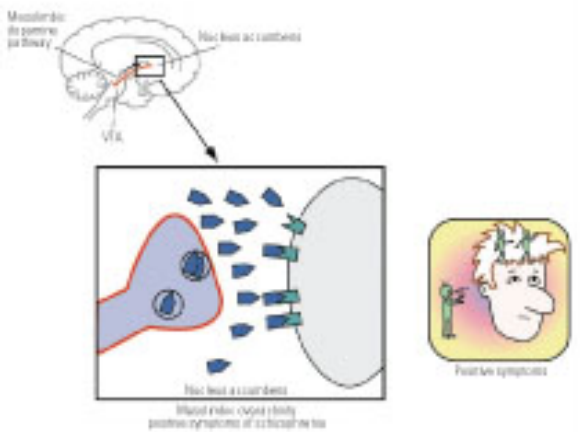


The Dopaminergic Hypothesis of Schizophrenia

1) Overactivity in the mesolimbic dopamine pathway is specifically proposed as the mediator of positive symptoms of schizophrenia such as delusions and hallucinations.

2) Underactivity in the mesocortical dopamine pathway is hypothesized to be the mediator of negative, cognitive, and affective symptoms of schizophrenia.

FIGURE 1.
The mesolimbic dopamine hypothesis of positive symptoms of schizophrenia

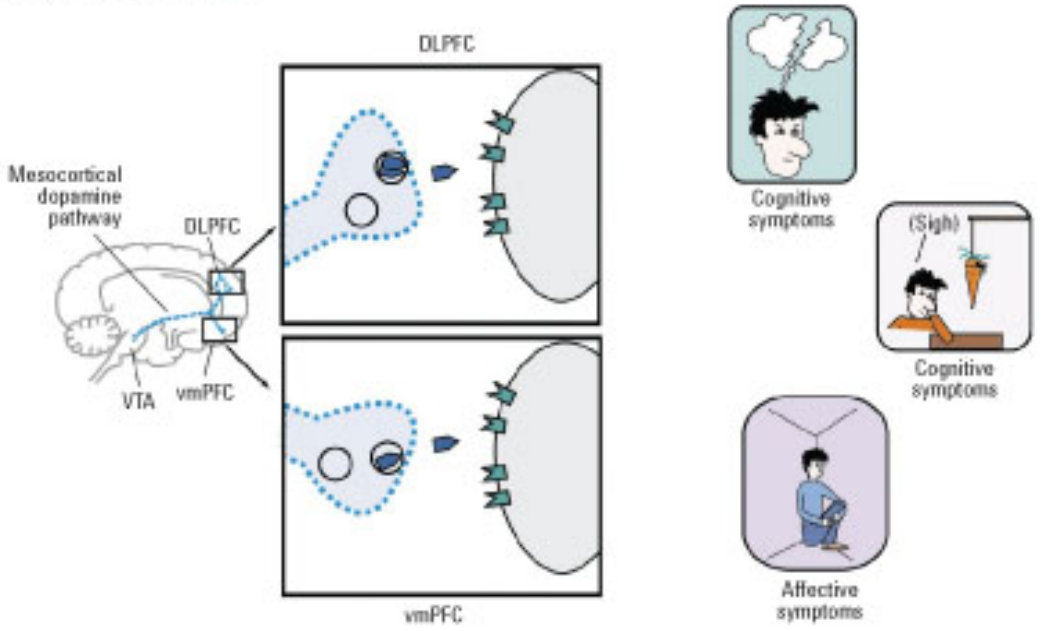


Stahl SM. *Essential Psychopharmacology*. 3rd ed. New York, NY: Cambridge University Press. In press. Reproduced with permission. Copyright Neuroscience Education Institute.

VTA=ventral tegmental area.

Stahl SM. *CNS Spectr*. Vol 12, No 4. 2007.

FIGURE 2.
The mesolimbic dopamine hypothesis of cognitive, negative, and affective symptoms of schizophrenia*[2]



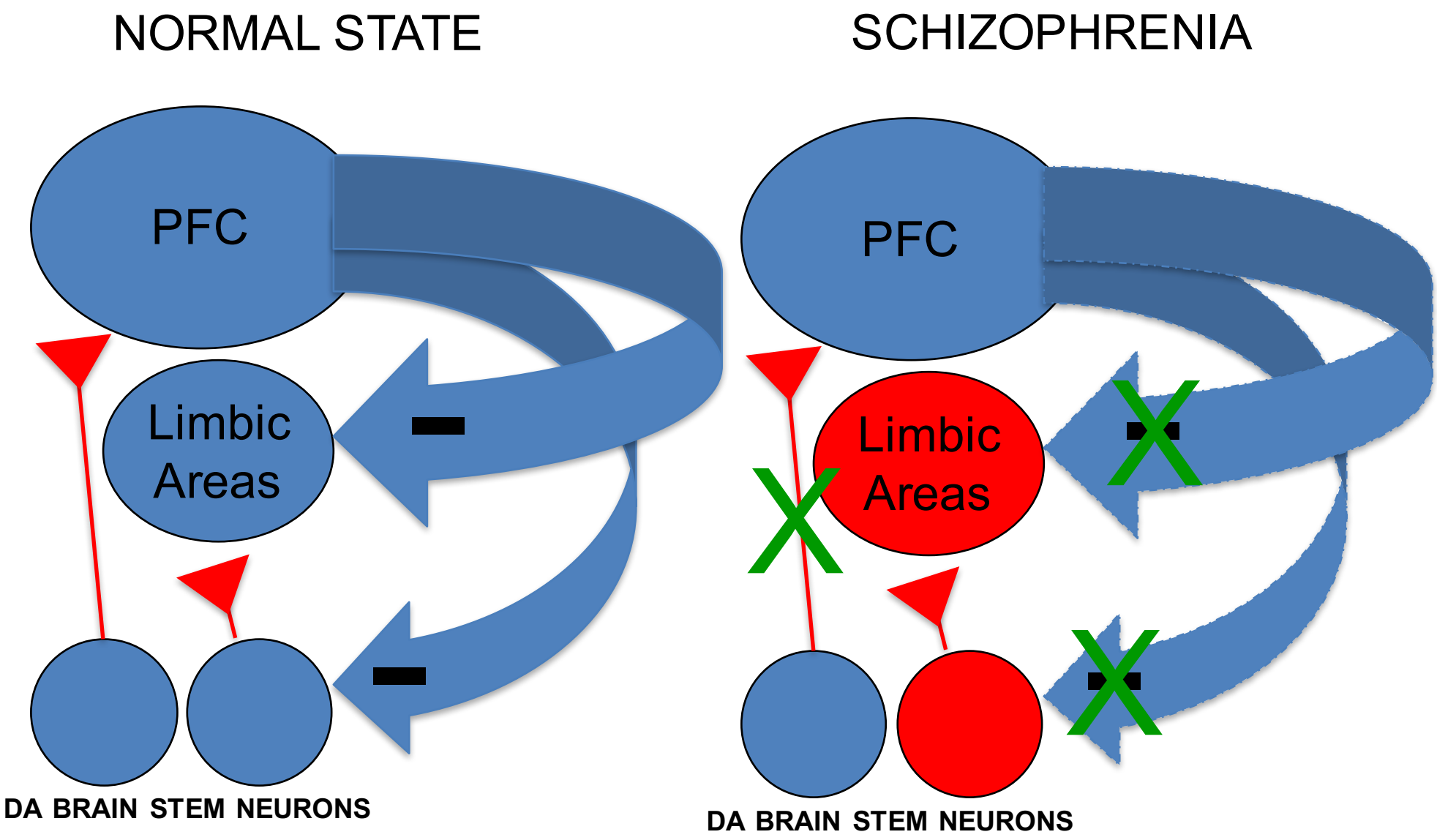
* Mesocortical underactivity: negative, cognitive and affective symptoms of schizophrenia.

Stahl SM. *Essential Psychopharmacology*. 3rd ed. New York, NY: Cambridge University Press. In press. Reproduced with permission. Copyright Neuroscience Education Institute.

DLPFC=dorsolateral prefrontal cortex; vmPFC=ventromedial prefrontal cortex; VTA=ventral tegmental area.

Stahl SM. *CNS Spectr*. Vol 12, No 4. 2007.

Alterations in dopamine neurotransmission



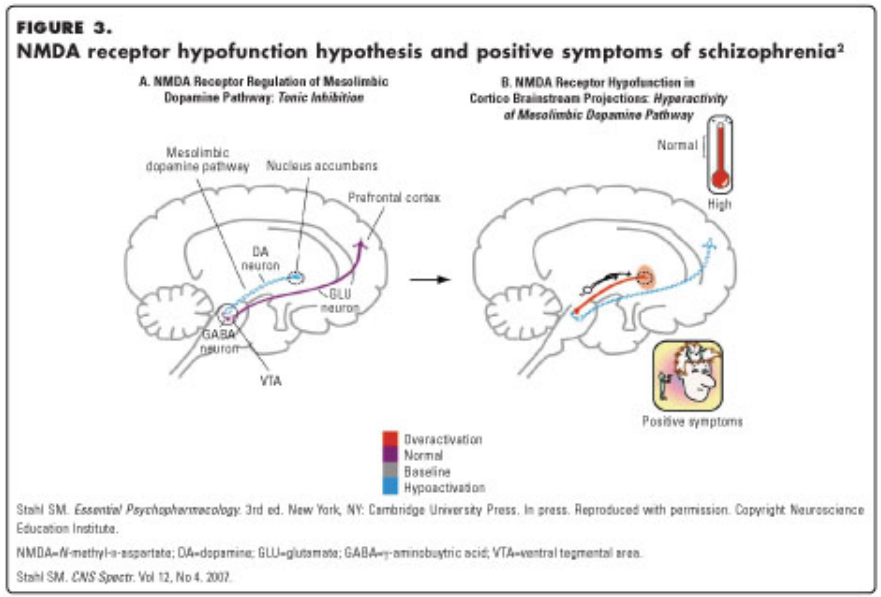
But, dopamine is not the whole story

- Some effective neuroleptic drugs do not act on DA receptors
- Other substances that can produce psychotic states also do not affect DA receptors
- Timing: neuroleptic drugs usually take a few weeks to be effective while the action in the brain is presumably immediate

The NMDA Receptor Hypofunction Hypothesis of Schizophrenia

- Phencyclidine (PCP) can produce a psychotic condition very similar t the positive symptoms of schizophrenia, including hallucinations an delusions by blocking NMDAr. Thus, NMDA receptors may b pathologically hypofunctional in schizophrenia, much like the conditio produced by the ingestion of PCP.
- Unlike amphetamine, which activates only positive symptoms, PC mimics the cognitive, negative and affective symptoms of schizophrenia.
- These clinical observations have led to the idea that NMDAr tha regulate mesocortical DA pathways may be hypoactive in schizophrenia.
- Several new drugs that target NMDAr are being tested as nove therapeutic agents for the treatment of schizophrenia

