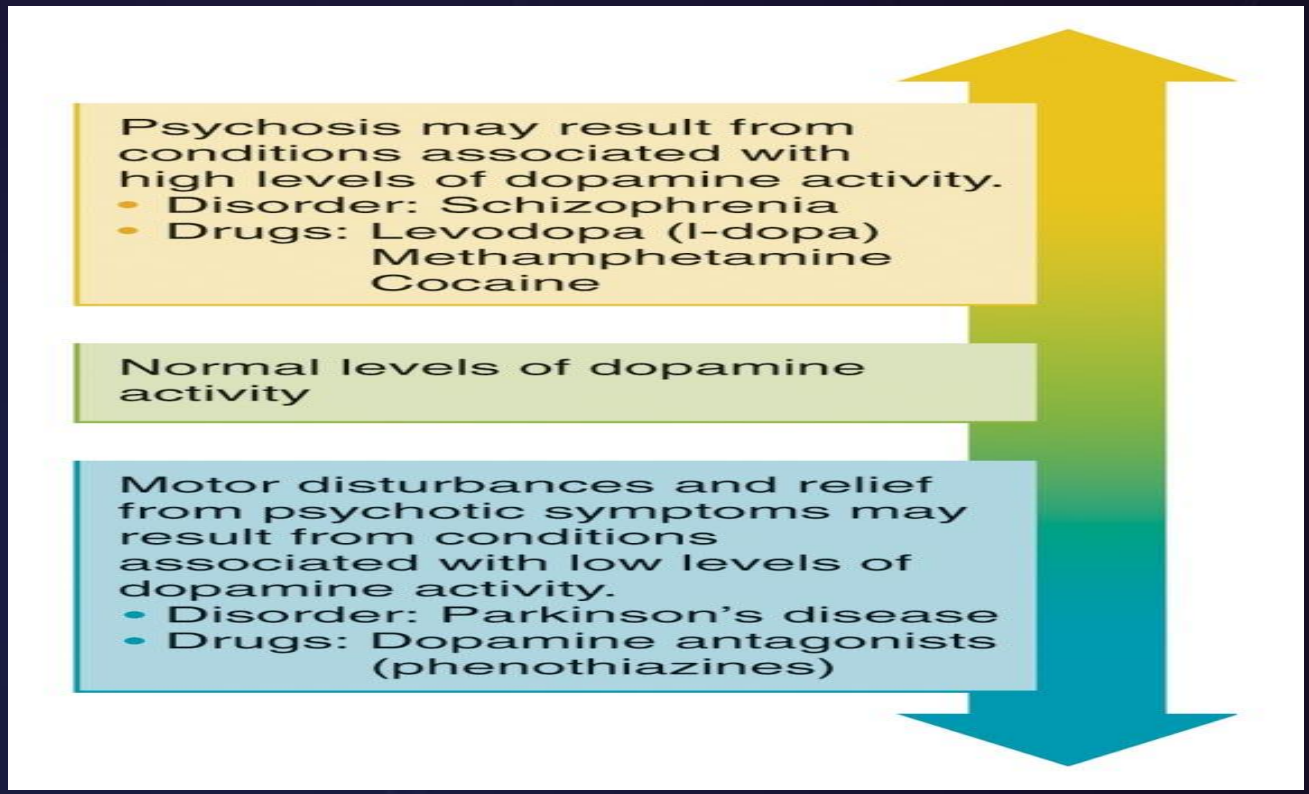
Antipsychotic drugs

Dr. Laila M. Matalqah

Dr. Romany H Thabet

Psychosis is a thought disorder characterized by disturbances of reality and perception, impaired cognitive functioning.



