

# 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

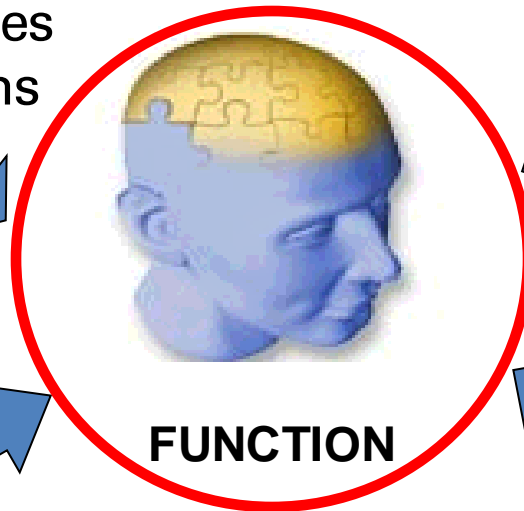
# Schizophrenia - symptoms

## 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

D<sub>2</sub>-receptor

### Present

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

Combined antagonists

5-HT<sub>2</sub>/D<sub>2</sub>

# 1st generation (Typicals)



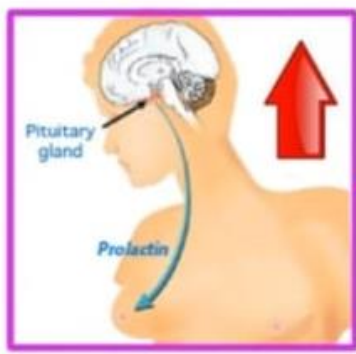
nigrostriatal



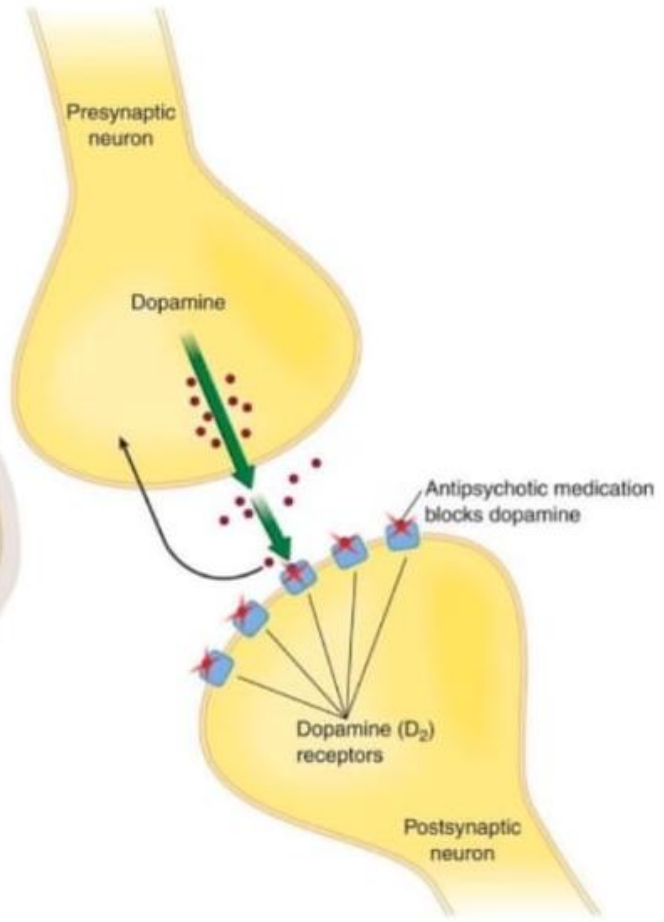
mesocortical



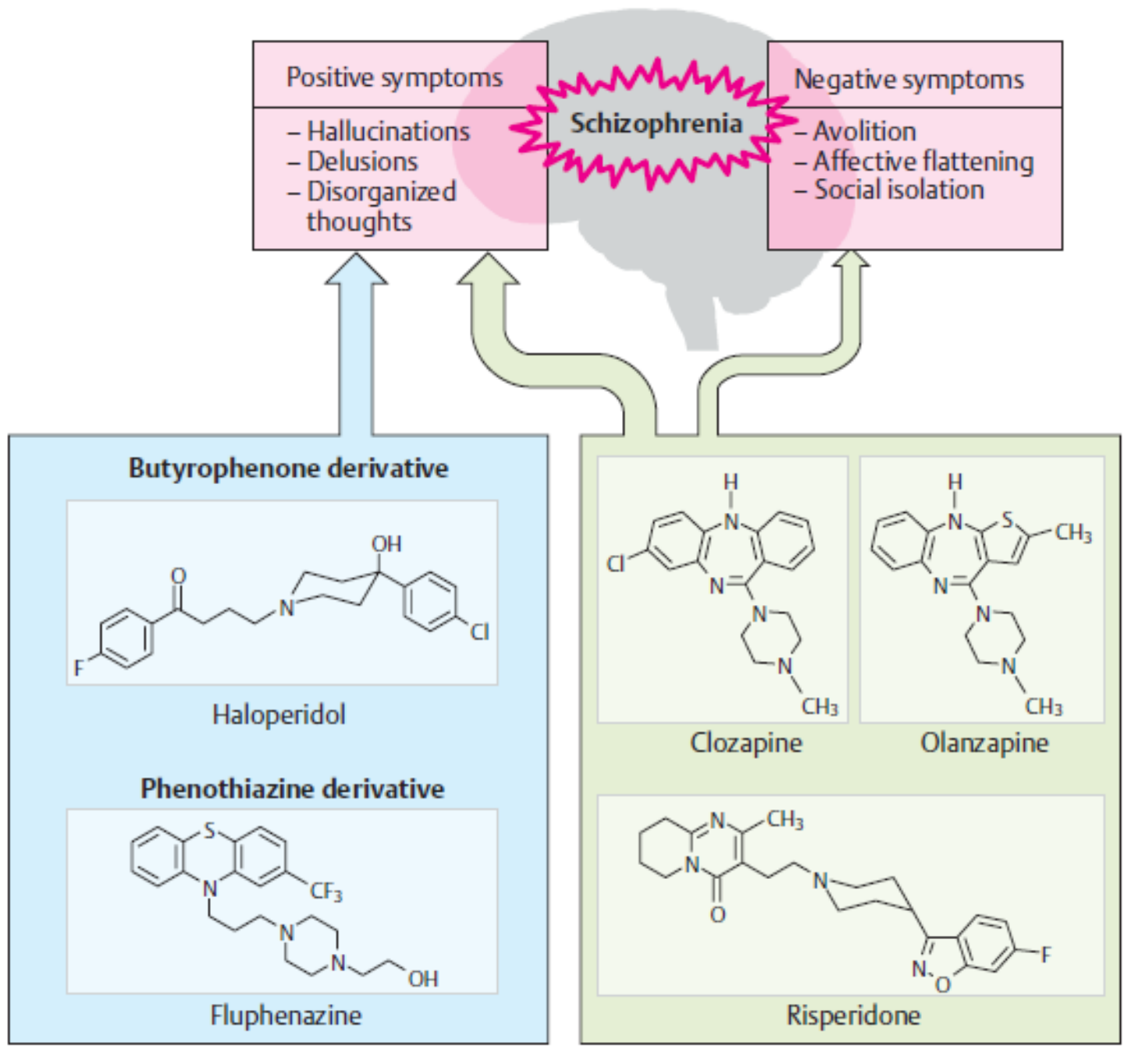
mesolimbic

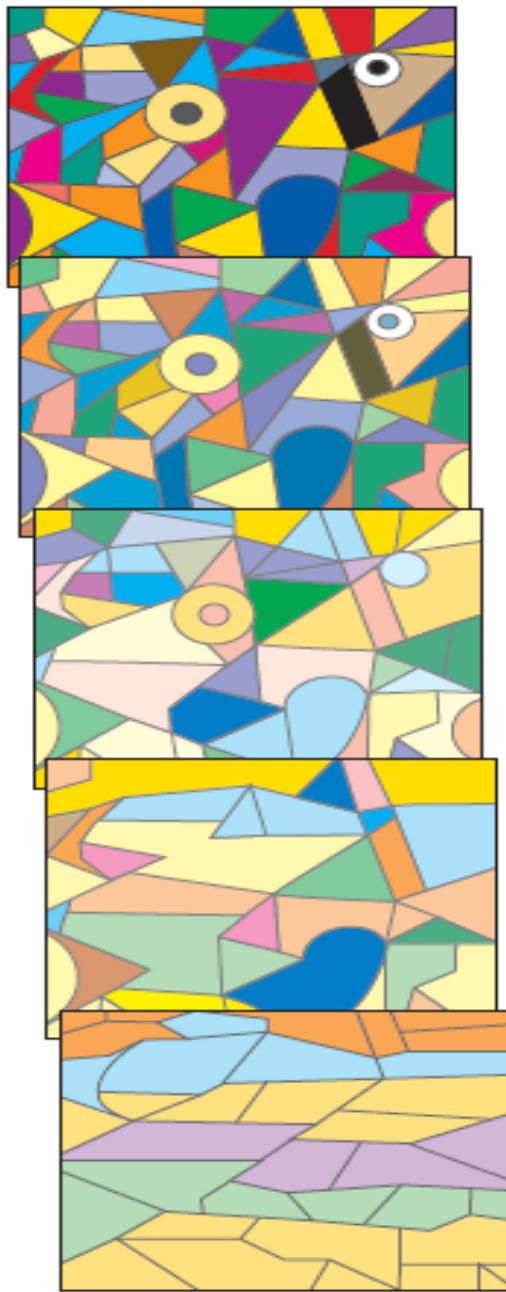


tuberoinfundibular



