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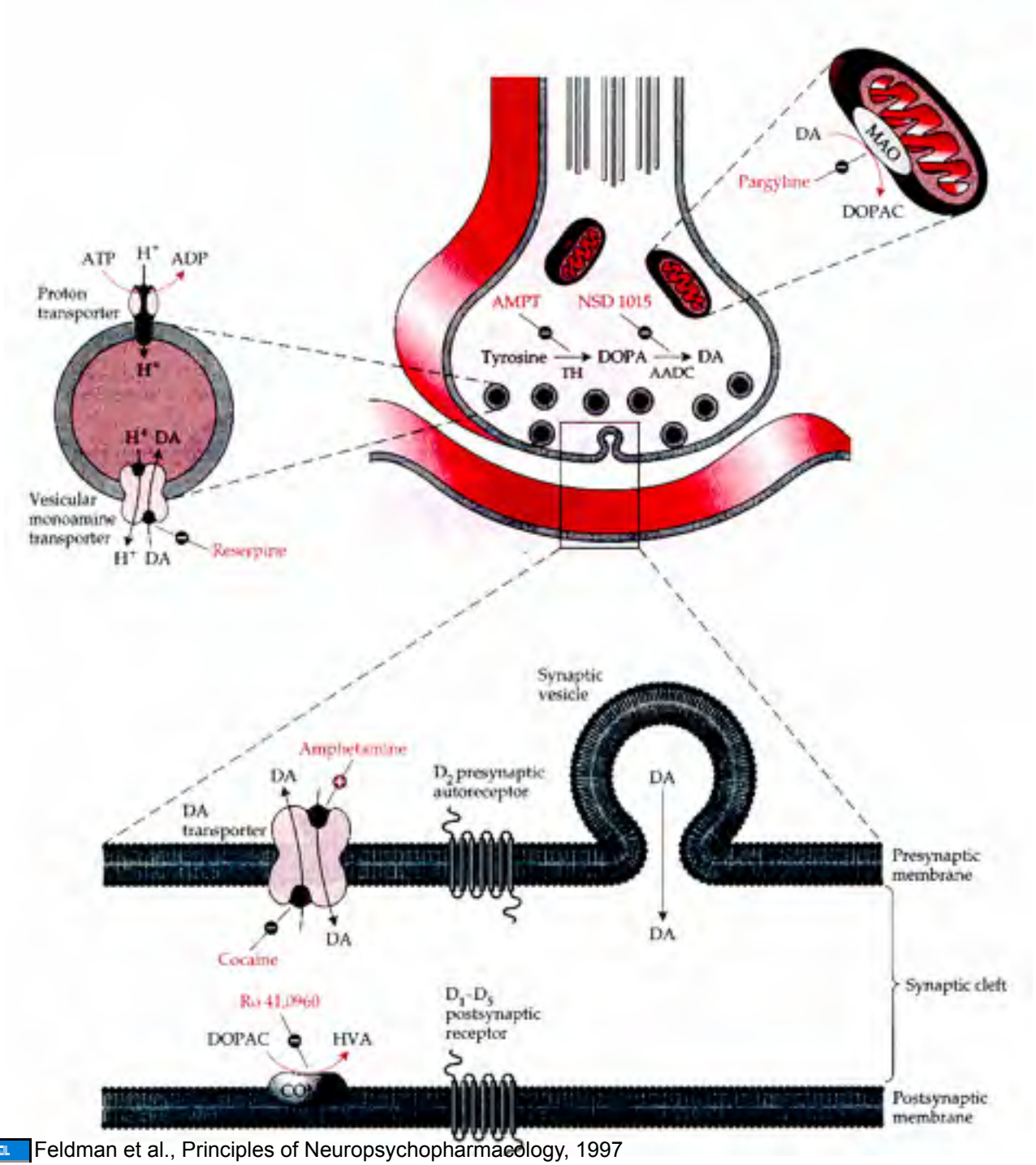
Margaret Gnegy
Professor
Department Pharmacology

Antipsychotic Drugs

Fall 2008

The Bottom line

- All active antipsychotic drugs block dopaminergic activity
- Drugs that more potently and specifically block dopamine (DA) D2Rs & FGAs have more extrapyramidal side effects
- Drugs that block many receptors have more autonomic and metabolic side effects
- Clozapine and olanzapine have the most metabolic side effects but may be the most efficacious
- DA and glutamate systems strongly interact: schizophrenia may involve low glutamate receptor (NMDA) activity and high dopamine receptor activity



Feldman et al., Principles of Neuropsychopharmacology, 1997

Synthesis:
TH – tyrosine hydroxylase

AADC – aromatic acid decarboxylase

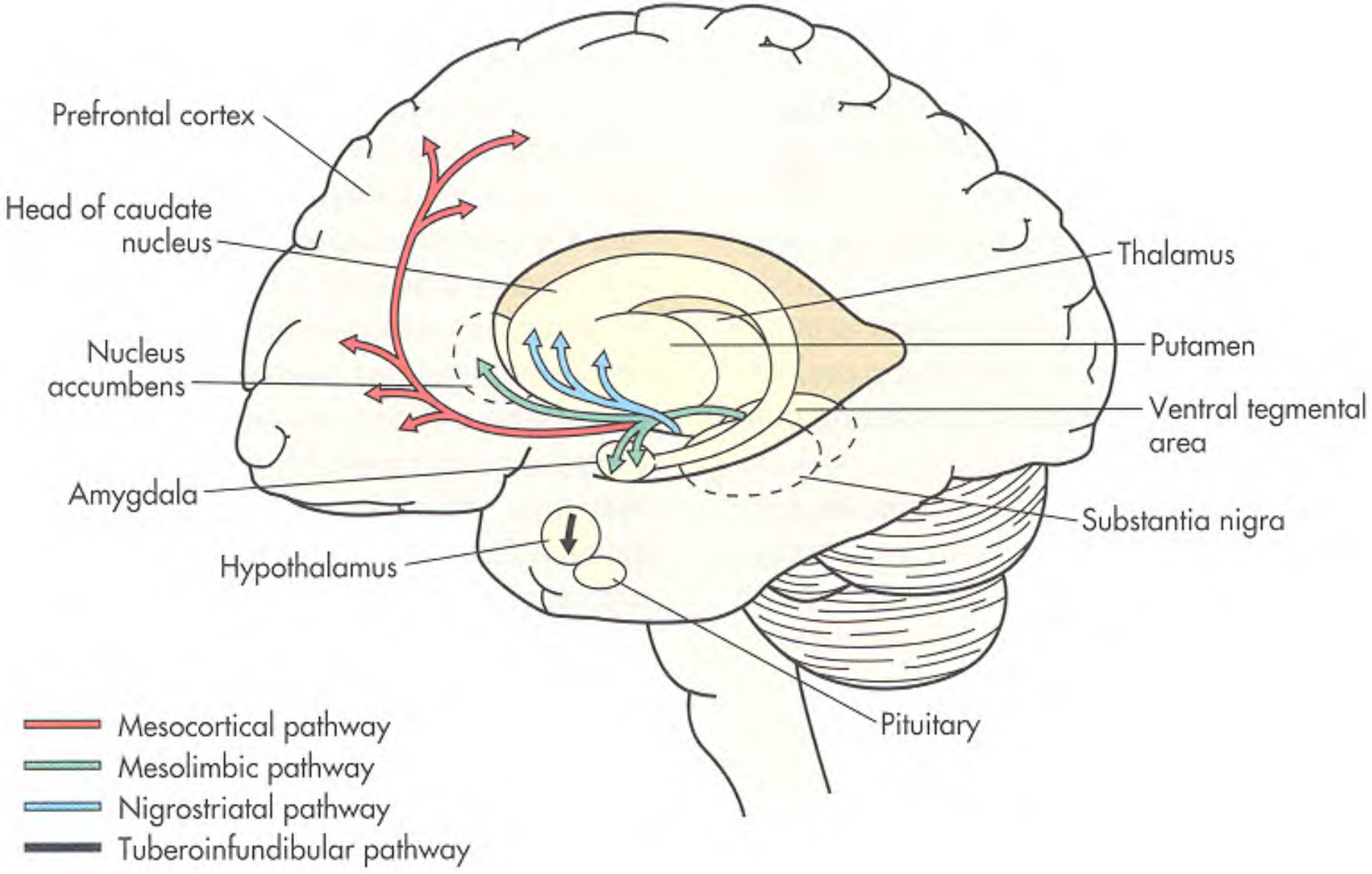
Metabolism:
MAO – monoamine oxidase

COMT – catechol-O-methyltransferase

Metabolites:
DOPAC – dihydroxyphenylacetic acid

HVA: homovanillic acid

Anatomy of dopamine neurons



Brody, Larner & Minneman, Human Pharmacology, Mosby, c1998, p. 343

Functional neuroanatomy of DA in the CNS

- Nigrostriatal pathway: motor planning and execution, habit formation, learning, habituation, memory
- Mesolimbic: complex target-oriented behavior, integrating emotional responses, motor and sensory processing
- Mesocortical: cognition; orchestration of thoughts and actions in accordance with internal goals
- Tuberoinfundibular: tonic inhibition of prolactin release, increase growth hormone release
- Chemoreceptor trigger zone: emesis & nausea

Early treatments of psychosis

PD-EXP National Library of Medicine

Bethlehem Asylum 'Bedlam', one of the first asylums (1403)

