



Artery Academy

Done By Hawazen

Antipsychotic Drugs

Pharmacology II
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Psychosis and Schizophrenia

- The term “**psychosis**” denotes a variety of **mental disorders** caused by some inherent dysfunction of the brain including schizophrenia and bipolar disorder.
- **Schizophrenia** is a particular type of psychosis; it is characterized by delusions (false beliefs), hallucinations (often in the form of voices), and thinking or speech disturbances.
- Schizophrenia often initially affects people during late adolescence or early adulthood.
- It is considered to be a neurodevelopmental disorder. This implies that structural and functional changes in the brain are present even in utero in some patients, or that they develop during childhood and adolescence, or both. Schizophrenia has a strong genetic component.

"Antipsychotic Drugs"

"الأدوية النفسية"

mental disorders (مشاكل عقلية)

مصطلح "psychosis" هو خلل وظيفي متأصل في الباطن ينتج عنه مجموعتان الاضطرابية العقلية.

مصطلح "Schizophrenia" يعتبر نوع من أنواع psychosis، وينتج عنه بعض الأعراض مثل إنه يشعر بالرفض

بالأوهام والهوسة واضطرابات ما هيئة في التفكير والكلام (الانفصام)

والانفصام يستهدف عادة الأشخاص في مرحلة الشباب (المراهقة) أو في بداية البلوغ

يعتبر الانفصام مرض من نفسية غالباً وراثي، والطفل وهو في بطن أمه حدث مشكلة في الخلية الجذرية

الانفصام

"Schizophrenia Symptoms"

الأعراض

Positive Symptoms

Hallucination and delusions

الهوسة والأوهام

(معنى positive و negative مثل إنه أعراض

عالمية وأعراض منجحة، معناه إنه إذا positive

إنه أعراض زائفة على مرضي Schizophrenia)

وغالباً أغلب الأدوية تنفع لل positive symptoms

(سهل نعالها كونترول)

* ملاحظة يادكاره (١)

هاد مرض مثل الانفصام يلي إحنا يعرفه لك، مثل

مرض إنه الشخص يكون إليه شخصيتين، عادي

إليه شخصيته وحدة وعنده الأعراض يلي ذكرتها

هداك مرض ثاني تماماً، عافانا الله وإياكم

Negative Symptoms

- Anhedonia

← الشخص الطبيعي غالباً لما يحدث الأشياء

ببساطة يبتسم، أما بالنقص ما يشعر بالسعادة

أبداً.

- Apathy

← شخص غير مهتم أو مبالٍ (مافي حماس

للحياة)

