Schizophrenia- Lecture 4

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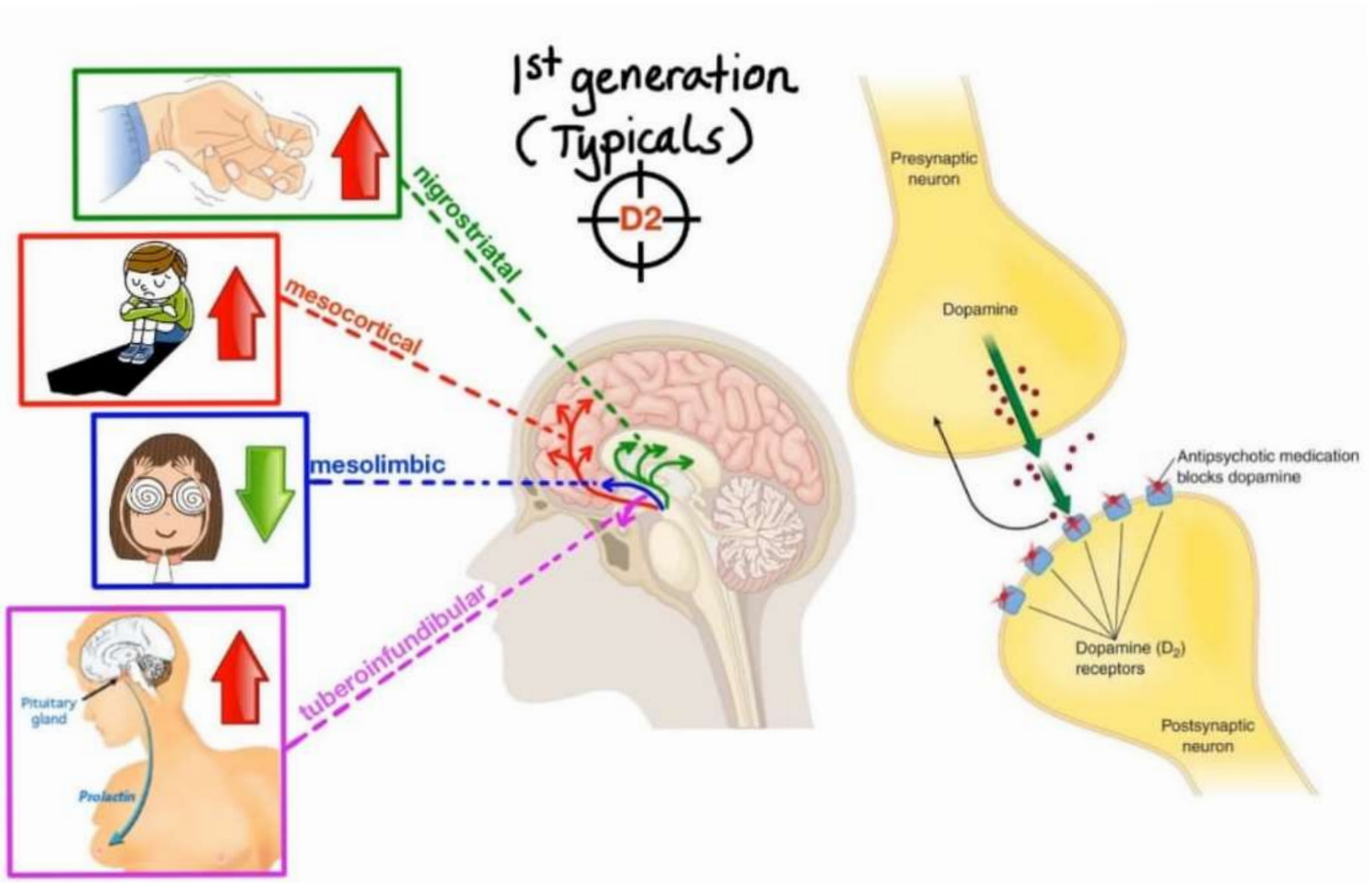
Classification of Antipsychotic drugs