PD-EXP Jerrold & Quenzer, Psychopharmacology, Sinauer, c2005, p. 445

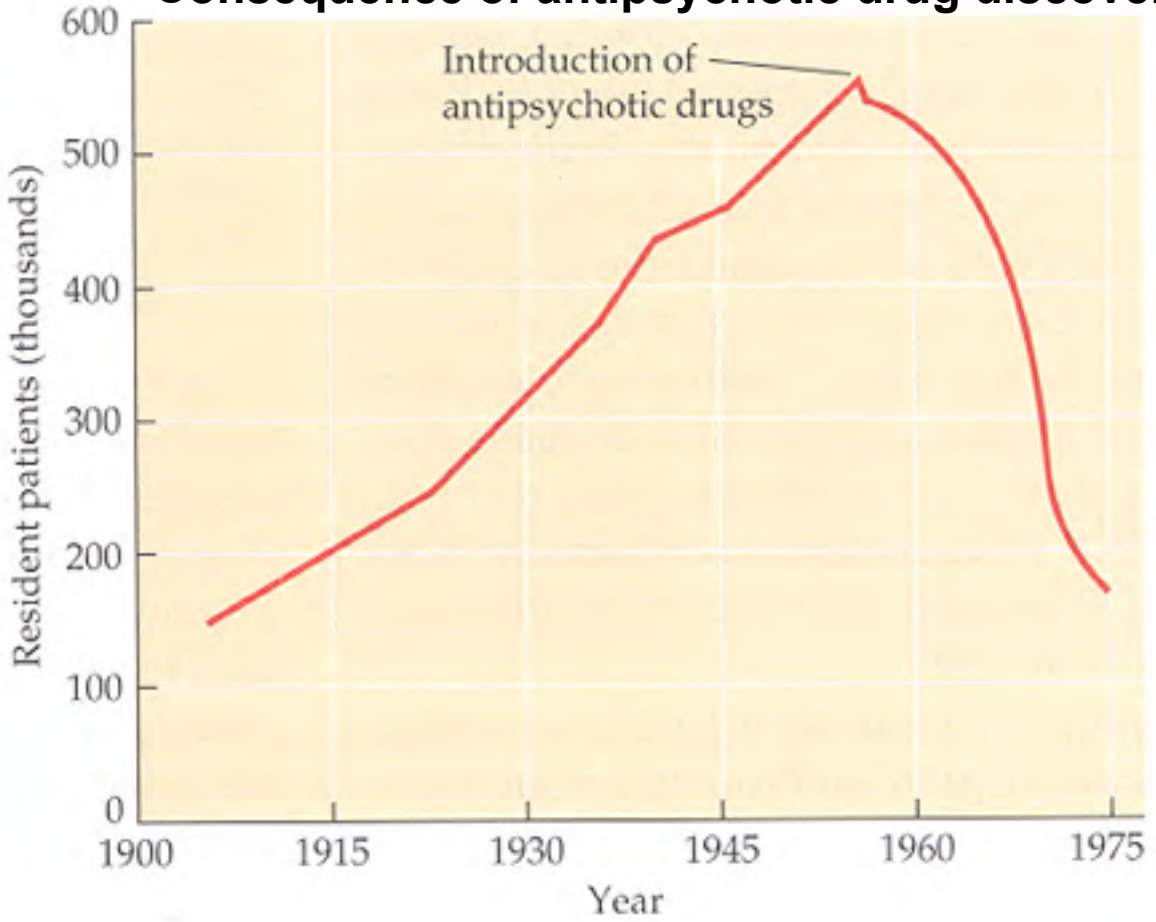
18th century asylum

Early treatment of psychosis

- Reserpine
- Insulin shock
- ECT
- Ice or fever therapy

Chlorpromazine
Haloperidol

Consequence of antipsychotic drug discovery

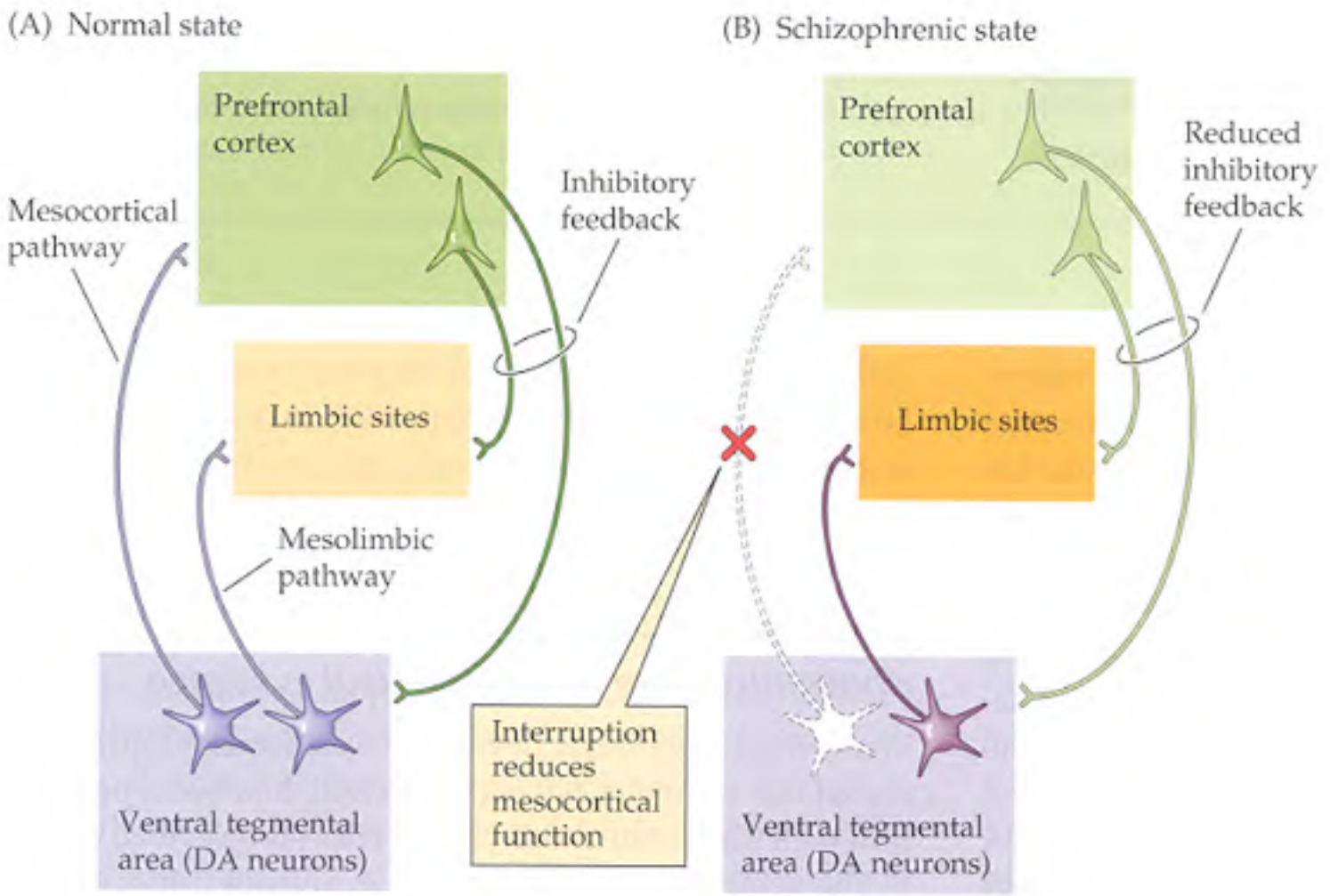


Jerrold & Quenzer, Psychopharmacology, Sinauer, c2005, p. 445

Pharmacological evidence supporting a role of DA in the positive aspects of schizophrenia

- **Increasing dopamine worsens psychosis**
  - High doses of amphetamine or cocaine can lead to a paranoid psychosis
  - Amphetamine will exacerbate an existing schizophrenic state
- **Decreasing dopamine ameliorates psychosis**
  - Blockade of DA receptors treats psychosis
  - Inhibition of DA synthesis ameliorates symptoms of schizophrenia
- There is enhanced amphetamine-induced DA release in schizophrenia

