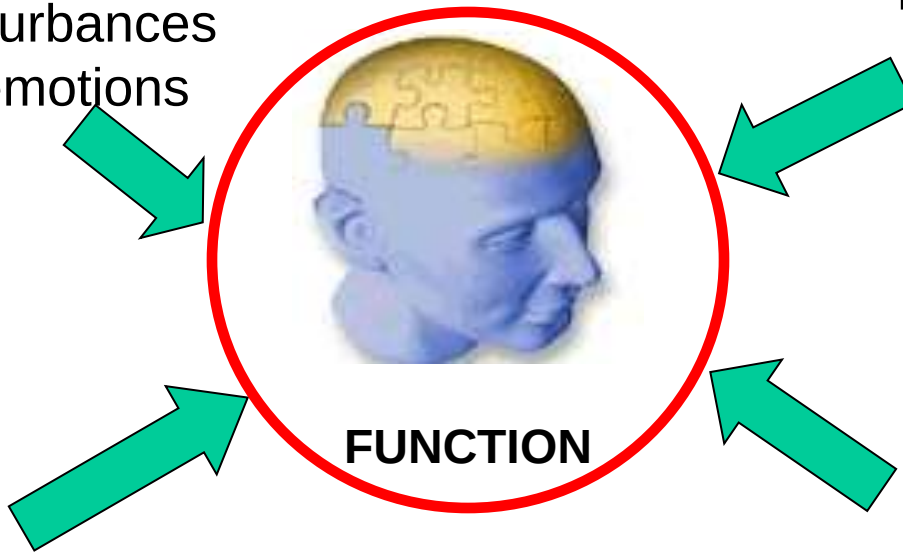
Antipsychotic drugs

Martin Votava

Schizophrenia - symptoms

Positive Symptoms
Hallucinations
Delusions (bizarre, persecutory)
Disorganized Thought
Perception disturbances
Inappropriate emotions

Negative Symptoms
Blunted emotions
Anhedonia
Lack of feeling



Cognition
New Learning
Memory

Mood Symptoms
Loss of motivation
Social withdrawal
Insight
Demoralization
Suicide

- **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

DSM-IV Diagnosis

- Schizophrenia
  - Symptoms $\geq$ 6 months
- Schizophreniform disorder
  - Symptoms 1 month - 6 months
- Brief psychotic disorder
  - Symptoms 1 day - 1 month

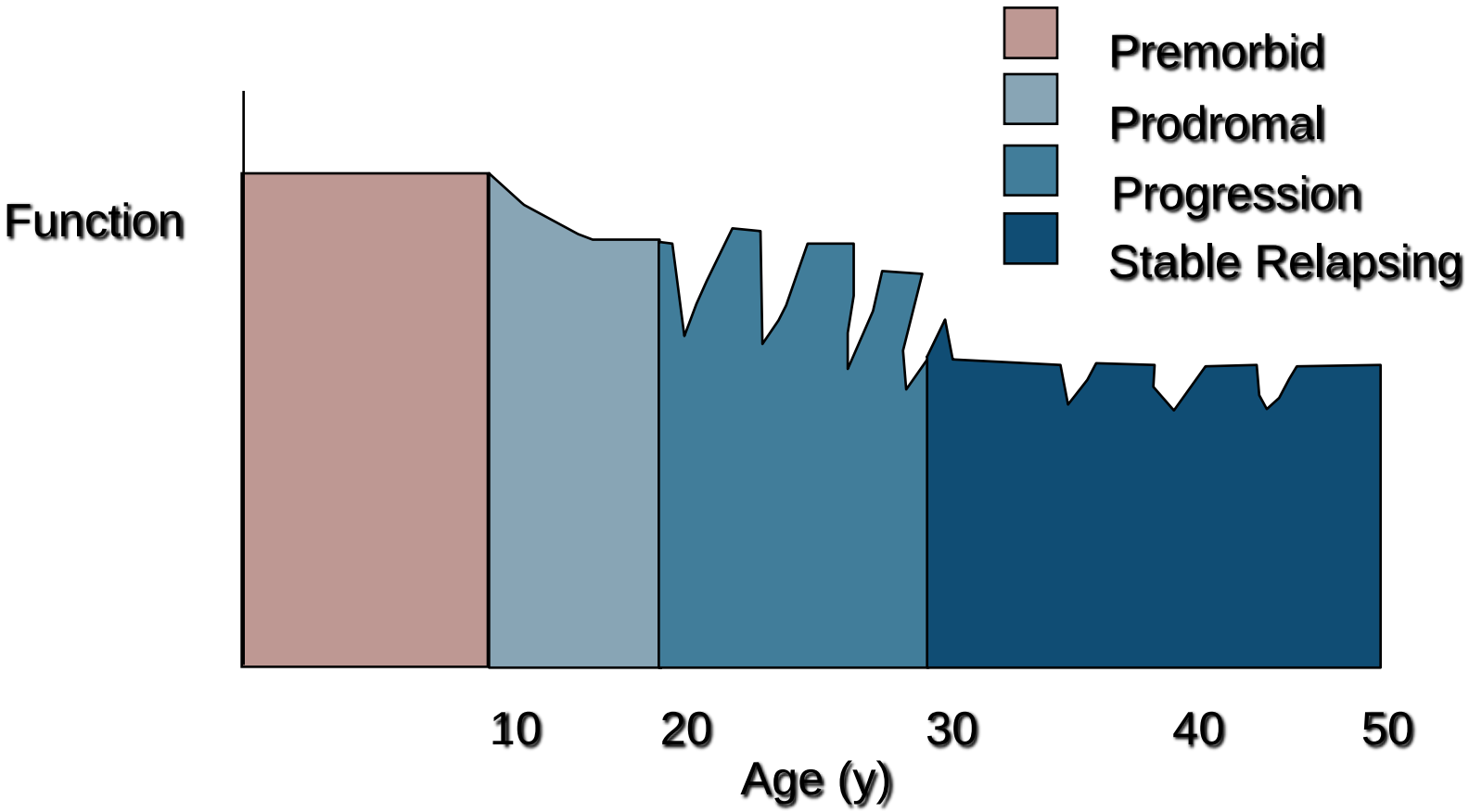
Prevalence of Schizophrenia

- 1-2% of U.S. population
- 2 million diagnosed in U.S.
- Median age at diagnosis = mid-20's
- Men = Women prevalence
  - Men earlier diagnosis
    - Worse premorbid history
    - Worse prognosis

Prognosis of Schizophrenia

- 10% continuous hospitalization
- ≤ 30% recovery = symptom-free for 5 years
- 60% continued problems in living/episodic periods

Personal history of schizophrenia



Lieberman JA. Atypical Antipsychotic Drugs As A First-Line Treatment of Schizophrenia: A Rationale and Hypothesis. Journal of Clinical Psychiatry 1996; 57 (suppl 11):68-71

Etiology

- Hereditary Influences may account for 10% of schizophrenia cases
- Prenatal Biological Trauma 5-10% cases of schizophrenia
- Perinatal biological trauma
- Diathesis - Stress Model