- Impaired attention

← ما يقف على لتفاصيل

- Cognitive impairment

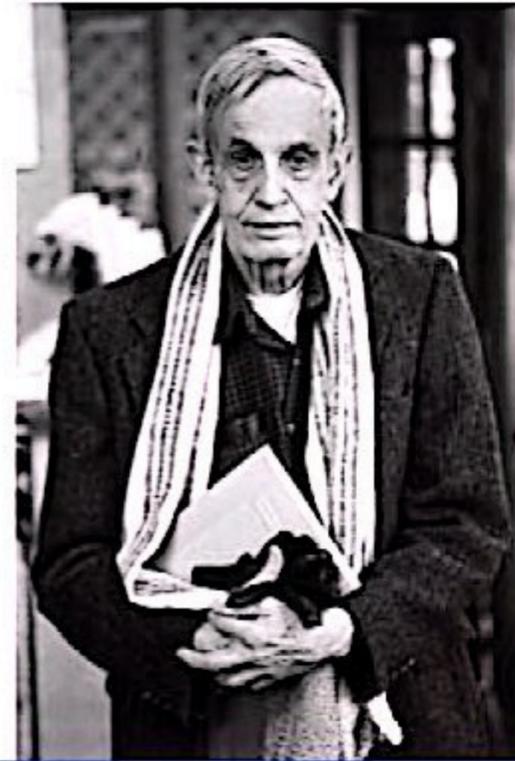
← ضعف بالادراك

- Social isolation

← مثل إجتماعي بالمرارة

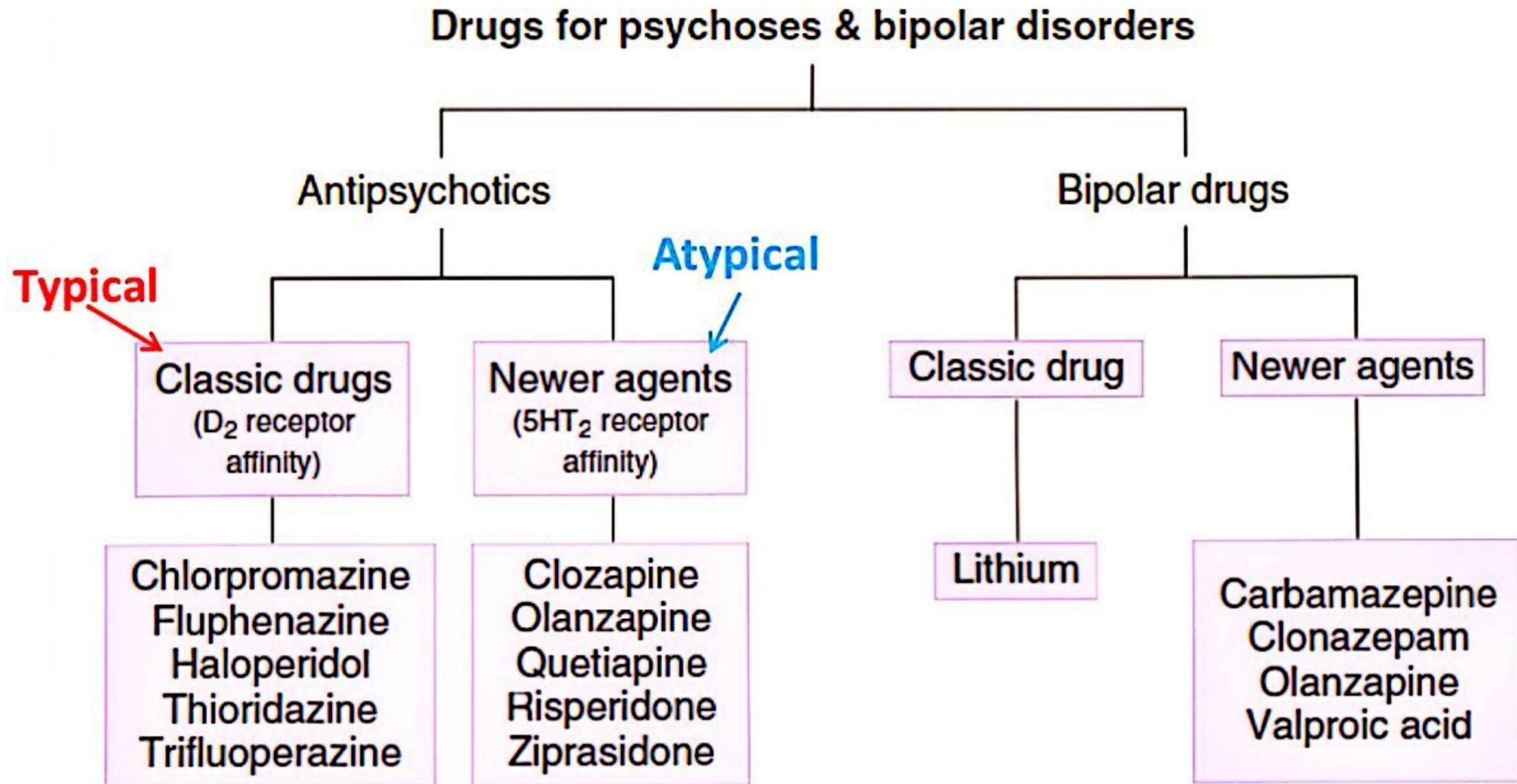
Schizophrenia Symptoms

- Positive symptoms:
 - Hallucinations and delusions
- Negative symptoms:
 - Anhedonia (not getting pleasure from normally pleasurable stimuli)
 - Apathy (lack of interest, enthusiasm or concern)
 - Impaired attention
 - Cognitive impairment
 - Social isolation



John Nash, an American mathematician and joint winner of the 1994 Nobel Prize for Economics, who had schizophrenia

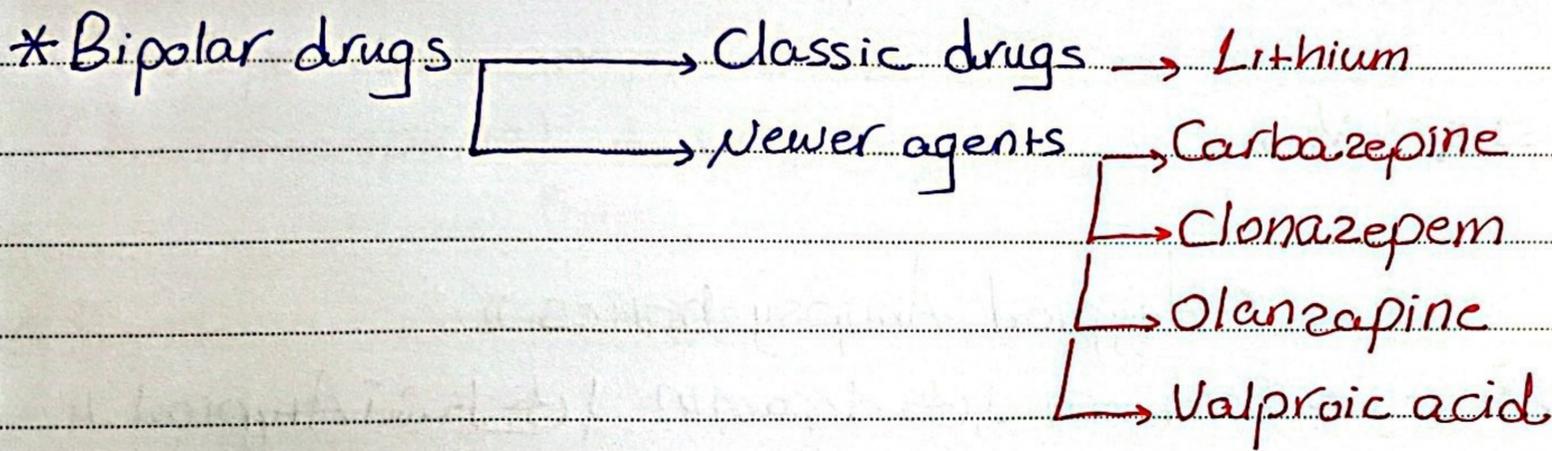
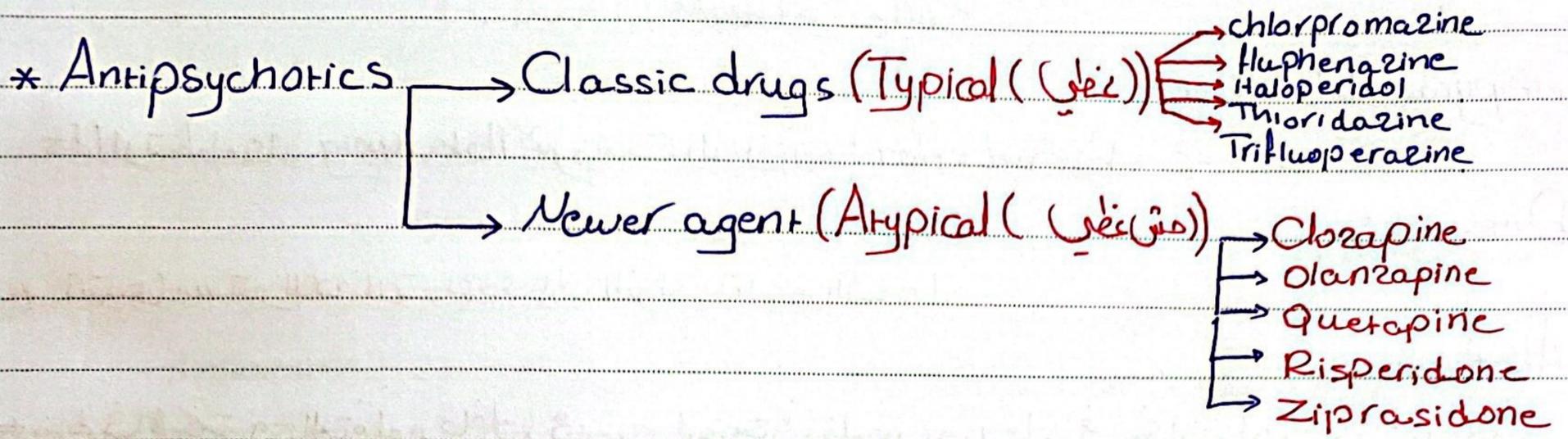
Antipsychotic Agents