Schema of neurodevelopmental model of schizophrenia

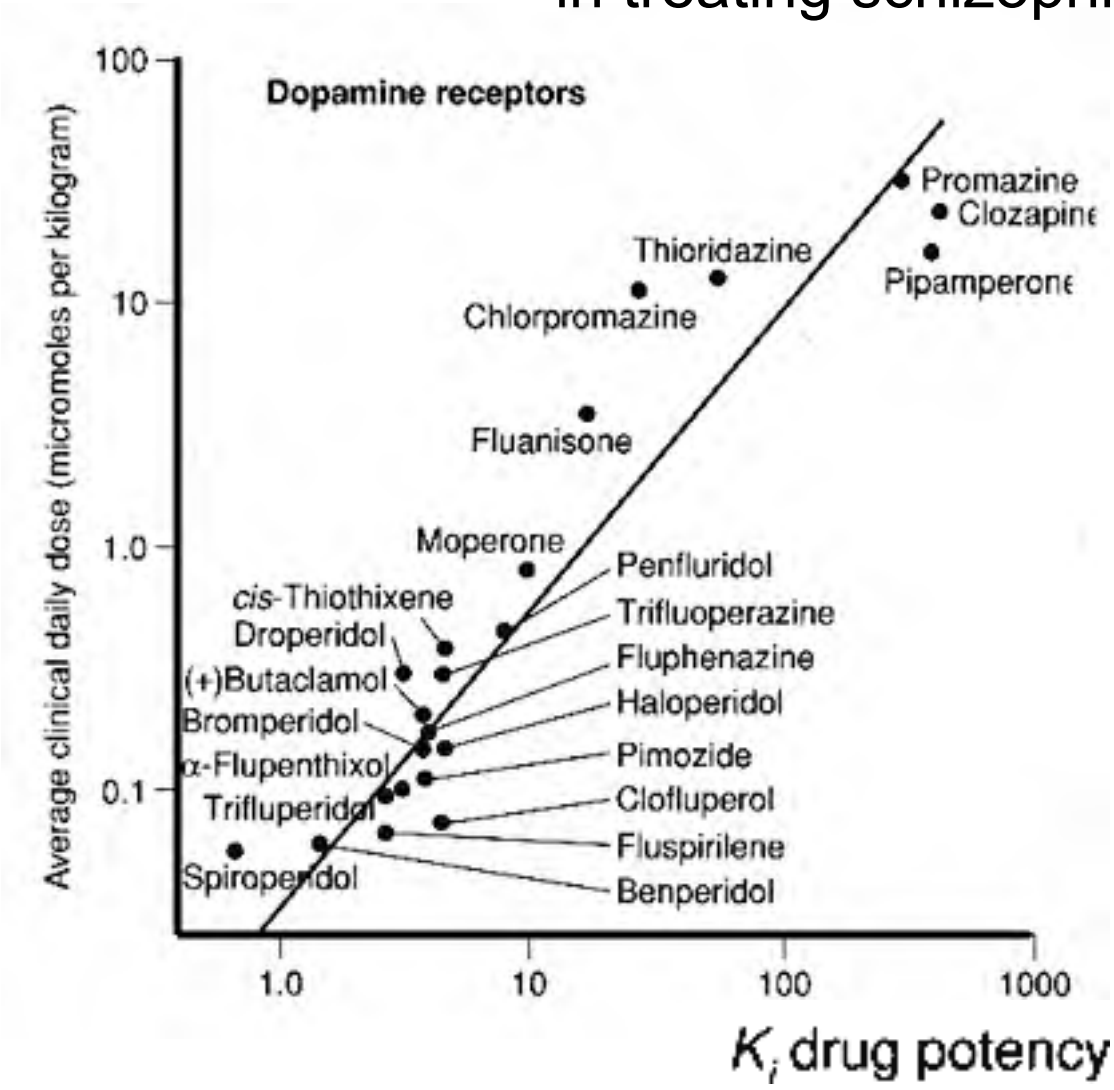


Jerrold & Quenzer, Psychopharmacology, Sinauer, c2005, p. 466

Characteristics of Antipsychotic Drugs

- Active against psychosis of any origin: idiopathic, metabolic, drug-induced
- More active against ‘positive’ symptoms
- Antipsychotic drugs interfere with dopamine transmission, most block dopamine receptors
- Drugs start to work relatively quickly, but it takes a few months to reach maximum effect

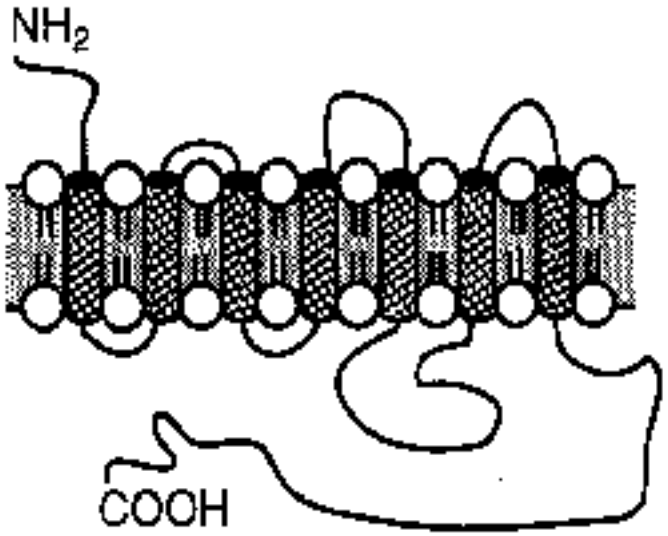
The potency of antipsychotic drugs in binding to the D2 family of receptors is proportional to the potency of the drugs in treating schizophrenia



This is not true for the potency of the drugs in blocking histamine H1, serotonin or α-adrenergic receptors

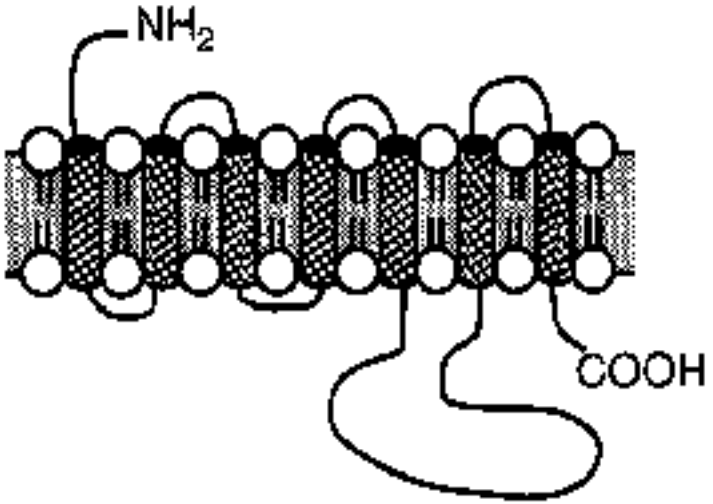
Adapted from Nestler Hyman & Malencka, Molecular Neuropharmacol.ogy, McGraw Hill, c2001, p. 402

D1 Receptor Family



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

D2 Receptor Family



- ⬇ cAMP
- ⬆ K^+ currents
- ⬇ ψ-gated Ca^{2+} currents
- ⬆ β-arrestin/Akt/GSK-3β pathway

Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th Ed. Brunton et al. Eds. McGraw-Hill, c2006, p. 531

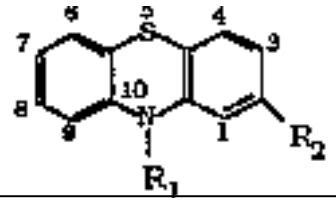
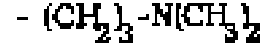
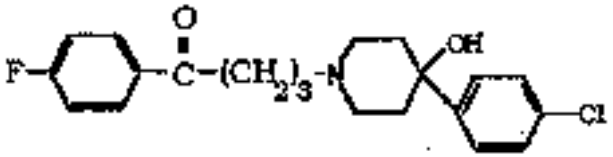
Modern Course of Treatment

- New ‘atypical’ antipsychotic drugs (second generation)

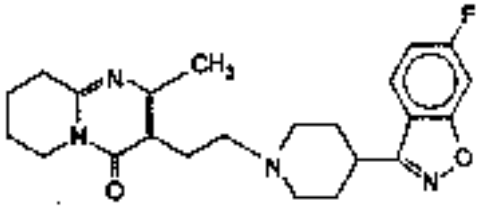
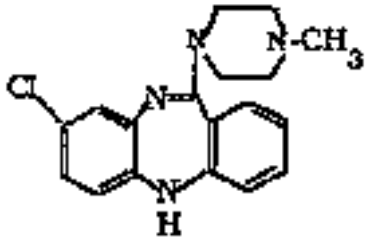
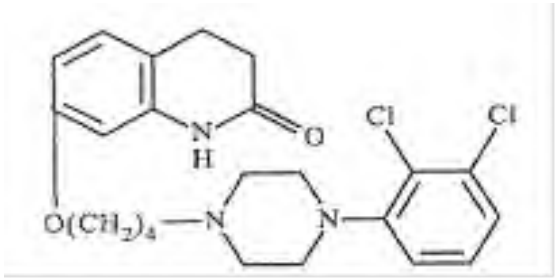
- Conventional old-line drugs (first generation)

- Clozapine

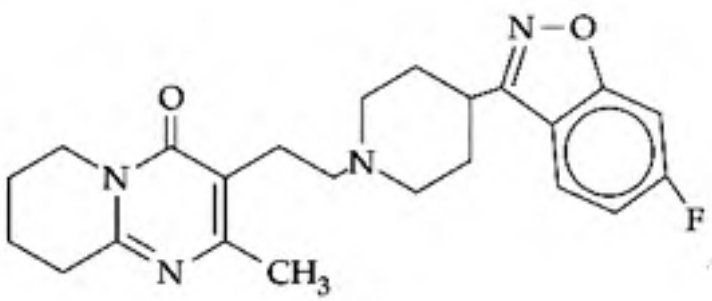
First Generation Antipsychotic Drugs

Compound			Seda-tion	Hypo-tension	Motor (EP) Effects
Phenothiazines					
Chlorpromazine	R1 	R2 Cl	+++	++	++
Fluphenazine		CF_3	+	+	++++
Haloperidol Haldol			+	+	++++