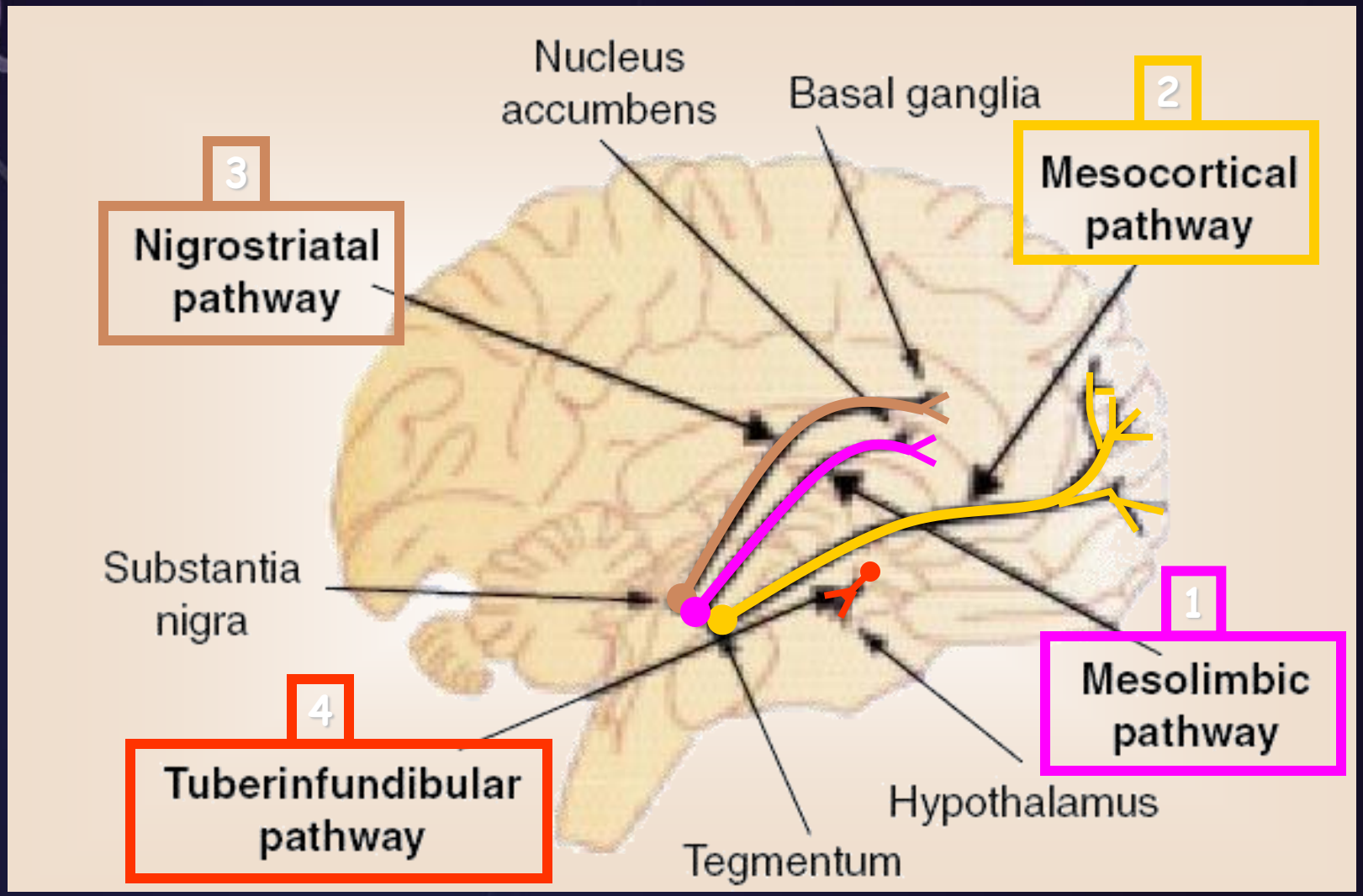
The Dopamine Hypothesis of schizophrenia

- The **dopamine hypothesis** suggests that excessive dopaminergic activity underlies schizophrenia includes the following:

- **Drugs that increase dopaminergic activity either aggravate existing schizophrenia or induce psychosis**

- **Traditional antipsychotic drugs block D2 receptors in the CNS**

- **Post-mortem studies show increase dopamine receptor density in brains of schizophrenics who were not treated with antipsychotics**


Nucleus accumbens
Basal ganglia
2
Mesocortical pathway
3
Nigrostriatal pathway
Substantia nigra
1
Mesolimbic pathway
4
Tuberinfundibular pathway
Hypothalamus
Tegmentum

Dopamine Pathways

- **Mesolimbic :** Overactivity produces delusions and hallucinations.
- **Nigrostriatal:** Controls Extrapyramidal movements

<u>Chronic blockade can cause</u>

  - Potentially irreversible movement disorder
    - "Tardive Dyskinesia"
  - Akathisia
  - Dystonia
  - Tremor, rigidity, bradykinesia