Antipsychotic Agents

- The antipsychotic drugs are used in schizophrenia and are also effective in the treatment of other psychoses and agitated states.
 1. Older (classical or **typical**) drugs have high affinity for dopamine **D2 receptors**.
 2. Newer (**atypical**) antipsychotic drugs have greater affinity for **serotonin 5-HT2 receptors**.
- Although schizophrenia is not cured by drug therapy, the symptoms, may be ameliorated by antipsychotic drugs.

Antipsychotic Agent



الفرق بين Older و Newer

Older → have a high (D_2 receptors) dopamine res. blocking affinity

Newer → high and greater affinity for Serotonin 5-HT₂ receptors.

بشكل عام، لا يتم علاجهم بشكل جيد عن طريق الأدوية، ولكن يتم فيها تخفيف الأعراض على الأقل!

Typical Antipsychotics

- Typical antipsychotics are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blocking of D₂ dopamine receptors.
- They are more likely to be associated with **movement disorders (Extrapyramidal symptoms)**, particularly for drugs that bind tightly to dopaminergic neuroreceptors, such as **haloperidol**, and less true of medications that bind weakly, such as **chlorpromazine**.

FIRST-GENERATION ANTIPSYCHOTIC (low potency)

Chlorpromazine THORAZINE

Prochlorperazine COMPAZINE

Thioridazine MELLARIL

FIRST-GENERATION ANTIPSYCHOTIC (high potency)

Fluphenazine PROLIXIN

Haloperidol HALDOL

Pimozide ORAP

Thiothixene NAVANE

Side Effects

1. Reversible neurologic effects

- Dose-dependent **extrapyramidal effects** occur with chronic treatment which include:
 1. **Dystonias** (sustained contraction of muscles leading to twisting, distorted postures)
 2. **Akathisia** (unpleasant sensations of inner restlessness that manifests itself with an inability to sit still or remain motionless)
 3. **Parkinson-like symptoms** (bradykinesia, rigidity, and tremor)



Atypical Antipsychotics

- Atypical antipsychotics have fewer extrapyramidal symptoms (EPS) than the first-generation agents, but are associated with a higher risk of **metabolic side effects**, such as diabetes, hypercholesterolemia, and weight gain.
- They appear to owe their unique activity to **blockade** of both serotonin and dopamine (and, perhaps, other) receptors.
- Consistent differences in therapeutic efficacy among the individual atypical drugs have not been established.
- These **atypical** antipsychotic drugs may be somewhat more effective and less toxic than the older drugs. However, they are much more costly than standard older drugs.

SECOND GENERATION ANTIPSYCHOTIC

Aripiprazole ABILIFY

Asenapine SAPHRIS

Clozapine CLOZARIL

Iloperidone FANAPT

Lurasidone LATUDA

Olanzapine ZYPREXA

Quetiapine SEROQUEL

Paliperidone INVEGA

Risperidone RISPERDAL

Ziprasidone GEODON

"Side effects"

Extrapyramidal effects

كلما ارتبطوا مع blockin أكثر زادت الأعراض و side effect من :-

① Dystonias

* تمتص مسقر للدماغ يؤدي إلى التواء وتشويه الأعضاء

② Akathisia

* فرط في الحركة وسرعة قلبه داخل في عدم الرغبة في الجلوس والبقاء في مكان واحد دون حركة

③ parkinson.

* بطئ الحركة، تصلب، رعاش

« Atypical Antipsychotics »

ال Atypical تشتغل على dopamin و serotonin بحيث تقلل blockade

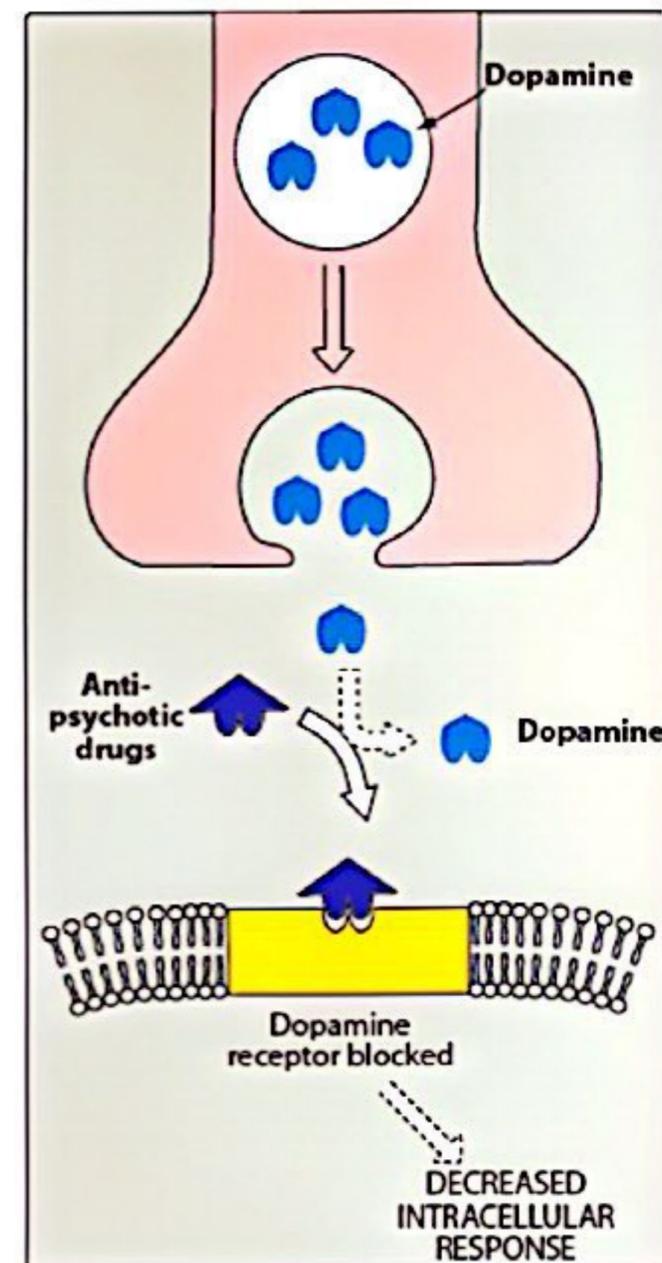
ال metabolic side effect مثل diabetes, hypercholesterolemia, weight gain