Second Generation Antipsychotic Drugs

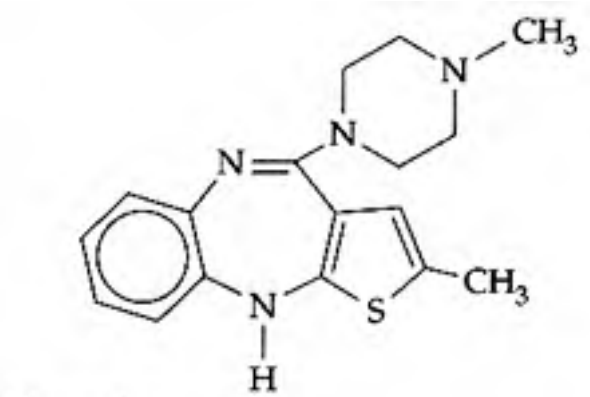
Compound	Sedation	Hypo-tension	Motor effects
Risperidone  Risperdal	++	+++	+/++ Dose dependent
Clozapine  Clozaril	++	++	-
Aripiprazole  Abilify	0/+	0/+	0/+

Second Generation Antipsychotic Drugs



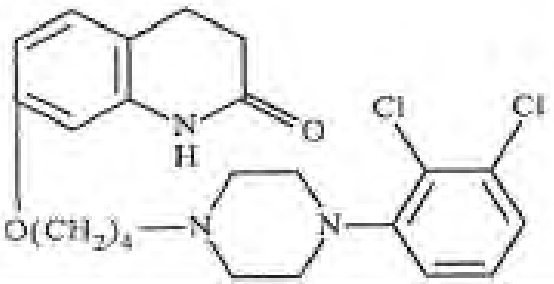
Risperidone

Risperdal



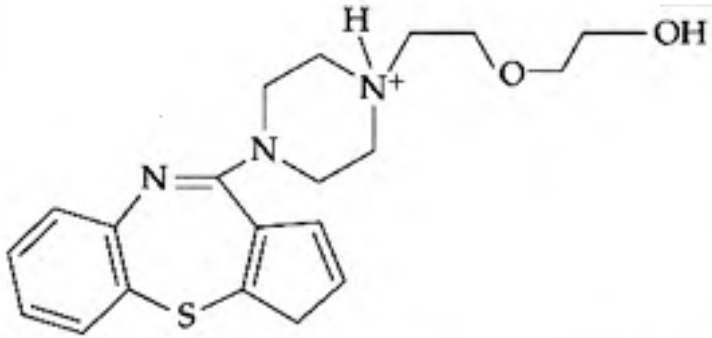
Olanzapine

Zyprexa

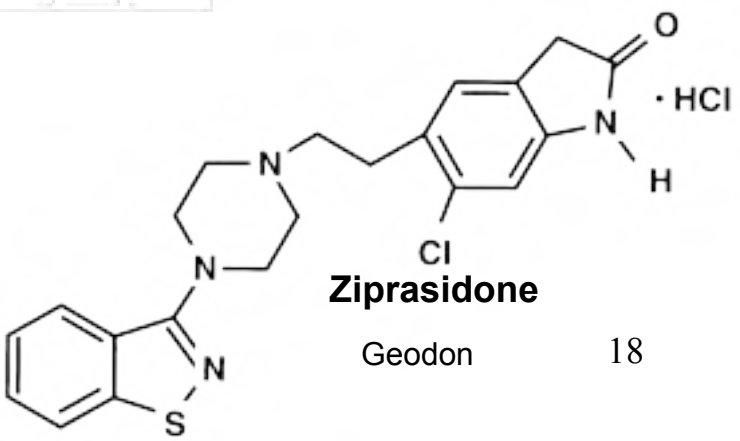


Aripiprazole

Abilify



Quetiapine Seroquel



Ziprasidone

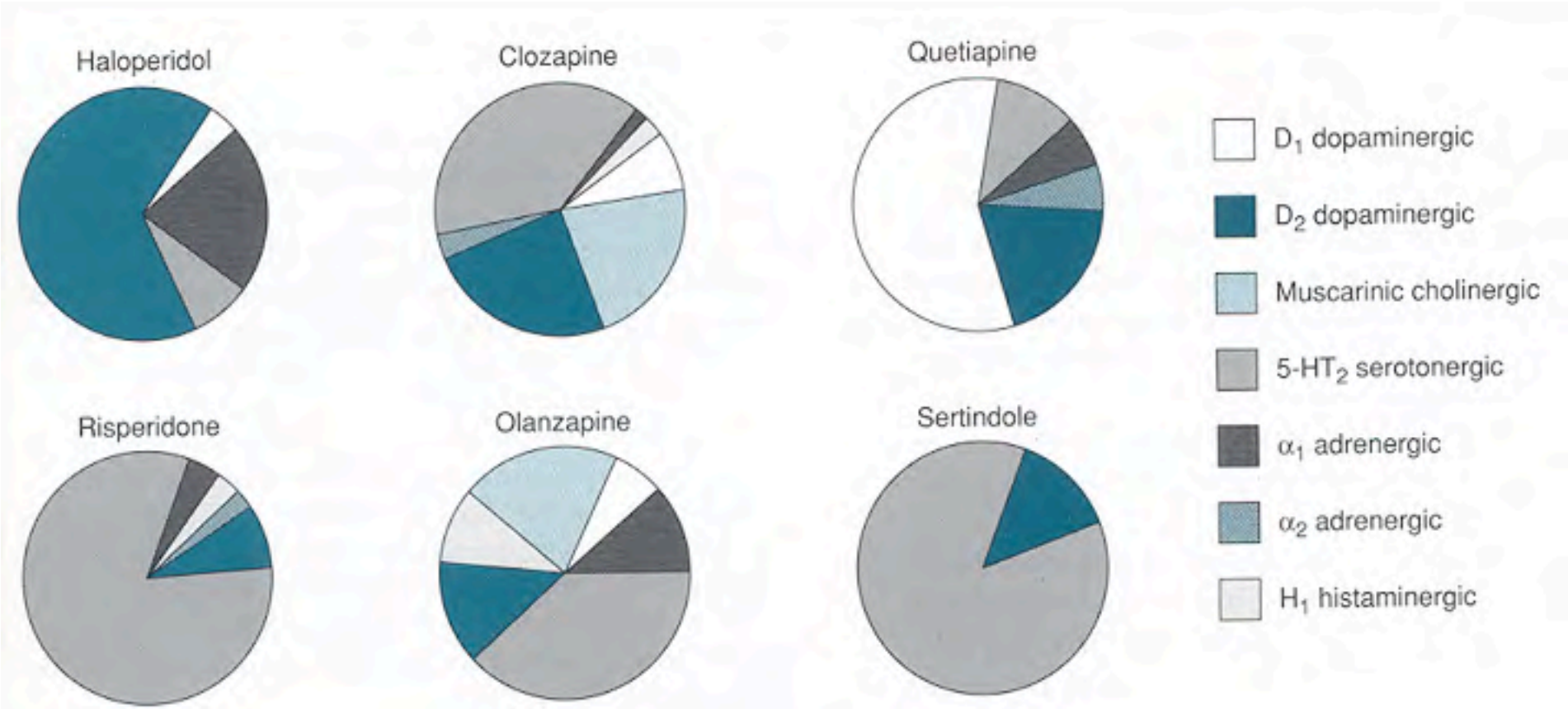
Geodon

Image Sources Undetermined

Pharmacological effects of antipsychotic drugs: blockade of DA action

Area	**What dopamine does**	**What antipsychotic drug does**	**Drug profile**
Basal ganglia	Control of movement	Extrapyramidal (motor) side effects: DA deficiency	High specificity > low specificity. Less with 2nd gen. None with clozapine or quetiapine.
Limbic and frontal cortex	Affective behavior; cognition	Site of antipsychotic action	Most equally efficacious, ex. Clozapine & olanzapine
Hypothalamus & endocrine	Temp. regulation; ↓ prolactin	poikilothermic effect; ↑prolactin	1st Generation and risperidone
Chemoreceptor trigger zone	Nausea, emesis	Reduce nausea, emesis	1st Generation and risperidone

In vitro profiles of the relative ability of antipsychotic drugs to bind to specific receptors

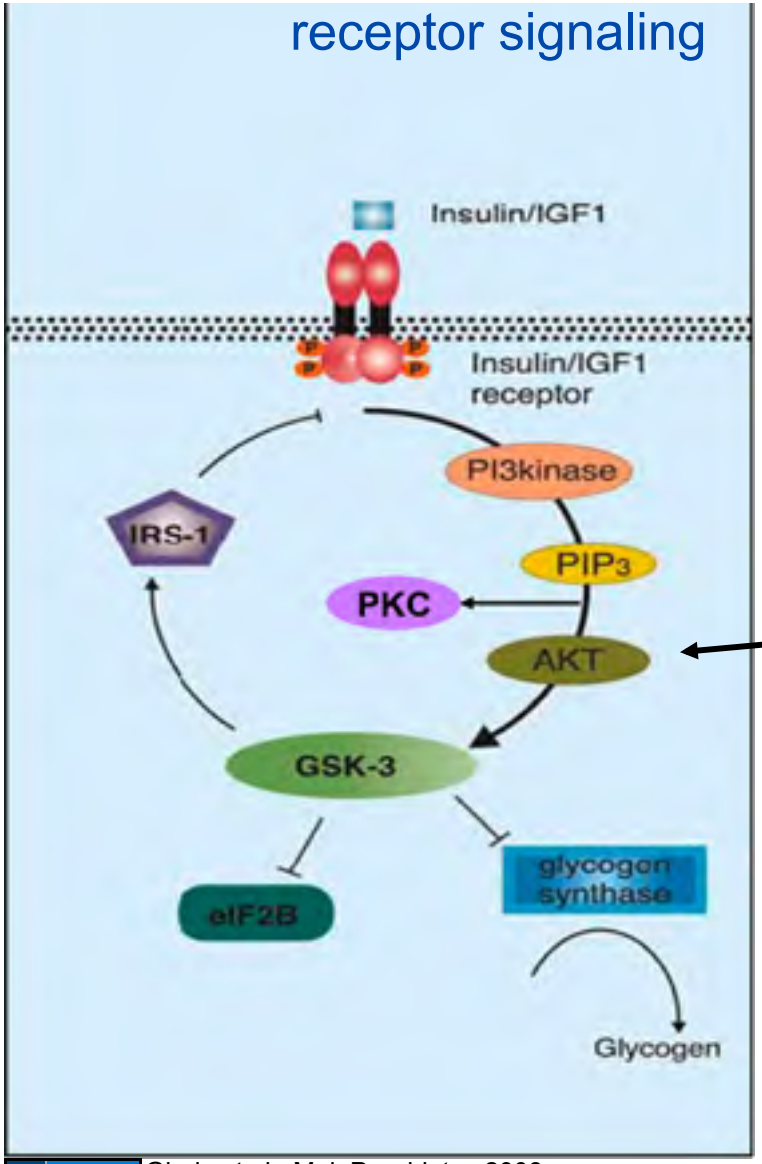


Nestler Hyman & Malencka, Molecular Neuropharmacol.ogy, McGraw Hill, c2001, p. 405