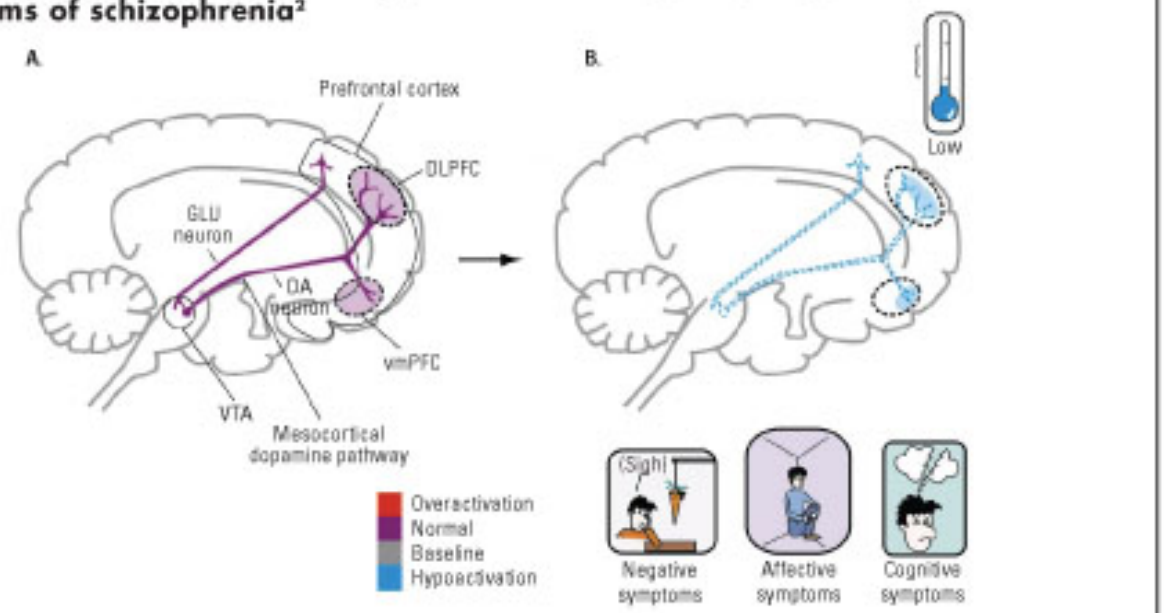
The NMDA Receptor Hypofunction Hypothesis of Schizophrenia



A) A descending glutamatergic pathway projects from cortical pyramidal neurons to dopamine neurons in the ventral tegemental area and acts as a brake on the mesolimbic dopamine pathway through an inhibitory γ-aminobutyric acid interneuron in the ventral tegmental area (VTA).
B) NMDA receptors in the VTA are hypoactive in untreated schizophrenia, and thus cannot inhibit mesolimbic dopamine neurons, this would cause mesolimbic dopamine hyperactivity and the positive symptoms of psychosis.

The NMDA Receptor Hypofunction Hypothesis of Schizophrenia

FIGURE 4.
NMDA receptor hypofunction hypothesis and negative, cognitive, and affective symptoms of schizophrenia[2]



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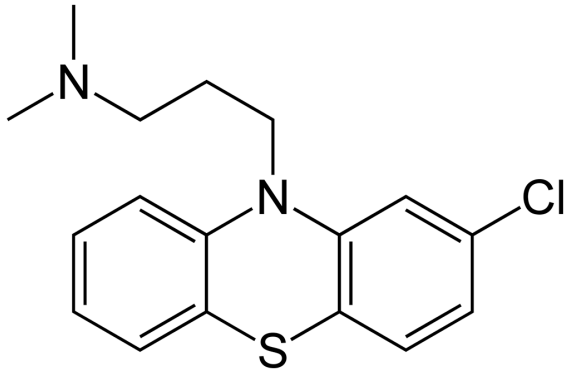
NMDA=*N*-methyl-D-aspartate; DLPFC=dorsolateral prefrontal cortex; VTA=ventral tegmental area; GLU=glutamate; DA=dopamine; vmPFC=ventromedial prefrontal cortex.

Stahl SM. *CNS Spectr*. Vol 12, No 4. 2007.

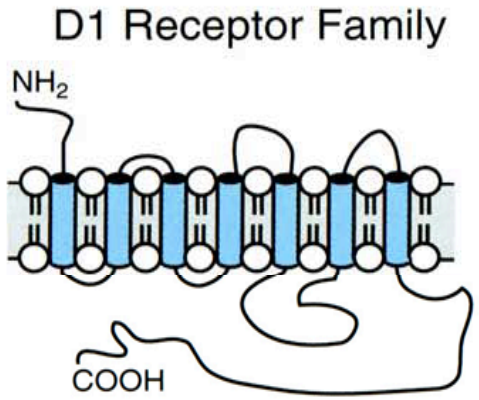
A) Cortico-brainstem glutamate neurons synapse directly upon mesocortical dopamine neurons, and tonically excite them.

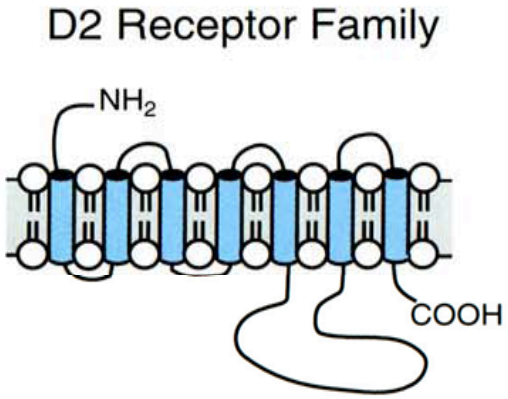
B) when cortico-brainstem projections to mesocortical dopamine neurons have NMDA receptor hypoactivity, they become hypoactive. Mesocortical dopamine neurons hypoactivity may be responsible of the cognitive, negative, and affective symptoms of schizophrenia.



Chlorpromazine treatment of schizophrenia

- In 1950 a French neurosurgeon, Henri Laborit, was looking for drugs to relax patients prior to surgery and tried various anti-histamines
  - He found chlorpromazine effective
  - It was so effective in calming patients that he thought it might work on calming schizophrenic patients
  - It was spectacularly successful and only later was it known to block dopamine





⬆ cAMP
⬆ PIP_2 hydrolysis
- Ca^{2+}mobilization
- PKC activation

⬇ cAMP
⬆ K^+ currents
⬇ ψ-gated Ca^{2+} currents

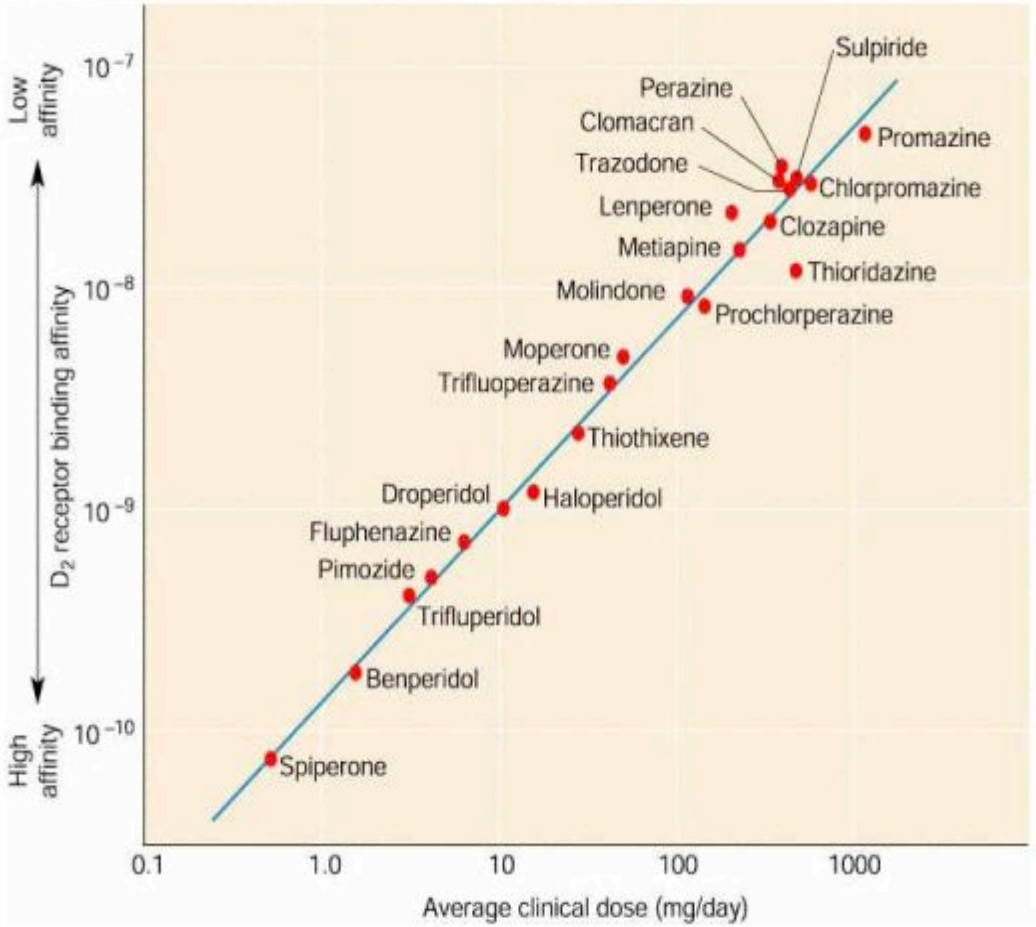
Distribution and characteristics of dopamine receptors.

SNpc, substantia nigra pars compacta; cAMP, cyclic AMP; Ψ, voltage.

	D1	D5
Distribution	• striatum • neocortex	• hippocampus • hypothalamus

D2	D3	D4
• striatum • SNpc • pituitary	• olf. tubercle • n. accumbens • hypothalamus	• frontal cortex • medulla • midbrain

Effectiveness of neuroleptics is highly correlated with binding affinity to DA receptors



Typical Antipsychotics
(Phenotiazine derivatives, Butyrophenones, Tioxantenes)

Chlorpromazine (Largactil)
Droperidol (Droleptan, Thalamonal)
Flupenthixol (Depixol, Fluanxol)
Fluphenazine (Modecate, Moditen, Motipress, Motival)
Haloperidol (Haldol, Serenace)
Sulpiride (Bosnyl, Dogmatil, Dolmatil, Eglonyl, Modal)
Thioridazine (Melleril)
Trifluoperazine (Stelazine, Parstelin)
Zuclopenthixol (Clopixol)

KEY CONCEPTS:

- *All neuroleptics* are equally effective in treating psychoses, including schizophrenia, but differ in their tolerability.
- *All neuroleptics* block one or more types of DOPAMINE receptor, but differ in their other neurochemical effects.
- *All neuroleptics* show a significant delay before they become effective.
- *All neuroleptics* produce significant adverse effects.

