

Schizophrenia

- Pathogenesis is unknown.
- Onset of schizophrenia is in the late teens - early '20s.
- Genetic predisposition -- Familial incidence.

Hereditary Influences may account for 10% of schizophrenia cases

- Multiple genes are involved.
- Afflicts 1% of the population worldwide.
- A thought disorder

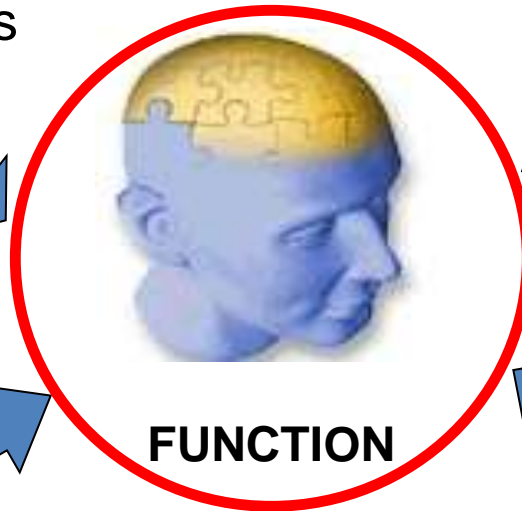
Schizophrenia - symptoms

Positive Symptoms

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

Negative Symptoms

Blunted emotions
Anhedonia
Lack of feeling



FUNCTION

Cognition

New Learning
Memory

Mood Symptoms

Loss of motivation
Social withdrawal
Insight
Demoralization
Suicide

Schizophrenia

- Drugs currently used in the prevention of psychosis.

**** These drugs are not a cure ****

- Schizophrenics must be treated with medications **indefinitely**, in as much as the disease is lifelong and it is preferable to prevent the psychotic episodes than to treat them.

SCHIZOPHRENIA IS FOR LIFE

There is no remission

Dopamine Theory of Schizophrenia

Many lines of evidence point to the aberrant increased activity of the dopaminergic system as being critical in the symptomatology of schizophrenia.

There is a greater occupancy of D2 receptors by dopamine => greater dopaminergic stimulation

Schizophrenia Pathophysiology

Schizophrenia Pathophysiology

Pharmacologic Profile of APDs

.Past

Excess dopaminergic activity

Dopamine antagonists

D₂-receptor

Present

Renewed interest in the role of serotonin (5-HT)

Combined antagonists

5-HT₂/D₂

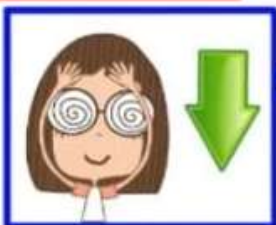
1st generation (Typicals)