Biological Treatment

Insulin coma therapy, Prefrontal lobotomy, Electroconvulsive therapy

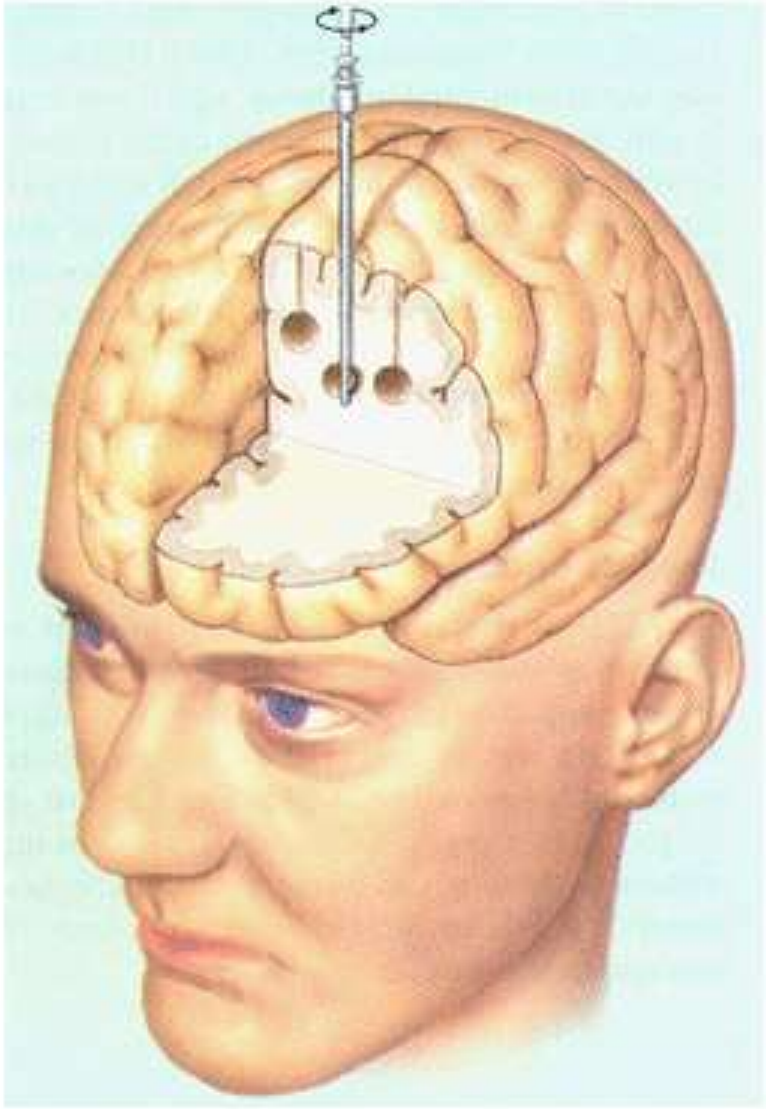
- Dr. Egas Moniz –Developed prefrontal lobotomy technique
- 1935 – heard about work on a chimp “Becky” – Performed surgery on many patients
- they were just calmer, but also more sluggish and apathetic
- Awarded the Nobel Prize in Physiology and Medicine
- Next 15 years - 50,000 lobotomies

► Prefrontal Lobotomy Procedure of Moniz and Lima

The Prefrontal Lobotomy Procedure of Moniz and Lima

The leucotome was inserted 6 times into the patient's brain with the cutting wire retracted.

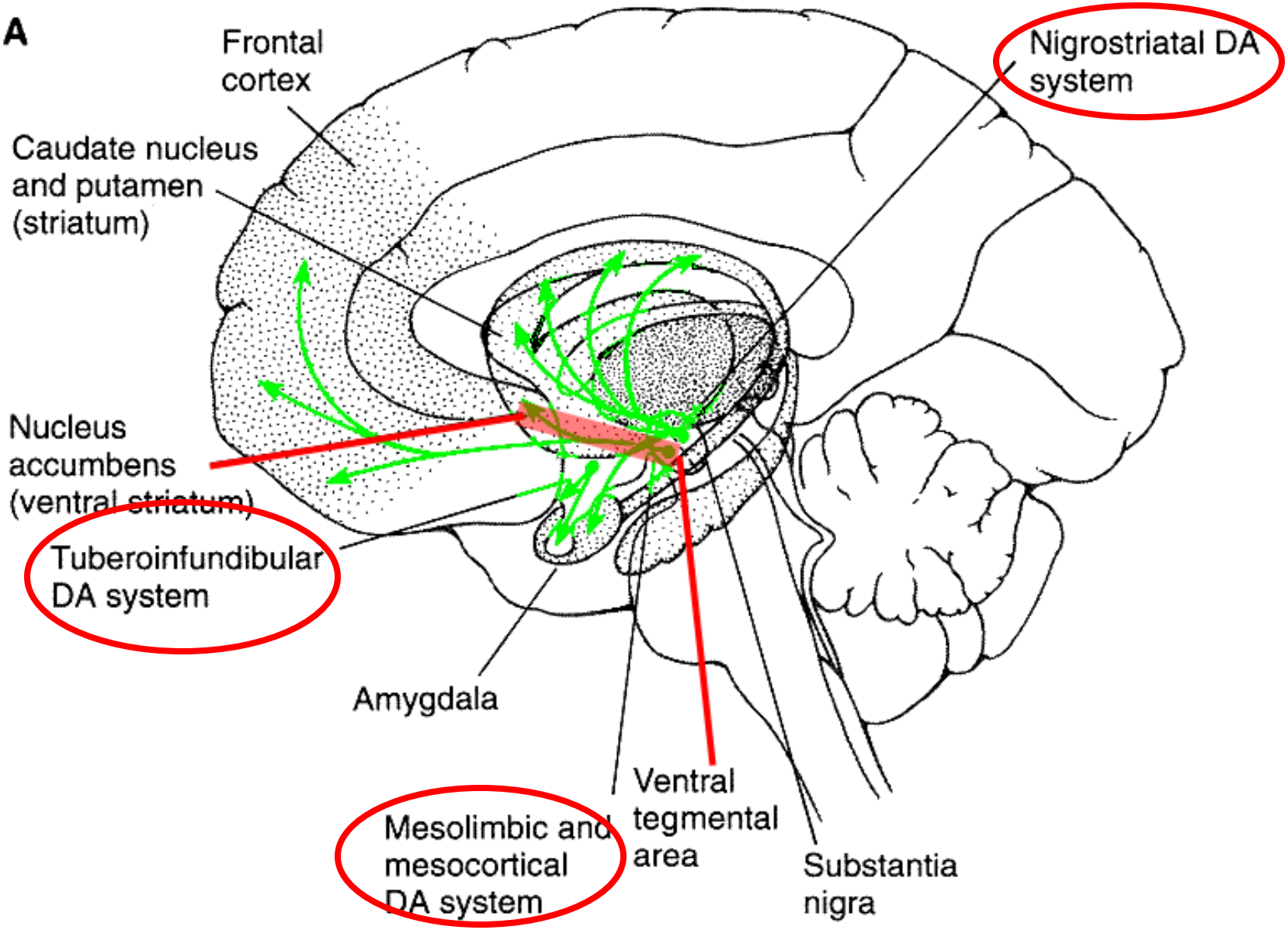
After each insertion the cutting wire was extruded and the leucotome rotated to cut out a core of tissue.



Schizophrenia Pathophysiology

	Schizophrenia Pathophysiology	Pharmacologic Profile of APDs
Past	Excess dopaminergic activity	Dopamine D_2-receptor antagonists
Present	Renewed interest in the role of serotonin (5-HT)	Combined 5-HT_2/D_2 antagonists
Future	Imbalance in cortical communication and cortical-midbrain integration, involving multiple neurotransmitters	More selective antagonists Mixed agonist/antagonists Neuropeptide analogs