→ Dose & D2r affinity

→ Occupancy of 65-70% D2r

→ 4-6 weeks

→ 75-80% D2r Occupancy >> EPS

70-80 % of patients respond to therapy
but 30-40% show a partial response

GENERAL CHARACTERISTICS OF *TYPICAL* NEUROLEPTICS

- Typical neuroleptics are generally more effective against positive (active) symptoms of schizophrenia than the negative (passive) symptoms.
- Positive/active symptoms include:
  - Thought disturbances, delusions, hallucinations
- Negative/passive symptoms include:
  - Social withdrawal, loss of drive diminished affect, paucity of speech. impaired personal hygiene

MECHANISMS OF ACTION OF TYPICAL NEUROLEPTICS

- DOPAMINE-2 receptor blockade in meso-limbic and meso-cortical systems for antipsychotic effect.
- DOPAMINE-2 receptor blockade in basal ganglia (nigro-striatal system) for EPS
- DOPAMINE-2 receptor supersensitivity in nigrostriatal system for tardive dyskinesia

LONG TERM EFFECTS OF D2 RECEPTOR BLOCKADE:

- Dopamine neurons reduce activity.
- Postsynaptic D-2 receptor numbers increase (compensatory response).
- When D2 blockade is reduced, DA neurons resume firing and stimulate increased # of receptors >> hyper-dopamine state >> tardive dyskinesia

EPS
(Extra Pyramidal Symptoms)

- **EPS include:**
  - **Acute Dystonias: happens within hours**
  - **Parkinsonism: develops gradually (Days – Weeks)**
  - **Tardive Dyskinesia: chronic development**
  - **Tardive Dystonia: chronic development**

- **Changes in Dopamine Receptor Blockade in the Certain Areas of Brain (Substantia Niagra and Caudate Nucleus)**

Parkinsonian Syndrome

- Parkinsonian Syndrome
  - Tremors
  - Rigidity
  - Cogwheeling
  - Bradykinesia
  - Akinesia
- Management
  - Anticholinergic drugs
  - Antiparkinson drugs

Akathisia

- Inability to sit still
  - A feeling of restlessness,
  - A need to keep moving,
  - An urge to raise the feet high
- Treatment:
  - Anticholinergics: not always effective
  - Propranolol
  - Clonidine

NMS
(Neuroleptic Malignant Syndrome)

- A rare but potentially fatal complication
- Main clinical findings:
  - Hyperthermia
  - Severe muscular rigidity
  - Autonomic instability:
    - Pulse/ BP/ Breathing/ Sweating
  - Changing levels of consciousness
  - Unstable vital signs

NMS
(Neuroleptic Malignant Syndrome)

- Treatments
  - Stop the antipsychotics
  - Supportive and symptomatic TX
  - Medications:
    - Dantrolene (Dantrium):
    - Bromocriptine (Parlodel):
    - Amantadine (Symmetrel)
- Mortality: 20 – 30 %
  - May be higher when depot forms are used

TD
(Tardive Dyskinesia)

- Involuntary and persistent movement disorder that may occur later after long-term treatment
- At least 10 – 20% of the patients (pts) treated with the typical antipsychotics for more than a year experience TD

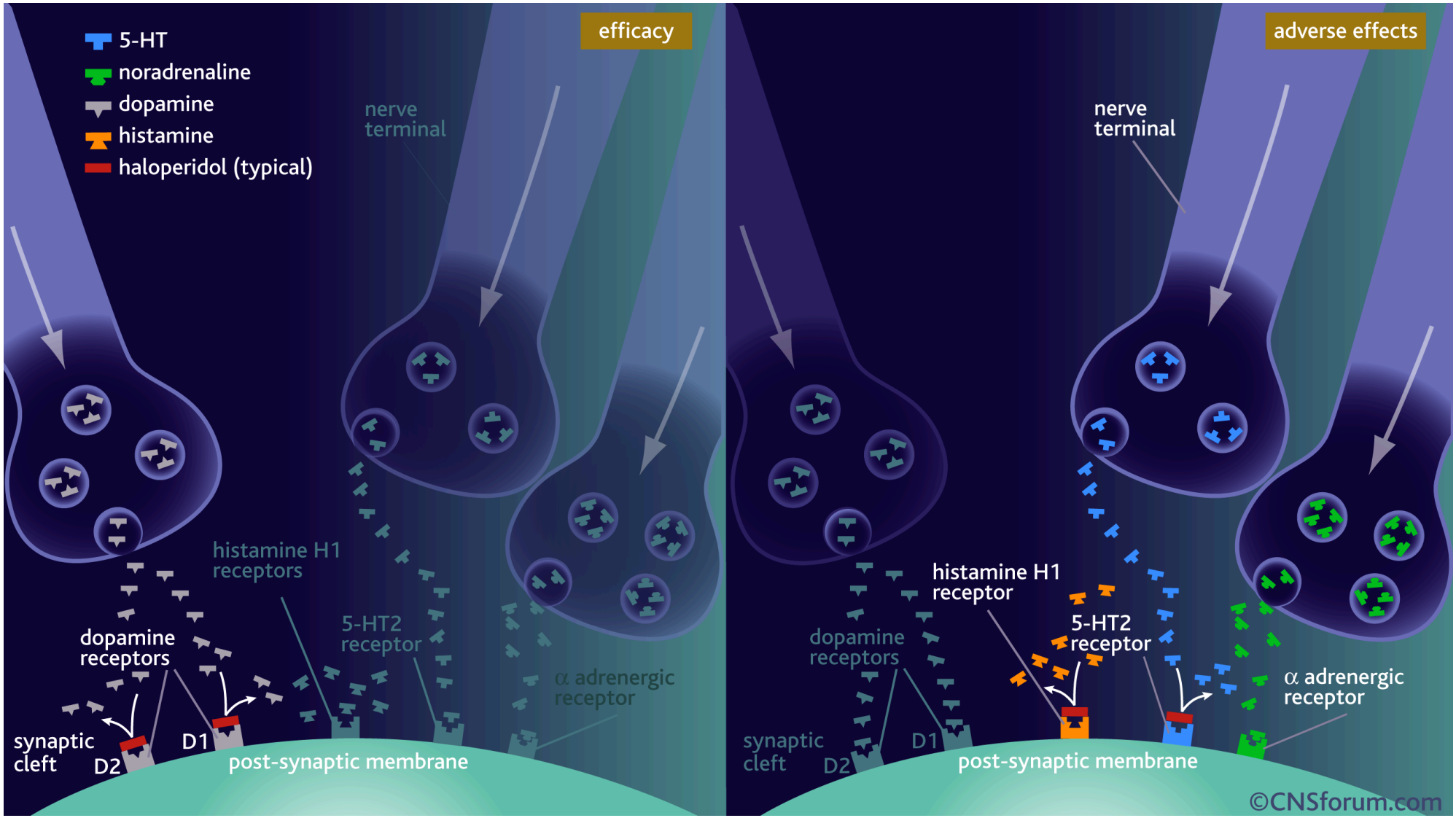
Cardiovascular Effects

- Prolonged QTc intervals
  - Low Potency Conventional Antipsychotics
    - Mellaril (Thioridazine)
    - Thorazine (Chlorpromazine)
  - With QTc intervals exceeding 0.440 seconds, the risk of sudden cardiac death increases because of ventricular tachycardia or ventricular fibrillation

GENERAL CHARACTERISTICS OF *TYPICAL* NEUROLEPTICS

- Typical neuroleptics do not produce a general depression of the CNS, e.g. respiratory depression

- Abuse, addiction, physical dependence do not develop to typical neuroleptics.



'Typical', or 'first-generation', neuroleptics are non-selective and binds to a broad range of receptors (D1 and D2, 5-HT2, H1 and α2 R in the brain)

The efficacy of neuroleptics is due to antagonism of DAr in the mesolimbic system

The adverse effects of typical neuroleptics are caused by non-selective interaction at other Rs

ADVERSE EFFECTS OF TYPICAL NEUROLEPTICS

- Anticholinergic (antimuscarinic) side effects:
  - Dry mouth, blurred vision, tachycardia, constipation, urinary retention, impotence

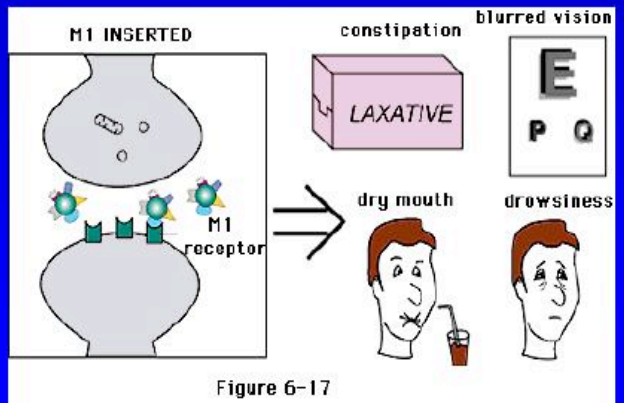
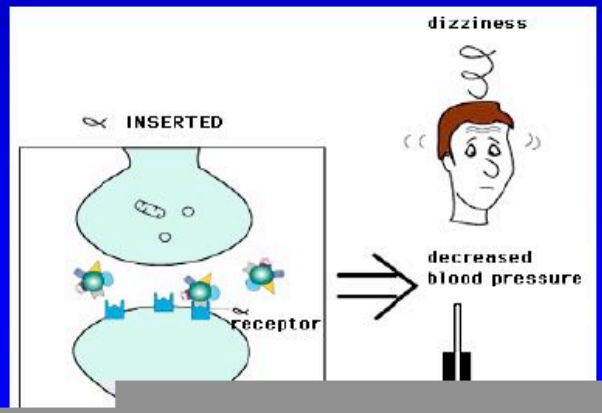


Figure 6-17

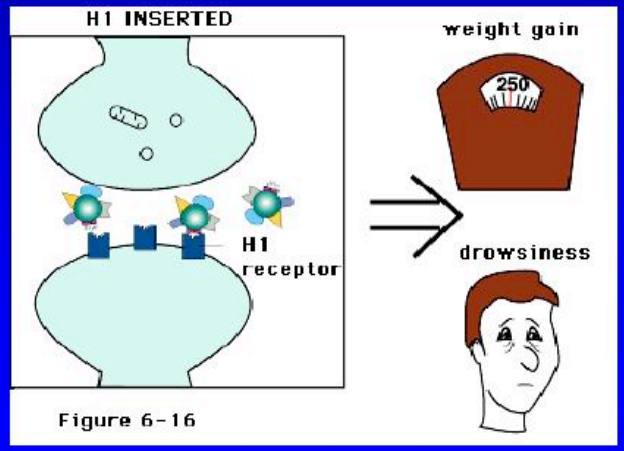
ADVERSE EFFECTS OF TYPICAL NEUROLEPTICS

- Antiadrenergic (Alpha-1) side effects:
  - Orthostatic hypotension w/ reflex tachycardia
  - sedation

