

**SECOND -GENERATION ANTIPSYCHOTIC  
AGENTS**

or

**ATYPICAL ANTIPSYCHOTICS**

## *second-generation antipsychotic agents*

- Second generation antipsychotics have weak D2 blocking but potent 5-HT<sub>2</sub> antagonistic activity. Extrapyramidal side effects are minimal, and they may improve the impaired cognitive function in psychotics.

# Clozapine

- First atypical antipsychotic agent; Weak D2 blocking action; few/no extrapyramidal effects
- Both -ve and +ve symptoms of schizophrenia are improved; **used as a reserve drug in resistant schizophrenia.**
- The differing pharmacological profile may be due to its relative selectivity for D4 receptors (which are sparse in basal ganglia) and additional 5-HT<sub>2</sub> as well as a blockade.
- Clozapine is metabolized primarily by CYP3A4 with an average t<sub>1/2</sub> of 12 hours. Its major limitation is higher incidence of **agranulocytosis** (0.8%) and other blood dyscrasias; weekly monitoring of leucocyte count is required. High dose can induce seizures even in nonepileptics. Other side effects are sedation, unstable BP, tachycardia, urinary incontinence, weight gain and precipitation of diabetes.

**Agranulocytosis is a rare condition that occurs when the bone marrow does not make enough neutrophils**

# Risperidone

- Combination of D2 + 5-HT2 receptor blockade.
- In addition it has high affinity for  $\alpha_1$ ,  $\alpha_2$  and H1 receptors; blockade of these may contribute to efficacy as well as side effects like postural hypotension.
- Risperidone is **more potent D2 blocker than clozapine**; extrapyramidal side effects are less only at low doses ( <6 mg/day). Prolactin levels rise during risperidone therapy, but it is less epileptogenic than clozapine.
- Caution: increased risk of stroke in the elderly.

# Olanzapine

(broader spectrum of efficacy covering schizo-affective disorders)

- resembles clozapine in blocking multiple monoaminergic (D2, 5-HT2,  $\alpha_1$ ,  $\alpha_2$ ) as well as muscarinic and H1 receptors. Both positive and negative symptoms of schizophrenia appear to be benefited.
- A broader spectrum of efficacy covering schizo-affective disorders, and it is approved for use in mania. Monotherapy with olanzapine may be as effective as a combination of lithium/valproate + benzodiazepines.
- Weaker D2 blockade results in few extrapyramidal side effects and little rise in prolactin levels.
- Incidence of stroke may be increased in the elderly.
- Agranulocytosis has not been reported with olanzapine.
- Olanzapine is metabolized by CYP1A2 and glucuronyl transferase. The  $t_{1/2}$  is 24-30 hours.

# Quetiapine

- This new short-acting ( $t_{1/2}$  is 6 hours) atypical antipsychotic requires twice daily dosing.
- It blocks 5-HT<sub>1A</sub>, 5-HT<sub>2</sub>, D<sub>2</sub>,  $\alpha_1$ ,  $\alpha_2$  and H<sub>1</sub> receptors in the brain, but D<sub>2</sub> blocking activity is low: extrapyramidal and hyperprolactinaemic side effects are minimal.
- ADR:
  - quite sedating, postural hypotension, urinary retention
  - Weight gain and rise in blood sugar are infrequent
- Use: benefit negative symptoms of schizophrenia, but can be used in mania /bipolar disorder.
- It is metabolized mainly by CYP3A4; can interact with macrolides, antifungals, anticonvulsants, etc.

Atypical antipsychotic agent	Distinctive features
<b>Aripiprazole</b>	<ul style="list-style-type: none"> <li>• partial agonist at D2 and 5-HT<sub>1A</sub> receptor</li> <li>• It is minimally sedating, may even cause insomnia</li> <li>• Metabolized by CYP2D6 and CYP3A4.</li> <li>• ADR: nausea, dyspepsia, constipation and light-headedness. hyperprolactinaemia, hypotension and Q-T prolongation are not frequent.</li> </ul>
<b>Ziprasidone</b>	<ul style="list-style-type: none"> <li>• D2 + 5-HT<sub>2A/2C</sub> + H<sub>1</sub> + α<sub>1</sub> receptor blocking activity.</li> <li>• Efficacy in schizophrenia has been related equivalent to haloperidol</li> </ul>
<b>Amisulpiride</b>	<ul style="list-style-type: none"> <li>• Congener of <i>sulpiride</i> (typical antipsychotic)</li> <li>• High affinity to D2 (and D3) receptor and has low affinity for 5-HT<sub>2</sub> receptor.</li> <li>• Not sedative.</li> </ul>
<b>Zotepine</b>	<ul style="list-style-type: none"> <li>• D1+D2 and 5-HT<sub>2</sub>, α<sub>1</sub> receptor blocking activity.</li> <li>• It also inhibits NA reuptake.</li> <li>• Both positive and negative symptoms of schizophrenia appear to be benefited.</li> <li>• It has lower seizure threshold.</li> <li>• ADR: Weight gain, hyperglycemia.</li> </ul>