- 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**)



Proceed to the next slide for the Dr's recap

In the previous lecture, we started talking about anti-psychotics and how we focused on targeting **dopamine receptors (especially D2)**, and we divided anti-psychotic drugs into 2 types; typical and atypical, and we mentioned how the typical type was built on the theory of **dopamine-schizophrenia reasoning (D2 activation is the only reason of schizophrenia)**, but these drugs are not that selective, they bind to other receptors but more importantly **they'll bind to D2 receptors in the whole brain** which will cause many side effects

(We can't get them to only target D2 at the mesolimbic area (our goal)),

most important one being the prolactinemia which causes multiple sexual disturbances including both physically and mentally (They have such issues even before treatment), it will also target the mesocortical area, which is low on dopamine already causing depression and the effect of the drug in this area will worsen the depression, nigrostriatal effects causing extra-pyramidal side effects such as parkinsonism, dystonia etc.

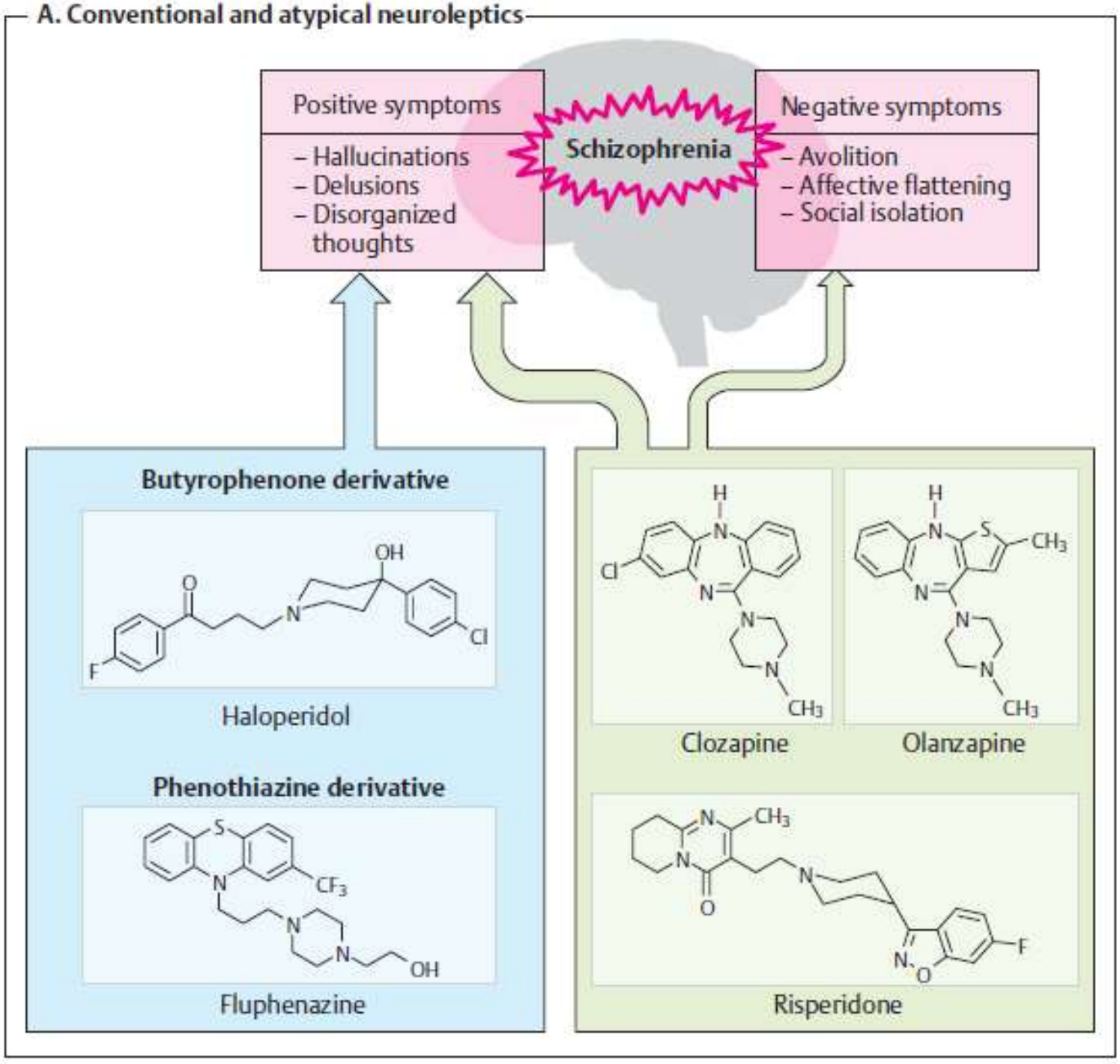
'**Hal**'operidol is used for '**Hal**'lucination attacks!

