CNS
Doctor 2021

Pharmacology

Modified (6)

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Schizophrenia

More in males and early in onset ~21 year , and in females is less comon and Late ~ 28 year

Come in certain age because : environment factors + genetic make up

- Pathogenesis is unknown.

Without environmental triggers no disease, and this is the difference between genetic risk diseases (polymorphism) , and genetic diseases

- Onset of schizophrenia is in the late teens - early ‘20s.

Environment triggers the disease in patient genetically predisposed

Schizophrenia is not a genetic disease

Polymorphism increase RISK of disease (increase in incidence)

- Genetic predisposition -- Familial incidence.

Hereditary Influences may account for 10% of schizophrenia cases

- Multiple genes are involved.

Doesn’t born to be schizophrenic

- Afflicts 1% of the population worldwide.

In 100 male there is 1 case , and in 200 females there is 1 case

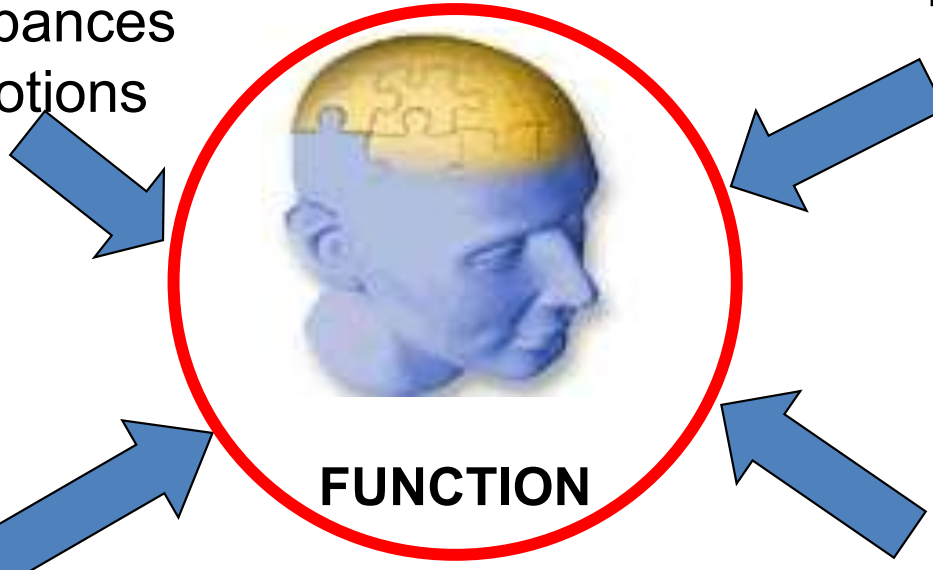
- A thought disorder

Schizophrenia - symptoms

Affect many areas in brain
-> increase Dopamine levels

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

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 in 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

Seretonin also has a role

Schizophrenia Pathophysiology

Schizophrenia Pathophysiology	Pharmacologic Profile of APDs	
.Past		
		Typical drugs
Excess dopaminergic activity	Dopamine antagonists	D_2-receptor
Present		
		Atypical drugs
Renewed interest in the role of serotonin (5-HT)	Combined antagonists	5-HT_2/D_2