تعتبر هذه الأدوية Less toxic أكثر من older drugs وسعواتها

Mechanism of Action

1. Dopamine receptor–blocking activity in the CNS:

- All of the **typical** and most of the **atypical** antipsychotic drugs block dopamine receptors in the brain and the periphery.
- The therapeutic efficacy of the older antipsychotic drugs correlates with their relative affinity for the D2 receptor.
- Unfortunately, there is also a correlation between blockade of D2 receptors and **extrapyramidal dysfunction**.



Mechanism of Action

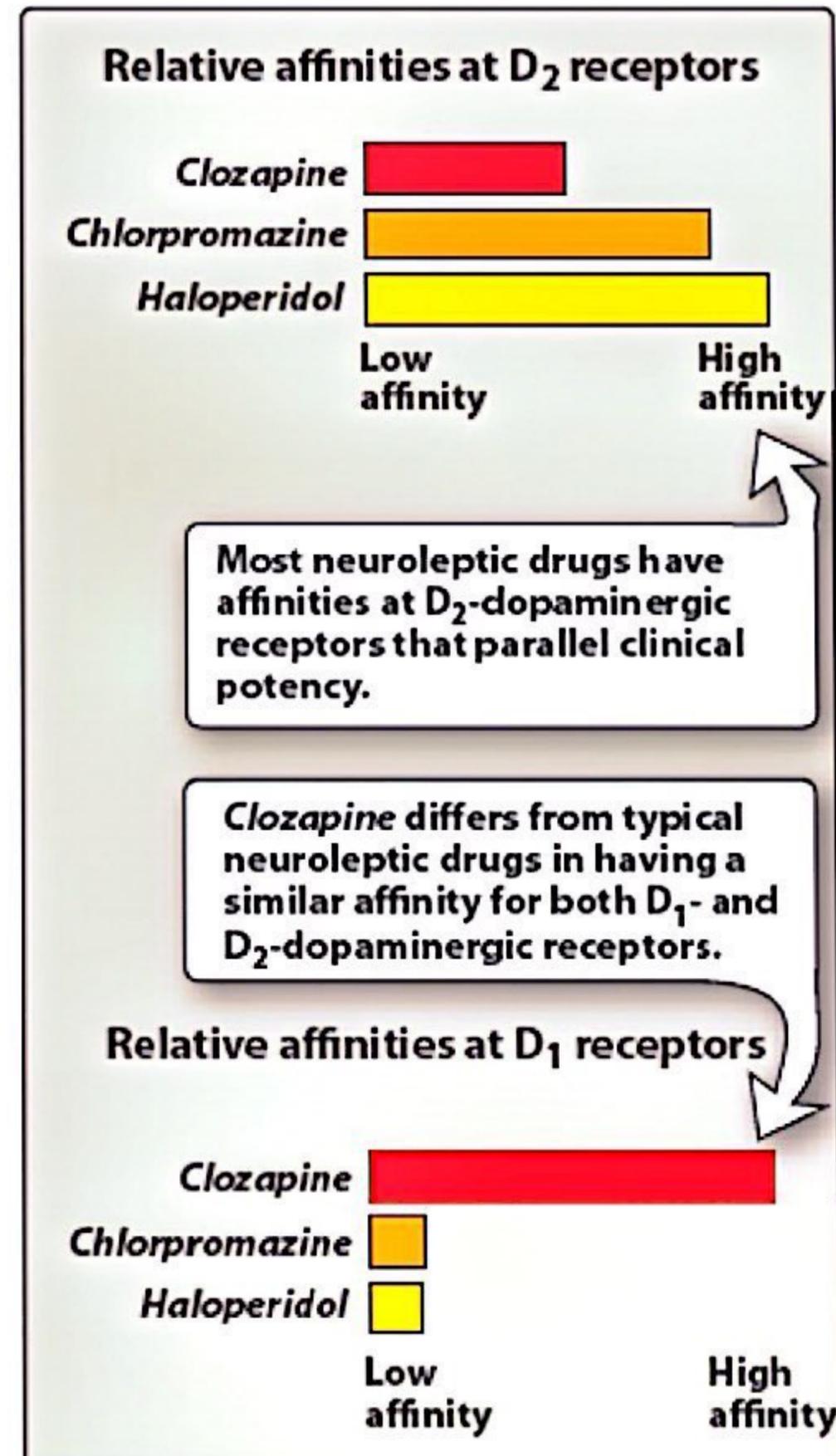
1. Dopamine receptor–blocking activity in the CNS:

- The actions of the antipsychotic drugs are antagonized by:
 - agents that raise synaptic dopamine concentrations (for example, levodopa and amphetamines)
 - or mimic dopamine at post-synaptic binding sites (for example, bromocriptine).