Most potent against D2

-Haloperidol - **High potency, typical anti-psychotic**, **used for** acute attacks of schizophrenia, post-partum/surgery, drug induced psychosis (excess amphitamine as an example)

-Chlorpromazine - **low potency, typical anti-psychotic**, **used for** constant hiccups, schizophrenia on the longer run (chronically?)

*EXTRA- **Flupenthixol** is a typical anti-psychotic found in the commonly described deanxit which is currently not approved by the FDA*



Again, look at how **Atypical anti-psychotics** have 2 arrows meaning they affect both positive and negative symptoms because they target (block) the serotonin receptors 5-HT2A+C

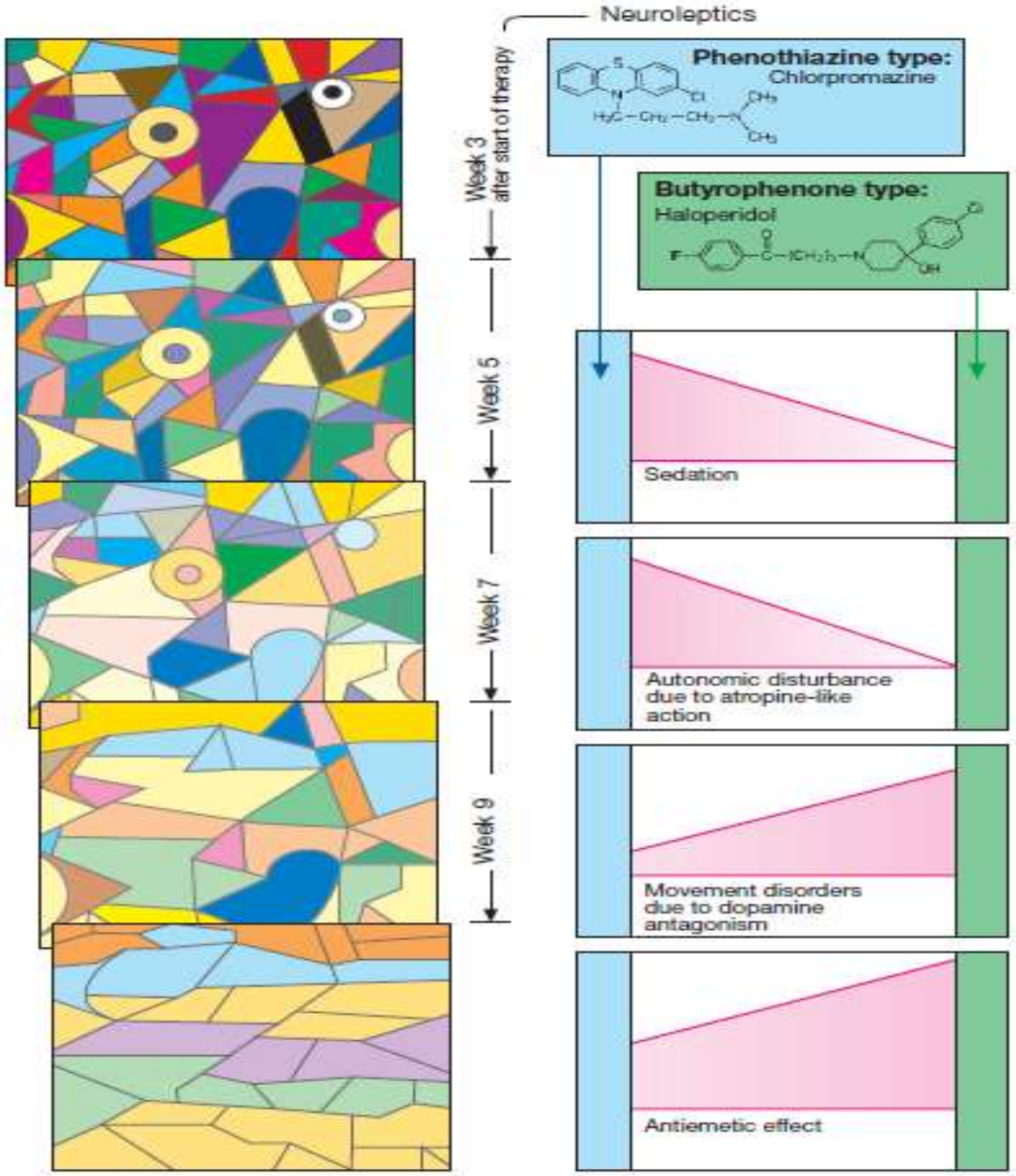
Atypicals have 2 advantages; First we have decreased the D2 selectivity meaning that we will have less extra-pyramidal side effects and less side effects regarding prolactin, while gaining the second advantages which is targeting 5-HT2 receptors giving this the little arrow towards the negative symptoms!