Pharmacological effects of antipsychotic drugs

Area	**Antipsychotic drug action**	**Pharmacological effect**	**Drug profile**
Autonomic effects	Blockade of α-adrenergic, muscarinic, hist H1 and serotonin receptors	Hypotension, orthostatic hypotension, ↓ ejaculation, sedation, dry mouth, etc.	Low specificityy > high specificity
Metabolic effects	Blockade of serotonin, muscarinic, dopamine, hist H1 receptors	Diabetes, weight gain	**Cloz ≈ olanz** > risper, quet, chlorpromaz > zipras, aripip, halop
Cardiovascular system	Direct and indirect effects	Mild orthostatic hypotension; Chance for prolonged QT interval	Low specificity > high specificity Dose related

Insulin signaling intersects with DA D2R and serotonin (5-HT) receptor signaling



Girgis et al., Mol. Psychiatry, 2008

Antipsychotic drugs

⊥

DA and 5-HT Rs

+

β-arrestin

+/-

Absorption, Distribution and Fate of Antipsychotic drugs

- Erratic absorption
- Highly lipophilic
- t 1/2 = 6-40 hrs, most taken once a day
- Metabolized by cytochrome P450 enzymes
- Clearance from brain may be slower than clearance from plasma

Depot forms of antipsychotic drugs

- Are depot forms for non-compliant patients
  - Haloperidol, fluphenazine, risperidone, [olanzapine]
- Paliperidone ER (Invega, active metabolite of risperidone) uses oral osmotic pump extended release technology
- Can give lower doses than with oral forms, less plasma level drug fluctuation
- Elimination following i.m. injection is very slow, half-life of 7-10 days
- Lower relapse rates
- Poor patient acceptance and no flexibility in dosing

Tolerance and dependence to antipsychotic drugs

- Not addicting
- Relapse in psychosis if discontinued abruptly

- Tolerance develops to sedative effects
- No tolerance to prolactin secretion
- No tolerance to antipsychotic effect

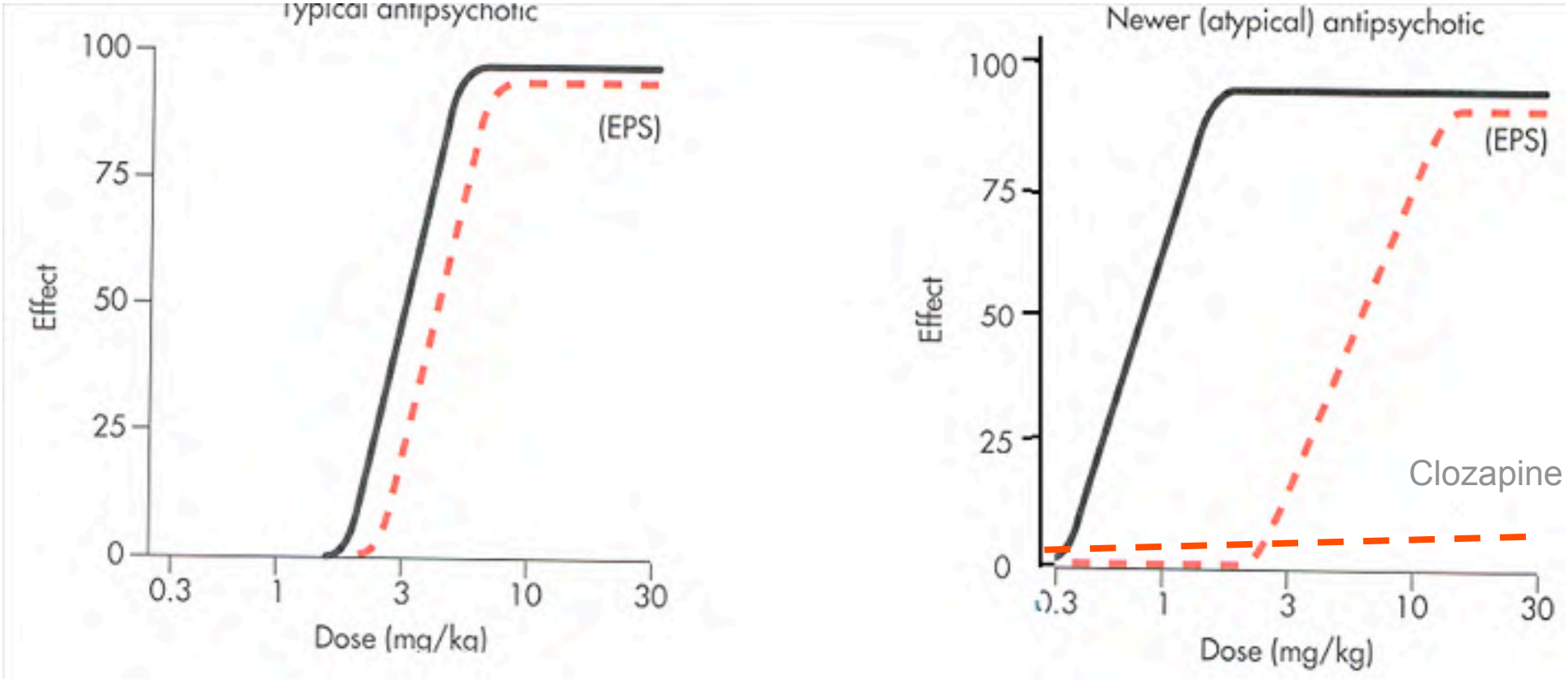
Drug Interactions of Antipsychotic drugs

- CNS Depressants: will potentiate actions of other CNS depressants: sedatives, analgesics, hypnotics, cold remedies
- Blocks effects of l-dopa and dopaminergic agonists
- Most are metabolized by P450 system, will be affected by drugs that alter P450

Extrapyramidal side effects

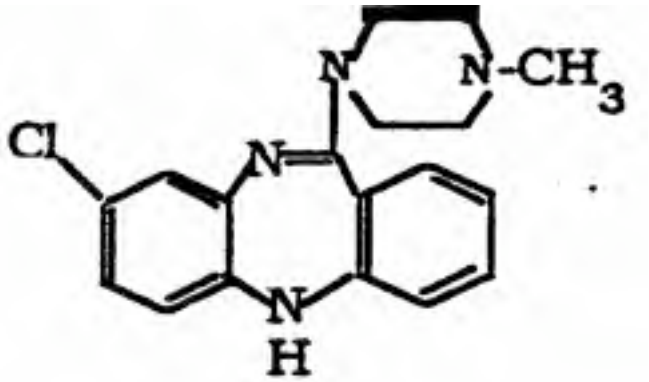
EFFECT	FEATURE	TIME OF RISK	MECHANISM?	TREATMENT
Acute dystonia	Spasm of muscles of tongue, face, neck, back	1 to 5 days	Unknown	Antimuscarinic agents
Akathisia	Motor restlessness, Anxiety	5 to 60 days	Unknown	Reduce dose, propranolol
Parkinsonism	Bradykinesia, rigidity, tremor	5 to 30 days	DA antagonism	Quetiapine or clozapine
Neuroleptic malignant syndrome	Catatonia, stupor, fever, can be fatal	Weeks, can persist for days	DA antagonism	Stop neuroleptic immediately
Tardive dyskinesia	Stereotyped or choreic involuntary movements of face, tongue, trunk	After months or years of treatment, seen when withdraw drug	Excess function of DA?	Prevention crucial, switch to clozapine or quetiapine

The dose response curves for efficacy and extrapyramidal symptoms are separated



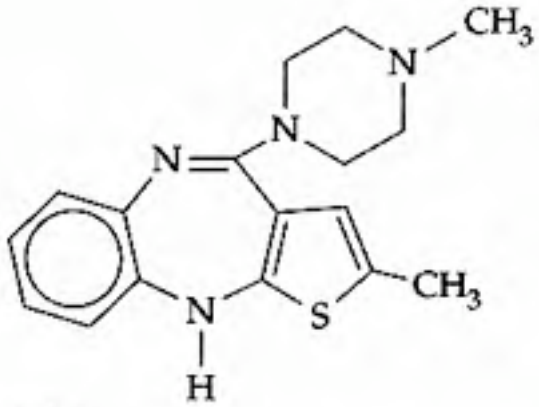
Adapted from Brody, Larner & Minneman, Human Pharmacology, Mosby, c1998, p. 346