## A. Conventional and atypical neuroleptics





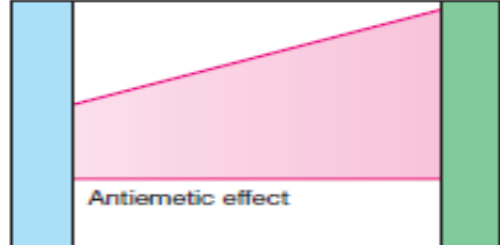
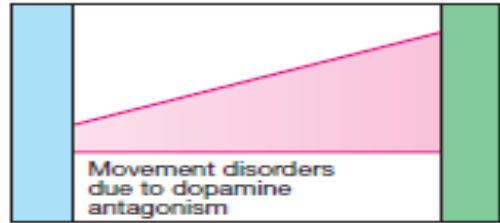
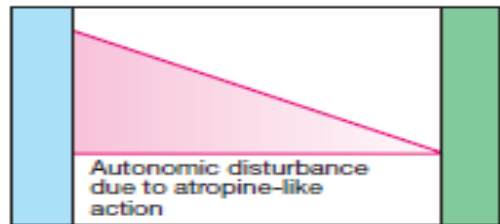
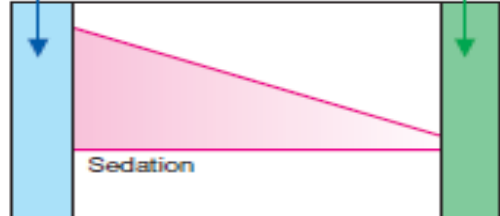
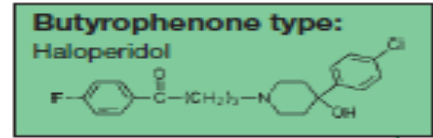
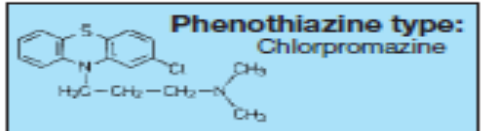
Week 3 after start of therapy