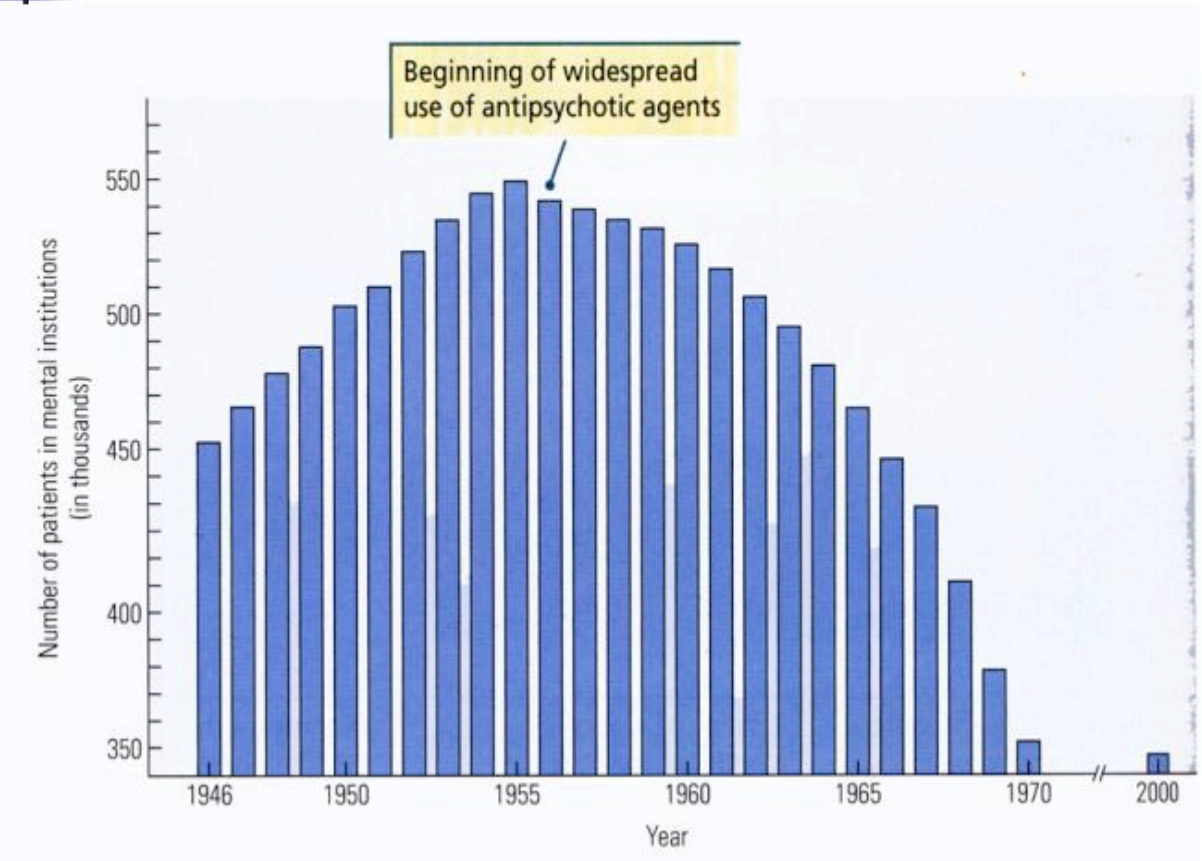


ADVERSE EFFECTS OF TYPICAL NEUROLEPTICS

- Antihistamine effect: sedation, weight gain



Decrease in patients in mental hospitals following antipsychotic drug use

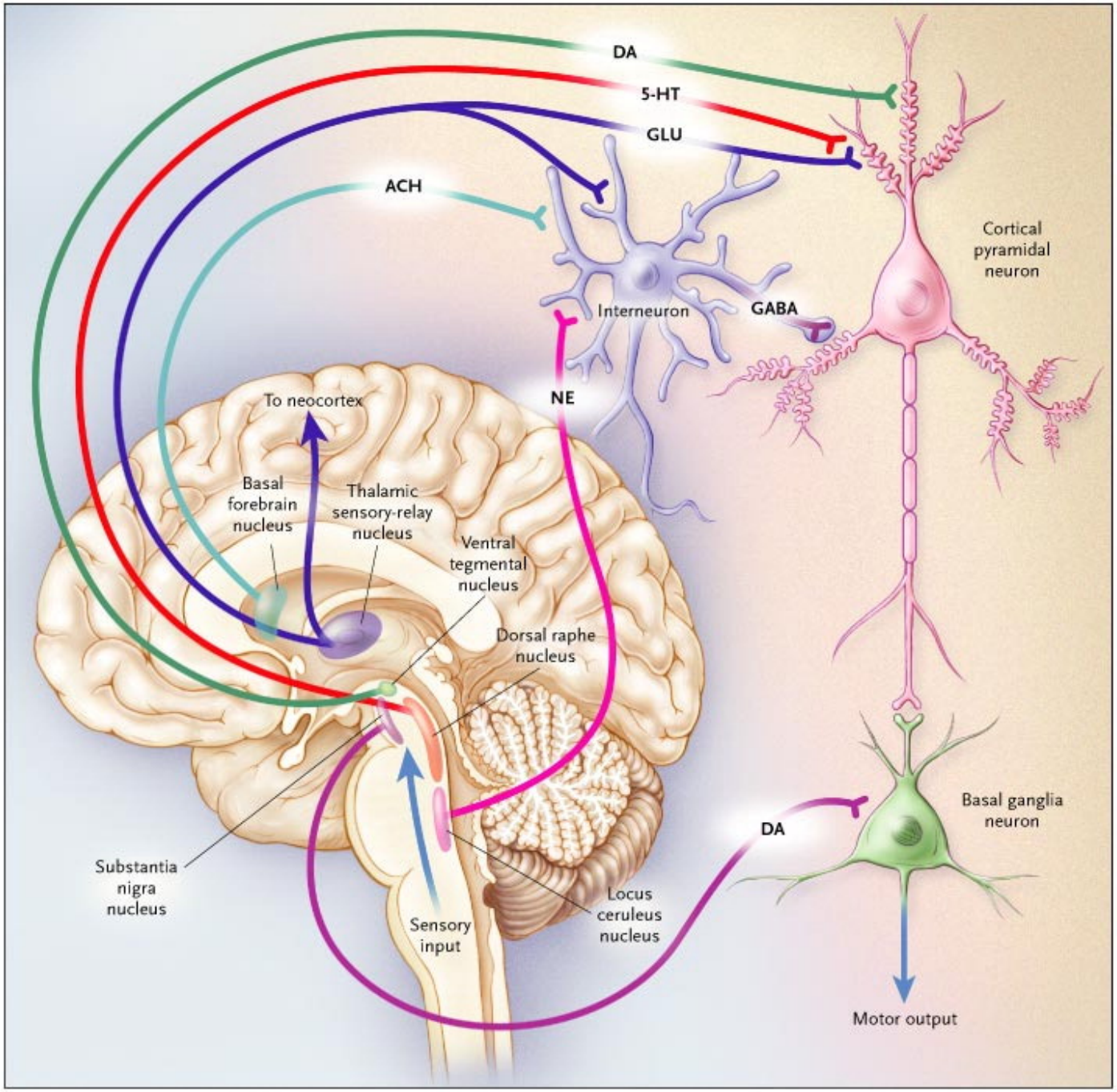


Second generation Antipsychotics

- A second generation of antipsychotic agents has been introduced into clinical practice over the past 15 years in an attempt to improve therapeutic effects and decrease the side effects associated with first-generation antypsychotics.
- All second-generation drugs share the D2r antagonism of first-generation drugs, but second-generation drugs are less tightly bound to the D2r, and D2r antagonism is no longer the sole therapeutic mechanism.
- Hence, there are similarities in the general scope and time course of the effects of first- and second-generation drugs, but there are clinically important differences in both the therapeutic effects and the side effects.

Second generation Antipsychotics

- Clozapine – introduced 1970s
- 1st of the second generation antipsychotics
- Second generation antipsychotics = "atypical" antipsychotics
- "Atypical" because EPS is absent!
- Other beneficial properties include reduction of negative symptoms
- This is because serotonin receptors are blocked as well as dopamine receptors



Neuronal Circuits That Appear to Be Involved in Schizophrenia and Its Treatment.

- **Thalamic nuclei relay sensory information to networks of pyramidal neurons in the limbic system through GLU excitatory afferents.**
- **An excessive response of pyramidal neurons is a putative mechanism of psychosis.**
- **Various subcortical nuclei facilitate this response.**
- **DA from the VTA activates D1 and D2r that increase neuronal responses to glutamate (GLU).**
- **5HT from the dorsal raphe nucleus activates 5HT2Ar that facilitate the release of glutamate from synaptic terminals.**
- **Antipsychotic drugs block the facilitative effects of both DA and 5HT**

Table 2. Putative Neuronal Mechanisms in Psychosis and Its Treatment.

Pharmacologic Agents That Cause Psychosis, Hallucinations, or Delirium by Increasing the Response of Pyramidal Neurons in the Cerebral Cortex to Incoming Stimuli

Mechanism	Type of Agent	Result
Dopamine agonism	Stimulant (cocaine, amphetamine)	Increased pyramidal-neuron response to glutamate excitation
Norepinephrine agonism	Stimulant (cocaine, amphetamine)	Decreased interneuron regulation of glutamate excitation of pyramidal neurons
Serotonin agonism	Hallucinogenic (lysergic acid diethylamide)	Presynaptic facilitation of glutamate release onto pyramidal neurons
Glutamate *N*-methyl-D-aspartate antagonism	Dissociative anesthetic (phencyclidine)	Diminished glutamatergic activation of interneurons, which increases excitation of pyramidal neurons
Acetylcholine antagonism	Anticholinergic (atropine)	Decreased cholinergic stimulation of interneurons, which increases excitation of pyramidal neurons

Antipsychotic Agents That Decrease Neuronal Response in the Cerebral Cortex to Incoming Stimuli

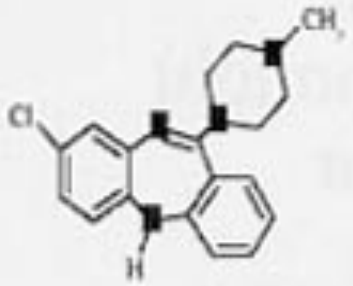
Mechanism	Type of Agent	Result
Dopamine D2 antagonism	First-generation (haloperidol)	Blockade of dopamine facilitation of pyramidal-neuron response
D2 and 5-HT_{2A} antagonism	Second-generation (olanzapine, risperidone, quetiapine, ziprasidone)	Blockade of dopamine facilitation of pyramidal-neuron response and serotonin facilitation of glutamate release
Multiple actions	Clozapine	D1, D2, and 5-$HT_{2\text{-}3}$ antagonism, leading to decreased pyramidal-neuron responses; increased acetylcholine release and norepinephrine antagonism, leading to increased interneuron regulation of pyramidal neurons
Mixed dopaminergic agonism and antagonism	Aripiprazole	Facilitation of low-level stimulation of dopamine receptors, blockade of higher levels of stimulation
Dopamine D2 and D3 antagonism	Amisulpride	Blockade of cortical dopamine receptors, but not those in basal ganglia

GENERAL CHARACTERISTICS OF ATYPICAL NEUROLEPTICS

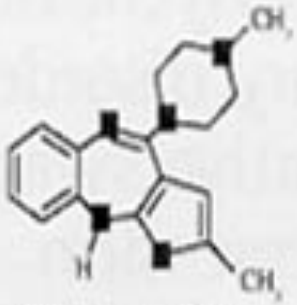
- Effective antipsychotic agents with greatly reduced or absent EPS, esp. reduced Parkinsonism and tardive dyskinesia
- All atypical neuroleptics block dopamine *and* serotonin receptors; other neurochemical effects differ
- Are effective against positive *and* negative symptoms of schizophrenia

Chemical Structures of Olanzapine and Other Antipsychotic Agents

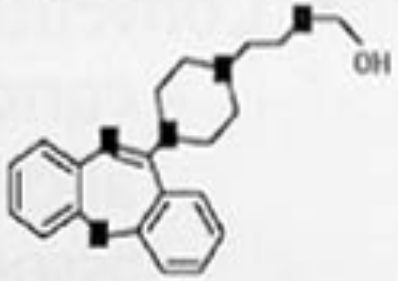
1. Multi-acting receptor targeted antipsychotics (MARTA)