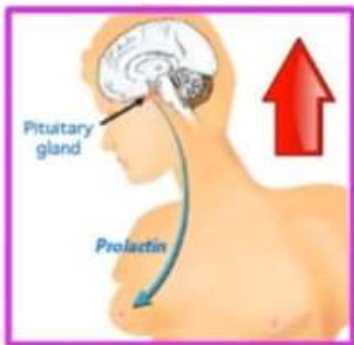
nigrostriatal



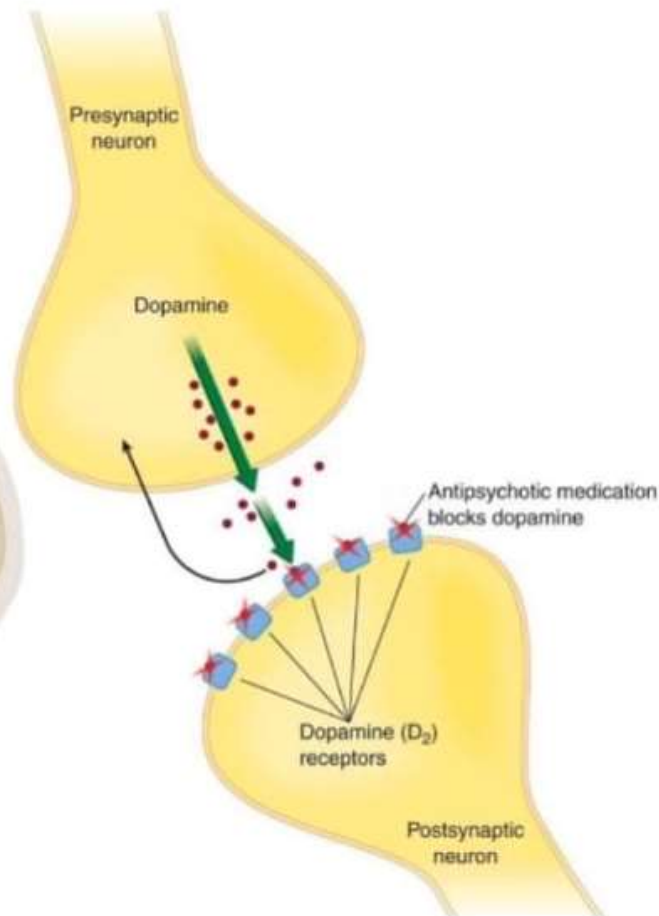