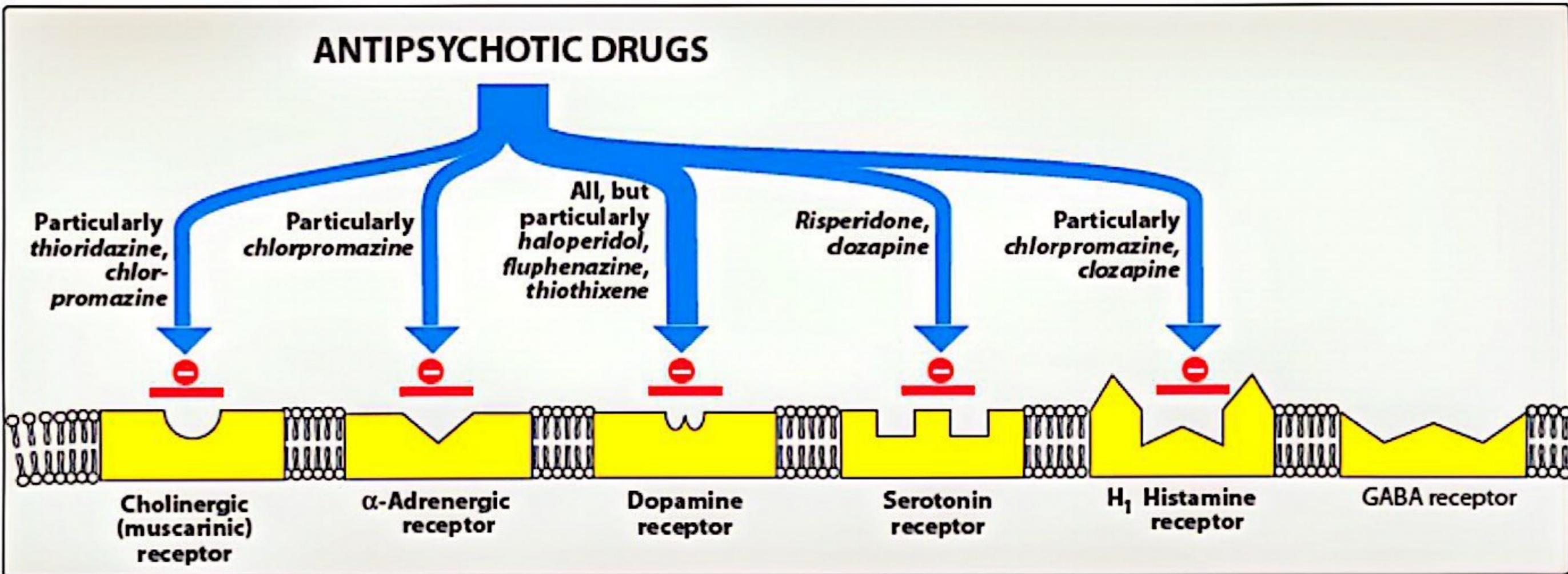
Mechanism of Action

2. Serotonin receptor–blocking activity in the CNS:

- Most of the **atypical** agents appear to exert part of their unique action through inhibition of serotonin receptors (5-HT), particularly 5-HT_{2A} receptors.
- Clozapine has high affinity for D₁, D₄, 5-HT₂, muscarinic, and α-adrenergic receptors, but it is also a weak dopamine D₂-receptor antagonist.



Actions of Antipsychotic Drugs



"Mechanism of action"

Atypical and typical block dopamine receptors

extrapyramidal effect كلما زاد ارتباطهم زادت نسبة يمسرعني

* Dopamine receptor-blocking activity in the CNS:-

بما انه الادوية هاي تقل block للدوبامين، بالتالي، الادوية يلي تزيد من dopamine، وتركيزها هو المذكور بالسلايدات.

(Levodopa and amphetamines) ← تزيد من تركيزه

(bromocriptine) ← تقلل الدوبامين في موقع الارتباط

* Serotonin receptor-blocking activity in the CNS:-

(Clozapine) has high affinity for D₁, D₄, 5-HT₂ muscarinic and α-adrenergic receptors

Atypical ← فقط لا

Absorption and Metabolism

- The antipsychotic drugs are well absorbed when given orally, and because they are lipid soluble, they readily enter the CNS and most other body tissues (have a large volume of distribution), and bind well to plasma proteins.
- These drugs require metabolism by liver enzymes before elimination and have long plasma half-lives that permit once-daily dosing.
- **Parenteral** forms of many agents (eg, fluphenazine, haloperidol) are available for both rapid initiation of therapy and depot treatment.

Absorption and Metabolism

Long-acting Injectable (LAI) formulation:

- Fluphenazine decanoate, haloperidol decanoate, risperidone microspheres, paliperidone palmitate, and olanzapine pamoate are long-acting injectable (LAI) formulations of antipsychotics that are administered via intramuscular injection.
- These formulations have a therapeutic duration of action of up to **2 to 4 weeks** and, therefore, are often used to treat outpatients and individuals who are noncompliant with oral medications.

Absorption and Metabolism

← تنعش الأدوية antipsychotic وتمتص بشكل oral وهي قابلة للذوبان في الدهون وسهلة
الذوبان إلى CNS وللشعبه الاخرى في جسم البشري الدم
and bind well to plasma proteins.