- Tuberoinfundibular

  Blockade produces galactorrhea

  Increased prolactin levels

Dopaminergic System

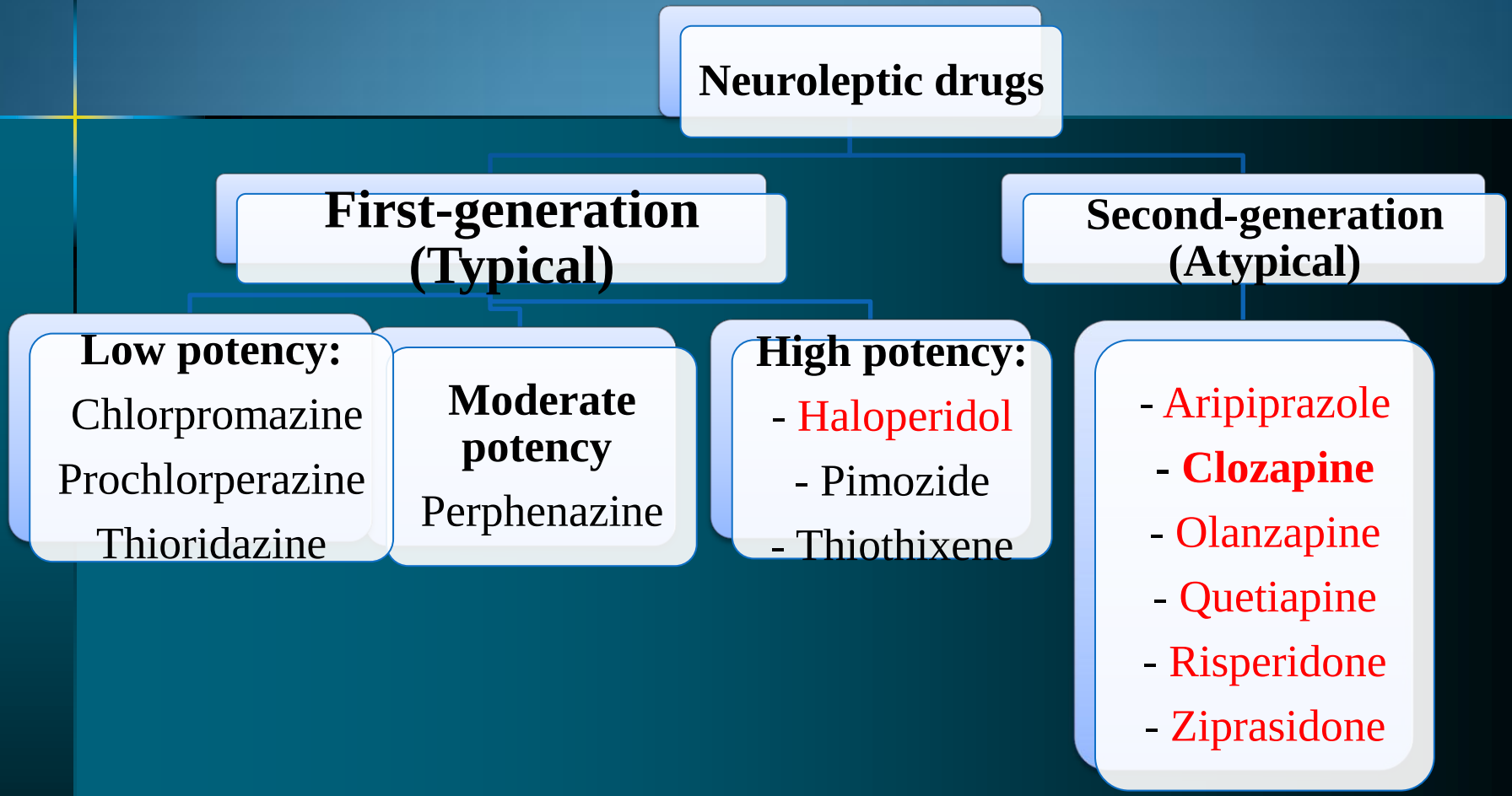
- Dopamine receptors
  - **D_2**=antipsychotic action
  - **D_1,D_3,D_4, D_5**=Action unknown
  - Typical antipsychotics block D_2 nonspecifically in the brain
    - **Causes EPS**
    - **Elevated Prolactin**
    - **Possibly worsen negative symptoms**

Schizophrenia

- Pathophysiology
  - No consistent neuropathology or biomarkers for schizophrenia
    - ? Increased dopamine in mesolimbic pathways causes delusions and hallucinations
    - ? Dopamine deficiency in mesocortical and nigrostriatal pathways causes negative symptoms (apathy, withdrawal)
    - Hallocinogens produce effect through action on 5-HT2 receptors