mesocortical



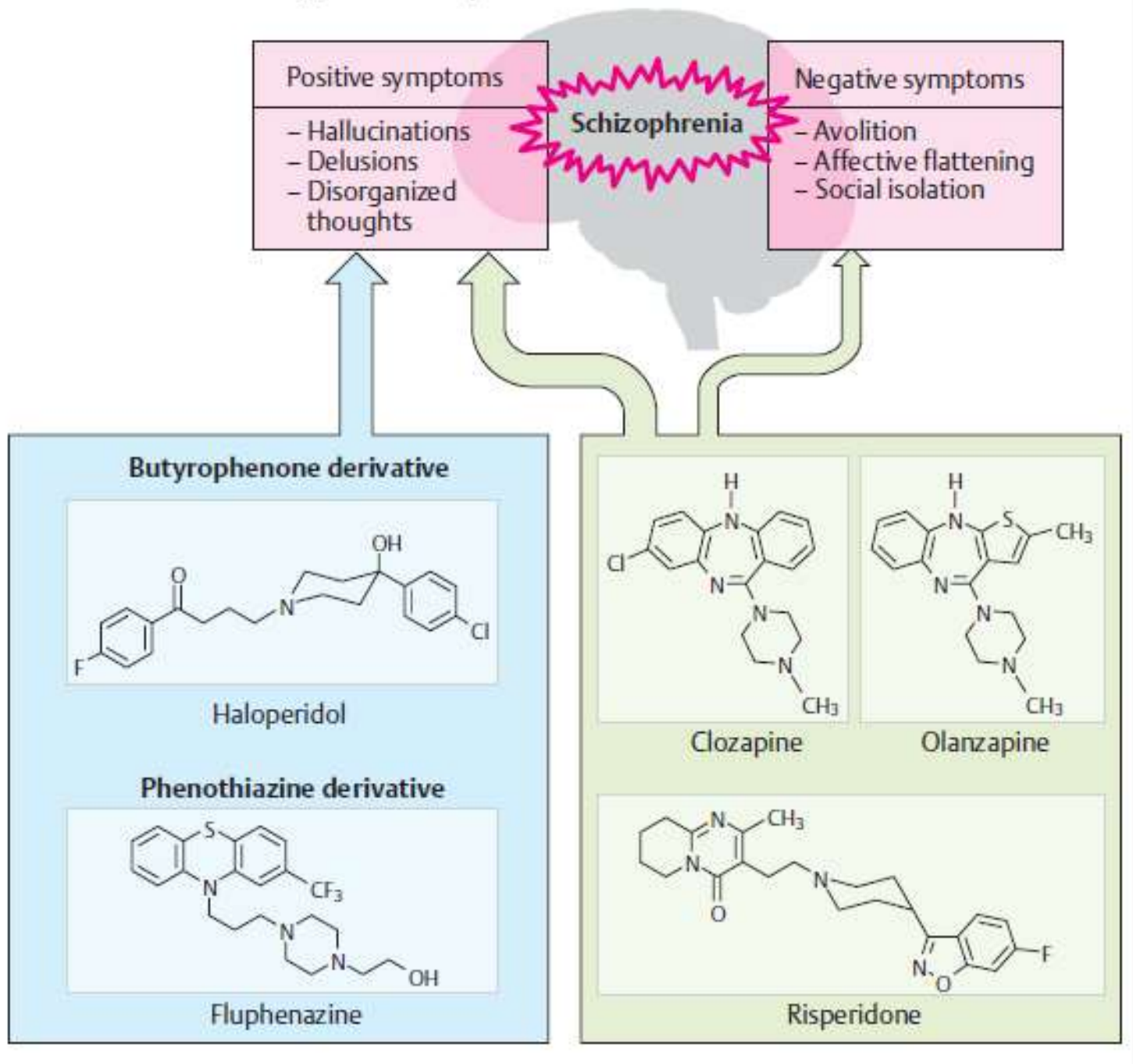
mesolimbic

