

Pharmacology

Modified no. 08 part 2

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EMS

Antipsychotic drugs -2

- This is a continuation of the “Antipsychotics” lecture , with more clarifications of the last parts

Color code

	Slides
	Doctor
	Additional info
	Important

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.

Typical drugs often cause issues due to reduced dopamine levels, leading to conditions such as Parkinsonism and long-term complications, including extrapyramidal side effects.

However **Atypical** drugs (risperidone, clozapine, and aripiprazole) that work on serotonin , differ in their mechanism of action and adverse effects.

Second Generation Antipsychotic Drugs

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

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, ^b benzodiazepines or propranolol ^c 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

Aripiprazole is a **partial agonist** that binds to dopamine and serotonin receptors , while avoiding antagonism of the 5-HT_{3A}/5-HT_{3C} receptors associated with **diabetes**. This mechanism results in fewer side effects, though its efficacy is somewhat reduced. Because it takes time for patients to show improvement, **augmentation** is often necessary. To enhance its effects, aripiprazole is administered both **orally and via injection**, particularly during the first month of treatment, to strengthen the inhibition of hallucinations and improve positive symptoms.

Aripiprazole

- **Partial agonist at D2 receptor**
- **Partial Affinity toward muscarinic, α_1 -adrenergic, serotonin and histamine receptors**
- **Few extrapyramidal side effects**
- **Weight gain** (is reduced compared to others)
- **feeling dizzy**

Clozapine and olanzapine primarily target serotonin receptors and also bind to D2 dopamine receptors. Binding to 5-HT_{3C} receptors induces metabolic changes, leading to diabetes and weight gain.

- **Olanzapine:** Primarily associated with an increased risk of diabetes.
- **Clozapine:** Causes both diabetes and agranulocytosis, a potentially fatal side effect.

Clozapine is considered the most effective antipsychotic and is used as a last resort when other treatments fail. Typically, treatment starts with olanzapine, and if it is ineffective, clozapine is introduced. However, aripiprazole is generally preferred due to its better safety profile.

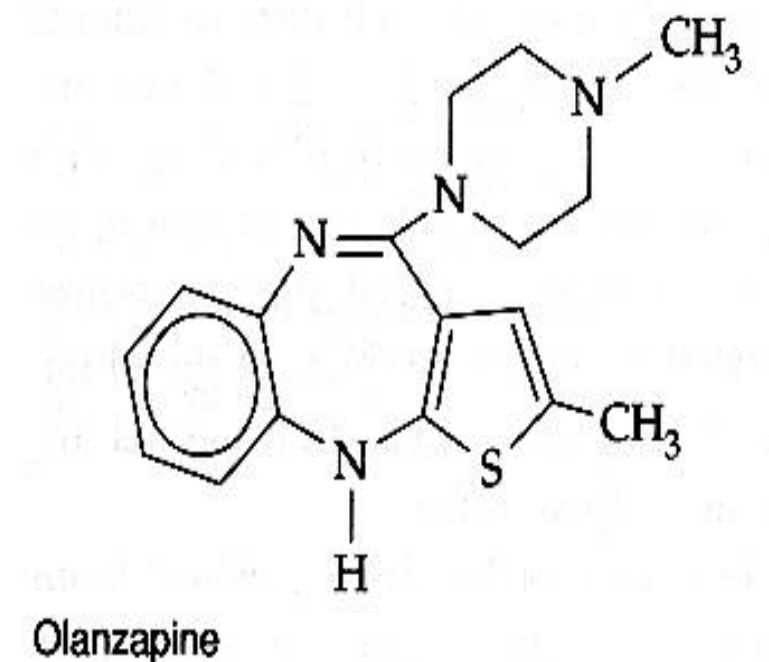
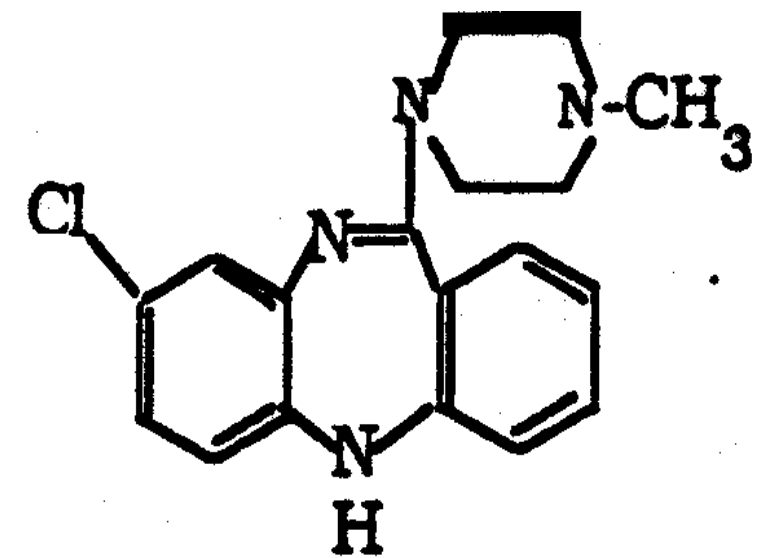
Both clozapine and olanzapine can also cause hypotension and sedation as side effects.