Clozapine and olanzapine



Source Undetermined

- VERY low EPS
- Blocks D1, D2, D4, α-adrenergic, 5HT2, muscarinic, and histamine H1 receptors
- May show greater efficacy against negative symptoms than other antipsychotic drugs
- Agranulocytosis is a potentially fatal side effect forclozapine

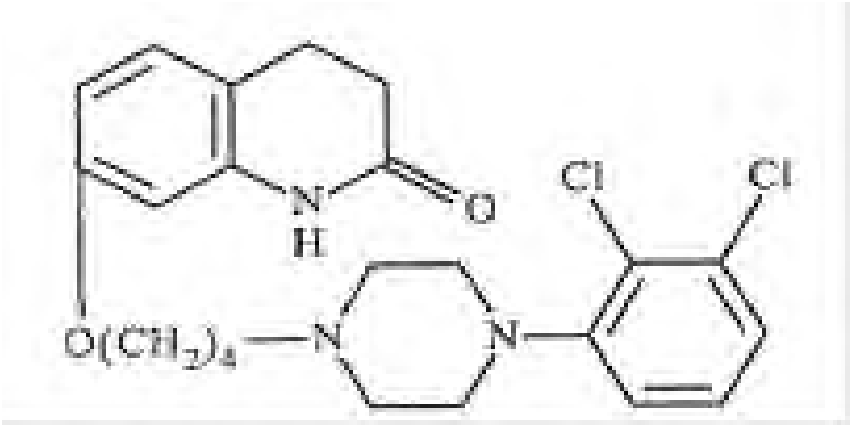


Olanzapine

Source Undetermined

Both drugs have high efficacy, but cause significant weight gain and diabetes

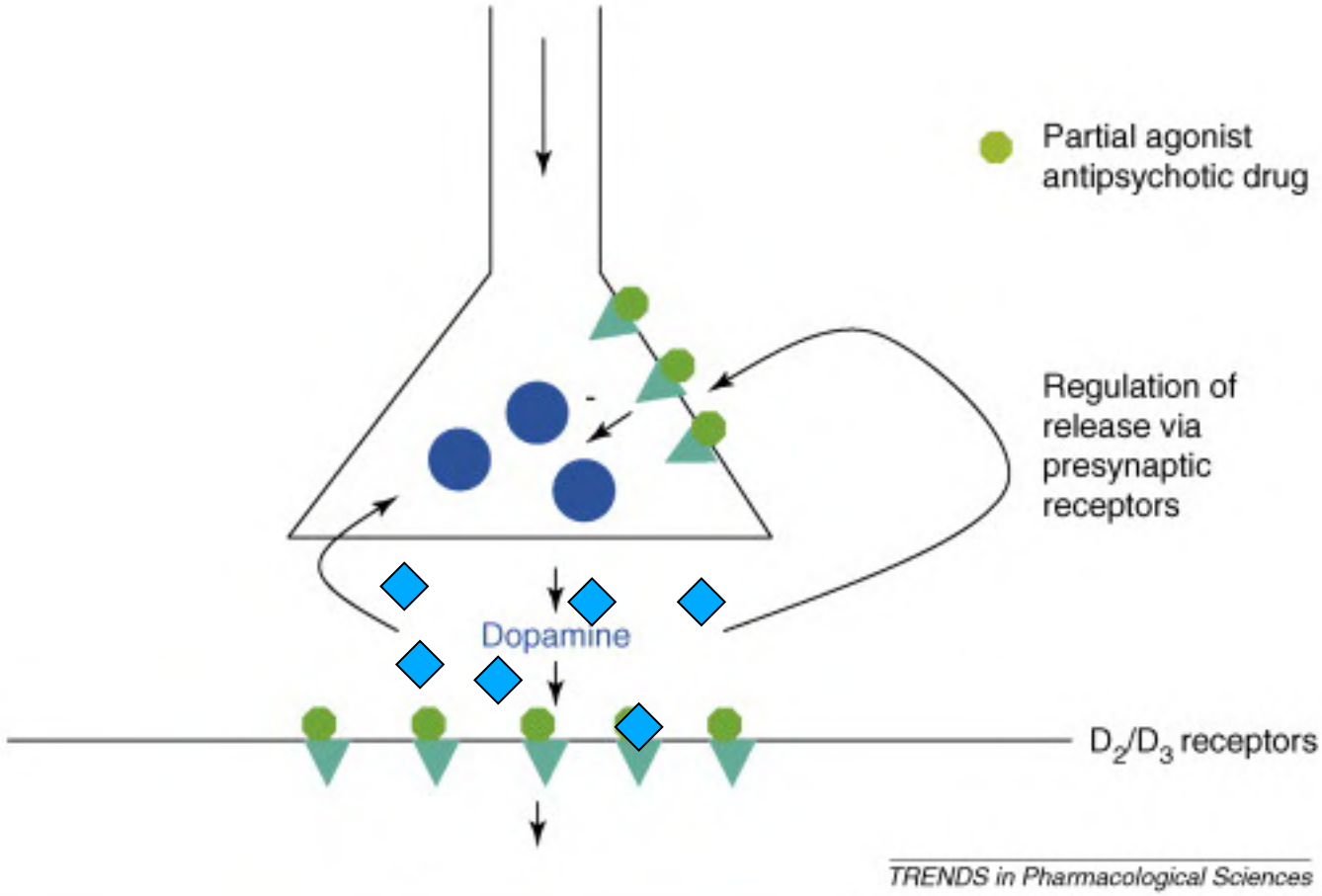
Aripiprazole (Abilify)



Source Undetermined

- **Partial agonist at D2 receptor**
- Intrinsic activity depends on synaptic levels of DA
- Affinity for muscarinic, α_1-adrenergic, serotonin and histamine receptors
- Good oral absorption, 3-5 hr to peak plasma concentration, long elimination half life
- Few extrapyramidal side effects

Action of aripiprazole, a D2R partial agonist, at dopaminergic synapse



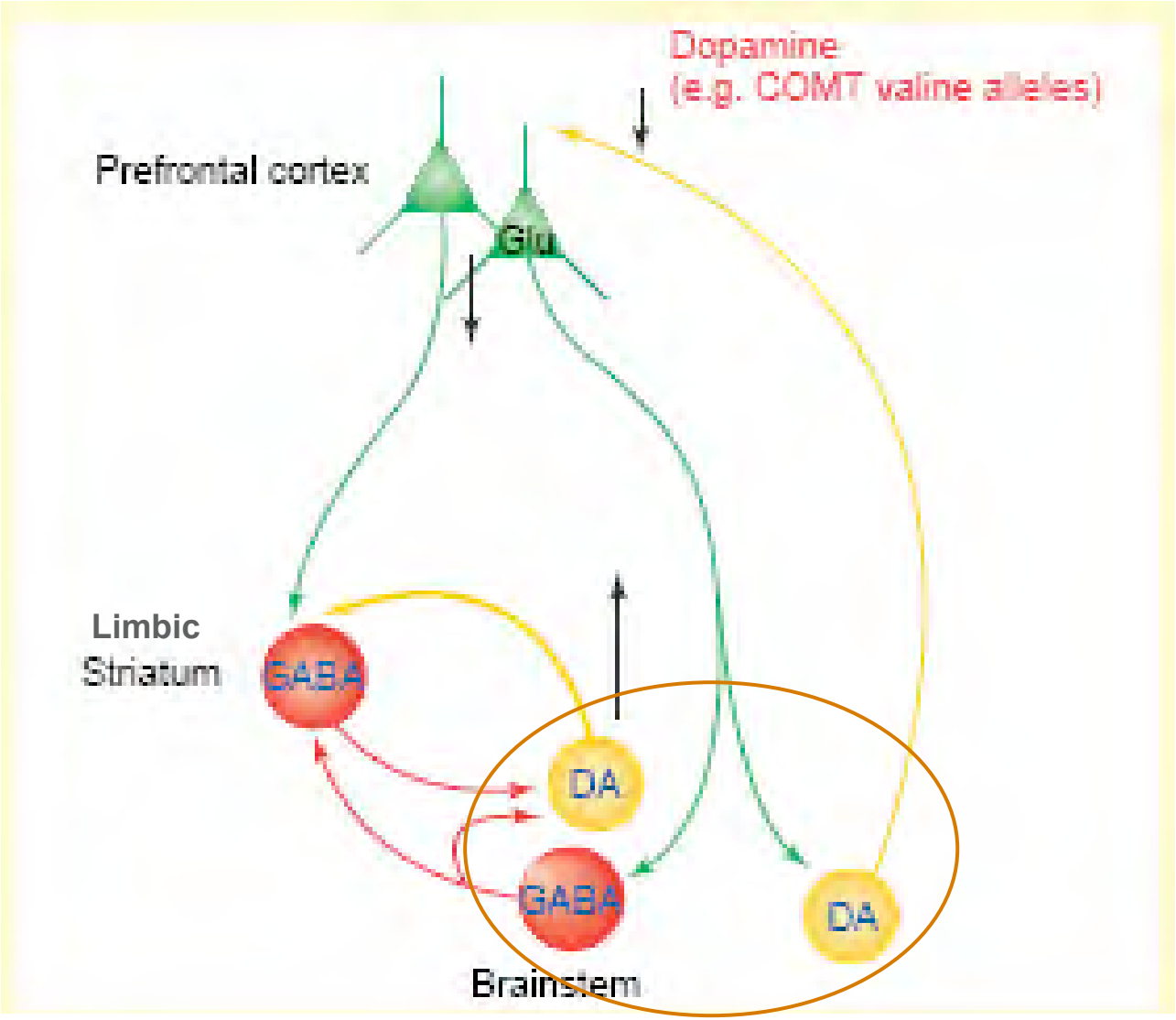
Second generation antipsychotic drugs

- Fewer extrapyramidal side effects, usually dose dependent.
- Side effects: sedation, orthostatic hypotension, weight gain (especially clozapine, olanzapine and risperidone), potential for type II diabetes
- Efficacy of all drugs similar except forclozapine and olanzapine. But they have better efficacy but worse metabolic effects.
- Have high affinity for $5HT_2$, α_1-adrenergic receptors, varied affinity for DA receptors

Factors that may play a role in reduced EPS of 2nd generation drugs

- Receptor occupancy?
  - ~60% of D2Rs need to be occupied to get therapeutic effect
  - ≥ 80% occupation gives EPS
  - Aripiprazole occupies ~85%
- Receptor binding profile: most SGAs have high affinity for a number of serotonin receptor subtypes

Glutamate also plays a role in psychosis



Winterer and Weinberger, Trends in Neurosciences, 27:686, 2004.