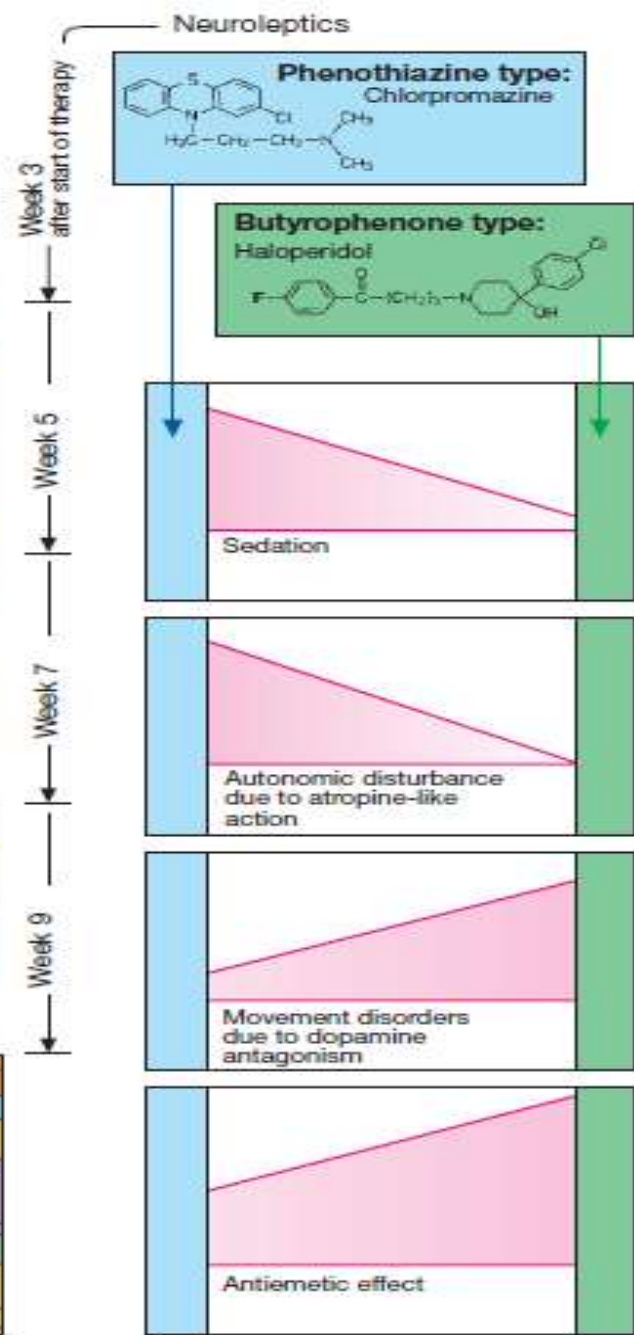
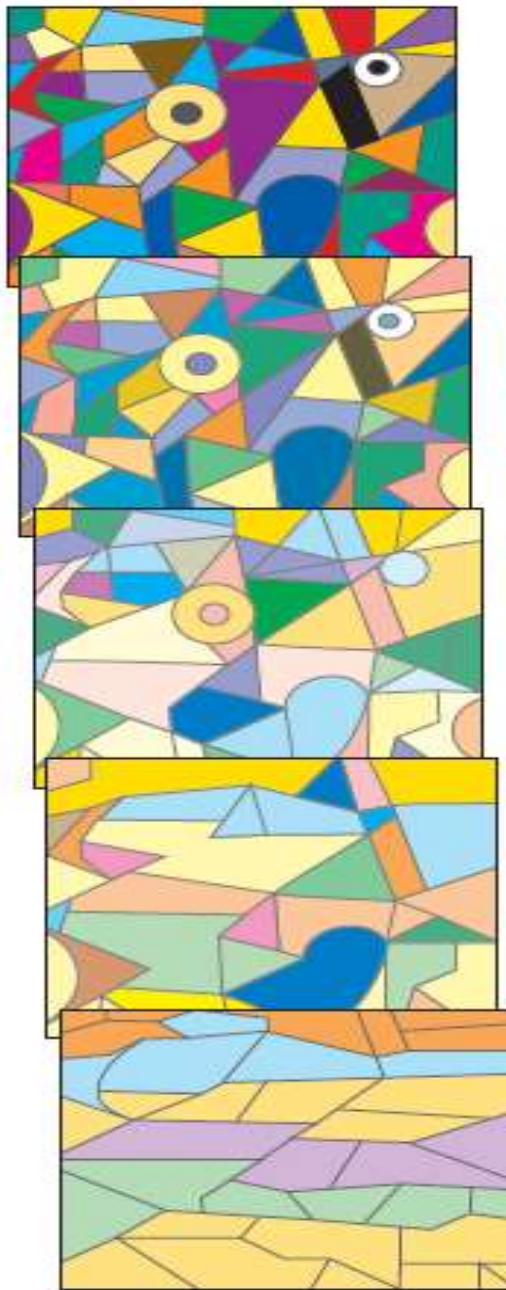