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 in 4% of the patients

More toward serotonin receptors rather than Dopamine

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



Before using clozapine or olanzapine, **risperidone** was typically the first choice. However, it has several side effects, including **sedation, hypotension, and extrapyramidal side effects** with long-term use. These may manifest as **akathisia** and **akinesia** .

Although risperidone is classified as an **atypical antipsychotic**, it strongly binds to **D2 dopamine receptors**, leading to **dopaminergic side effects** similar to those seen with typical antipsychotics.

Important

Risperidone = Risperdal

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, can cause DM
but **less than** olanzapine and clozapine
- Does cause anticholinergic side effects— dry mouth, constipation
- Does not elevate prolactin

Summary (Note that this summary is provided by the Doctor)

- **Aripiprazole** is a good antipsychotic with fewer side effects, but its effect is delayed. To compensate, it is given both orally and via injection at the start of treatment. Once the patient improves, treatment continues with oral administration.
- **Risperidone** has several side effects, including gynecomastia, increased prolactin levels, hypotension, sedation, and extrapyramidal side effects.
- **Olanzapine** can cause sedation, hypotension, diabetes mellitus, and weight gain.
- **Clozapine** has similar side effects to olanzapine (hypotension, sedation, diabetes mellitus, and weight gain) but also carries the risk of agranulocytosis, a potentially fatal condition.
- **Quetiapine** can induce sedation, hypotension, and diabetes mellitus, but its risk of causing diabetes is lower than that of other antipsychotics.

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

Drugs like **aripiprazole** have different dosages based on **CYP3A4** and **CYP2C6** metabolism.