But, does that mean that **Atypicals are better schizophrenic drugs?**
Actually studies say that **both types are equally effective** against schizophrenia!
but what about the depression, isn't it only treated with atypicals thus more efficacy? true, but..
The problem is that depression cannot be measured and its heavily heterogeneous.
And added to that the fact that the only measurable improvement that can be seen in schizophrenic patients after these drugs is the positive symptoms, and in that topic their efficacy was found to be pretty similar.
In real life, prescribing atypical types is NOT DEPENDANT on the efficacy (They're not more efficacious) and rather to avoid the adverse reactions that accompany the typical drugs. (USMLE question)

-Treatment of schizophrenia is not easy, we have a response rate of only 30-40% ! And similar high relapse rate no matter what drug we use.

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) (Most important point)
  - Efficacy in treatment-resistant group of patients
    This is not 100% true in real life
  - Efficacy against negative symptoms.



This was already discussed in the previous lecture, check whether you remember what we talked about here or not.

Neurological Side Effects of antipsychotics

In a couple of slides earlier we said that the most important advantage of atypicals is that they don't cause extrapyramidal side effects, why do we care about them that much?

REACTION Typical 20% Atypical 1%	FEATURES	TIME OF MAXIMAL RISK	PROPOSED MECHANISM	TREATMENT
Acute dystonia This side effect can even present with atypical drugs especially **in elderly!** **(so in older patients prescribe anti parkinsonian agents even with atypicals.)**	-Spasm of muscles of tongue, face, neck, back; may mimic seizures; *not* hysteria	-1 to 5 days Earliest one	-Unknown	**-Antiparkinsonian** agents are diagnostic and curative Anticholinergics
Akathisia	-Motor restlessness; not anxiety or "Agitation"	-5 to 60 days	-Unknown	-Reduce dose or change drug: antiparkinsonian agents, benzodiazepines or propranolol may help (anxiolytics) also used for migraine
Parkinsonism	-Bradykinesia, rigidity, variable tremor, mask facies, shuffling gait	-5 to 30 days	-Antagonism of dopamine	-Antiparkinsonian agents are helpful Anticholinergics
Tardive dyskinesia متأخر	-Oral-facial dyskinesia; widespread choreoathetosis or dystonia	-After months or years of treatment **(Worse on withdrawawl)**	-Excess function of dopamine hypothesized	-Prevention of crucial treatment, unsatisfactory (IRREVERSIBLE!)