Week 5

Week 7

Week 9

**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			+	+	++++
<b>Haloperidol</b>			+	+	++++

# Neurological Side Effects of antipsychotics

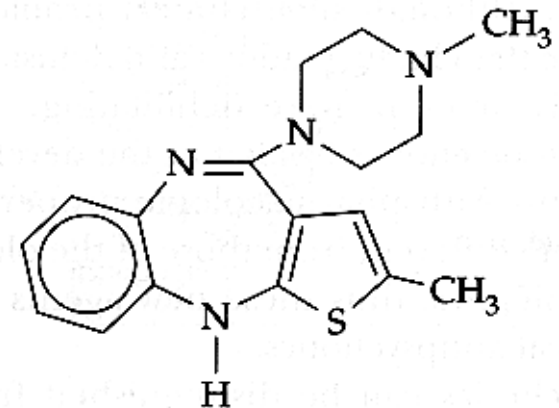
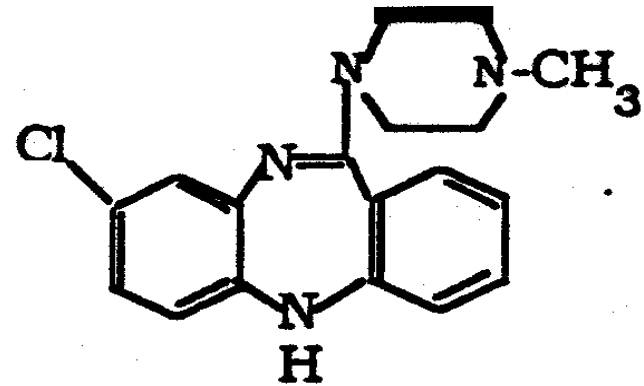
REACTION	FEATURES	TIME OF MAXIMAL RISK	PROPOSED MECHANISM	TREATMENT
Acute dystonia	Spasm of muscles of tongue, face, neck, back; may mimic seizures; <i>not</i> hysteria	1 to 5 days	Unknown	Antiparkinsonian agents are diagnostic and curative
Akathisia	Motor restlessness; <i>not</i> anxiety or "agitation"	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
<b>Risperidone</b>	++	+++	+/ +++ Dose dependent
Clozapine	++	++	-
Aripiprazole	0/+	0/+	0/+ 15

# Clozapine and olanzapine

- VERY low EPS
- Blocks D1, D2, D4,  $\alpha$ -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

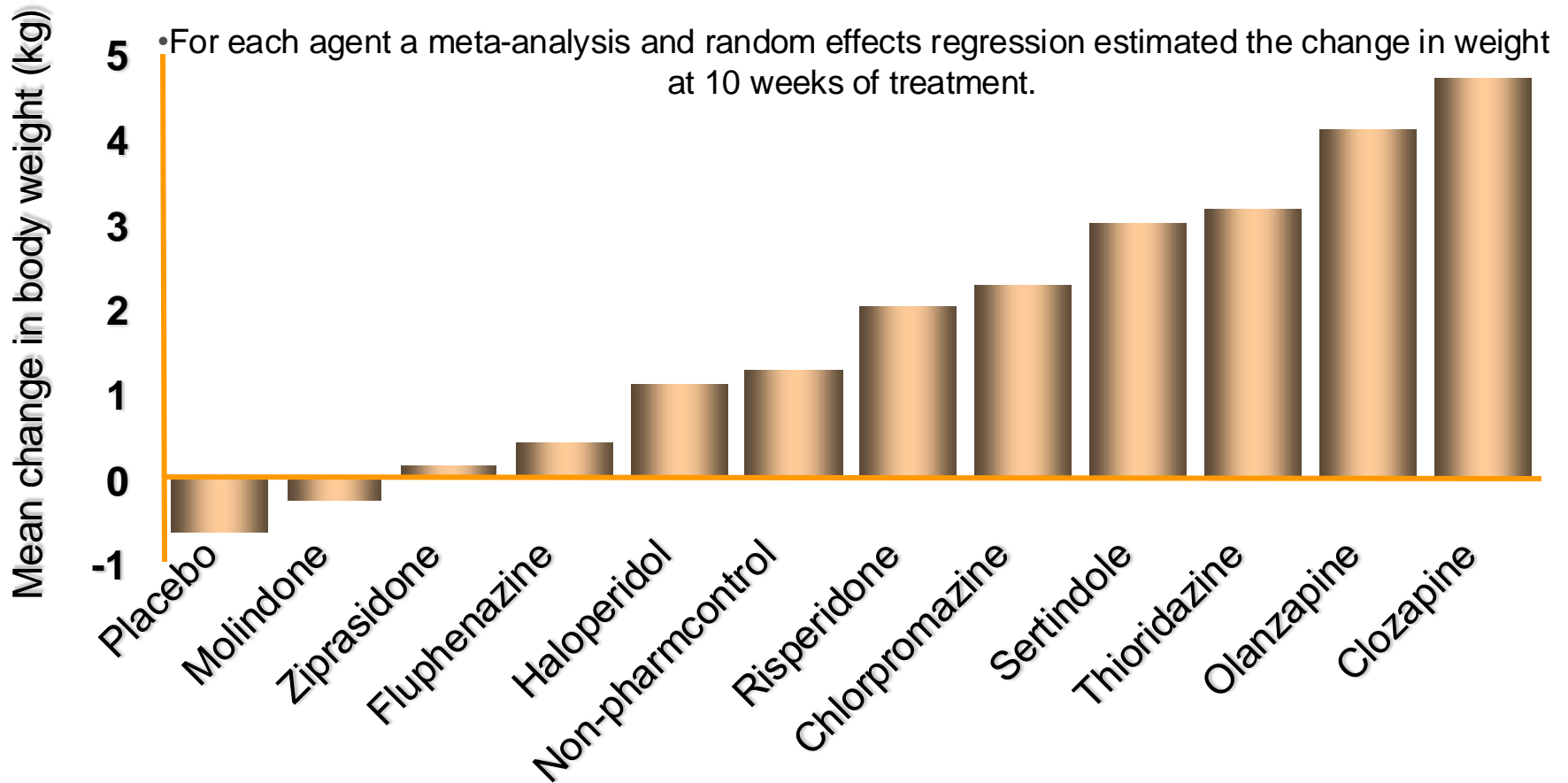
- **Partial agonist at D2 receptor**
- Affinity for muscarinic,  $\alpha_1$ -adrenergic, serotonin and histamine receptors
- Few extrapyramidal side effects
- **Weight gain**
- **feeling dizzy**