Clozapine

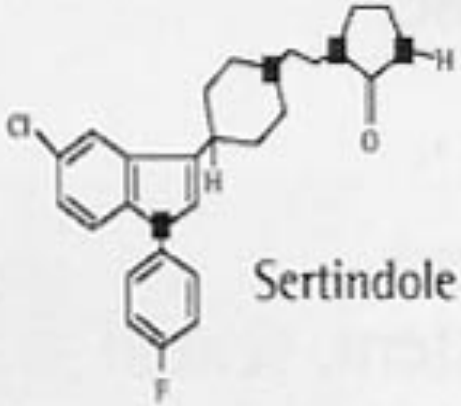


Olanzapine

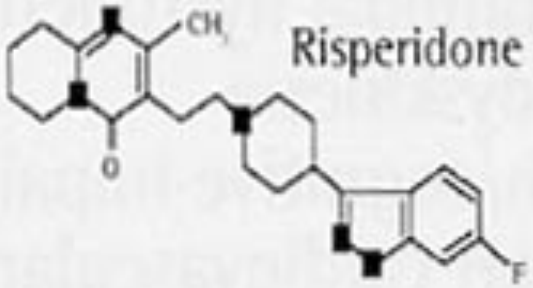


Quetiapine

2. Serotonin: dopamine antagonists (SDA)

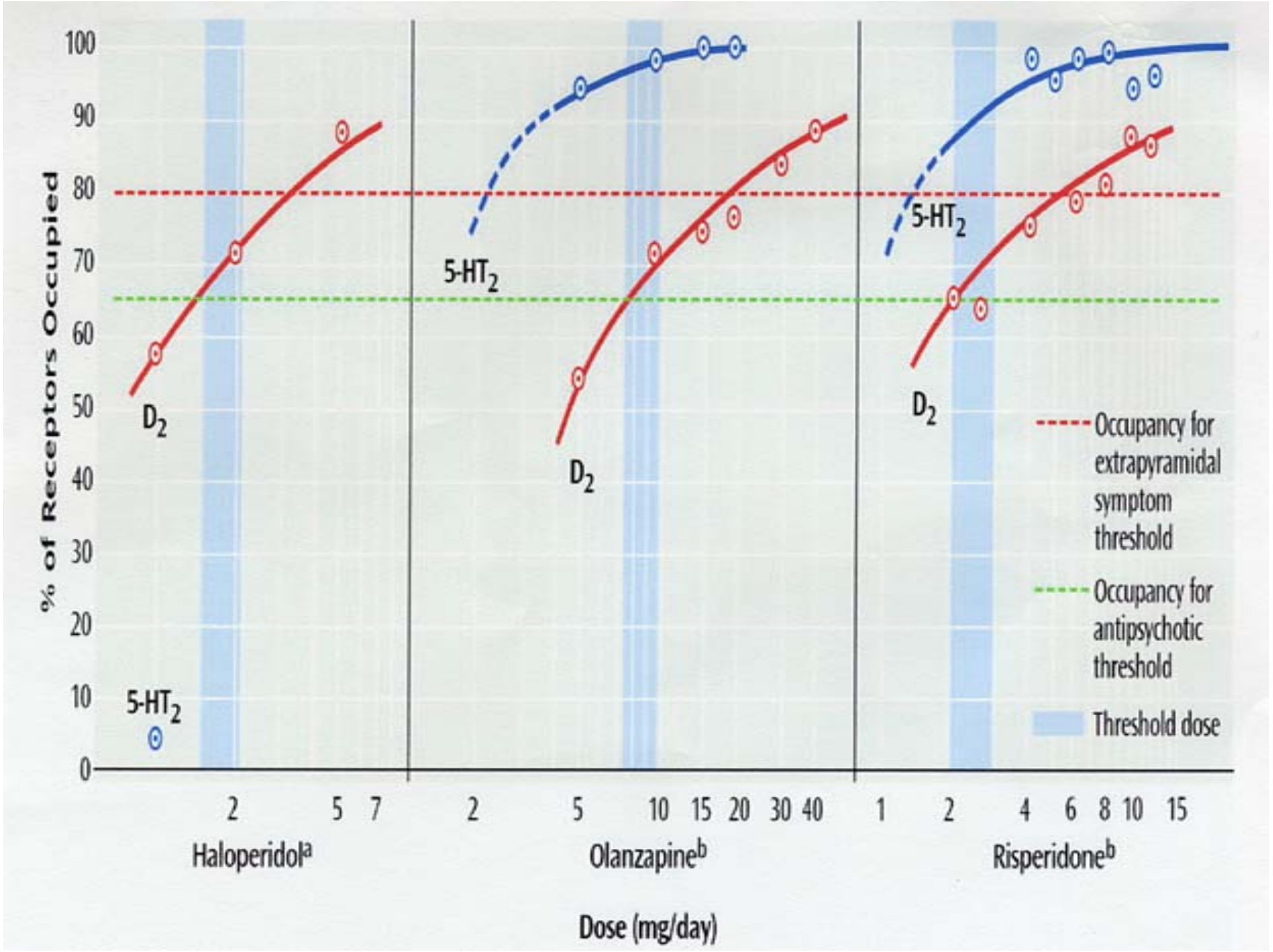


Sertindole



Risperidone

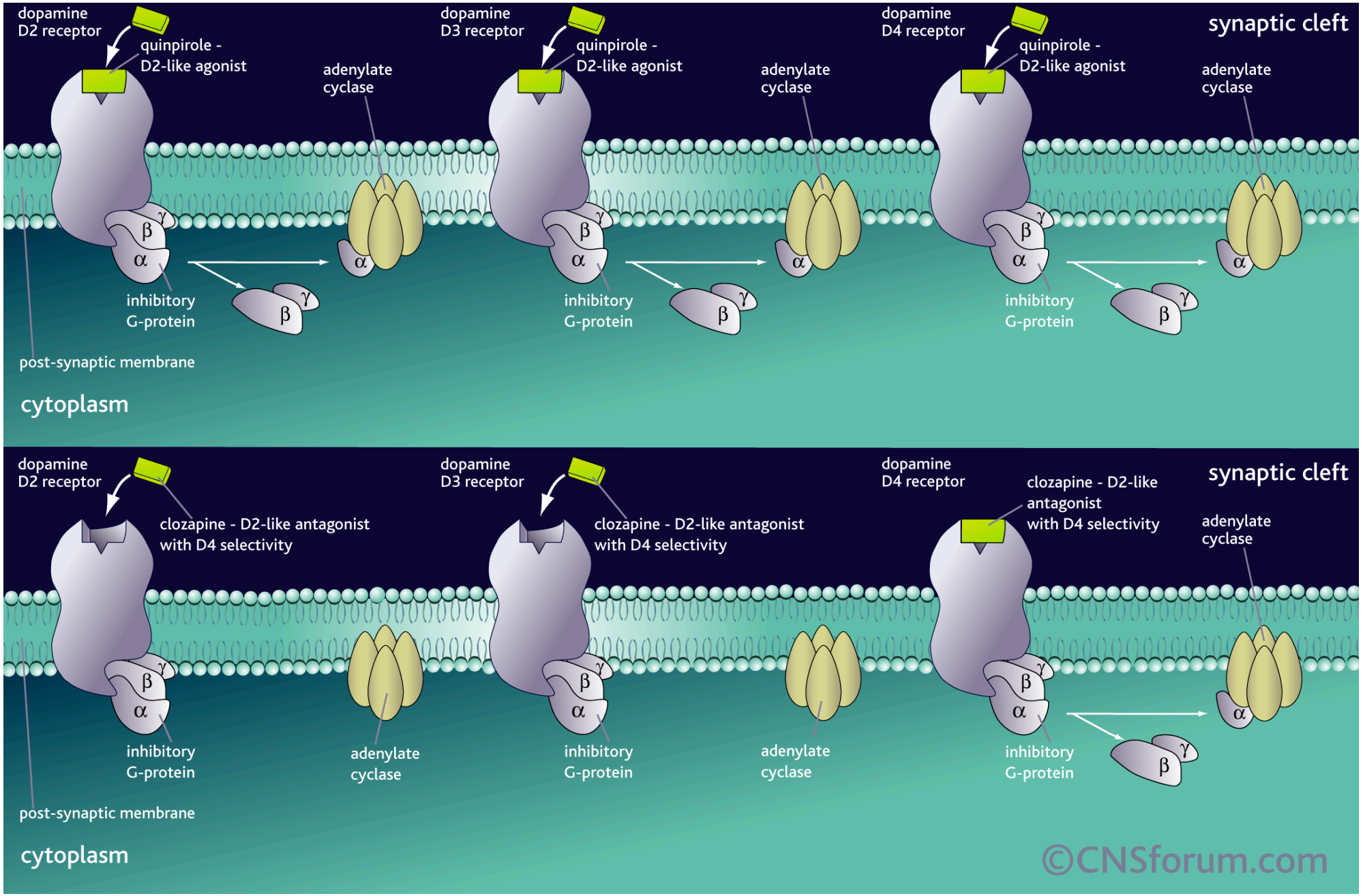
- Olanzapine has eliminated the halogen (Cl) from the clozapine molecule, a potentially reactive metabolite


% of Receptors Occupied
100
90
80
70
60
50
40
30
20
10
0
5-HT2
D2
5-HT2
D2
5-HT2
D2
Occupancy for extrapyramidal symptom threshold
Occupancy for antipsychotic threshold
Threshold dose
2
5
7
2
5
10
15
20
30
40
1
2
4
6
8
10
15
Haloperidol[a]
Olanzapine[b]
Risperidone[b]
Dose (mg/day)

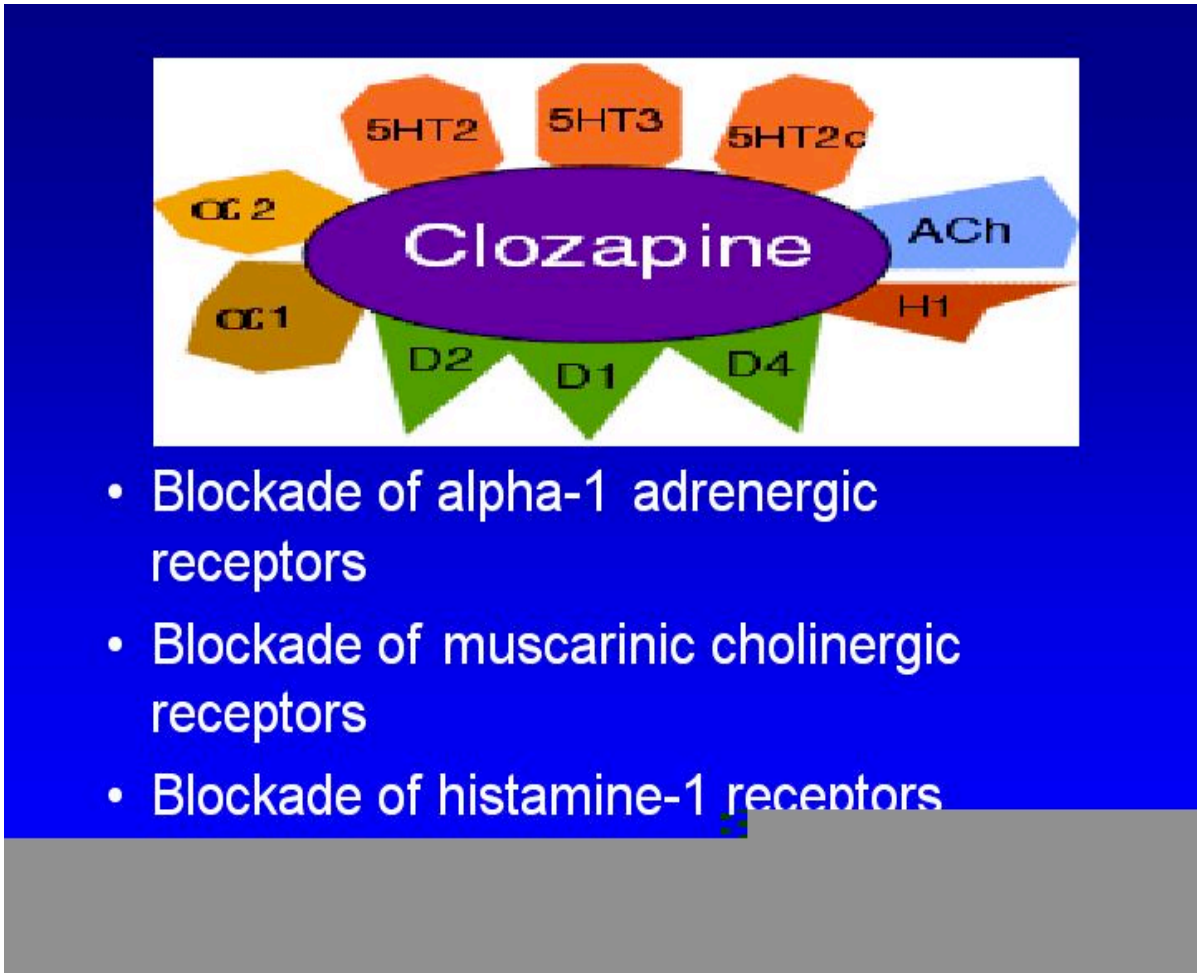
Clozapine – “Gold standard” in treating schizophrenia