Specially 5-HT2A

So drugs that target this receptor, enhance mood of patient

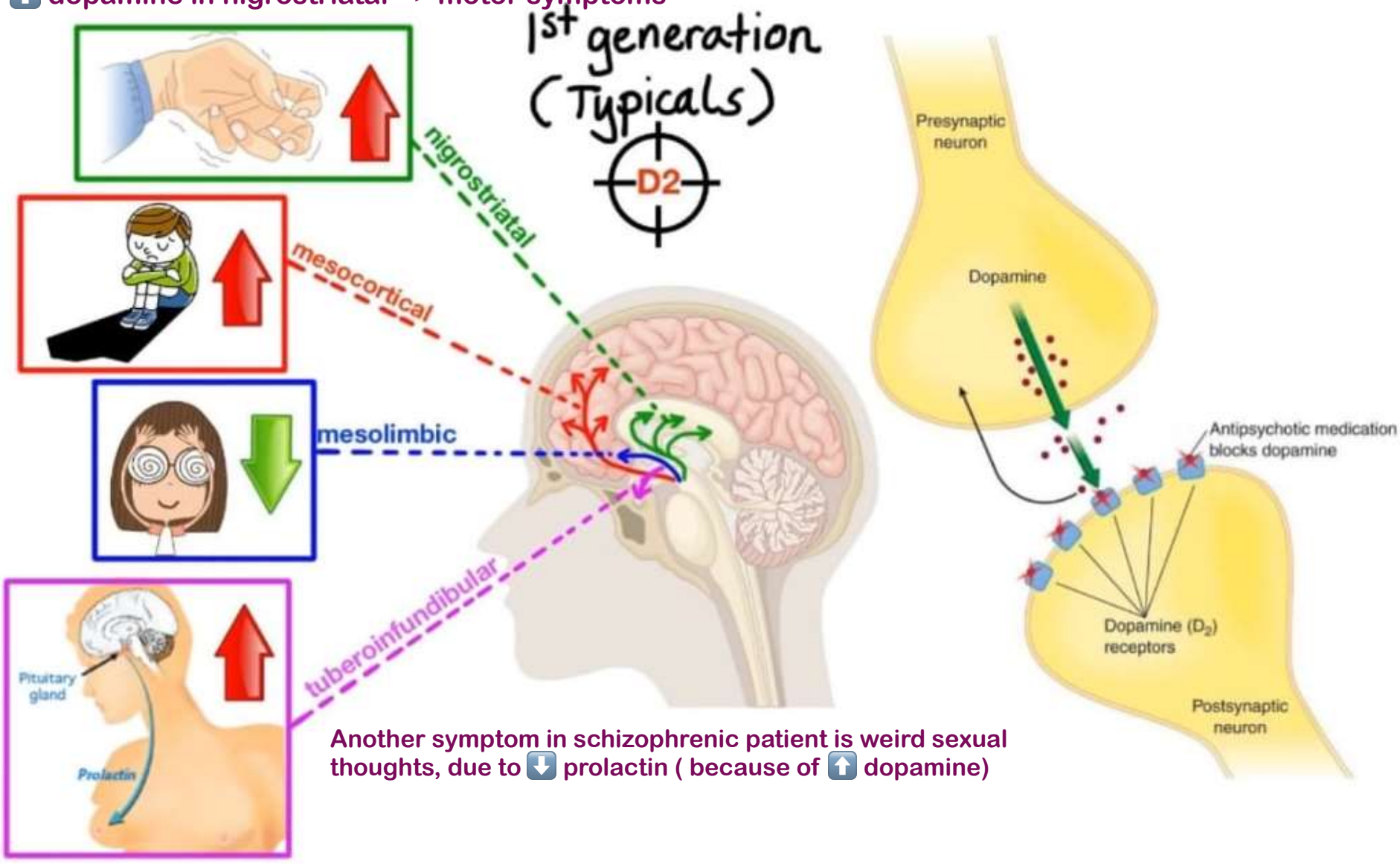
⬆️ dopamine in mesocortical --> hallucinations [agitation, screaming, can't explain the sentences ,...]

⬆️dopamine in mesolimpic --> Depression (-ve symptoms)