← وطبعًا كونها تؤخذ orally يمر عبر طبعًا metabolism بواسطة إنزيمات كبدا، و half-life
تأخر طويلاً لذلك يحتمل جرعة واحدة يوميًا

← يوجد بعض الأدوية تنعش Parenteral مثل Haloperidol, Fluphenazine

* Long-acting Injectable (LAI) Formulation:

هي عبارة عن تركيبة حقن طويلة الأمد وهي غالبًا تنعش Intramuscular (IM)
(مذكور أسماء الأدوية)

هذه المستحضرات ولحقن مدتها علاجية 2-4 أسابيع وهي للمرضى outpatients أو يلقى
ما يقدرها يشربوا الأدوية عن طريق الفم

Clinical Uses

1. Antipsychotic actions:

- All of the antipsychotic drugs can reduce the hallucinations and delusions associated with schizophrenia (the so-called “positive” symptoms) by blocking dopamine receptors in the mesolimbic system of the brain.
- The “negative” symptoms are not as responsive to therapy, particularly with the typical antipsychotics. Many second-generation (atypical) agents, ameliorate the negative symptoms to some extent.
- The antipsychotics are considered to be the only efficacious treatment for schizophrenia. The antipsychotic effects usually take several days to weeks to occur.
- Not all patients respond, and complete normalization of behavior is seldom achieved.

Clinical Uses

Drug Selection:

- Current antipsychotic therapy commonly comprises atypical agents to minimize the risk of debilitating movement disorders associated with the typical drugs that act primarily at the D₂ dopamine receptor.
- All of atypical antipsychotics exhibit an efficacy that is equivalent to, and occasionally exceeds, that of the typical antipsychotic agents.
- Individual patient response and comorbid conditions must often be used as a guide in drug selection.
- Further, atypical antipsychotics should not be considered interchangeable because patients may respond differently to each drug in this class.

Clinical Uses

Refractory patients:

- Approximately 20% of patients with schizophrenia will have an insufficient response to all typical and atypical antipsychotics.
- For these patients, **clozapine** has shown to be an effective antipsychotic with minimal risk of EPS. However, its clinical use is limited to refractory patients because of serious side effects.
- Clozapine can produce:
 - Bone marrow suppression
 - Seizures
 - Cardiovascular side effects.
 - Severe agranulocytosis which necessitates frequent monitoring of white blood cell counts.

Clinical Uses

2. Other psychiatric and neurologic indications

- The newer antipsychotic drugs are often used with lithium in the initial treatment of mania.
 - **Mania:** An abnormally elevated mood state characterized by such symptoms as inappropriate elation, increased irritability, severe insomnia.
- Several second generation antipsychotics are approved for maintenance treatment of **bipolar disorder**. They appear more effective in preventing mania than in preventing depression.

Clinical Uses

3. Antiemetic effects:

- Most older typical antipsychotic drugs, with the exception of thioridazine, have a strong **antiemetic** effect.
- This action is due to dopamine-receptor blockade, both centrally (in the chemoreceptor trigger zone of the medulla) and peripherally (on receptors in the stomach).
- The atypical antipsychotic drugs are not used as antiemetics.

((Clinical uses))

« 20% من المرضى تعاون الفهم عندهم الاستجابة غير كافية بتأثير جميع الأدوية، إلا أن نوعها
عشان هيك عندي دوا Clozapine يمكن يستجيبوا ههول، لكن عندهم لها ادوار
ليس مشكلت هي Side effect تابعته وهي تشمل الاعراض المذكورة بالسلايدارث
ومنها الآثار الجانبية القلبية او اثنية وغيرها.

* Other psychiatric and neurologic indications

يعتبر هذا المرض من الامراض النفسية يلي يرافقه تقلب المزاج بشكل غير طبيعي ابدأ (mania)
وايضاً اذره شديد.

عنت الموافقة على اعيد من هاي الأدوية حتى تعالج الاضطراب (bipolar disorder)
الساني، أكثر متابعته في ازالة الهوس و منع الاكتئاب.

هاي الأدوية يلي هي newer antipsychotic drugs تستخدم مع الليثيوم لتعالج manic

* Antiemetic effects :- ماله دخل بالنفسيته

استثناء Thioridazine، تعتبر كل ادمعظم الأدوية older typical anti لها تأثير قوي مضاد للقيء.
علاوة انه لا تستخدم ابدأ كمضادات للقيء.