Dopaminergic Pathways and Innervation



Pathophysiology: 'Dopamine Hypothesis' of Schizophrenia

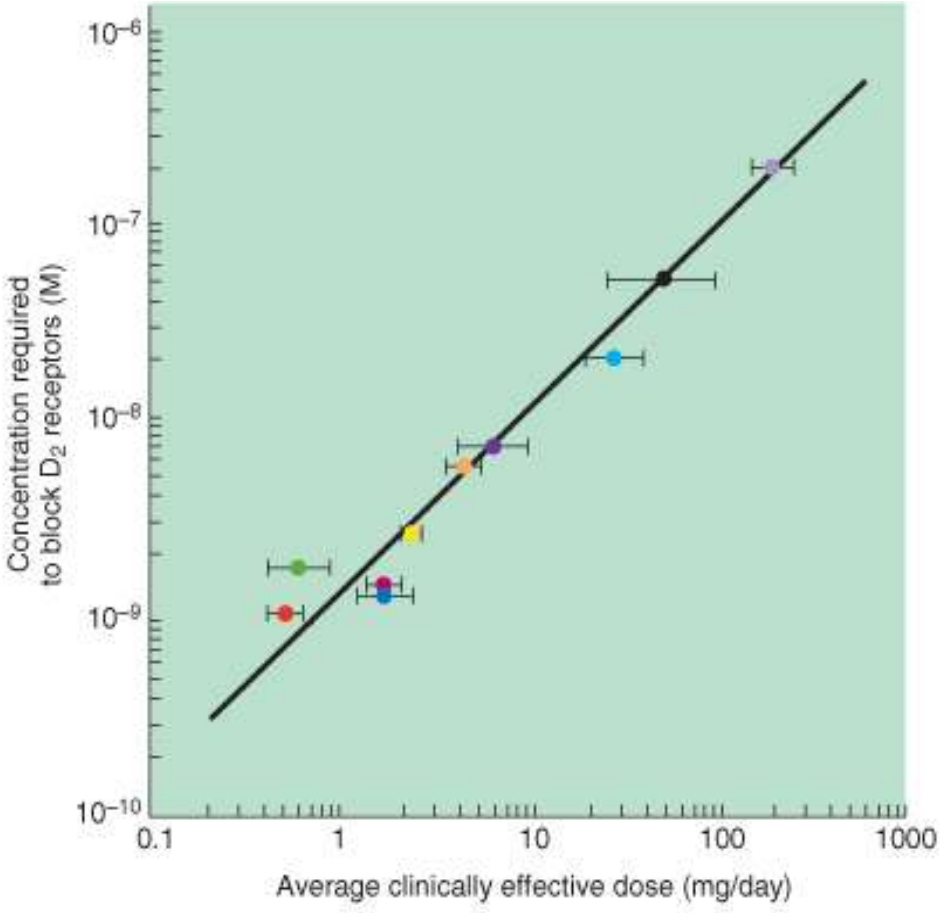
- 'Dopamine hypothesis':

  Schizophrenia is caused by excess dopaminergic activity

  - We now know that this hypothesis is not really true

- Arose in 1950s - 1960s: First effective antipsychotic drugs = dopamine antagonists
- Other supporting evidence:
  - Reserpine = "dopamine depleter" has some weak antipsychotic activity
  - DA enhancers (anti-Parkinson drugs, amphetamine) mimic some positive Sx: hallucinations, delusions

D2 affinity correlates with clinical dose to treat positive Sx



Dopamine Receptor Subtypes

- D1, D5: Gs coupled - increase cAMP
- D2, D3, D4: Gi coupled - decrease cAMP

- D2 mediates much of ‘typical APD’ therapeutic action . . .

. . . and side effects

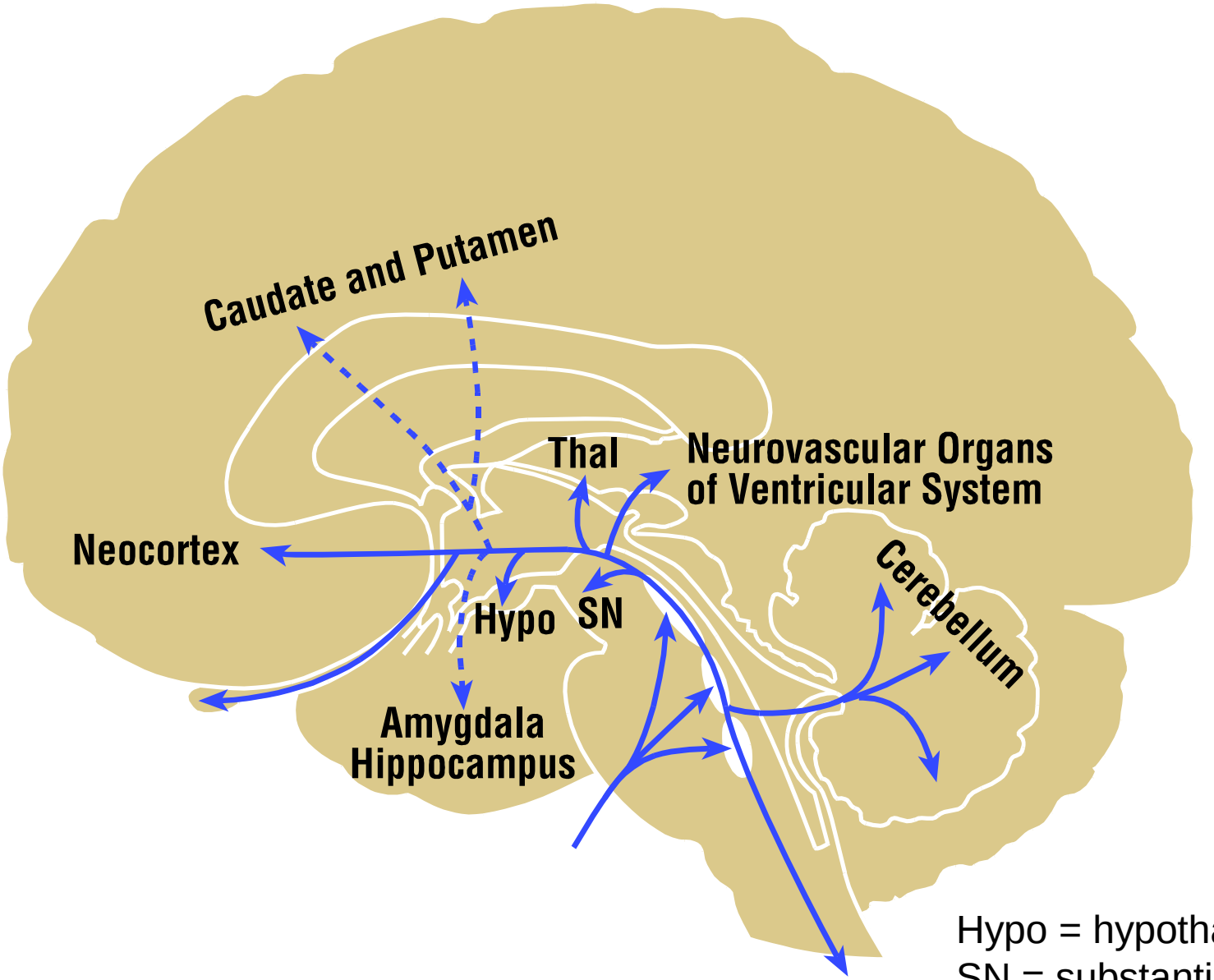
Other transmitter systems involved..

- Glutamatergic system dysfunction
  - e.g. effect of phencyclidine – blocker of NMDA type of glutamate receptors
- G-protein signaling abnormalities

- Serotoninergic system abnormalities
  - most antipsychotics also affect serotonin receptors