Tardive dyskinesia is a very important extra-pyramidal side effects, it presents later (1 to 2 or even 5 years after the beginning of drug use) (Remember, schizophrenia drugs are used **FOR LIFE**)
If the patient develops this side effect, we have to stop the drug immediately.
In patients with this side effects, **the symptoms** start **on the tongue first**, leading to the patient giving "Flying kisses" or "Flying tongue" which are **continuous movements** that later will spread to face muscles, along with tingling feeling on the tongue too!
So why does it present after all this time? Tardive dyskinesia happens due to **sensitization of dopamine receptors** thus causing activation of dopaminergic motor movements without consciousness leading to those constant unwanted movements, nothing can be administered to prevent this, and this side effect is **irreversible** and that's why we stop the drug immediately.
Extra: Remember that these symptoms are present in people that already struggle with mental illness, the added stigma is hard to bare causing the patient to withdraw from the public.

First Generation Antipsychotic Drugs

Dr skipped this slide

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

Second Generation Antipsychotic Drugs (ATYPICAL TYPE)

We're now comparing the selectivity of these drugs. We'll learn about 6

Compound	Sedation H1 receptors	Hypo-tension Alpha 1	Motor effects (1-2% only)
Risperidone **heavily blocks D2 in an affinity similar to that towards 5-HT2A/C, thus more side effects especially with higher doses (Highest affinity to D2 among atypicals)**	++	+++	+/++ **Dose dependent**
Clozapine Strongest agent against negative symptoms!	++	++	-
Aripiprazole **Partial agonist!**	0/+ Only non sedative	0/+	0/+

Good news; sedative effect undergoes tolerance!

Aripiprazole

Doctor prefers this drug as t**he best one** to prescribe, it's a great drug and does also come in the form of **injections** accompanied with **Resperidone** as one injection **every month.**
(Intramuscular injections are very helpful to solve drug adherence issues)

- **Partial agonist at D2 receptor**
- Affinity for muscarinic, α_1-adrenergic, serotonin and histamine receptors
- Few extrapyramidal side effects
- **Weight gain but not substantially** **feeling dizzy**

Risperidone
Endocrine effect

Again, binds to D2 more than serotonin receptors.

Side effects below are related to more D2 binding leading to prolactinemia.

- 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.**

Clozapine and olanzapine

*Strong against **5-HT2C**

This action is related to causing drug-induced metabolic syndrome

*Also their common side effect is orthostatic hypotension

- VERY low EPS Extra-pyramidal side effects
- Blocks D1, D2, D4, α-adrenergic, 5HT2, muscarinic, and histamine H1 receptors
- May show greater efficacy against negative symptoms than other antipsychotic drugs *(Last drug resort)
- Agranulocytosis is a potentially fatal side effect for clozapine *similar to hypersensitivity reactions, non dose dependant

Both drugs have high efficacy, but cause significant weight gain and diabetes (Because of high affinity towards 5-HT2**C**)

Quetiapine

- No increased risks for extrapyramidal symptoms
- Shares sedation, orthostatic hypotension, weight gain
- Does cause anticholinergic side effects– dry mouth, constipation

  (This drug is great overall, but at the cost of this, muscarinic blocking!)

- **Does not elevate prolactin**

Ziprasidone - 2001

- **Similar to advantages of others, but argued not** to cause weight gain, (Again, every gain comes at a cost, and here we lose some potency!)