tuberoinfundibular



A. Conventional and atypical neuroleptics





Tolerance and dependence to antipsychotic drugs

- Not addicting
- Relapse in psychosis if discontinued abruptly
- Tolerance develops to sedative effects
- No tolerance to antipsychotic effect

Withdrawal-like syndrome

- 1. Symptoms: nausea, vomiting, insomnia, and headache**
- 2. Symptoms may persist for up to 2 weeks.**
- 3. Symptoms can be minimized with a tapered reduction of drug dosage.**

Classification of Antipsychotic drugs

- Main categories are:
 - *Typical antipsychotics*
 - { Phenothiazines (**chlorpromazine**, perphenazine, fluphenazine, thioridazine et al)
 - { Thioxanthenes (**flupenthixol**, **clopenthixol**)
 - { Butyrophenones (**haloperidol**, droperidol)
 - *Atypical antipsychotics* (e.g. **clozapine**, **risperidone**, **sulpiride**, **olanzapine**)

Classification of Antipsychotic drugs

- Distinction between 'typical' and 'atypical' groups is not clearly defined, but rests on:
 - Incidence of extrapyramidal side-effects (less in 'atypical' group)
 - Efficacy in treatment-resistant group of patients
 - Efficacy against negative symptoms.

First Generation Antipsychotic Drugs

Compound			Seda- tion	Hypo- tension	Motor (EP) Effects
Phenothiazines					
Chlorpromazine			+++	++	++
Fluphenazine			+	+	++++
Haloperidol			+	+	++++

Neurological Side Effects of antipsychotics

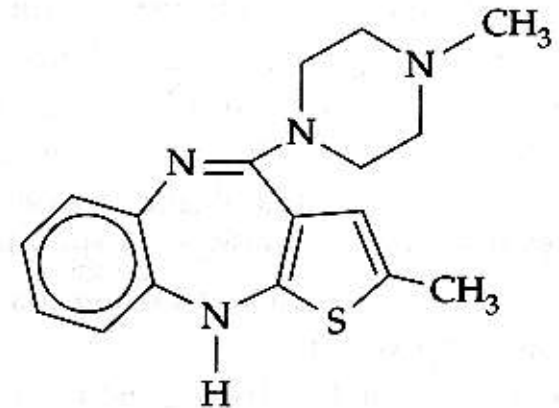
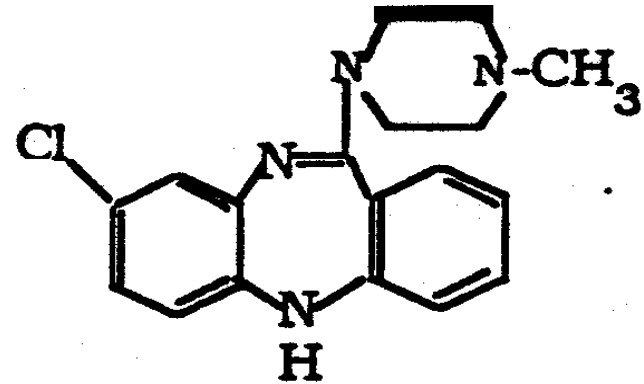
REACTION	FEATURES	TIME OF MAXIMAL RISK	PROPOSED MECHANISM	TREATMENT
Acute dystonia	Spasm of muscles of tongue, face, neck, back; may mimic seizures; <i>not</i> hysteria	1 to 5 days	Unknown	Antiparkinsonian agents are diagnostic and curative
Akathisia	Motor restlessness; <i>not</i> anxiety or "agitation"	5 to 60 days	Unknown	Reduce dose or change drug: antiparkinsonian agents, benzodiazepines or propranololc may help
Parkinsonism	Bradykinesia, rigidity, variable tremor, mask facies, shuffling gait	5 to 30 days	Antagonism of dopamine	Antiparkinsonian agents helpful
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

Second Generation Antipsychotic Drugs

Compound	Sedation	Hypotension	Motor effects
Risperidone	++	+++	+/ +++ Dose dependent
Clozapine	++	++	-
Aripiprazole	0/+	0/+	0/+ 15

Clozapine and olanzapine

- 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 for clozapine



Olanzapine

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

Risperidone

Endocrine effect

- ❖ One of the most prescribed drugs in Jordan.
- ❖ In **women**, these disturbances include:
 - galactorrhea
 - loss of libido
 - delayed ovulation and menstruation or amenorrhea.
- ❖ In **men**, these disturbances include:
 - gynecomastia
 - impotence.

Quetiapine

- No increased risks for extrapyramidal symptoms
- Shares sedation, orthostatic hypotension, weight gain
- Does cause anticholinergic side effects— dry mouth, constipation
- **Does not elevate prolactin**