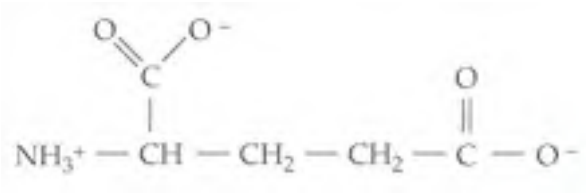
Model of psychosis:

Increased DAergic activity in limbic region

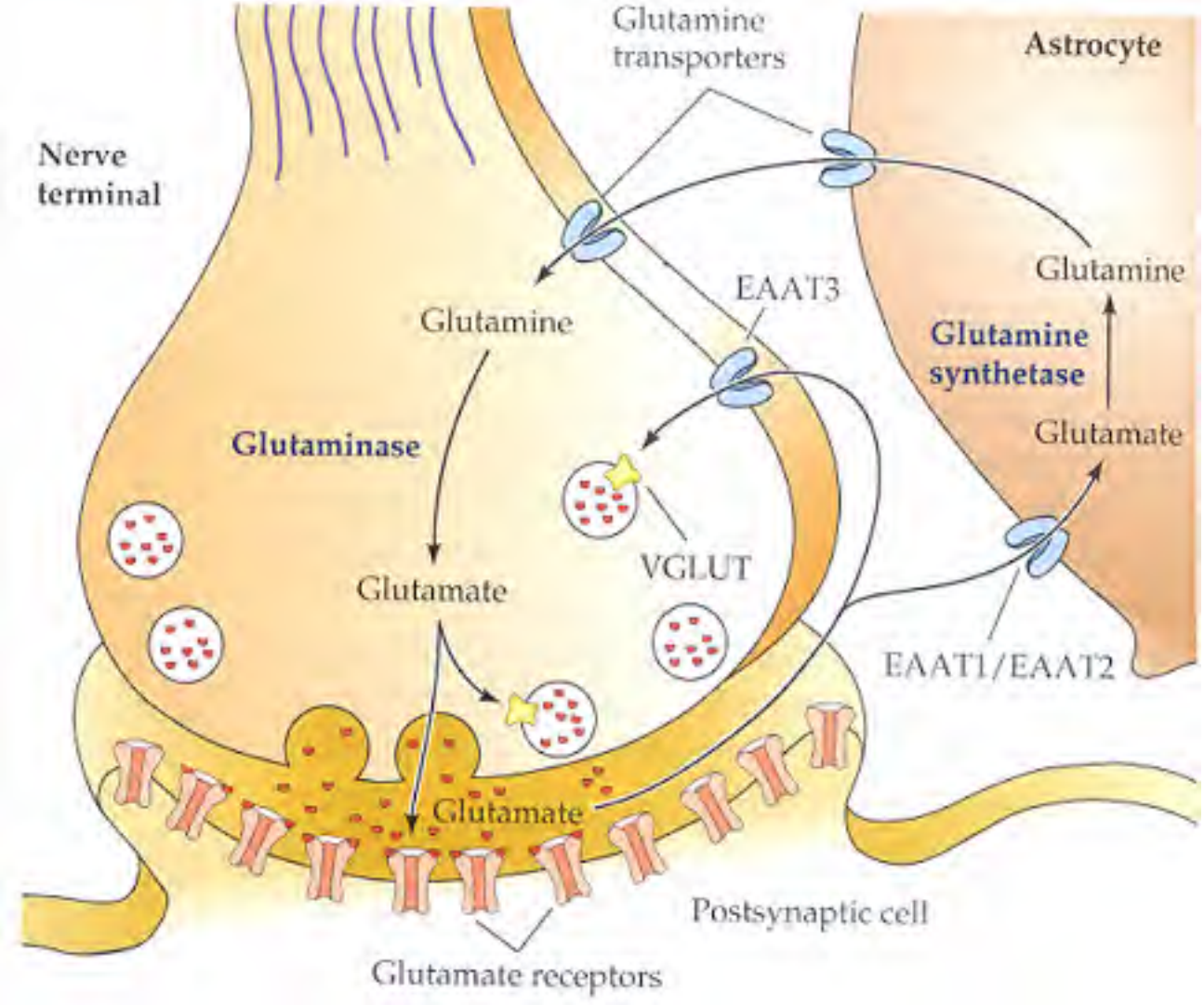
Decreased DAergic activity in prefrontal cortex