The explanation: ⬆️ Dopamine --> ⬇️ serotonin

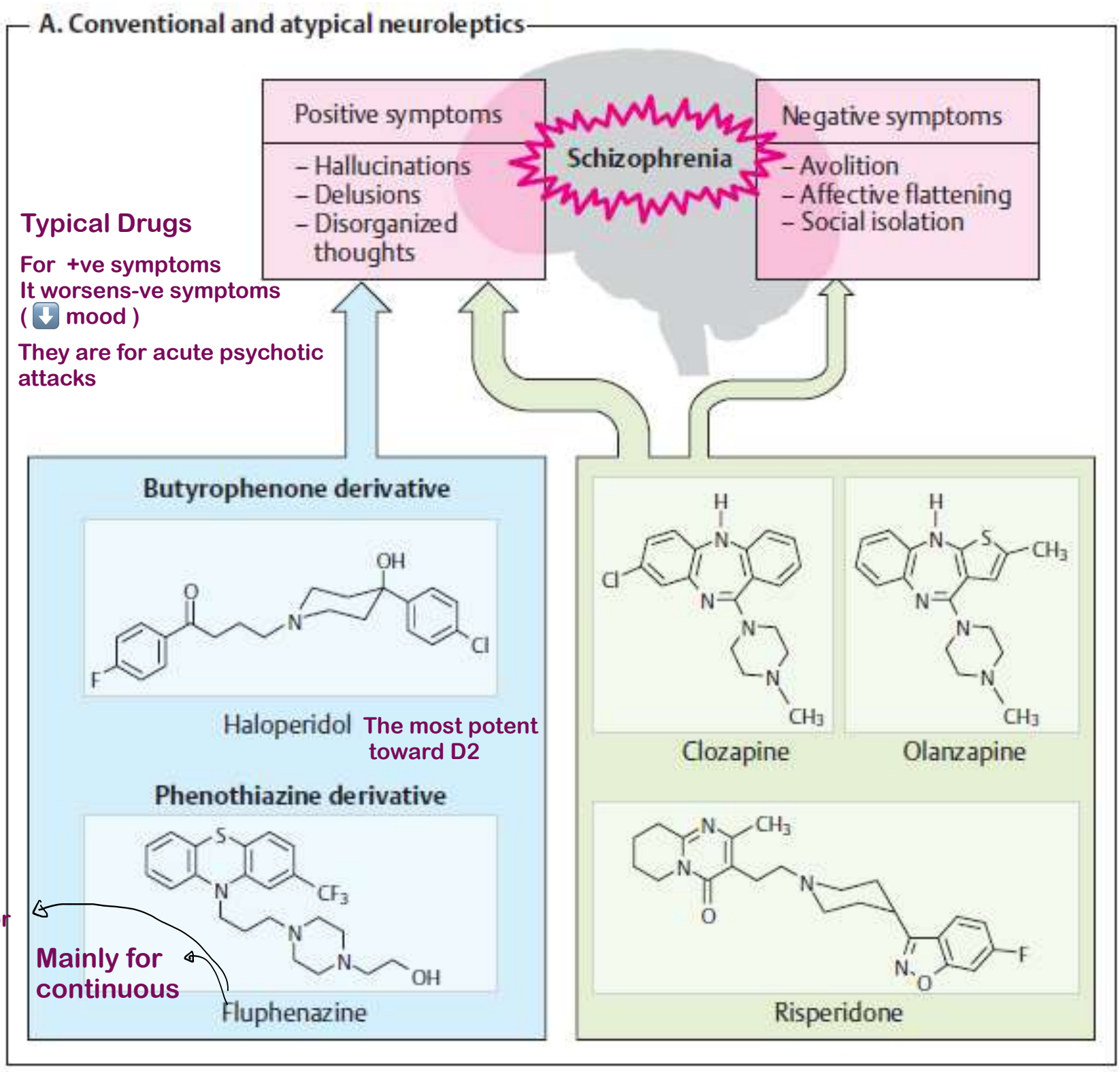
⬆️ serotonin--> ⬇️ Dopamine

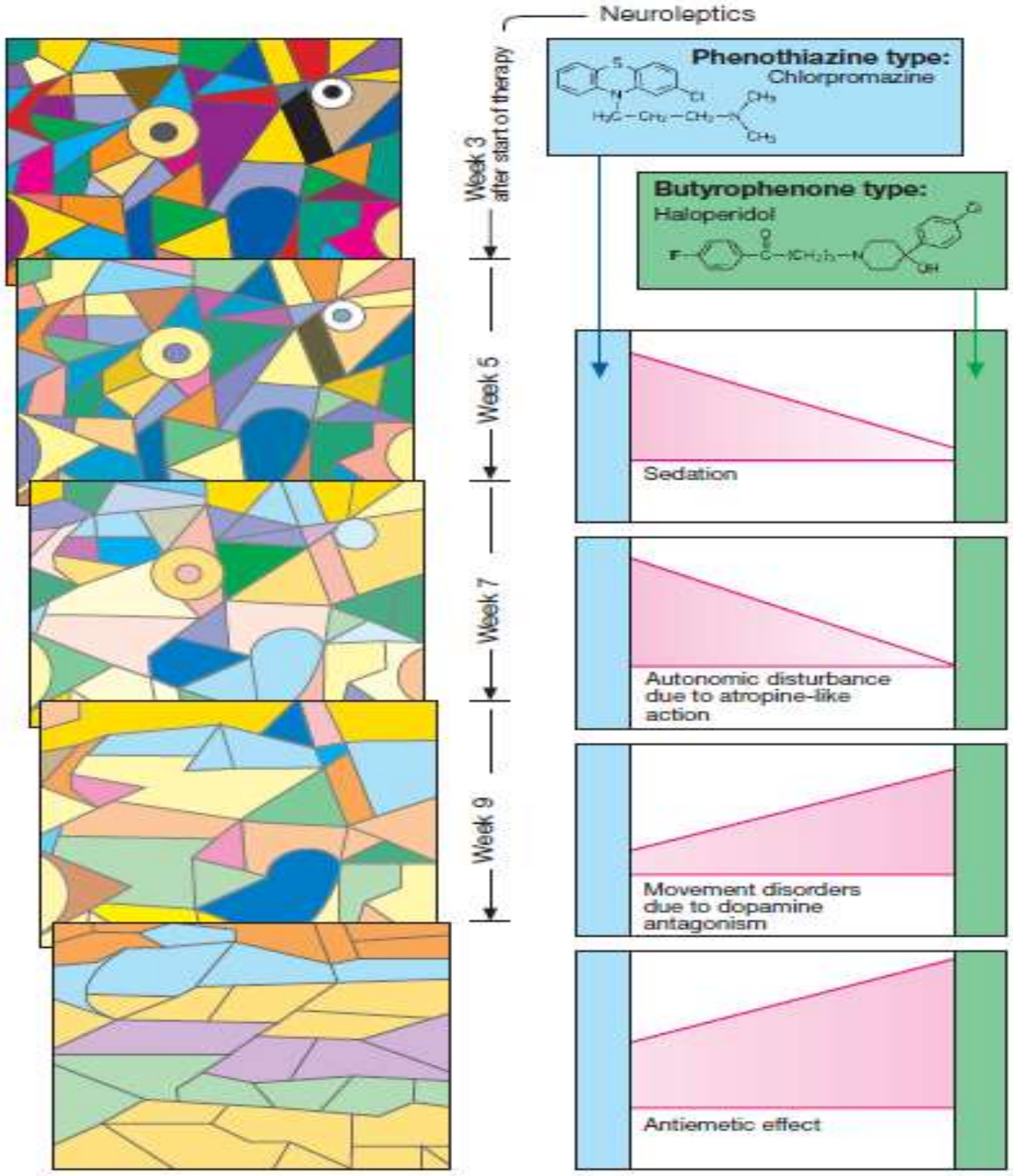
⬆️ dopamine in nigrostriatal --> motor symptoms



Another symptom in schizophrenic patient is weird sexual thoughts, due to ⬇️ prolactin (because of ⬆️ dopamine)

How differ from Bipolar ? Bipolar cycling (attacks) , but schizophrenia is continuous.


A. Conventional and atypical neuroleptics
Positive symptoms
– Hallucinations
– Delusions
– Disorganized thoughts
Schizophrenia
Negative symptoms
– Avolition
– Affective flattening
– Social isolation
Typical Drugs
For +ve symptoms
It worsens-ve symptoms
(⬇️ mood)
They are for acute psychotic attacks
Butyrophenone derivative
Haloperidol
The most potent toward D2
Phenothiazine derivative
Fluphenazine
Mainly for continuous
Clozapine
Olanzapine
Risperidone
* cheap
* used in poor areas ,
Use it orally and for long time


Neuroleptics
Week 3
after start of therapy
Week 5
Week 7
Week 9
Phenothiazine type:
Chlorpromazine
Butyrophenone type:
Haloperidol
Sedation
Autonomic disturbance due to atropine-like action
Movement disorders due to dopamine antagonism
Antiemetic effect