Urinary retention



Postural hypotension



Weight Gain



Sexual dysfunction



Seizure



Arrhythmias and sudden cardiac death



Sedation

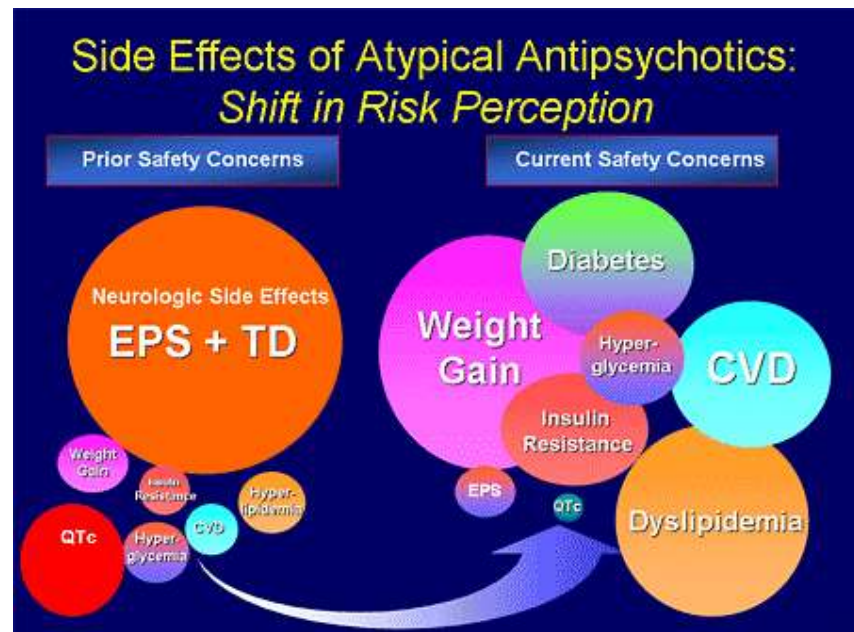


Dry mouth



Extrapyramidal symptoms

# Adverse events





## *Adverse events*

- CNS: Drowsiness, lethargy, mental confusion, weight gain (not with haloperidol), aggravation of seizures in epileptics.
- CVS: Postural hypotension, palpitation, inhibition of ejaculation (especially with thioridazine) are due to an adrenergic blockade; Q-T prolongation and cardiac arrhythmias are risk of overdose with thioridazine, pimozide and ziprasidone.
- Anticholinergic Dry mouth, blurring of vision, constipation, urinary hesitancy in elderly males.
- Endocrine Hyperprolactinemia (due to D2 blockade) is common with typical neuroleptics and risperidone. This can lower GH levels, but amenorrhoea, infertility, galactorrhoea and gynaecomastia occur infrequently after prolonged treatment.
- Metabolic effect: Elevation of blood sugar and triglyceride.

# Adverse events

- Extrapyramidal disturbances: Dose-limiting 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.
  - Parkinson-like symptoms of bradykinesia, rigidity, and tremor usually occur within weeks to months of initiating treatment. Tardive dyskinesia, which can be irreversible, may occur after months or years of treatment.
- Hypersensitivity reaction: Cholestatic jaundice, myocarditis, agranulocytosis.
- Miscellaneous: Weight gain often occurs with long term antipsychotic therapy; blood sugar and lipids may tend to rise. Risk of worsening of diabetes and blue pigmentation of exposed skin, and retinal degeneration.

**Tardive dyskinesia is a disorder that involves involuntary movements, especially of the lower face (tongue, lips, face, trunk, and extremities).**

# *Therapeutic uses*

- **Treatment of schizophrenia**
- **Prevention of severe nausea and vomiting**
- **Other uses:**
  - Treatment of mania, organic brain syndromes, anxiety.
  - Chlorpromazine is used to treat intractable hiccups.
  - Risperidone and haloperidol are also commonly prescribed for this tic disorder. Also, risperidone and aripiprazole are now approved for the management of the disruptive behavior and irritability secondary to autism (is a disorder of neural development characterized by impaired social interaction).

# -ve and +ve symptoms of schizophrenia

## Positive Symptoms

"Positive" refers to overt symptoms that should not be present. These include:

- Hallucinations
- Delusions
- Disorganized thoughts

## Negative Symptoms

"Negative" does not refer to a person's attitude, but instead to a lack of characteristics that should be present. These include:

- Reduced speech, even when encouraged to interact (alogia)
- Lack of emotional and facial expression (affective flattening)
- Diminished ability to begin and sustain activities (avolition)
- Decreased ability to find pleasure in everyday (anhedonia)
- Social withdrawal (asociality)

## Cognitive Deficits

Difficulties with following aspects of cognition can make it hard to live a normal life or earn a living:

- Memory
- Attention
- Planning
- Decision Making

[Back](#)