Side Effects

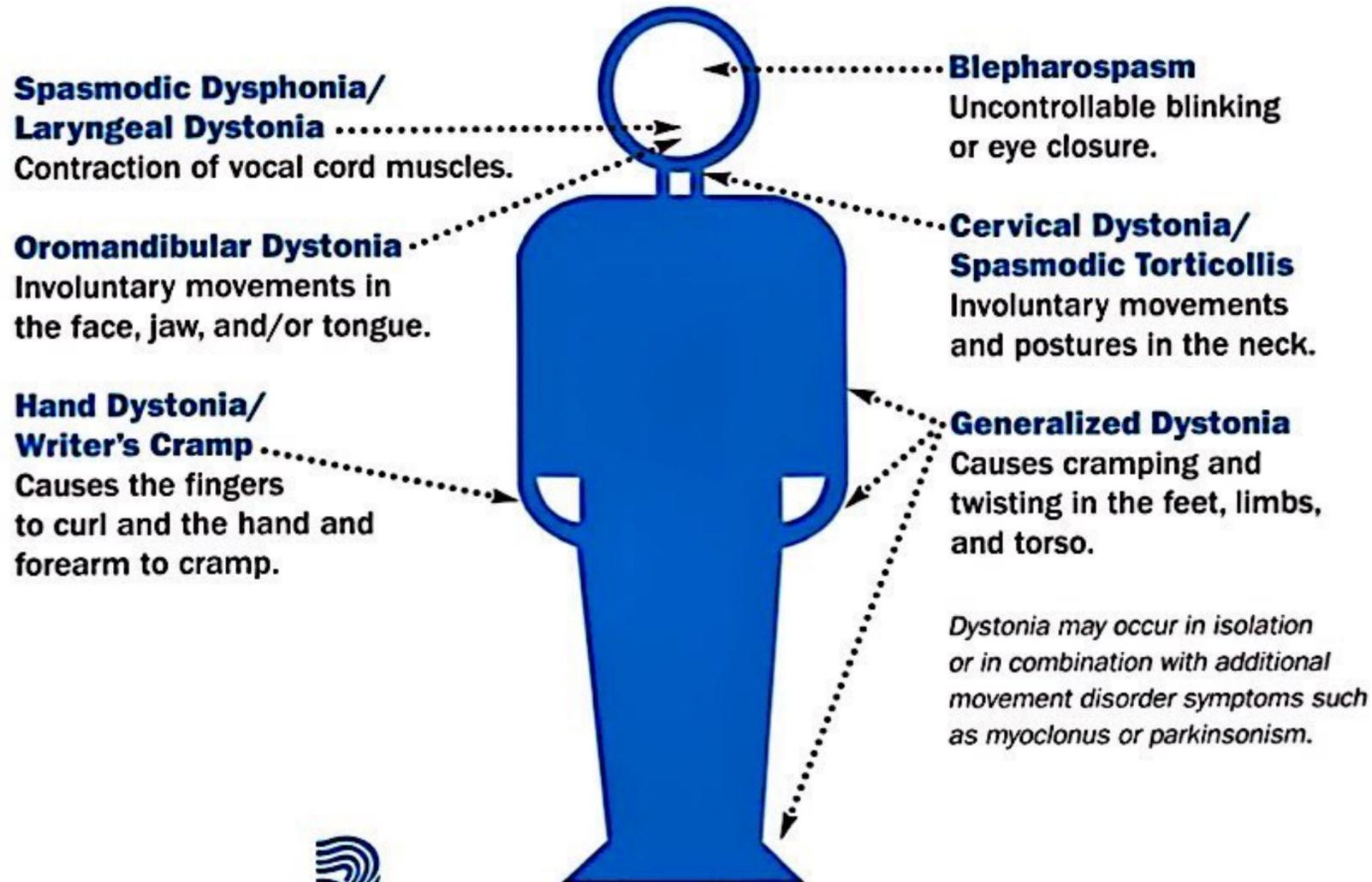
1. Reversible neurologic effects

- Dose-dependent **extrapyramidal effects** occur with chronic treatment which include:
 - **Dystonias** (sustained contraction of muscles leading to twisting, distorted postures)
 - **Akathisia** (unpleasant sensations of inner restlessness that manifests itself with an inability to sit still or remain motionless)
 - **Parkinson-like symptoms** (bradykinesia, rigidity, and tremor)



Understanding Dystonia

Dystonia is a disorder that causes muscles in the body to contract and spasm involuntarily.



**DYSTONIA
MEDICAL
RESEARCH
FOUNDATION**

-serving all dystonia-affected persons

MORE INFORMATION:

Dystonia Medical Research Foundation (DMRF)

Web: <http://www.dystonia-foundation.org>



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Side Effects

- The maximal risk of appearance of the movement disorders is time and dose dependent:
 - Dystonias occur within a **few hours** to days of treatment,
 - Akathisia occurring within **days to weeks**.
 - Parkinson-like symptoms usually occur within **weeks to months** of initiating treatment.
- Blocking of **dopamine** receptors in the **nigrostriatal** pathway probably causes these unwanted movement symptoms.
- The atypical antipsychotics exhibit a lower incidence of these symptoms.

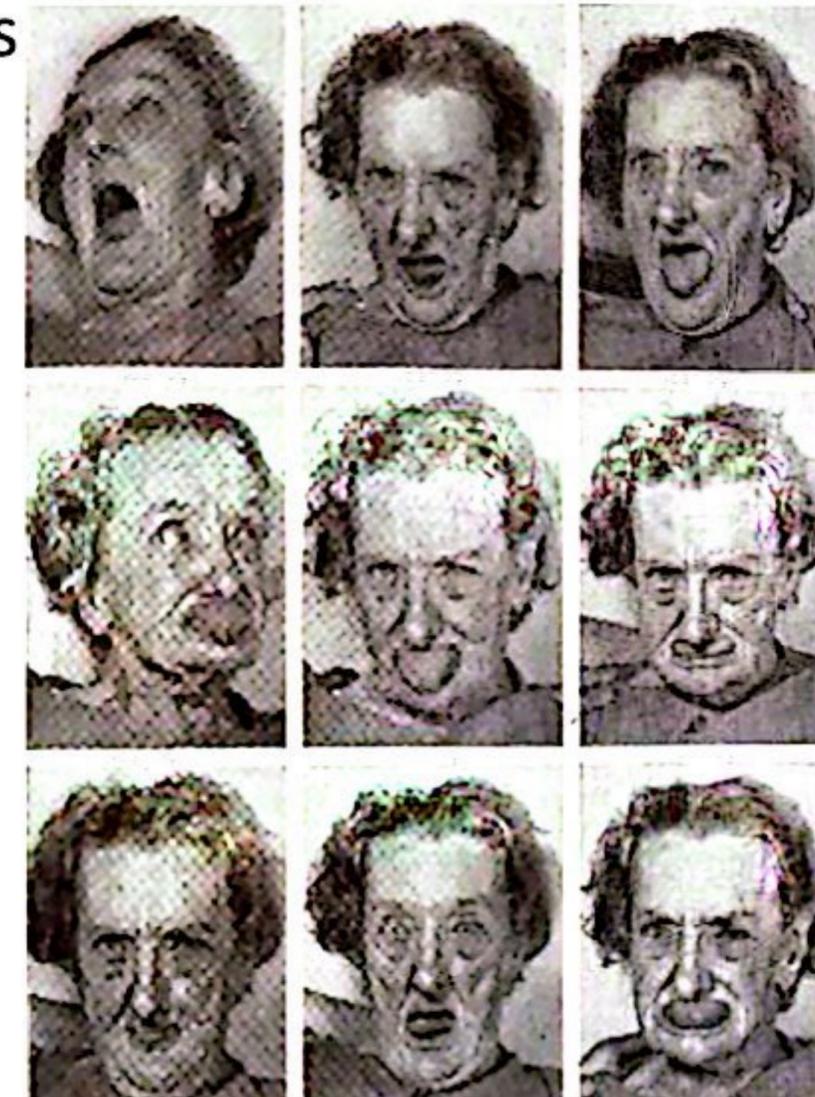
Side Effects

- The inhibitory effects of dopaminergic neurons are normally balanced by the excitatory actions of cholinergic neurons in the striatum. Blocking dopamine receptors alters this balance, causing a relative excess of cholinergic influence, which results in extrapyramidal motor effects.
- If cholinergic activity is also blocked, a new, more nearly normal balance is restored, and extrapyramidal effects are minimized. This can be achieved by administration of an **anticholinergic drug**, such as benztropine. But this will be in exchange for the side effect of muscarinic-receptor blockade.