This information is important. However it is not for exam purposes

Ziprasidone - 2001

Doctor did not explain
this slide

- **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

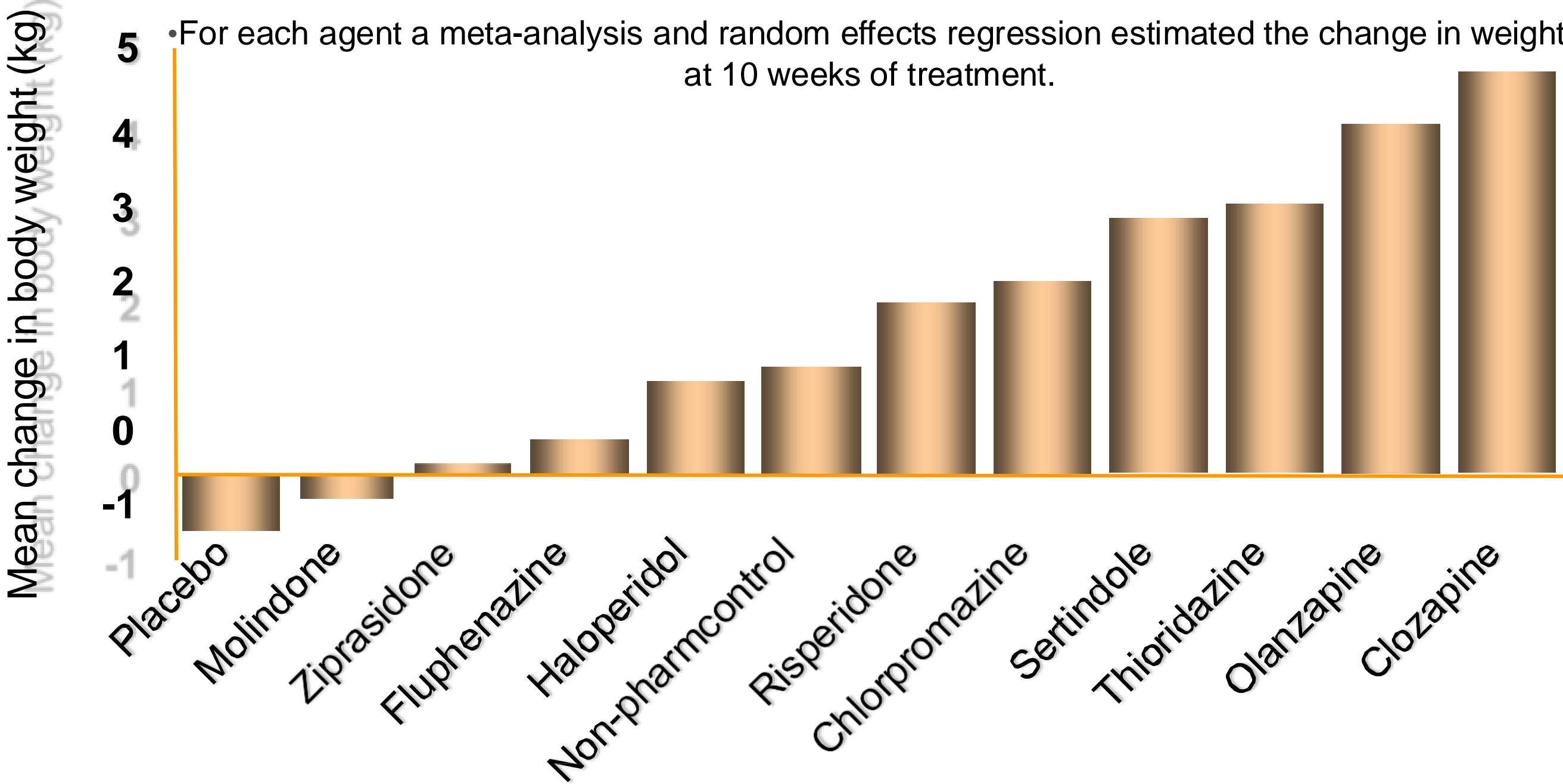
Quetiapine - 1.8 kg/month

ESTIMATED MEAN WEIGHT GAIN AT 10 WEEKS

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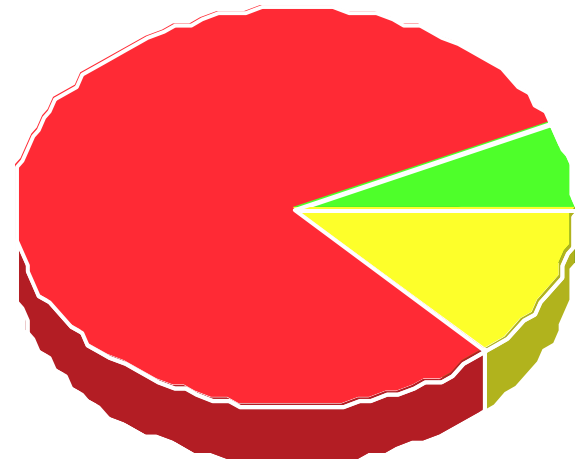
- A comprehensive literature search identified 78 studies that included data on weight change in patients treated with a specific antipsychotic.

- For each agent a meta-analysis and random effects regression estimated the change in weight at 10 weeks of treatment.

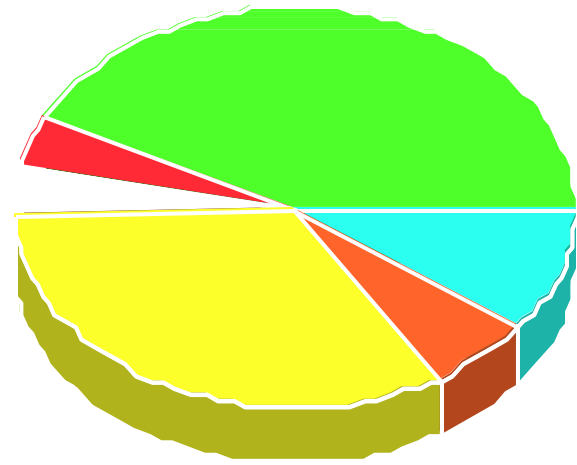


Allison DB, Mentore JL, Heo M, et al: Weight gain associated with conventional and newer antipsychotics: a meta Analysis. AJP, 1999.