➔ ***Dopamine and serotonin theory of schizophrenia***

Serotonergic Pathways and Innervation

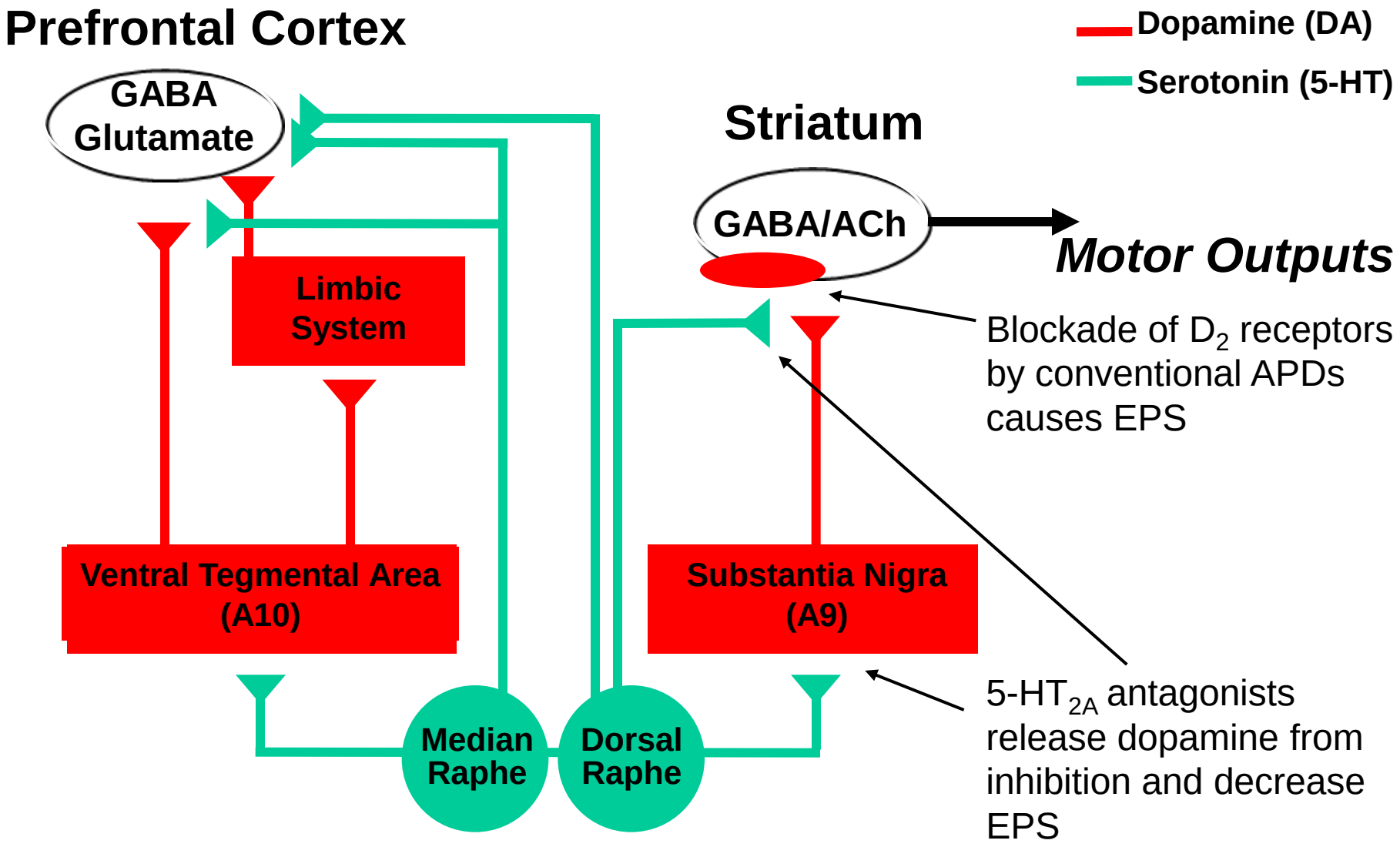


Hypo = hypothalamus
SN = substantia nigra
Thal = thalamus

Schizophrenia - Serotonin Hypothesis

- correlation between DA affinity and antipsychotic efficacy has become weaker as a result of recently developed atypical antipsychotic medications that also show **substantial affinity for 5HT2 receptors**
- Alteration of 5-HT transmission in the brains of schizophrenics patients have been reported in post-mortem studies and serotonin-agonists challenge studies
- There are widespread and complex changes in the 5-HT system in schizophrenics patients
- These changes suggest that 5-HT dysfunction is involved in the pathophysiology of the disease

Serotonin-Dopamine Interactions



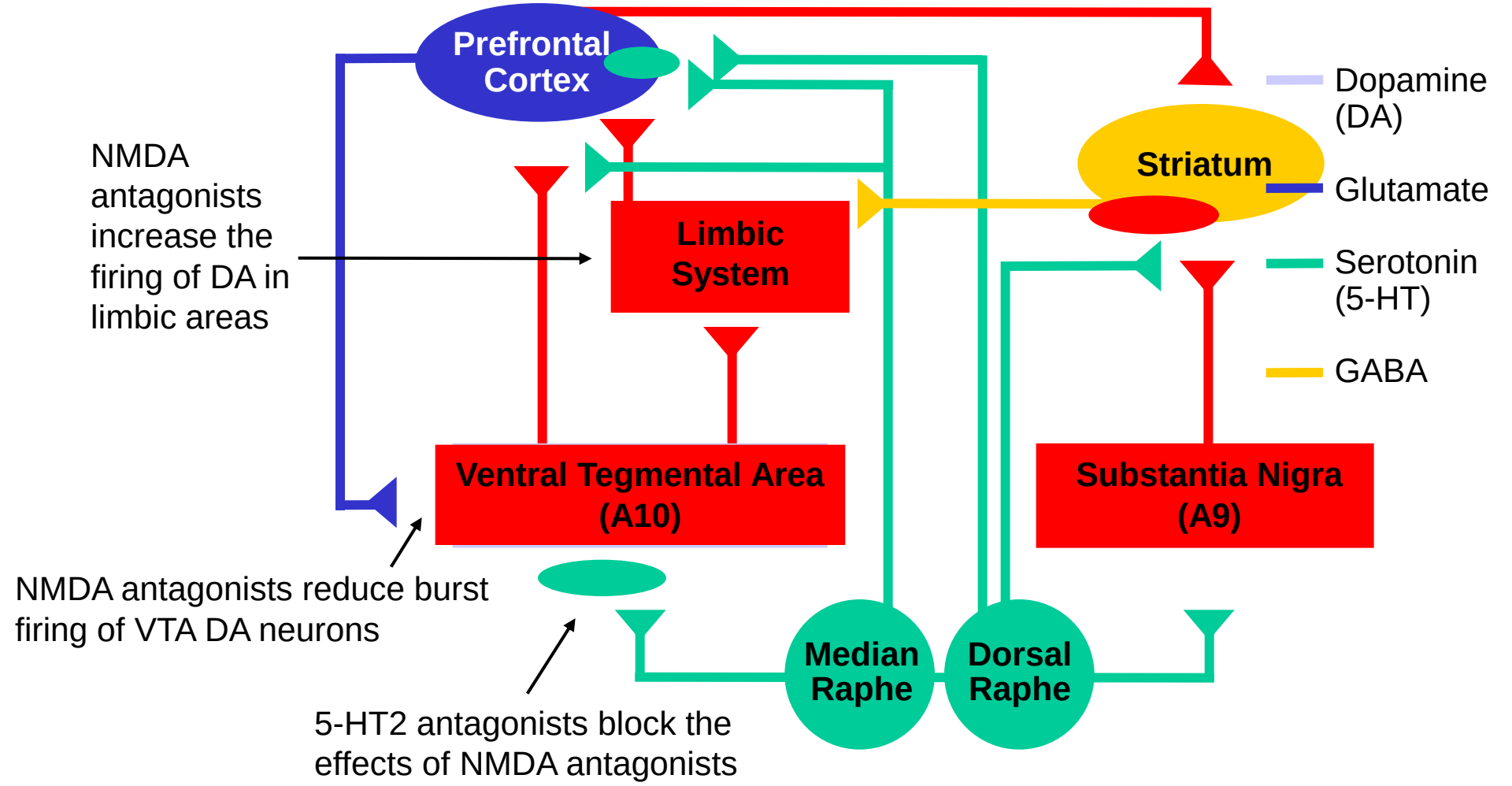
Schizophrenia May Involve Glutamate Hypofunction

- Dopamine stimulant (amphetamine) abuse:
  - Mimics some Positive Sx
- Glutamate NMDA type receptor antagonist (PCP, Ketamine) abuse:
  - Mimics some Positive Sx
  - Mimics some Negative Sx
    - (e.g. Cognitive Sx = Wisconsin card sorting test)
  - Ketamine Sx antagonised by clozapine (atypical antipsychotic) not by typical antipsychotics
- No Glutamate drugs for schizophrenia yet . .

Serotonin-Glutamate-Dopamine Interactions

NMDA antagonists elevate extracellular brain levels of 5-HT in the prefrontal cortex

5-HT2A antagonists restore dopaminergic function in the prefrontal cortex



ANIMAL MODEL OF SCHIZOPHRENIA

- High doses of **amphetamine** produce a syndrome of **repetitive behaviours** (sniffing, head movements, gnawing and licking) known as stereotypy or stereotyped behaviour.
- Because stereotyped behaviour also occurs in humans after higher doses of amphetamine and is similar to the repetitions of meaningless behaviour seen in schizophrenia, the amphetamine-induced stereotypy has been used as an animal model of schizophrenia.
- **DA receptor antagonists block amphetamine stereotypy** and there is a strong correlation between their potency in this model and in ameliorating schizophrenic symptoms.
- Other more complicated models are based on **attentional and cognitive abnormalities** observed in schizophrenia.