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; *not* hysteria	1 to 5 days **Sudden**	Unknown	Anticholinergic 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
Delayed 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

Stage drug

Tardive dyskinesia

Happen with old drugs , but can happen with the new drugs

Dont stop the drug suddenly

Mechanism:
Anti D2 --> ⬆️ number of D2 receptors to a level the dose of drug is no more enough, dopamine bind to free D2 --> oral , facial dyskinesia
1st sign of this toxicity: abnormal movement of the tongue

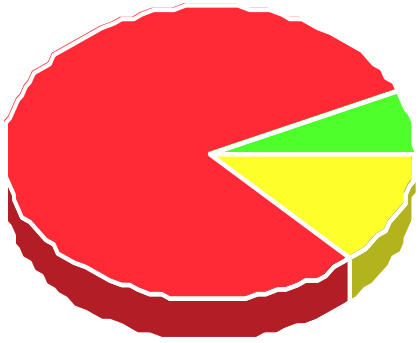
Treatment : tapering and change the drug , giving benzodiazepine
(the withdrawal symptom of inhibiting drug is excitation, so we need to benzo)

In severe case : ⬆️ dose acutly

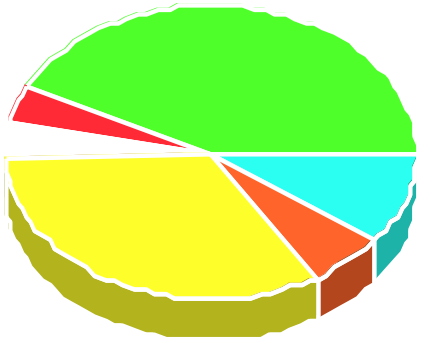
Second Generation Antipsychotic Drugs

Compound	Sedation	Hypo-tension	Motor effects
Risperidone	++	+++	+/++ Dose dependent **On high dose**
Clozapine	++	++	-
Aripiprazole **Partial agonist** **Weak but few side effects** **Need long time to work , so we use a Loading Dose (give injection once a week in combination of taking the drug orally)**	0/+	0/+	0/+

Atypical Antipsychotics In Vivo Binding Affinities

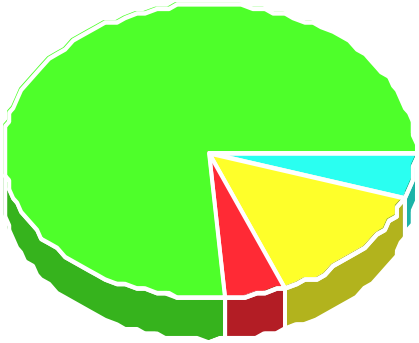


Haloperidol

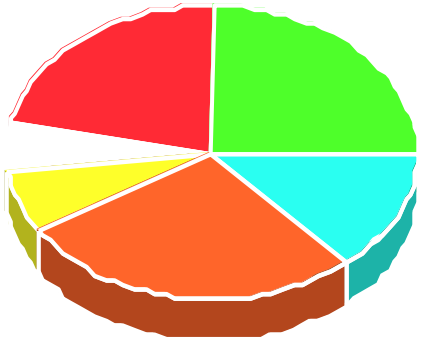


Clozapine

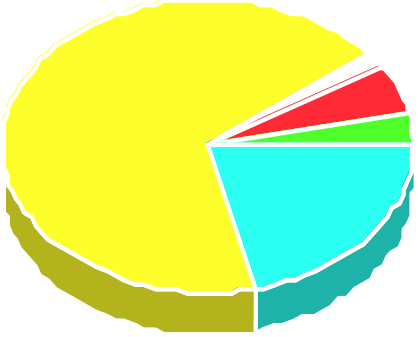
The best on -ve symptoms
BUT !! May cause Agranulocytosis which is fatal
So it becomes the last drug of choice



