	Typical Anti-psychotics		Atypical Anti-psychotics
	High potency	Low potency	
Examples	**Haloperidol**	**Chlorpromazine**	**Clozapine, olanzapine, risperidone, aripiprazole**
Affinity	**D2R ≥ 5HT-2R**		**D2R < 5HT-2R**
MOA	-Inhibit 4 DA Pathways -Block M1, H1, α1 **(Low potency drugs)** -Excellent correlation between the clinical potency and their affinity for D2R -Block D2R in **mesolimbic pathway**→ ↓positive symptoms -Block D2R in **nigrostriatal pathway** (basal ganglia)→ Extrapyramidal symptoms (EPS)		Block 5HT-2R in **mesocortical pathway**→ ↑DA → ↓negative symptoms
Pharmacological effects	**Delayed effect** (after 6 weeks) and Mechanism isn't fully understood		
When the drug is first taken	**↑↑DA synthesis and release**→ Compensatory to acute block of D2R		
During treatment	**Continued block of D2R**→↓DA release **"Depolarization blockade"** in **nigrostriatal** and **mesolimbic** neurons→ improvement in positive symptoms & causes EPS		
Finally	**↓DA release caused by Depolarization blockade**→ Up-regulation & Hypersensitivity of D2R→ **Tardive Dyskinesia**		

S/E		
Autonomic S/E **(Low Potency drugs)**	-**Block M1**→ Atropine-like action -**Block α-1**→ Dizziness, orthostatic hypotension, reflex tachy -**Block H1**→ Sedation & weight gain	
Block D2R in Nigrostriatal Pathway **(High potency drugs)**	**EPS** (most disturbing)	
Block D2R in Tubero-infundibular Pathway	**↑Prolactin**→ Gynecomastia , irregular menstrual cycle	
Jaundice	**Chlorpromazine**	
Pigment retinopathy & Cardiac toxicity	**Thioridazine** (Low potency drug)	
Neuroleptic malignant syndrome **(Caused by↓↓↓DA)**	-Potentially **fatal**, associated with high doses -Fever, muscle rigidity, sweating, confusion, and cardiovascular collapse & ↑ creatinine kinase (CK). **-Associated with high mortality rate (need immediate TTT):** 1) Stop anti-psychotic drug 2) Start DA receptor agonist **(bromocriptine)** & skeletal muscle relaxant **(dantrolene)**	
		Agranulocytosis → **Clozapine** (WBCs must be weekly monitored)
		Increased prolactin **QT prolongation** → **Risperidone**
		Autonomic S/E → **-Olanzapine** **-Clozapine**
		EPS **(Less compared to typical)** → **aripiprazole**

Individual differences with Atypical antipsychotics	
Clozapine	**-Block 5-HT2 Rs and D4 Rs** **-Associated with fatal agranulocytosis** → during the first-year of TTT → requires weekly monitoring of WBCs counts during the first 6 months of therapy → then every two weeks
Olanzapine	**like clozapine, but :** - has fewer autonomic side effects & No agranulocytosis
Risperidone	**like olanzapine, but:** -Cause a **higher incidence of EPS.** **+Other S/E**
Aripiprazole	**Partial agonist** at **D2R** and **5-HT1 R** but a **5-HT2 R antagonist**

	Extra-Pyramidal Symptoms (EPS)	
Features	**-Delayed** →after months - years of treatment **-Results from supersensitivity** to dopamine after long-term D2R blockers -Can be **irreversible** **-Not easily managed** → use drug in the lowest doses for the shortest period	
Examples	**Acute Effects:** akathisia, pseudoparkinsonism, and dystonia **(Occurs in 2nd stage of pharmacological effects)**	
	Tardive dyskinesia (Occurs in 3rd stage of pharmacological effects)	
TTT	**Acute Effects**	1) Lower the antipsychotic dose 2) Change to an atypical antipsychotic **3) Administer a drug to counteract these effects : benztropine** and/or **amantadine** (weak dopamine releaser)
	Tardive dyskinesia	**-Not easily managed** 1) Lower the antipsychotic dose **2) Valbenazine:** -Approved for the treatment of tardive dyskinesia -Vesicular monoamine transporter (VMA) type 2 inhibitors -Act centrally to deplete DA storage in presynaptic vesicles.

	High-Potency Typical	Low-Potency Typical	Atypical
EPS S/E	+++	+	+
ANS S/E	+	+++	++
Positive symptoms	✓	✓	✓
Negative symptoms	✗	✗	✓✓✓

Treatment considerations

-Atypical antipsychotic drugs (except clozapine) (1st Line):
Compared to typical drugs → they produce a lower incidence of EPS and more effective against the negative symptoms.

-Patients exhibit improvement of positive symptoms during the first 2 weeks of therapy → the maximal response after 6 weeks → then it is possible to reduce the dosage **(maintenance therapy)**.

-Usually continued for at least 12 months after the remission of acute psychotic symptoms → then either a **low-dose regimen** or **gradual withdrawal** of the drug is considered → **reduce risk of Tardive dyskinesia**.

-Should be **tapered slowly** before discontinuation → abrupt discontinuation can cause **withdrawal symptoms** → insomnia, nightmares, restlessness, GIT upset, salivation, and sweating.