ANTIPSYCHOTICS

- Pre-90's
  - "Typical", conventional, traditional neuroleptics, major tranquilizors
  - Modeled on D_2 antagonism
  - EPS/TD
- Post-90's
  - "Atypical", novel, 2nd generation
  - Modeled on 5-HT2/D2 antagonism
  - Less EPS, prolactin effects
  - Weight gain, sedation, diabetes

Impact of antipsychotics..

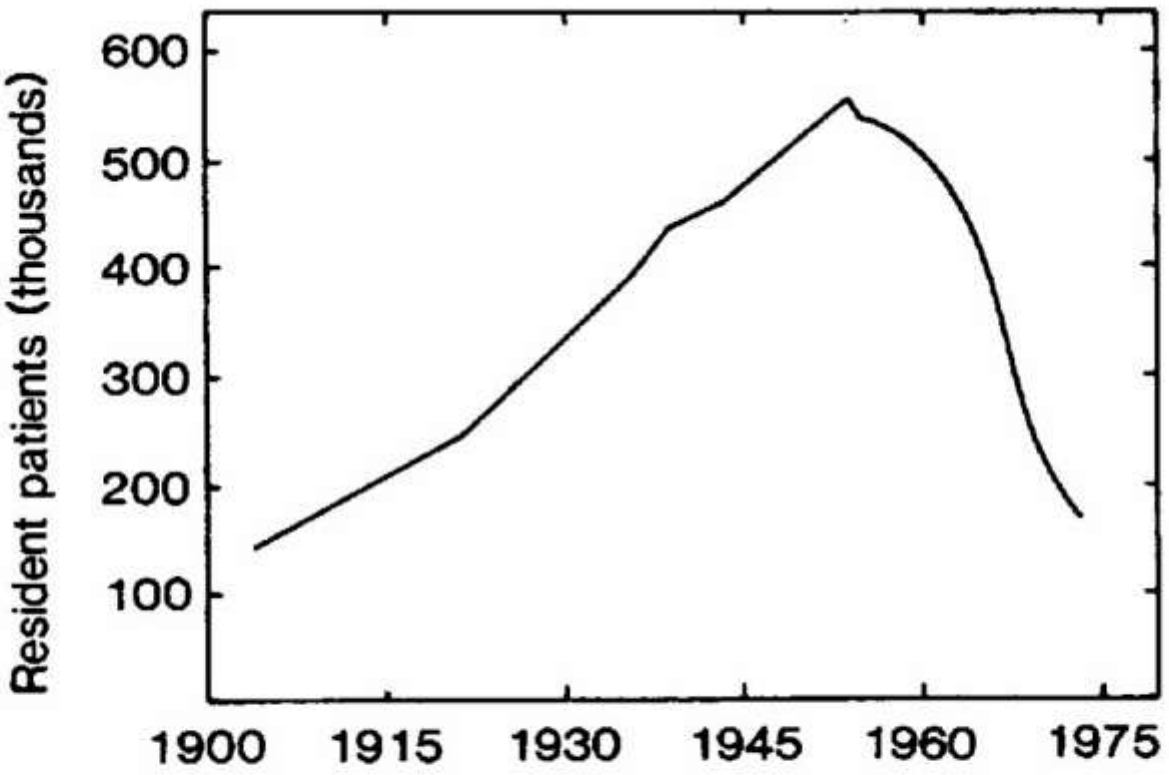


Fig. 28.6 Patient population in public mental hospitals in the U.S.A. (From: Bassuk E L, Gerson S 1978 Scientific American 238: 46)

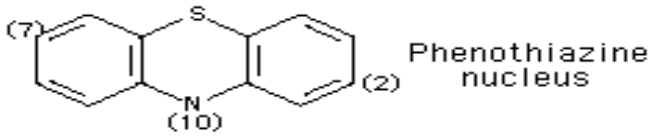
Typical antipsychotics

- Phenothiazines
  - e.g. chlorpromazine, fluphenazine, thioridazine
- Butyrophenones
  - e.g. haloperidol, droperidol
- Thioxanthines
  - e.g. chlorprotixen, thiothixene

Atypical antipsychotics

- receptor profile
  - MARTA
  - SDA
  - D2/D3 antag.
  - Partial DA antag.

PHENOTHIAZINE DERIVATIVES



Phenothiazine nucleus

Aliphatic side chain

Chlorpromazine (2)-Cl (10)-$CH_2-CH_2-CH_2-N-(CH_3)_2$

Thioridazine (2)-SCH_3 (10)-CH_2-CH_2 N CH_3

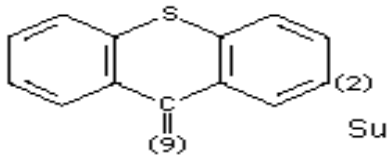
Piperazine side chain

Trifluoperazine (2)-CF_3 (10)-$CH_2-CH_2-CH_2-N$ $N-CH_3$

Perphenazine (2)-Cl (10)-$CH_2-CH_2-CH_2-N$ $N-CH_2-CH_2-OH$

Fluphenazine (2)-CF_3 (10)-$CH_2-CH_2-CH_2-N$ $N-CH_2-CH_2-OH$

THIOXANTHENE DERIVATIVE

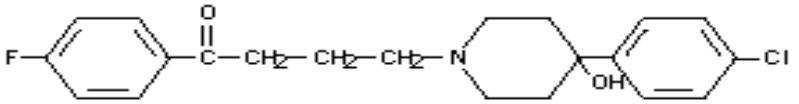


Substituting C for N in the nucleus

Thiothixene (2)-$SO_2N(CH_3)_2$

(9)=CH-CH_2-CH_2-N N-CH_3

BUTYROPHENONE



Haloperidol

Antipsychotics – „classical“

Basal - phenothiazines

- Chlorpromazine
- Thioridazine
- Levopromazine

Basal - thioxanthines

- Chlorprothixene

Antipsychotics – „classical“

Incisive – phenothiazines

- Fluphenazine

Incisive – thioxanthines

- Flupenthixole

Incisive – butyrophenones

- Haloperidol

Comparisons Between the Two Classes of Drugs

- **Phenothiazines**
  - Low potency
  - Are sedative
  - Block D2 receptors
  - metabolism and removal of phenothiazines is complex and among the slowest of any group of drugs
  - cause extra pyramidal symptoms
- **Butyrophenones**
  - High potency
  - Non-sedative
  - Block D2 receptors
  - Metabolism and removal is quicker
  - Cause extra pyramidal symptoms

Adverse Effects - EPS

Details on two main extrapyramidal disturbances (EPS):

- Parkinson-like symptoms
  - tremor, rigidity
  - direct consequence of block of nigrostriatal DA_2 R
  - reversible upon cessation of antipsychotics
- Tardive dyskinesia
  - involuntary movement of face and limbs
  - less likely with atypical antipsychotics (AP)
  - appears months or years after start of AP
  - ? result of proliferation of DA R in striatum
    - » presynaptic?
  - treatment is generally unsuccessful