PHARMACOLOGY OF CLOZAPINE (CLOZARIL ®)

- FDA-approved for patients not responding to other agents or with severe tardive dyskinesia
- Effective against negative symptoms
- Also effective in bipolar disorder
- Little or no parkinsonism, tardive dyskinesia , PRL elevation, neuro-malignant syndrome; some akathisia



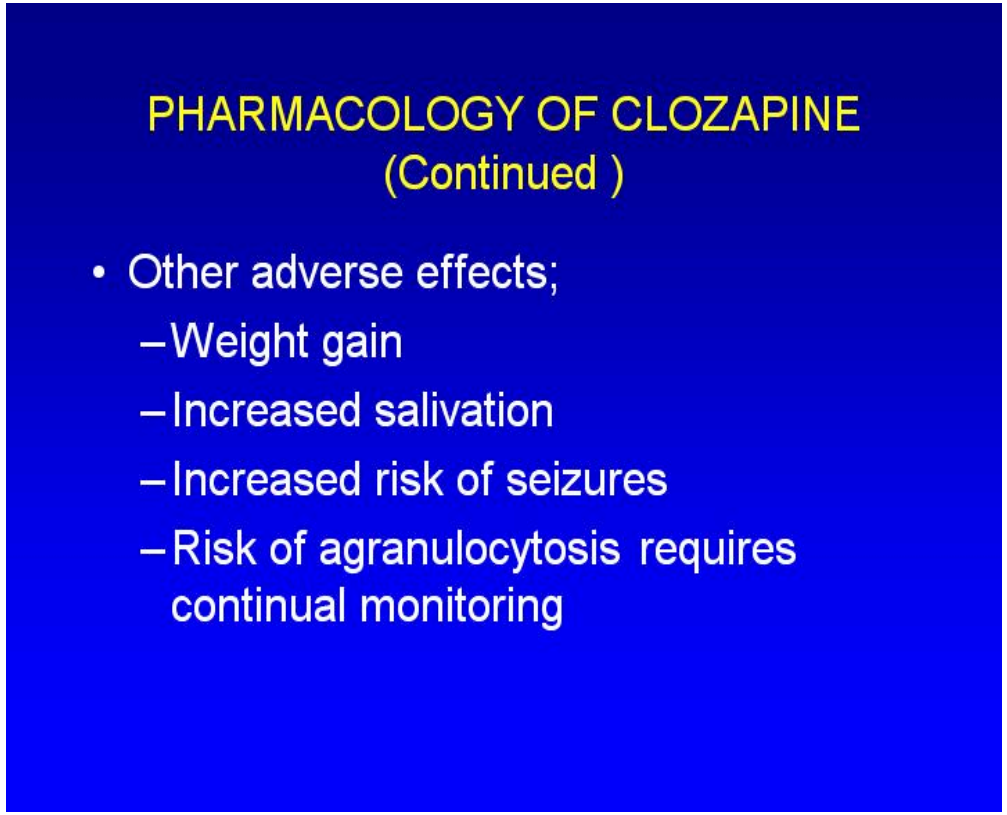
The D2-likeR include the D2, D3 and D4 R subtypes. Clozapine is a D2-like selective antagonist, binding to all 3 D2-like R. However, it is 28 times more potent at the D4 R than the D2 R. Its antipsychotic effects are thought to be mediated primarily by 5-HT 2A/2C and D2 R antagonism.



- **Clozapine has significant antagonist effects at D1, D2, and D4 receptors, as well as at NA and 5HT receptors.**

- **Patients who are smokers treated with clozapine also decrease their cigarette smoking. It has been hypothesized that smoking among persons with schizophrenia is an attempt at self-medication.**

- **Clozapine increases the synaptic release of ACh.**



- **Clozapine is not associated with the development of acute EPS or TD.**
- **The main factor limiting its use is the risk of potentially fatal agranulocytosis.**
- **Patients taking clozapine must undergo monitoring of the leukocyte count (weekly or every two weeks).**
- **The incidence of agranulocytosis is 0.39% and the death rate among patients who take clozapine is 0.013%.**
- **For 30% of patients not responding to other treatments, clozapine has substantially enhanced therapeutic effects that justify its use.**

Table 3. Examples of Antipsychotic Drugs and Doses.*

Medication	Daily Oral Dose
	mg
First-generation antipsychotic agents	
Chlorpromazine (Thorazine)	150–1000
Perphenazine (Trilafon)	8–64
Trifluoperazine (Stelazine)	5–60
Thiothixene (Navane)	5–60
Haloperidol (Haldol)	2–25
Second-generation antipsychotic agents	
Clozapine (Clozaril)	100–900
Risperidone (Risperdal)	2–10
Olanzapine (Zyprexa)	5–20
Quetiapine (Seroquel)	75–750
Ziprasidone (Geodon)	40–160
Aripiprazole (Abilify)	15–30
Amisulpride† (Solian)	400–1200
	Intramuscular Dose (every 2–4 wk)
	mg
Depot preparations	
Fluphenazine decanoate (Prolixin decanoate injection)	12.5–50
Haloperidol decanoate (Haldol decanoate injection)	50–200
Flupentixol decanoate (Fluanxol depot injection)†	20–100
Risperidone microspheres (Risperdal Consta)‡	25–50

* Data are from Herz and Marder.[42]
† This drug is not available in the United States.
‡ This drug is not available in the United States in this form.

PHARMACOLOGY OF OLANZAPINE (ZYPREXA ®)

- Olanzapine is clozapine without the agranulocytosis
  - Same therapeutic effectiveness
  - Same side effect profile

- Highly effective against positive and negative symptoms
- Adverse effects:
  - EPS incidence is dose-related
  - Alpha-1 receptor blockade
  - Little or no anticholinergic or antihistamine effects
  - Weight gain, PRL elevation

Potent 5-HT2A antagonists relative to their D2 receptor blocking property

Aripiprazole

- Partial agonist at D_2r and $5HT_{1A}$r
- Antagonist at $5HT_{2A}$r
- Effective, safe, and well tolerated for the positive and negative symptoms
- First non-D_2 receptor antagonist with clear antipsychotic effects

METABOLIC RISK WITH ATYPICAL ANTIPSYCHOTICS

Drug	Weight Gain	Risk for Diabetes	Worsening Lipid Profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	±	±
Quetiapine	++	±	±
Aripiprazole	++	-	-
Ziprasidone	++	-	-

- **Many second-generation drugs produce clinically significant weight gain up to 20 kg or more.**
- **H1R antagonism and activation of the appetite-stimulating enzyme AMP-protein kinase in the hypothalamus underlie the orexigenic effects of clozapine and olanzapine.**
- **Diabetes mellitus has been increasingly reported in patients treated for more than five years**
- **there is also some evidence of the development of insulin resistance.**
- **Cholesterol levels increase by 10%**
- **Ziprasidone and amisulpride at recommended doses cause less weight gain than do other antipsychotic drugs**

Table 4. Common Side Effects of First-Generation and Second-Generation Antipsychotic Drugs.*

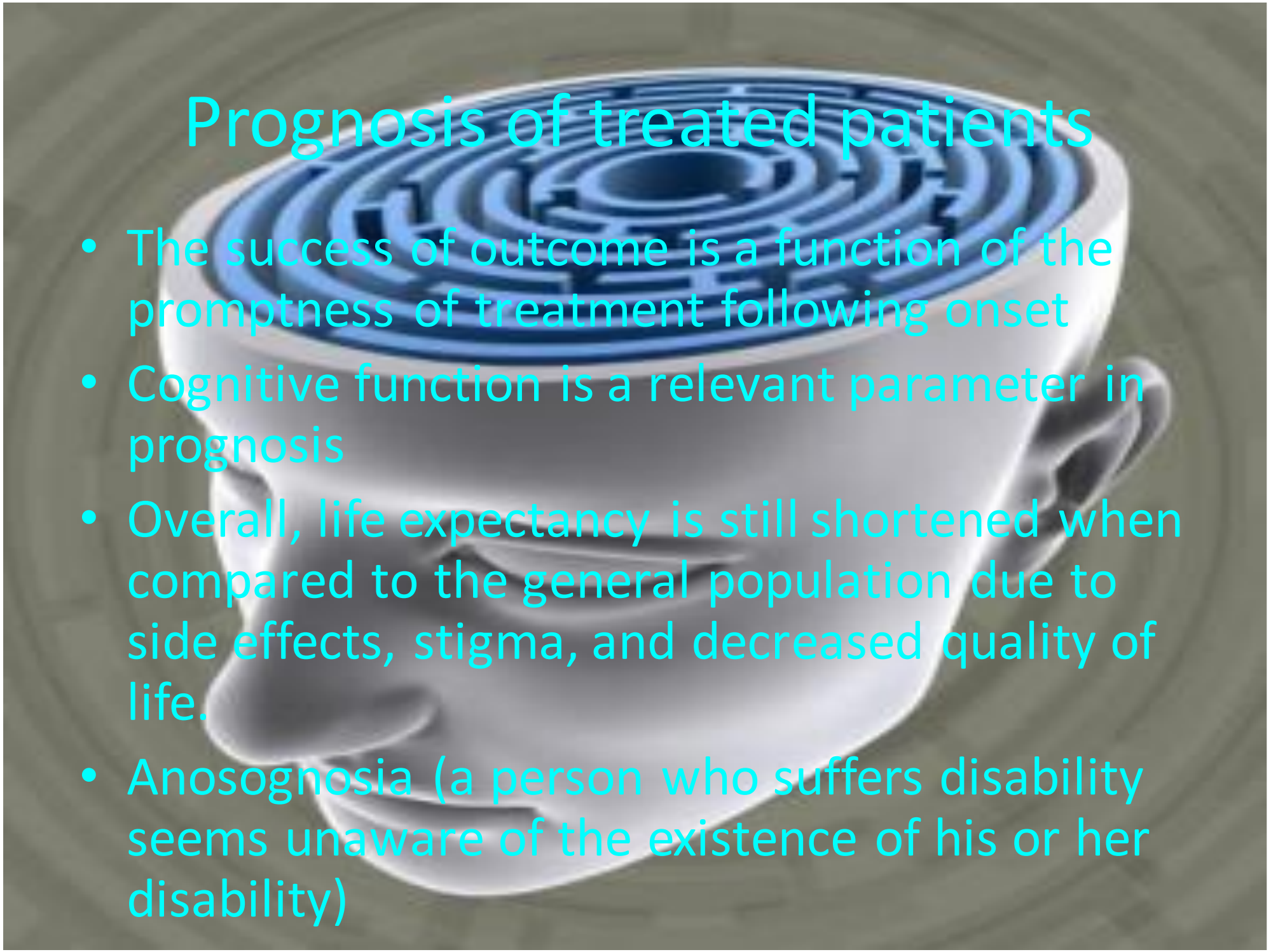
First-generation antipsychotics
Movement disorders, such as dystonia, bradykinesia, tremor, akathisia, choreoathetosis
Anhedonia
Sedation
Moderate weight gain
Temperature dysregulation, poikilothermy: cold in cold environments, warm in warm environments
Hyperprolactinemia, with galactorrhea and amenorrhea in women and gynecomastia in men; decreased sexual function in both
Postural hypotension
Sunburn
Prolonged QT interval, risk of potentially fatal arrhythmia (with thioridazine)
Second-generation antipsychotics
Moderate-to-severe weight gain (with olanzapine, clozapine)
Diabetes mellitus
Hypercholesterolemia
Sedation
Moderate movement disorder
Hypotension
Hyperprolactinemia (with risperidone)
Seizures (with clozapine)
Nocturnal salivation (with clozapine)
Agranulocytosis (with clozapine)
Myocarditis (with clozapine)
Lens opacities (with clozapine)

* Side effects can occur with any of the agents; a drug noted in parentheses indicates that a greater frequency of the side effect has been reported with that agent, but it can also occur with other agents.