Decreased glutamatergic input into limbic (striatal) region and mesencephalon

Deficits in GABAergic neurons in frontal cortex

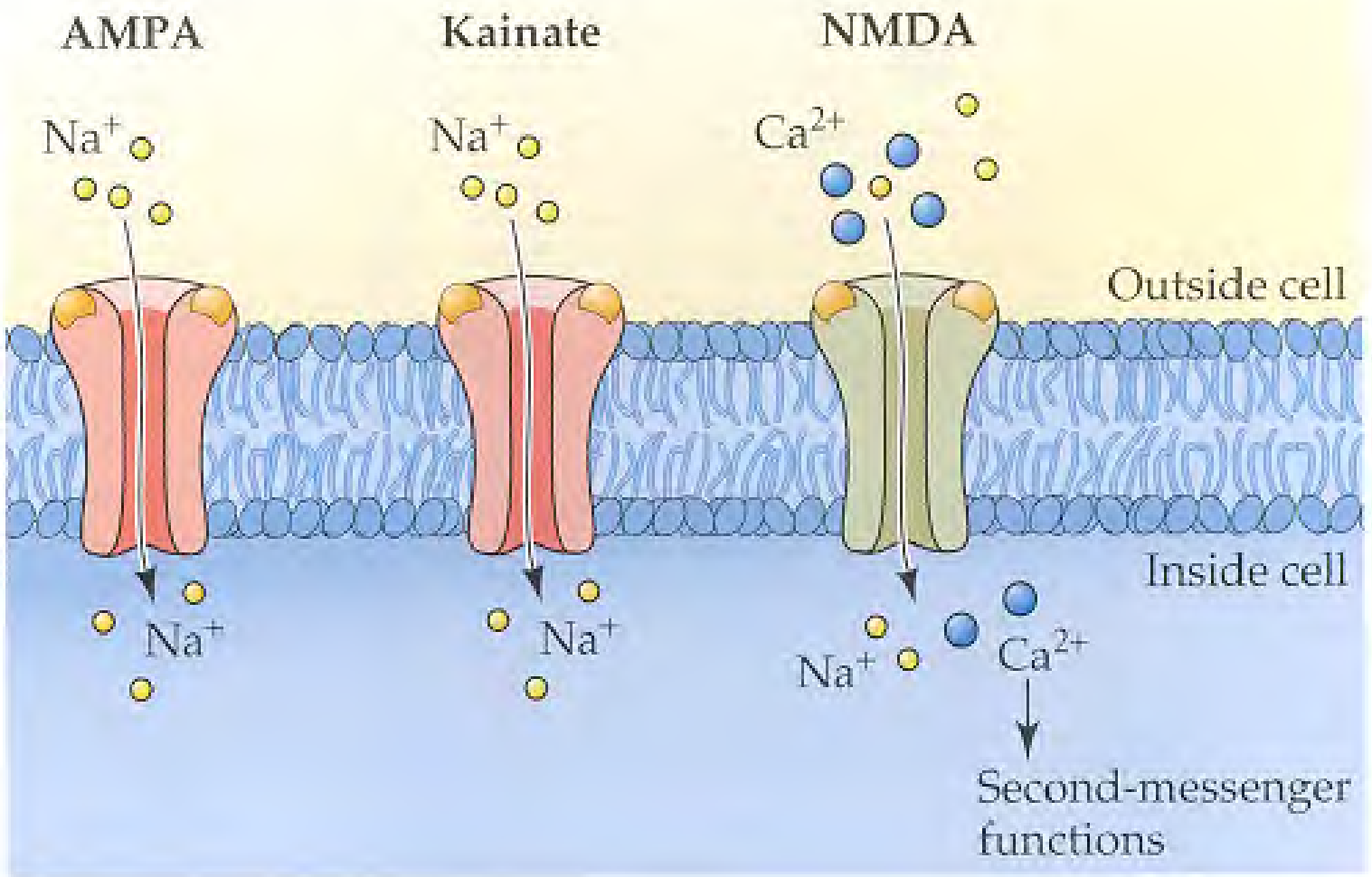


Glutamate neuron



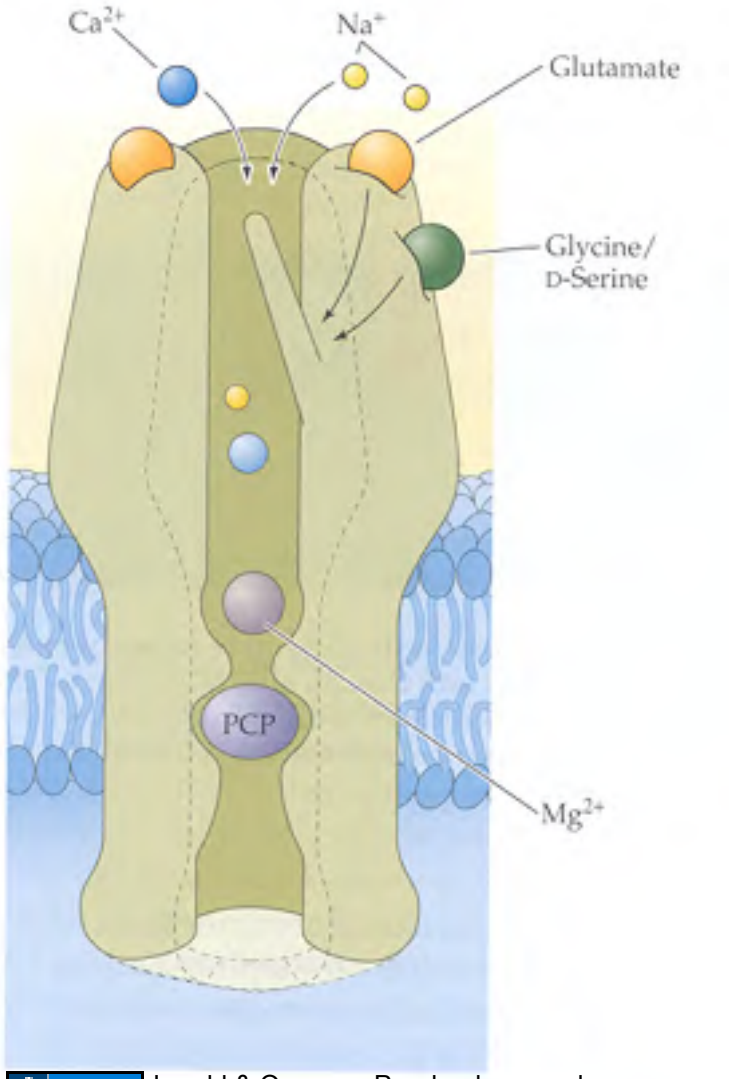
Jerrold & Quenzer, Psychopharmacology, Sinauer, c2005 , p. 166

Ligand-gated channel subtypes of the glutamate receptor



Jerrold & Quenzer, Psychopharmacology, Sinauer, c2005 , p. 167

N-methyl-D-aspartate receptor ligands



Jerrold & Quenzer, Psychopharmacology, Sinauer, c2005, p. 168

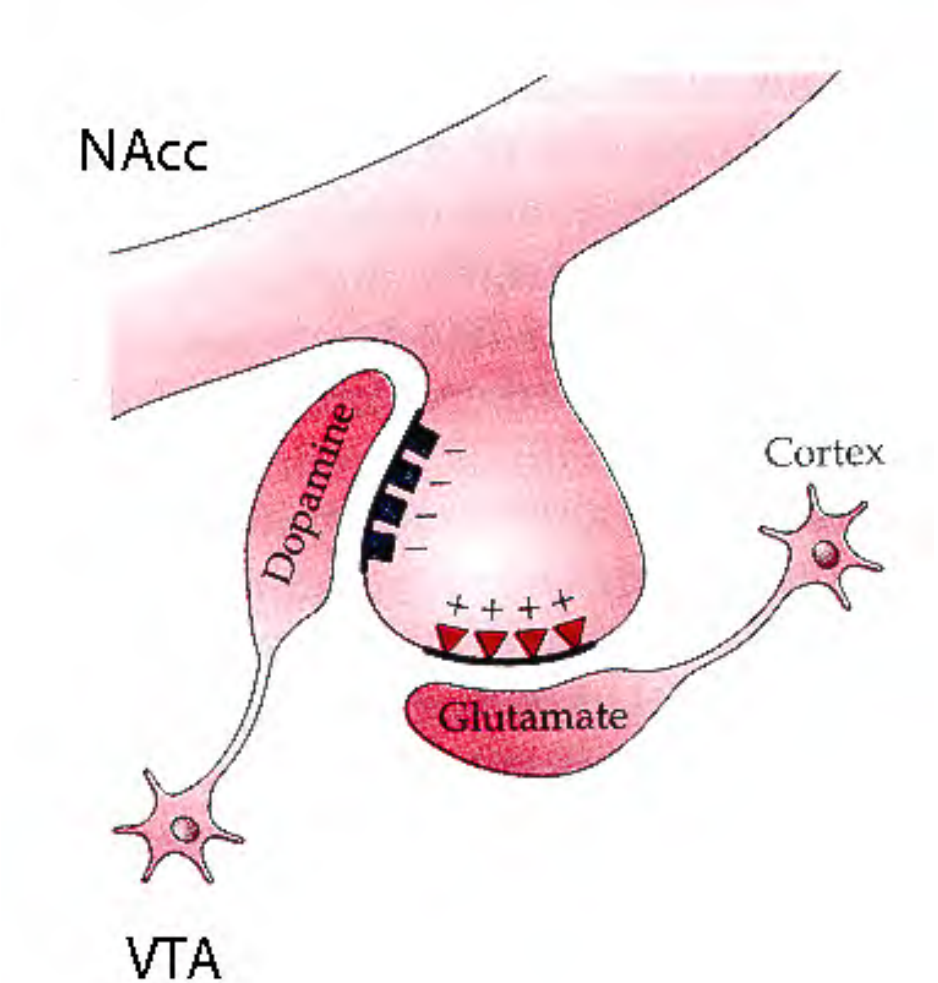
- Agonist: both glutamate and aspartate are agonists
- Co-agonist: glycine or D-serine
- Permeability: Ca^{2+} and Na^{+}
- Mg^{2+}: voltage-dependent block of the NMDA receptor
- Phencyclidine (PCP) and ketamine: noncompetitive antagonists

NMDA Hypothesis of Schizophrenia

- **Reducing glutamate worsens psychotic symptoms**
  - Competitive NMDA antagonists induce both positive and negative symptoms in healthy and schizophrenic subjects
  - NMDA antagonists worsen symptoms in unmedicated patients with schizophrenia
  - Chronic treatment with antipsychotic drugs can block effects of NMDA antagonists
  - Decreased levels of glutamate in CSF, prefrontal cortex and hippocampus of schizophrenics

- **NMDA agonists improve symptoms in schizophrenia**

New directions for antipsychotic drugs: Glutamate agonists



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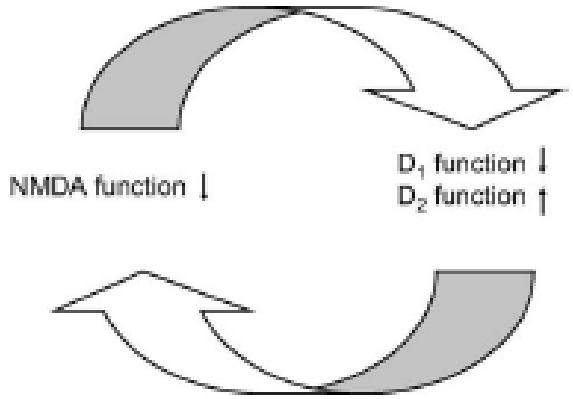
New avenues for treatment of schizophrenia

- Glutamate NMDA receptor co-agonists: glycine, alanine, D-serine
- Dopamine D1 agonists (many D1 receptors in prefrontal cortex) for cognition



Hypothesized imbalances in schizophrenia

- Nicotine receptor agonists to improve cognition

Upcoming therapies for schizophrenia

D1 receptor agonist	Cognitive enhancement
Glycine, alanine, D-serine	Enhance NMDA activity, effective in reducing negative symptoms in schizophrenia, reduce cognitive impairments
Glycine reuptake inhibitors	Increase synaptic glycine
Glutamate reuptake inhibitor	Increase synaptic glutamate
Nicotinic receptor agonist	Cognitive enhancement

Additional Source Information

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Slide 5: Feldman et al., Principles of Neuropsychopharmacology, 1997
Slide 6: Brody, Larner & Minneman, Human Pharmacology, Mosby, c1998, p. 343
Slide 8: National Library of Medicine; Jerrold & Quenzer, Psychopharmacology, Sinauer, c2005, p. 445
Slide 9: Jerrold & Quenzer, Psychopharmacology, Sinauer, c2005, p. 445
Slide 11: Jerrold & Quenzer, Psychopharmacology, Sinauer, c2005, p. 466
Slide 13: Adapted from Nestler Hyman & Malencka, Molecular Neuropharmacol.ogy, McGraw Hill, c2001, p. 402
Slide 14: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th Ed. Brunton et al. Eds. McGraw-Hill, c2006, p. 531
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Slide 16: Source Undetermined
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