Ziprasidone - 2001

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

Clozapine – 1.7 kg/month
kg/month

Risperidone – 1

Olanzapine – 2.3 kg/month
kg/month

Ziprasidone – 0.8

Quetiapine - 1.8 kg/month

Aripiprazole

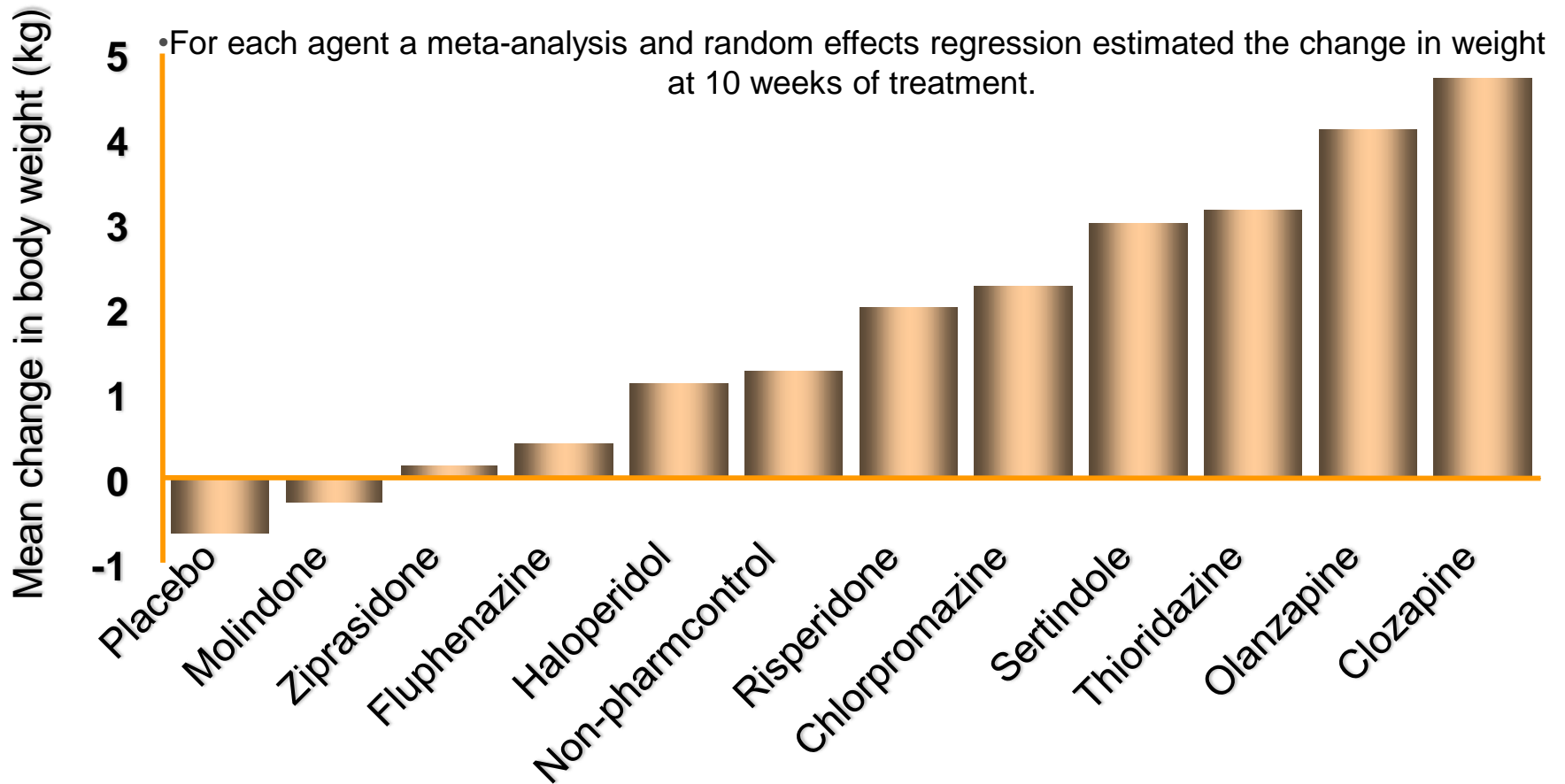
- **Partial agonist at D2 receptor**
- Affinity for muscarinic, α_1 -adrenergic, serotonin and histamine receptors
- Few extrapyramidal side effects
- **Weight gain** **feeling dizzy**