Table 1. Efficacy, Side Effects, and Costs of Antipsychotic Medications.

Drug	Efficacy*	Extrapyramidal Symptoms†	Weight Gain†‡	Prolactin Increase†	Daily Dose§	30-Day Cost¶
					mg	*$*
Second-generation antipsychotic agents						
Clozapine‖	4	0	4	0	500	613
Olanzapine	3	1	4	0	20	684
Amisulpride	3	2	1	3	400	—
Risperidone	3	2	3	3	4	420
Aripiprazole	2	1	1	0	10	371
Quetiapine	2	0	2	0	400	492
Ziprasidone	2	1	1	0	120	438
First-generation antipsychotic agents (e.g., haloperidol)	2	4	1	2	10	35

* Efficacy is rated on a scale of 1 to 4, with higher numbers indicating higher efficacy.
† Side effects are rated on a scale of 0 to 4, with 0 indicating that the side effect is rarely observed and 4 indicating that it is the most severe.
‡ First-generation antipsychotic agents cause a gain in body weight of about 10 percent at the time of initial treatment for schizophrenia. This column ranks weight gain after treatment with a second-generation antipsychotic medication after the first episode of schizophrenia. Weight gain is highly variable among patients.
§ The daily dose is the lowest that is fully effective. The average is about 1.2 times as high as the lowest fully effective dose, since some patients require a higher dose.
¶ Cost is the average wholesale cost of an average dose for 30 days. Amisulpride is not sold in the United States.
‖ Agranulocytosis can occur with clozapine.



Prognosis of treated patients

- The success of outcome is a function of the promptness of treatment following onset
- Cognitive function is a relevant parameter in prognosis
- Overall, life expectancy is still shortened when compared to the general population due to side effects, stigma, and decreased quality of life.
- Anosognosia (a person who suffers disability seems unaware of the existence of his or her disability)

The Choice of an Antipsychotic Drug

- All antipsychotic drugs are effective for positive symptoms of acute psychosis.

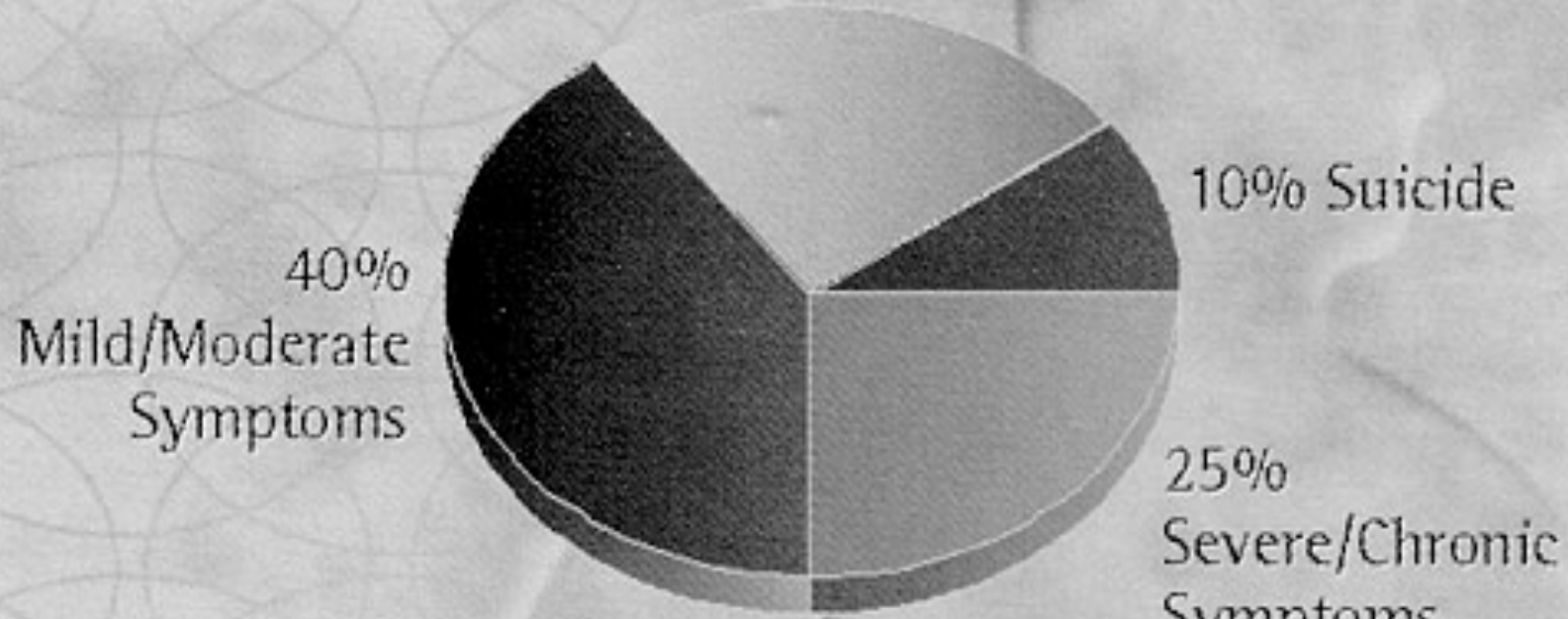
- Second-generation drugs are preferred because of their greater effects on negative symptoms and cognitive function and
- because they are associated with a lower rate of relapse and a lower incidence of movement disorders.

- Consistent therapeutic differences among second-generation drugs, other than clozapine, have not been established.

- The response of the individual patient must be used to guide selection

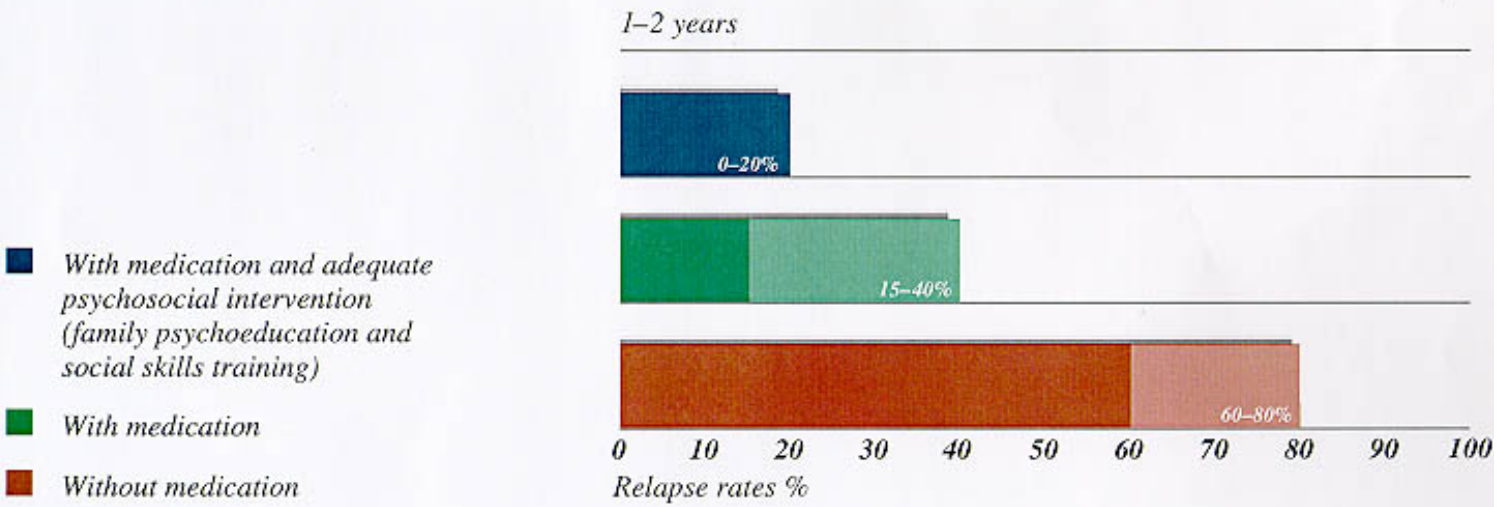
▪Primary endpoint: avoid relapses

Prognosis of Schizophrenia

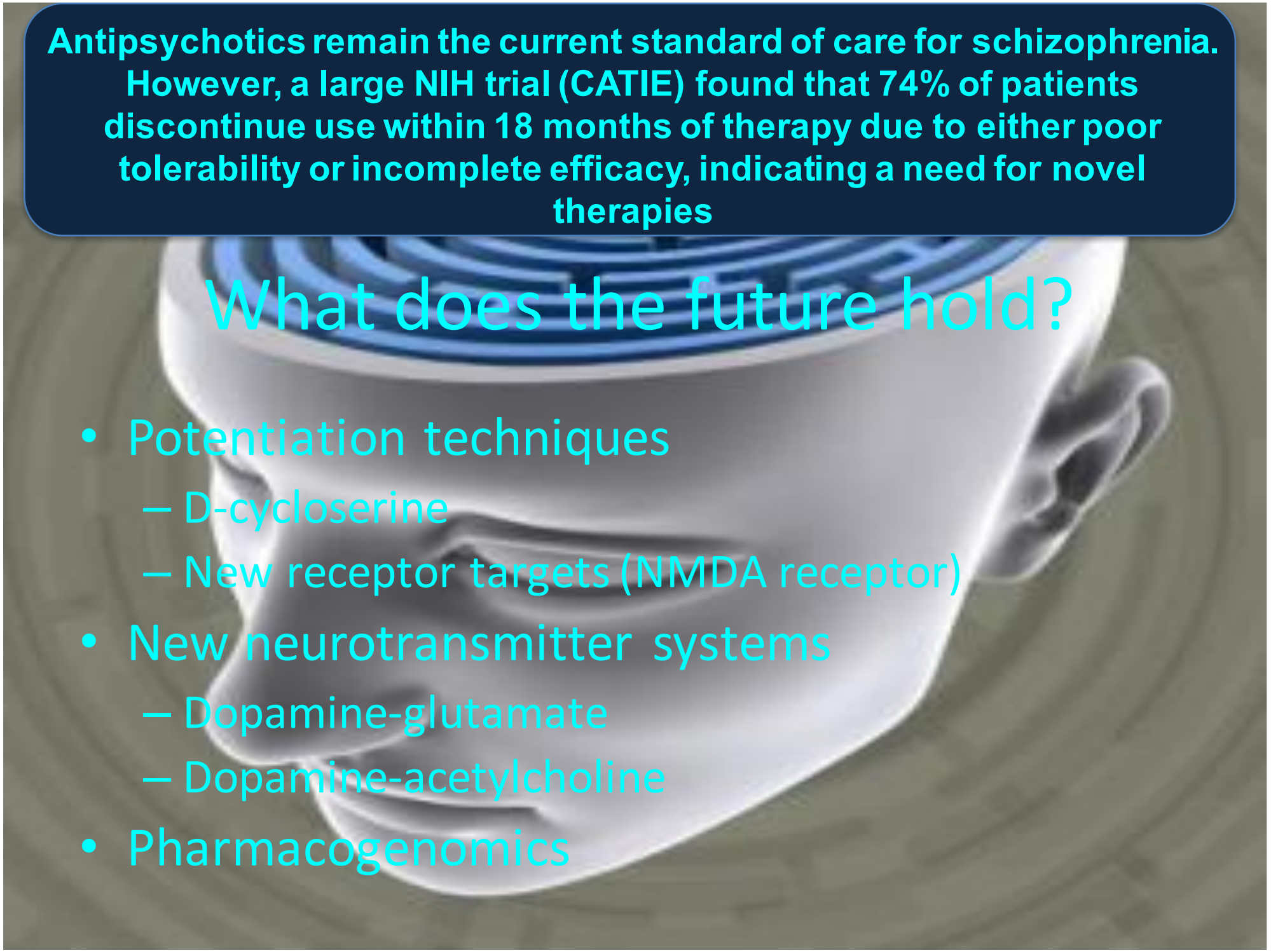


Adapted from J.A. Lieberman

Relapse rates and long-term outlook



PRELAPSE
Preventing relapse in schizophrenia



Antipsychotics remain the current standard of care for schizophrenia. However, a large NIH trial (CATIE) found that 74% of patients discontinue use within 18 months of therapy due to either poor tolerability or incomplete efficacy, indicating a need for novel therapies

What does the future hold?