Weight gain comparasions

Clozapine – 1.7 kg/month

Olanzipine – 2.3 kg/month

Quetiapine - 1.8 kg/month

Risperidone – 1 kg/month

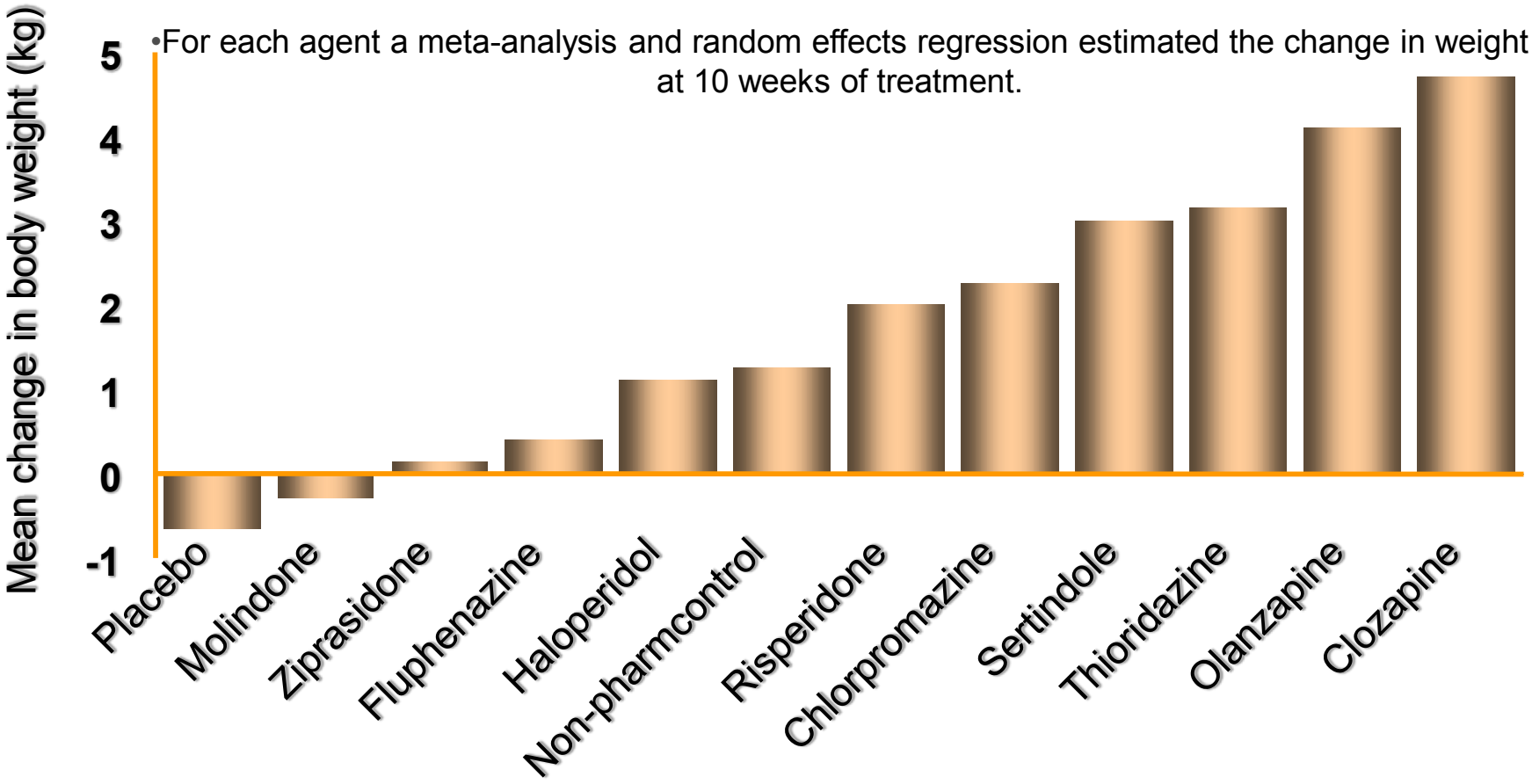
Ziprasidone – 0.8 kg/month

Lowest!