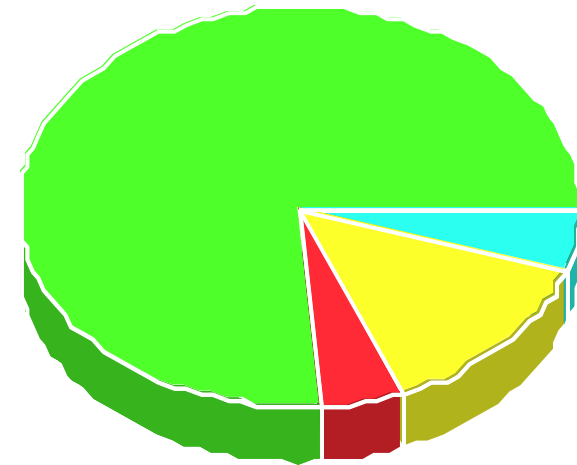
Atypical Antipsychotics In Vivo Binding Affinities



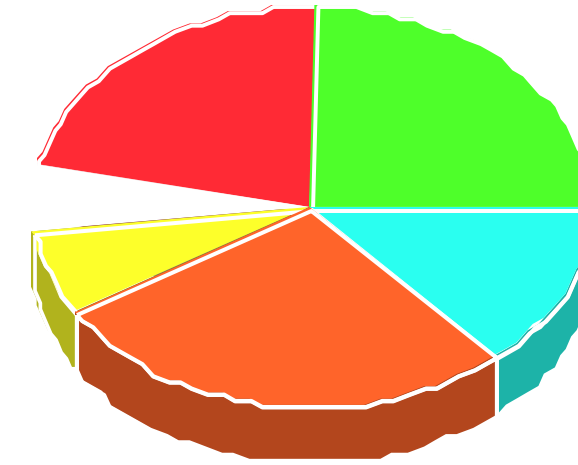
Haloperidol



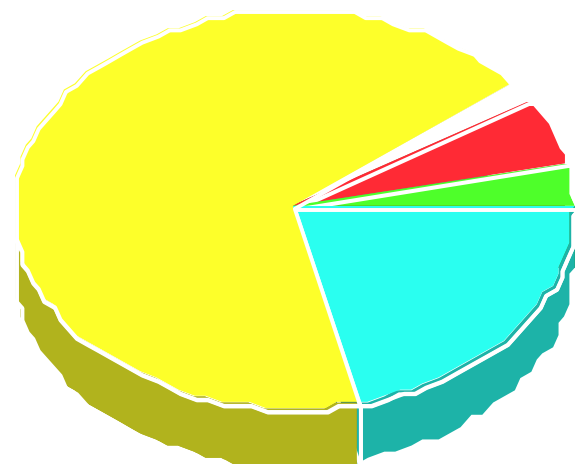
Clozapine



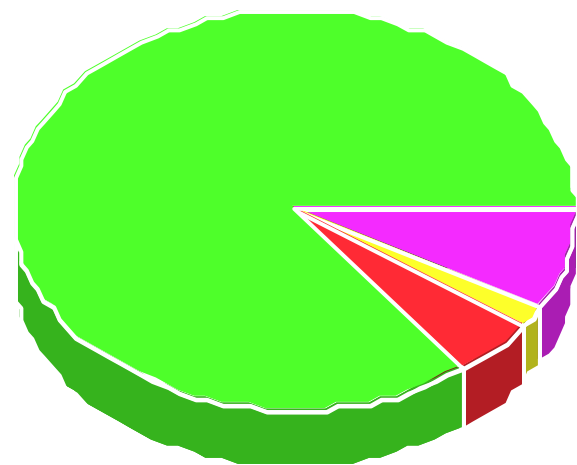
Risperidone



Olanzapine



Quetiapine



Ziprasidone

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عيدكم مبارك !! تقبل الله منكم صالح الأعمال وأعادہ عليكم باليمن والنصر والفتوحات.

دراسة CNS موفقة 😊

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→V2			
V2→V3			



امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!