Neurological Side Effects of antipsychotics

REACTION	FEATURES	TIME OF MAXIMAL RISK	PROPOSED MECHANISM	TREATMENT
Acute dystonia	Spasm of muscles of tongue, face, neck, back; may mimic seizures; *not* hysteria	1 to 5 days	Unknown	Antiparkinsonian agents are diagnostic and curative
Akathisia	Motor restlessness; *not* anxiety or "agitation"	5 to 60 days	Unknown	Reduce dose or change drug: antiparkinsonian agents,b benzodiazepines or propranololc may help
Parkinsonism	Bradykinesia, rigidity, variable tremor, mask facies, shuffling gait	5 to 30 days	Antagonism of dopamine	Antiparkinsonian agents helpful
Neuroleptic malignant syndrome	Catatonia, stupor, fever, unstable blood pressure, myoglobinemia; can be fatal	Weeks; can persist for days after stopping neuroleptic	Antagonism of dopamine may contribute	Stop neuroleptic immediately: dantrolene or bromocriptined may help: antiparkinsonian agents not effective
Perioral tremor ("rabbit" syndrome)	Perioral tremor (may be a late variant of parkinsonism)	After months or years of treatment	Unknown	Antiparkinsonian agents often help
Tardive dyskinesia	Oral-facial dyskinesia; widespread choreoathetosis or dystonia	After months or years of treatment (worse on withdrawal)	Excess function of dopamine hypothesized	Prevention crucial; treatment unsatisfactory

Adverse Effects Summary

- **Sedation** - initially considerable; tolerance usually develops after a few weeks of therapy; dysphoria
- **Postural hypotension** - results primarily from adrenergic blockade; tolerance can develop
- **Anticholinergic effects** - include blurred vision, dry mouth, constipation, urinary retention; results from muscarinic cholinergic blockade
- **Endocrine effects** - increased prolactin secretion can cause galactorhea; results from antidopamine effect
- **Hypersensitivity reactions** - jaundice, photosensitivity, rashes, agranulocytosis can occur
- **Idiosyncratic reactions** - malignant neuroleptic syndrome
- **Weight gain**
- Neurological side effects - see next

Haloperidole

- entered US market in 1967
- more potent than phenothiazines, so doses are lower
- also have long half-life
- like phenothiazines, they block dopamine and norepinephrine receptors and show the related side effects
- extrapyramidal effects are worse (due to low blockade of ACh and thus worse ratio)
- but blood pressure effects are less
- reduced sedation
- no blood abnormalities or jaundice

Limitations Of Conventional Antipsychotics

- Approximately one-third of patients with schizophrenia fail to respond
- Limited efficacy against
  - Negative symptoms
  - Affective symptoms
  - Cognitive deficits
- High proportion of patients relapse
- Side effects and compliance issues
- Some safety issues are prominent

Antipsychotic Drugs – New Generations „atypical“

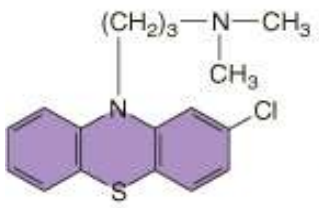
About 40-60% do not respond to phenothiazines or cannot handle side effects

- Questions remain about the efficacy of phenothiazines and haloperidole for negative symptoms
- Drugs needed that are low in extrapyramidal side effects and at least equal in efficacy for positive symptoms, perhaps better for negative

Atypical Antipsychotics

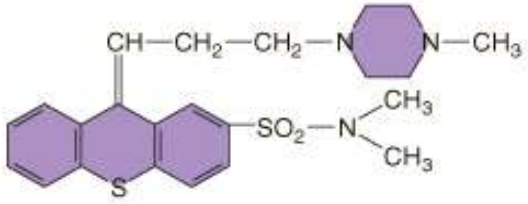
Typical (Traditional) Antipsychotics

PHENOTHIAZINE



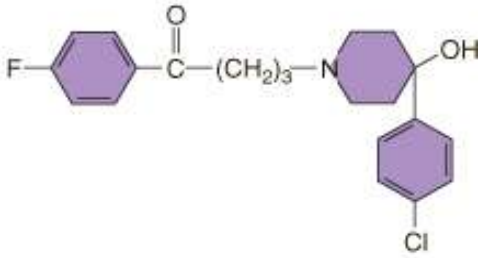
Chlorpromazine

THIOXANTHINE



Thiothixene

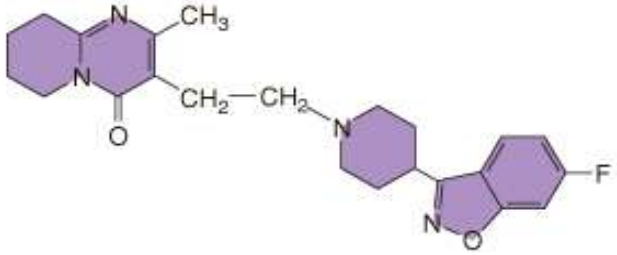
BUTYROPHENONE



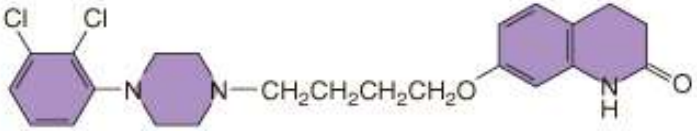
Haloperidol

Atypical (Novel) Antipsychotics

Clozapine



Risperidone



Aripiprazole

What Defines "Atypical" Antipsychotics?

Atypical APD's have some of the following:

- Positive Sx: Increased Therapeutic Efficacy
  - i.e. in treatment resistant patients
- Negative Sx: Some Therapeutic Efficacy
  - motivation, social withdrawl, cognition
- Side Effects: Generally less than typical drugs
  - Acute EPS: Parkinsonian, Dyskinesias, Akathisia
  - Chronic EPS: Tardive Dyskinesia
  - Endocrine: Hyperprolactinemia

Atypical APD's: Efficacy

- Positive Symptoms of Schizophrenia
  - Typicals:
    - Significant help for about 70% of patients
    - Reduces relapse rate from ~75%/yr to ~20%
  - Clozapine:
    - Helps about 80 - 85% of patients
    - Helps ~ 1/3 to 1/2 of those not helped by typicals
    - Reduces relapse rates to ~10 - 15%
  - Other atypicals may be more effective than typical agents, but less effective than clozapine

Antipsychotic Drugs – New Generations „atypical“

- clozapine
- risperidone
- olanzapine
- sertindole
- quetiapine
- aripiprazole
- ziprasidone etc.

Atypical antipsychotics

MARTA (multi acting receptor targeted agents)

- clozapine, olanzapine, quetiapine

SDA (serotonin-dopamine antagonists)

- risperidone, ziprasidone, sertindole

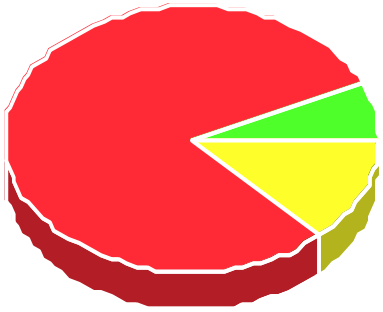
Selective D2/D3 antagonists

- sulpiride, amisulpiride

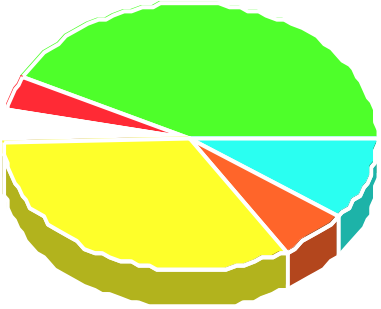
Partial Dopamine antagonists

- aripiprazole

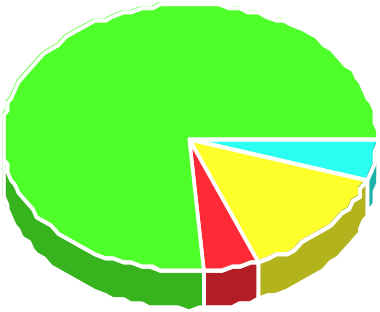
Atypical Antipsychotics In Vivo Binding Affinities