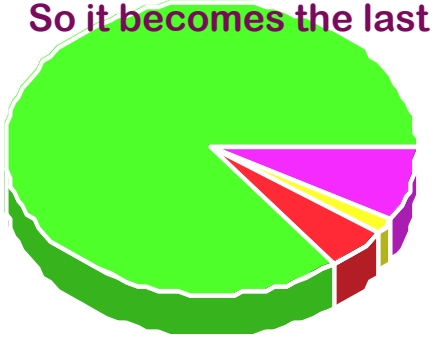
Risperidone



Olanzapine



Quetiapine



Ziprasidone

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

Different efficacy
Efficacy here is measured in relation to effect of the drug on -ve symptoms ,since all these drug work on D2 and lead to get rid of hallucinations

Casey 1994

All drugs work on D2 in varying extent :

Resperidone

Relief of depression
5- HT2A (excitatory) --> antidepressant
Alpha 1 --> orthostatic hypotension
h1 --> sedation
D2 --> antipsychotic
* it is potent antagonist for 5-HT2A and D2
So the side effects similar to typical drugs
+ ⬆️ prolactin--> gynecomastia , ... (mentioned in the slides)

Olanzapine

Work on many receptors (distributed but less affinity

Clozapine

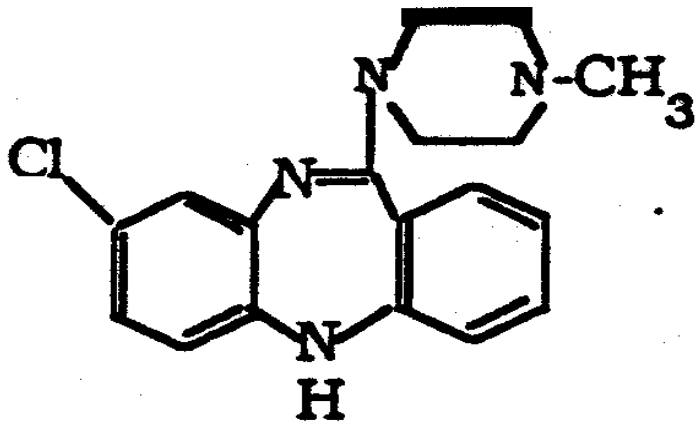
Both olanza and clozapine bind to 5-HT2c
* side effects: don't lead to parkinsonism (weak affinity to D2)
But lead to metabolic problems: increase weight and lead to diabetes on long run

Ziprasidone :

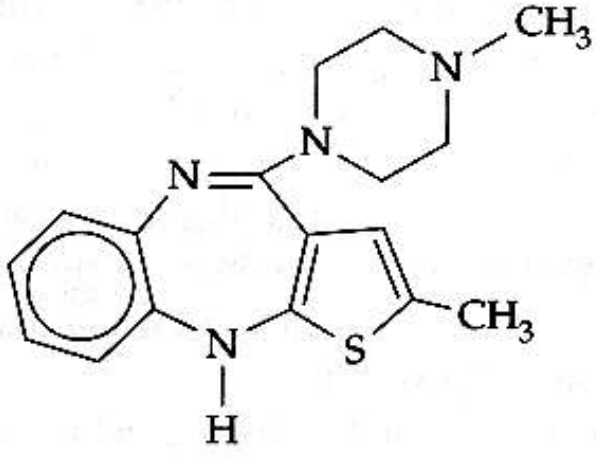
For 5-HT2a mainly
and D2

Sedation and orthostatic hypotension in all drugs

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

Olanzipine – 2.3 kg/month

Quetiapine - 1.8 kg/month

Risperidone – 1 kg/month

Ziprasidone – 0.8 kg/month

Aripiprazole

Prodrug , activated cytochrome p450 (CYP 2D6 , CYP 3A4)

It needs dosing according to genetic makeup of patient

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

Is the patient good or poor metabolizer
Take inhibitor drugs to CYP (ex; antifungal) or inducers (ex; phenobarbital)