Dosage adjustments - interactions

	Adjusted Dose
CYP2D6 Poor Metabolizers	
CYP2D6 Poor Metabolizers	300 mg
CYP2D6 Poor Metabolizers taking concomitant CYP3A4 inhibitors	200 mg
Patients Taking 400 mg of ABILIFY MAINTENA	
Strong CYP2D6 <u>or</u> CYP3A4 inhibitors	300 mg
CYP2D6 <u>and</u> CYP3A4 inhibitors	200 mg
CYP3A4 inducers	Avoid use
Patients Taking 300 mg of ABILIFY MAINTENA	
Strong CYP2D6 <u>or</u> CYP3A4 inhibitors	200 mg
CYP2D6 <u>and</u> CYP3A4 inhibitors	160 mg
CYP3A4 inducers	Avoid use

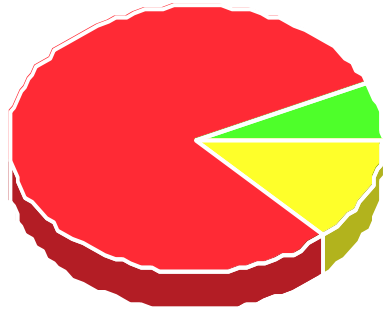
ESTIMATED MEAN WEIGHT GAIN AT 10 WEEKS

•A comprehensive literature search identified 78 studies that included data on weight change in patients treated with a specific antipsychotic.

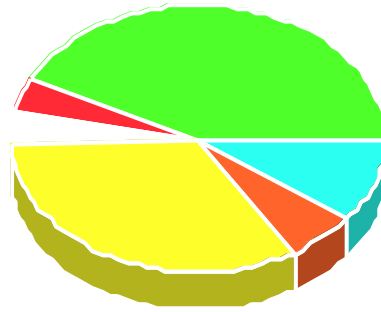


Allison DB, Mentore JL, Heo M, et al: Weight gain associated with conventional and newer antipsychotics: a meta Analysis. AJP, 1999.

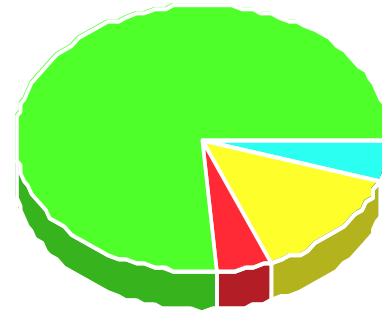
Atypical Antipsychotics In Vivo Binding Affinities



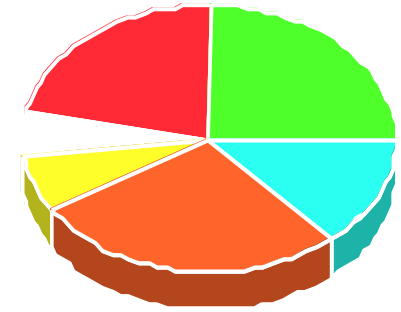
Haloperidol



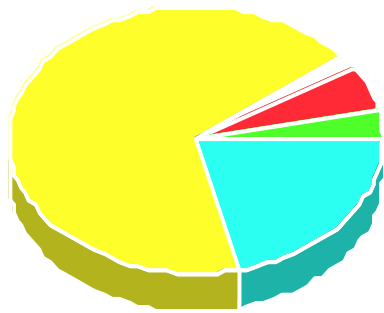
Clozapine



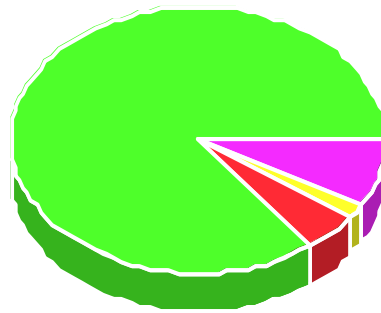
Risperidone



Olanzapine



Quetiapine



Ziprasidone

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