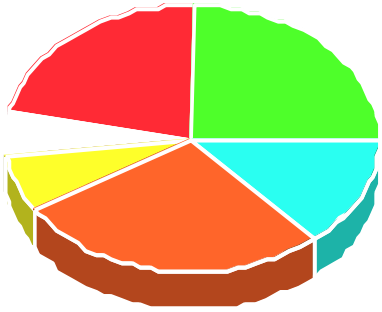
Haloperidol



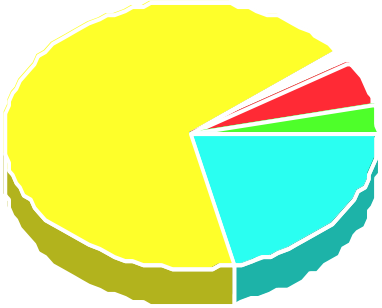
Clozapine



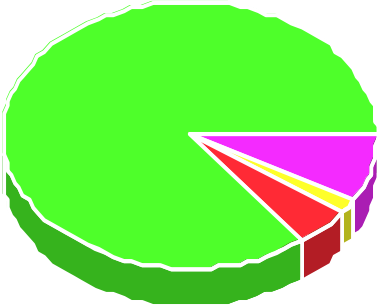
Risperidone



Olanzapine



Quetiapine



Ziprasidone

5HT2A D2 D1 Alpha 1 Musc H1 5HT1A (agonist)

Casey 1994

Clozapine (1989)

- Selectively blocks dopamine D2 receptors, avoiding nigrostriatal pathway
- Also blocks NE
- More strongly blocks 5-HT2 receptors in cortex which then acts to modulate some dopamine activity
- Among non-responders to first generation meds or those who cannot tolerate side effects, about 30% do respond to Clozapine

Clozapine

- Extrapyramidal side effects are minimal
- May help treat tarditive dyskinesia
- Still shows orthostatic hypotension effects, sedation, weight gain, increased heart rate
- Increased risk for seizures (2-3%)
- **Agranulocytosis in 1%**
- Agranulocytosis risks increase when co-administered with carbamazepine
- Interactions with SSRIs and valproic acid increase Clozapine levels and risks

Risperidone (Risperdal; 1994)

- Fewer side effects than Clozapine
- Marketed as first line approach to treatment
- Blocks selective D2, norepinephrine, and 5-HT2
- Argued as effective for positive and negative symptoms (controversial)
- Extrapyramidal side effects low (but are shown at high doses) - controversial
- Shares sedation, weight gain, rapid heart beat, orthostatic hypotension, and elevated prolactin
- No agranulocytosis risks
- May cause anxiety/agitation (possible OCD)

Risperidone (Risperdal)

- Research designs clearly stacked in favor of Risperidone re showing better profile for extrapyramidal side effects and for symptom reduction
- Advantages unclear other than agranulocytosis issue

Olanzipine - Zyprexa – 1996

- Same poorly supported arguments about improved negative symptom reduction
- Argued to be better than risperidone in extrapyramidal issues
- Does not cause prolactin elevation
- Same claim to fame reduced agranulocytosis risks

Sertindole – Serlect – 1995

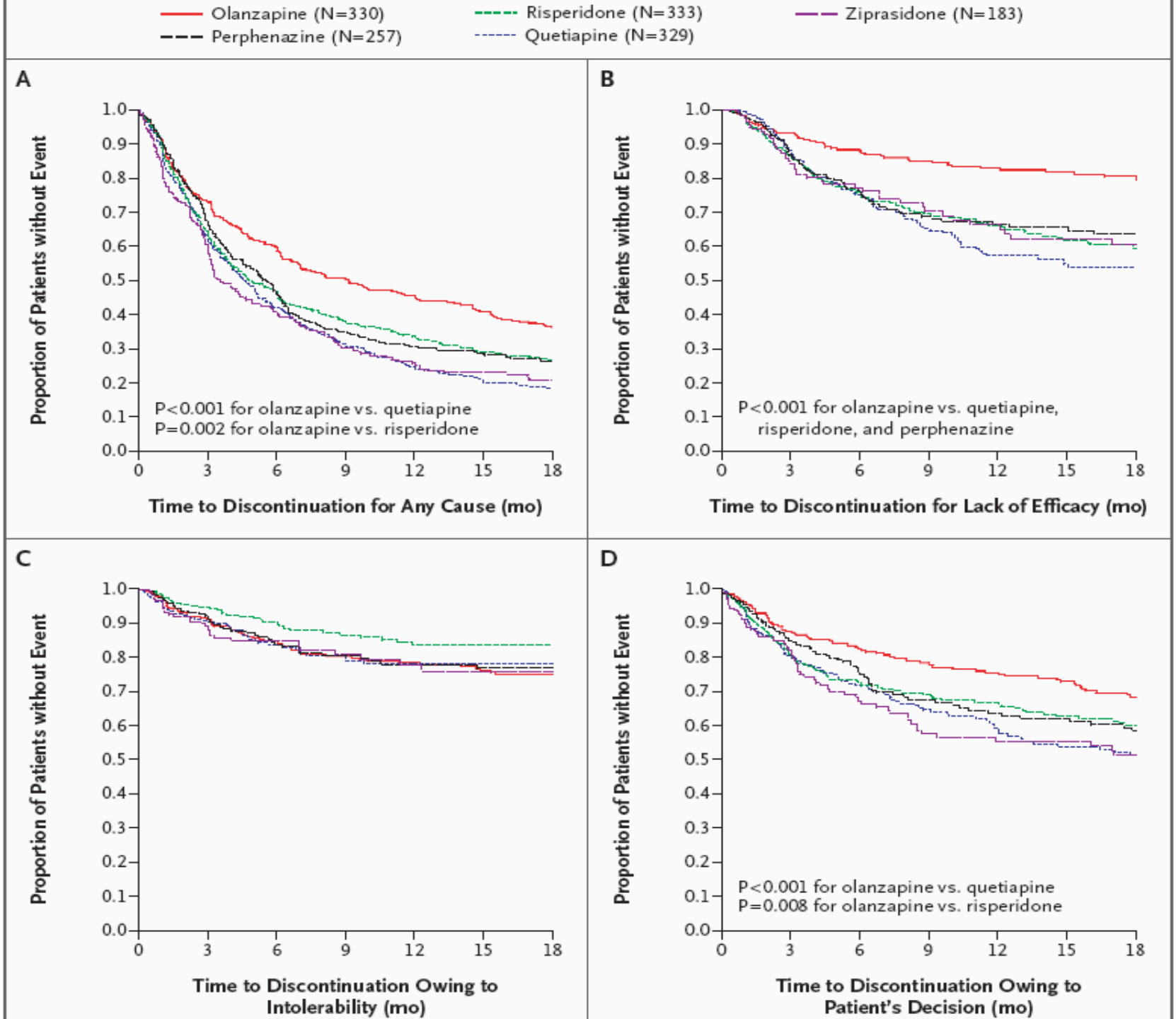
- Some poorly supported arguments about improved negative symptom reduction
- Low risk for extrapyramidal side effects – major advantage
- No sedation and very mild prolactin elevation– major advantages
- Shares orthostatic hypotension, tachycardia, and weight gain
- Common side effects are rhinitis and reduced ejaculatory volume (not associated with disturbed function)
- concern about sudden cardiac death or episodes due to cardiac arrhythmia led to its voluntary removal in 1998

Quetiapine – Seroquel - 1997

- No increased risks for extrapyramidal symptoms
- Shares sedation, orthostatic hypotension, weight gain
- Does cause anticholinergic side effects (like older and Clozapine) – dry mouth, constipation
- Does not elevate prolactin

Ziprasidone - 2001

- Similar to advantages of others, but argued not to cause weight gain



N Engl J Med 2005;353:1209-23.