ESTIMATED MEAN WEIGHT GAIN AT 10 WEEKS

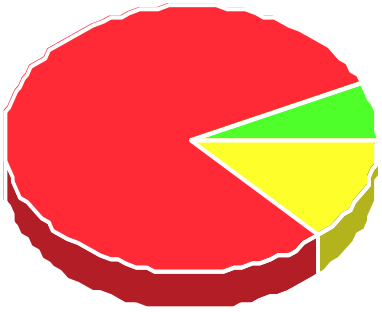
•A comprehensive literature search identified 78 studies that included data on weight change in patients treated with a specific antipsychotic.

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

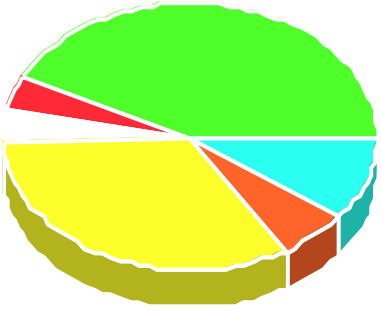


Allison DB, Mentore JL, Heo M, et al: Weight gain associated with conventional and newer antipsychotics: a meta Analysis. AJP, 1999.

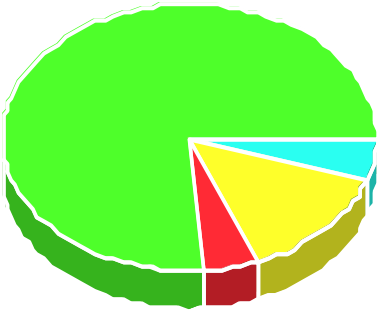
Atypical Antipsychotics In Vivo Binding Affinities



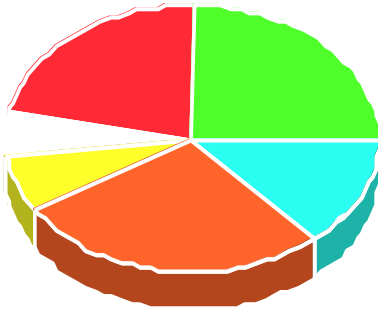
Haloperidol



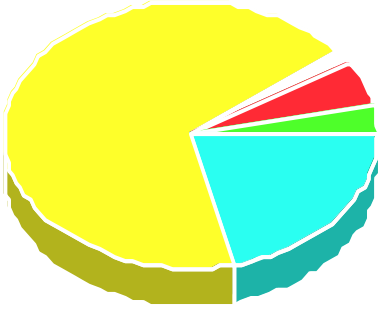
Clozapine



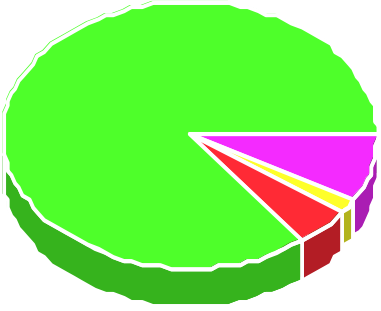
Risperidone



Olanzapine



Quetiapine



Ziprasidone

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

Small changes in the chemical structure can cause significant differnces in receptor binding leading to different side effects that we are going to manage along the "lifetime" course of describtion of them to our patients.

Casey 1994

Dosage adjustments - interactions

Doses are adjusted depending on both CYP3A4 and CYP2D6 status of the patint, we decrease the dose in poor metabolizers, we increase it in rapid+ultra rapid metabolizers And also if there's drug-drug interactions; look below!

	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 CYP2D6 inhibitor such as **fluoxetine**	300 mg
CYP2D6 and CYP3A4 inhibitors	200 mg
CYP3A4 inducers **Carbamazepine** as an example	Avoid use **or reduce!**
Patients Taking 300 mg of ABILIFY MAINTENA	
Strong CYP2D6 or CYP3A4 inhibitors	200 mg
CYP2D6 and CYP3A4 inhibitors	160 mg
CYP3A4 inducers	Avoid use

Dr stopped here, Good luck!

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.**