- Potentiation techniques
  - D-cycloserine
  - New receptor targets (NMDA receptor)
- New neurotransmitter systems
  - Dopamine-glutamate
  - Dopamine-acetylcholine
- Pharmacogenomics

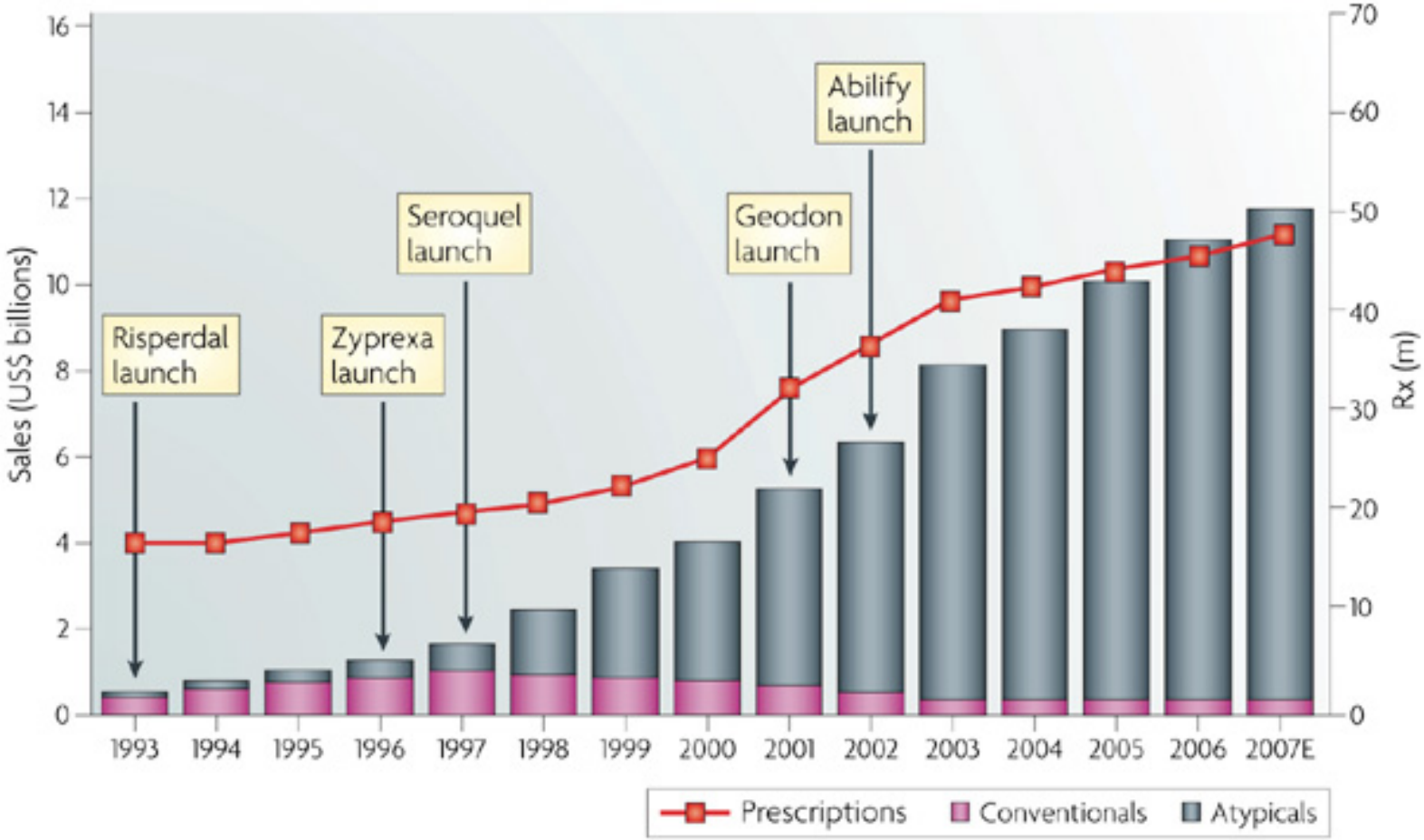


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Table A. Summary of strength of evidence of efficacy, by drug and condition

	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Anxiety					
- generalized anxiety disorder	0	-	++	-	-
Anxiety					
- social phobia	0	+	-	0	0
Attention Deficit/Hyperactivity Disorder					
-no co-occurring disorders	0	0	0	+	0
Attention Deficit/Hyperactivity Disorder					
-bipolar children	-	0	0	0	0
Attention Deficit/Hyperactivity Disorder					
-mentally retarded children	0	0	0	+	0
Dementia overall	++	+	+	++	0
Dementia psychosis	+	+-	+-	++	0
Dementia agitation	+	++	+-	++	0
Depression					
-MDD augmentation of SSRI/SNRI	++	+	++	++	+
Depression					
-MDD: Monotherapy	0	-	++	0	0
Eating Disorders	0	--	-	0	0
Insomnia	0	0	-	0	0
Obsessive Compulsive Disorder					
-augmentation of SSRI	0	+	--	++	-
Obsessive Compulsive Disorder					
-augmentation of citalopram	0	0	+	+	0
Personality Disorder					
-borderline	+	+-	+	0	-

Psychiatric Uses Of Antipsychotic Drugs

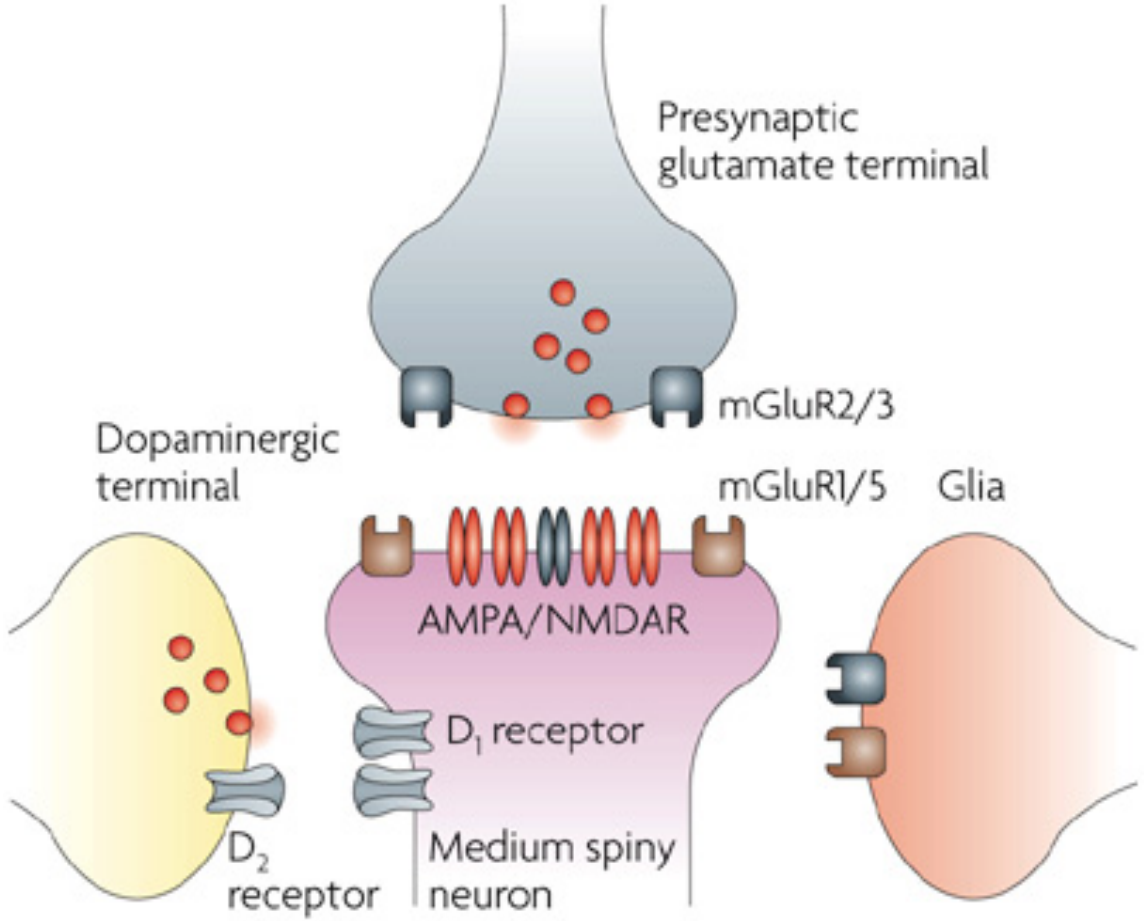
1. Schizophrenia: Acute and Chronic Maintenance
2. Psychotic Depression (With Antidepressants)
3. Acute Mania (With Lithium)
4. Autism (For Control of Aggressive Behaviors)
5. Gilles de la Tourette's Syndrome – Chronic Tics
6. Severe Agitation In Mentally Retarded and In Alzheimer's Patients

Company	Launched drug	Mechanism of action	2006 sales worldwide (US$)	Patent expiration
Johnson & Johnson	Risperdal (risperidone)	D_2, 5-HT, α-$_{2A}$ antagonist	4.1 billion	2008
Eli Lilly	Zyprexa (olanzapine)	D_2, 5-HT_2, M_{1-4}, H_1 antagonist	4.3 billion	2011
Pfizer	Geodon (ziprasidone)	D_2, 5-HT_2 antagonist	0.8 billion	2012
AstraZeneca	Seroquel (quetiapine fumarate)	D_2, 5-HT_2, 5-HT_6, H_1 antagonist	3.6 billion	2012
Bristol–Myers Squibb	Abilify (aripiprazole)	D_2 partial agonist	1.2 billion	2014

5-HT, 5-hydroxytryptamine receptor; α-2_A, α-2_A adrenoceptor; D_2, dopamine receptor 2; H_1, histamine receptor 1; M_{1-4}, muscarinic receptors 1–4.

Company	Pipeline drug	Mechanism of action	Phase	POC
Eli Lilly	LY2140023	mGluR2/3 agonist	II/III	Yes
Acadia	Primavanserin	5-HT inverse agonist	II/III	Yes
Merck/Addex	ADX63365	mGluR5 PAM	Preclinical	No
Johnson & Johnson/Addex	NA	mGluR2/3 PAM	Preclinical	No
Merck/Taisho	NA	mGluR agonist	Preclinical	No
Pfizer/Taisho	TS-032	mGluR agonist	Preclinical	No

5-HT, 5-hydroxytryptamine; mGluR, metabotropic glutamate receptor; NA, not applicable; PAM, positive allosteric modulator; POC, proof-of-concept.



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