Expanding Indications …

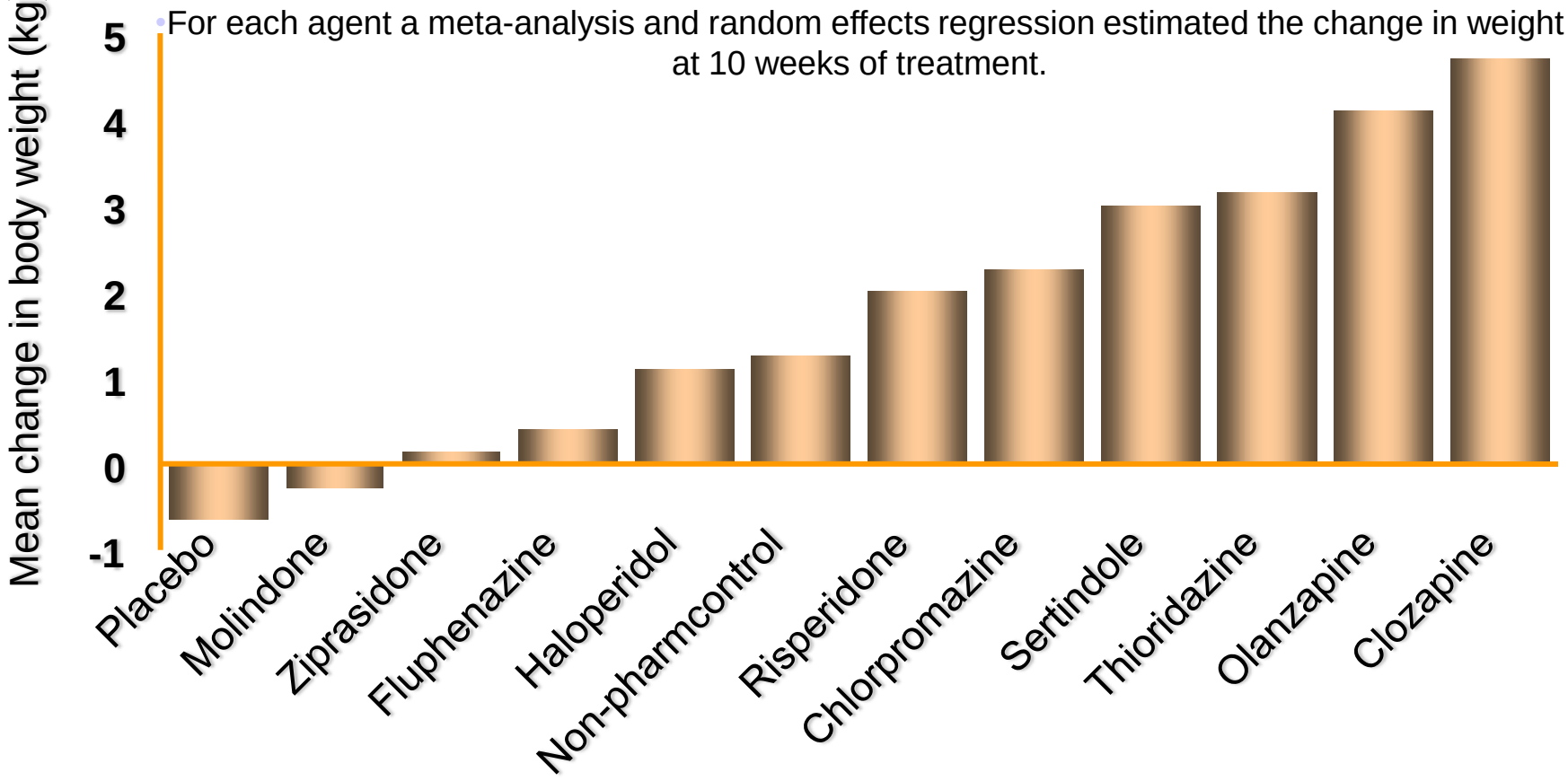
- Psychosis
- Schizophrenia
- Mania – mostly adjunctive benefits
- Aggression
- Tourette’s
- Delirium
- Affect instability in BPD

Side effects

- weight gain
- type II diabetes mellitus
- hyperlipidemia
- extrapyramidal side effects
- QTc interval prolongation
- myocarditis
- sexual side effects
- cataract

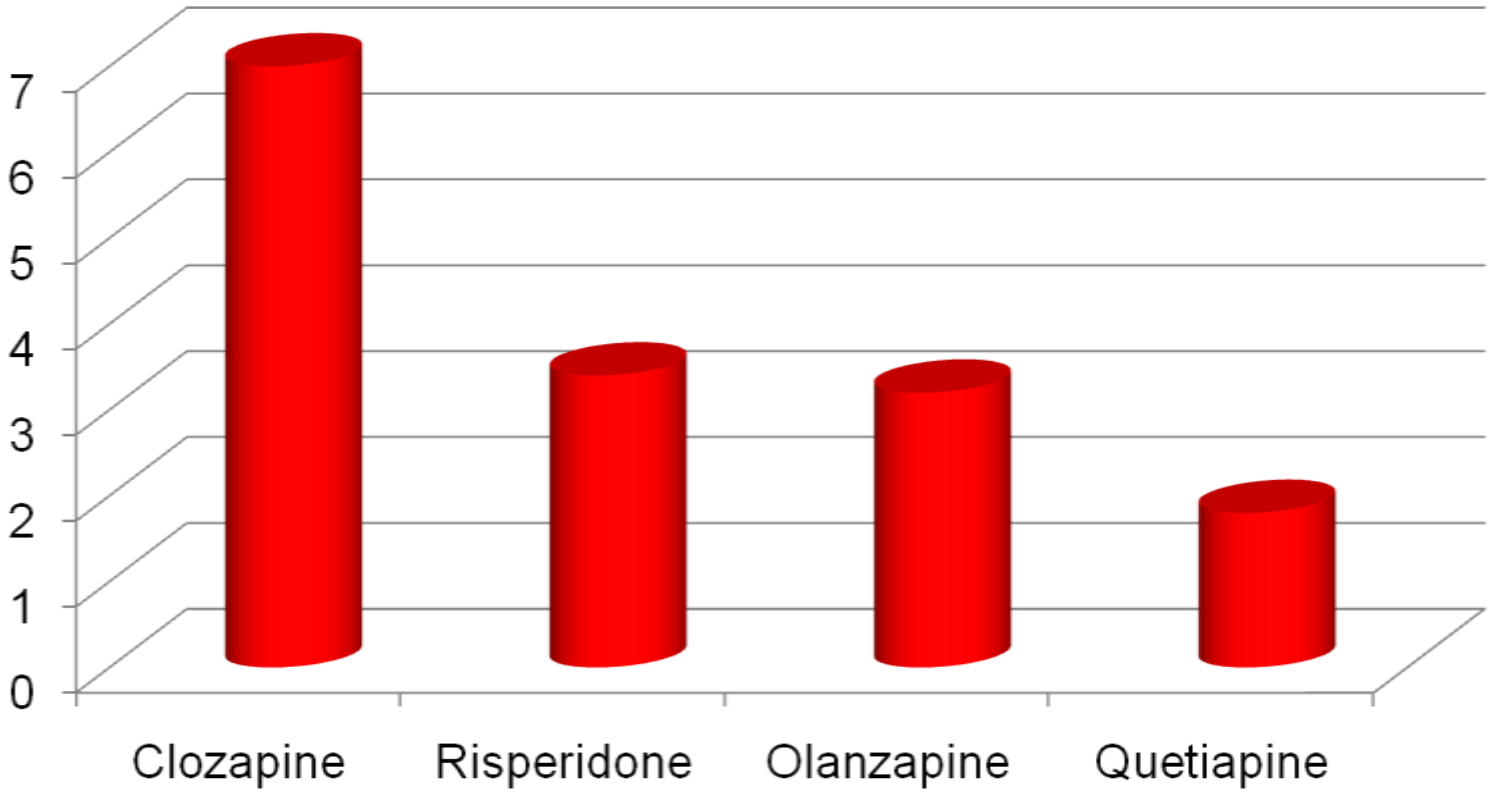
Estimated mean weight gain at 10 weeks

- A comprehensive literature search identified 78 studies that included data on weight change in patients treated with a specific antipsychotic.
- For each agent a meta-analysis and random effects regression estimated the change in weight at 10 weeks of treatment.



Allison DB, Mentore JL, Heo M, et al: Weight gain associated with conventional and newer antipsychotics: a meta Analysis. AJP, 1999.

Risk of diabetes mellitus (HR vs. conventional AP)



Hyperlipidemia

High risk - chlorpormazine, thioridazine
atypical antipsychotics, quetiapine, olanzapine and clozapine

Low risk – haloperidol
atypical antipsychotics, ziprasidone, risperidone and aripiprazole

Parkinsonism events