Side Effects

2. Tardive dyskinesia

- This important toxicity includes movements of the muscles of the lips and buccal cavity and may be irreversible.
- Tardive dyskinesias tend to develop after several years of antipsychotic drug therapy but have appeared as early as 6 months.
- **Antimuscarinic drugs** that usually ameliorate other extrapyramidal effects generally **increase** the severity of tardive dyskinesia symptoms.



Side Effects

3. Anticholinergic effects:

- Some of the antipsychotics, particularly thioridazine, and olanzapine, produce anticholinergic effects, including:
 - Blurred vision
 - Dry mouth (the exception is clozapine, which increases salivation)
 - Confusion
 - Inhibition of gastrointestinal and urinary tract smooth muscle, leading to constipation and urinary retention.
- This anticholinergic property may actually assist in reducing the risk of EPS with these agents.

Side Effects

4. Other effects:

- Blockade of α -adrenergic receptors causes **orthostatic hypotension**.
- The antipsychotics also alter temperature-regulating mechanisms and can produce **poikilothermia** (condition in which body temperature varies with the environment).
- In the pituitary, antipsychotics block D_2 receptors, leading to an **increase in prolactin** release (dopamine is the normal inhibitory regulator of prolactin secretion). Second-generation antipsychotics are less likely to produce prolactin elevations.

Side Effects

4. Other effects:

- **Sedation** occurs with those drugs that are potent antagonists of the H₁-histamine receptor.
- Significant **weight gain** and **hyperglycemia** due to a diabetogenic action occur with several of the atypical agents, especially clozapine and olanzapine.

TABLE 29–2 Adverse pharmacologic effects antipsychotic drugs.

Type	Manifestations	Mechanism
Autonomic nervous system	Loss of accommodation, dry mouth, difficulty urinating, constipation Orthostatic hypotension, impotence, failure to ejaculate	Muscarinic cholinergic blockade α -Adrenoceptor blockade
Central nervous system	Parkinson's syndrome, akathisia, dystonias Tardive dyskinesia Toxic-confusional state	Dopamine-receptor blockade Supersensitivity of dopamine receptors Muscarinic blockade
Endocrine system	Amenorrhea-galactorrhea, infertility, impotence	Dopamine-receptor blockade resulting in hyperprolactinemia
Other	Weight gain	Possibly combined H_1 and $5-HT_2$ blockade

Monitoring Antipsychotics S/E

Antipsychotics	Sedation	EPS	Weight gain	Prolactin	DM	Lipid
Aripiprazole	+	+	+	+	+	+
Chlorpromazine	++++	+++	++	+++	-	-
Clozapine	++++	+	++++	+	+++	+++
Fluphenazine	+	++++	+	++++	-	-
Haloperidol	+	++++	+	++++	-	-
Olanzapine	++	++	++++	+	+++	+++
Quetiapine	++	+	++	+	+	+
Risperidone	+	++	++	++++	++	++

Tandon R. Safety and tolerability: how do newer generation "atypical" antipsychotics compare? Psychiatr Q 2002;73:297-311.

زَهَقْتُوا بِأَقْتَمِ بِاللَّحُونِ

"Side effect"

* (سلايد تكرار)

* The maximal risk of appearance of the movement disorders is Time and Dose dependent :-

علاج هاي Side effect ، الفاعل يتعال منها ويرجع balance الجسم للإنسان :

مثل Dystonias تتأخر few hours

AKathrisias تتأخر days to weeks

parkinson تتأخر weeks to months

2- Tardive dyskinesia

3- Anticholinergic effect:

~~Side~~ lanszapine, Thiodazine etc
:- side effect مثل :-

① دؤبة مشوشة

③ ارتباك

② عفاف بالعم

④ إمساك و إبتها بالبول

4- other effect

← تحدث زيادة آيسرة بالعوزن وارتفاع في السكر (في الدم) بسبب تأثير مسبب مرض السكر

Cautions and contraindications

- All antipsychotics may lower the seizure threshold and should be used cautiously in patients with seizure disorders.
- The high incidence of agranulocytosis with clozapine may limit its use to patients who are resistant to other drugs.
- Antipsychotics used in patients with mood disorders should also be monitored for worsening of mood and suicidal ideation or behaviors.

TABLE 29-4 Dose relationships of antipsychotics.

	Minimum Effective Therapeutic Dose (mg)	Usual Range of Daily Doses (mg)
Chlorpromazine	100	100-1000
Thioridazine	100	100-800
Trifluoperazine	5	5-60
Perphenazine	10	8-64
Fluphenazine	2	2-60
Thiothixene	2	2-120
Haloperidol	2	2-60
Loxapine	10	20-160
Molindone	10	20-200
Clozapine	50	300-600
Olanzapine	5	10-30
Quetiapine	150	150-800
Risperidone	4	4-16
Ziprasidone	40	80-160
Aripiprazole	10	10-30

"Cautions and contraindications"

⚠ (تحذيرات وموانع)

⚡ يجب استخدام الـ antipsychotics بحذر في المرضى الذين يعانون من اضطرابات تنوبارية

⚡ ارتفاع معدل وجود الـ agranulocytosis مع الـ Clozapine يؤدي إلى ارتفاع المقاومة لدى المرضى للأدوية المضوية

⚡ يجب مراقبة الجوع والاضطرابات الحسنة للمرضى الذين يعانون من اضطرابات الجوع

* في نظام دعواتكم يا أحياب
وساخو نيلو لم أحسن لتفني
إن أحسنت فمن الله
وإن أسأت فمن نفسي
والشيطان

Questions??



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