# Dosage adjustments - interactions

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

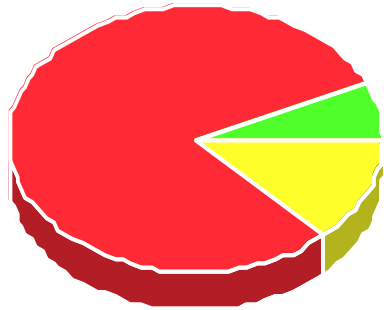
# ESTIMATED MEAN WEIGHT GAIN AT 10 WEEKS

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

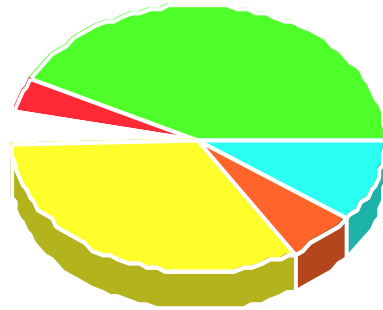


Allison DB, Mentore JL, Heo M, et al: Weight gain associated with conventional and newer antipsychotics: a meta Analysis. AJP, 1999.

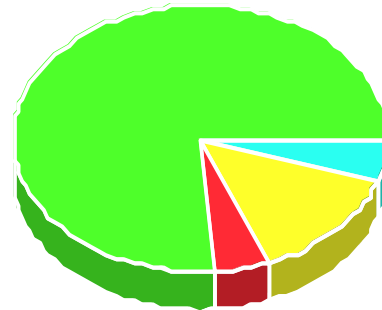
# Atypical Antipsychotics In Vivo Binding Affinities



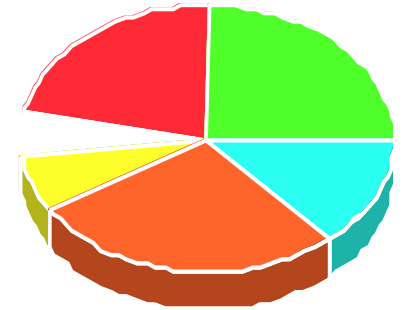
Haloperidol



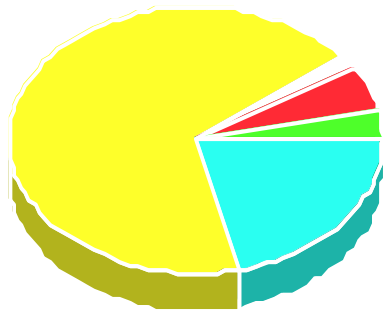
Clozapine



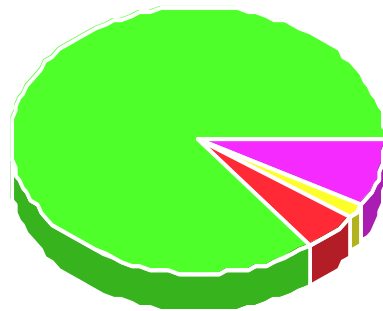
Risperidone



Olanzapine



Quetiapine



Ziprasidone

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