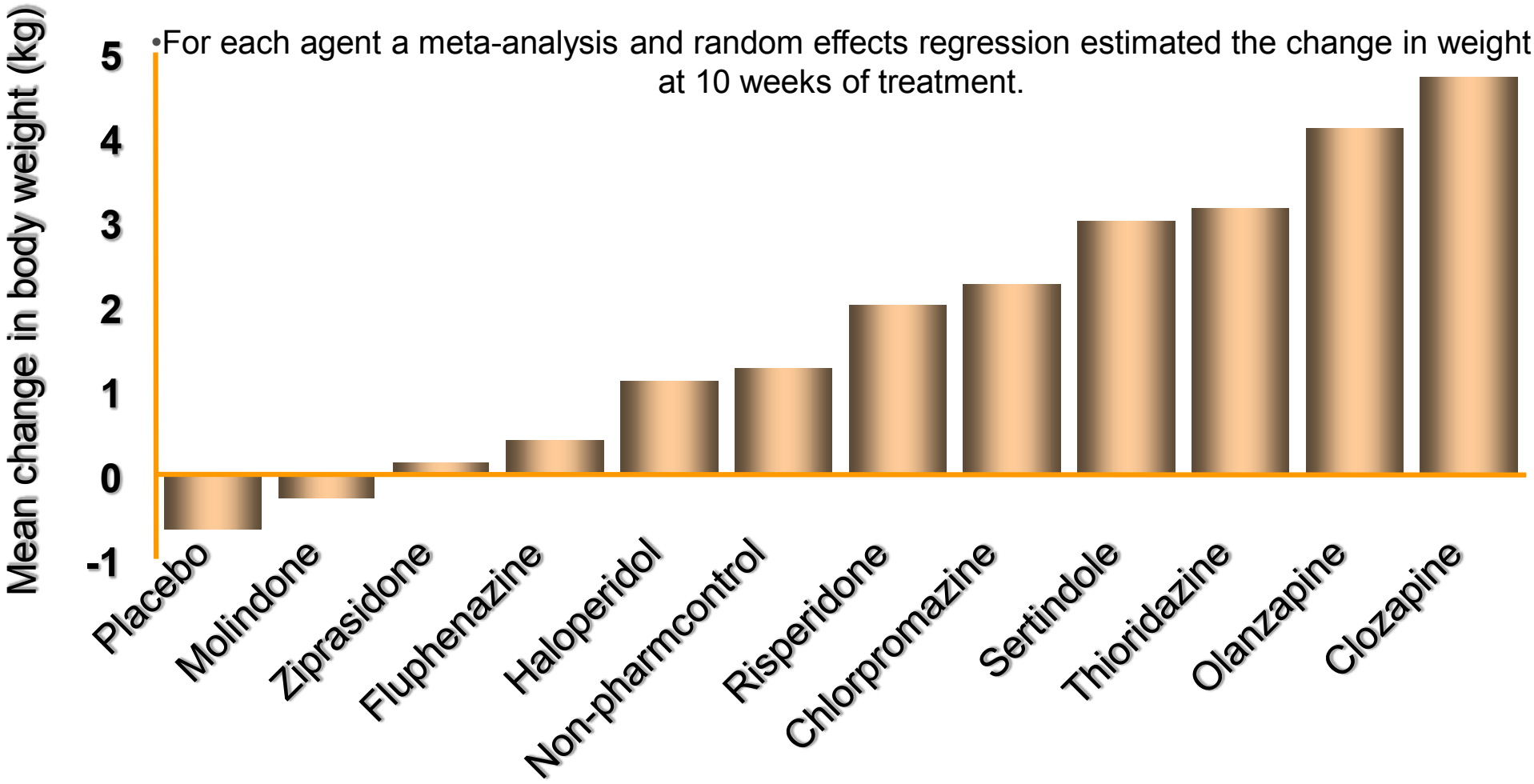
Dosage adjustments - interactions

	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 **or** CYP3A4 inhibitors	300 mg
CYP2D6 **and** CYP3A4 inhibitors	200 mg
CYP3A4 inducers	Avoid use
Patients Taking 300 mg of ABILIFY MAINTENA	
Strong CYP2D6 **or** CYP3A4 inhibitors	200 mg
CYP2D6 **and** 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.

•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.

“لو كنتَ وحدَك لهانت ، لكنّها أمّةٌ يا فتى “

V1