Schizophrenia

- Positive symptoms
  - Hallucinations
  - delusion
  - Disordered thinking
  - Disorganized speech
  - Combativeness
  - Agitation
  - Paranoia
- Negative symptoms
  - Social withdrawal
  - Emotional withdrawal
  - Lack of motivation
  - Poverty of speech
  - Blunted affect
  - Poor insight
  - Poor judgement
  - Poor self-care


Neuroleptic drugs
First-generation (Typical)
Second-generation (Atypical)
Low potency:
Chlorpromazine
Prochlorperazine
Thioridazine
Moderate potency
Perphenazine
High potency:
- Haloperidol
- Pimozide
- Thiothixene
- Aripiprazole
- Clozapine
- Olanzapine
- Quetiapine
- Risperidone
- Ziprasidone

A. First-generation antipsychotics

- also called conventional, typical, or traditional antipsychotics

- competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blocking of D2 dopamine receptors.

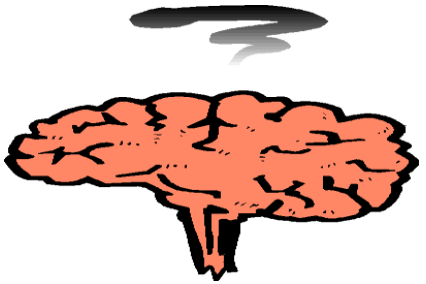
- more likely to be associated with movement disorders, particularly for drugs that bind tightly to dopaminergic neurorecepors, such as haloperidol.

Typical antipsychotics

Potency	Drug	Equiv oral dose (mg)	EPS	Sedation	Anticholinergic s/e
Low	Chlorpromazine	100	Moderate	**High**	Moderate
	Thioridazine	100	Low	High	High
	Sulpiride	200	Low	Moderate	Low
Moderate	Perphenazine	10	Moderate	Moderate	Low
High	Trifluoperazine	5	High	Low	Low
	Thiotheixene	2	High	Low	Low
	Fluphenazine	2	High	Low	Low
	Haloperidol	2	High	Low	Low
	Pimozide	0.5	High	Moderate	Moderate

B. Second-generation antipsychotic drugs

- also referred to as “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.
- owe their unique activity to blockade of both serotonin and dopamine receptors.



Atypical antipsychotics

Comparison of representative atypical antipsychotics	
Drug	**Disadvantages**
Clozapine	Risk of fatal agranulocytosis, Weight gain
Risperidone	EPS and hypotension at high doses
Olanzapine	Weight gain
Quetiapine	Dose adjustment with associated hypotension
Ziprasidone	QT prolongation

Mechanism of action

Dopamine receptor–blocking activity in the brain:

- All of the first-generation and most of the second-generation antipsychotic drugs block dopamine receptors in the brain and the periphery.
- The clinical efficacy of the typical antipsychotic drugs correlates closely with their relative ability to block D2 receptors in the mesolimbic system of the brain.

Serotonin receptor–blocking activity in the brain:

- Most of the second-generation agents appear to exert part of their unique action through inhibition of serotonin receptors (5-HT), particularly 5-HT2A 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 .

- **Risperidone** blocks 5-HT2A receptors to a greater extent than it does D2 receptors, as does **olanzapine**

- The second generation antipsychotic **aripiprazole** is a partial agonist at D2 and 5-HT1A receptors as well as a blocker of 5-HT2A recepors

Antipsychotic actions:

- All of the neuroleptic 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**, such as blunted affect, anhedonia (not getting pleasure from normally pleasurable stimuli), apathy, and impaired attention, as well as cognitive impairment are not as responsive to therapy, particularly with the typical neuroleptics.

- Many atypical agents, such as clozapine, ameliorate the negative symptoms to some extent. All of the drugs also have a calming effect and reduce spontaneous physical movement.

- In contrast to CNS depressants, such as barbiturates, the neuroleptics do not depress the intellectual functioning of the patient as much

- The antipsychotic effects usually take several days to weeks to occur

Extrapyramidal effects:

- **Dystonias** (sustained contraction of muscles leading to twisting distorted postures),**parkinson-like symptoms**, **akathisia** (motor restlessness), and **tardive dyskinesia** (involuntary movements of the tongue, lips, neck, trunk, and limbs) occur with chronic treatment.

- Blocking of dopamine receptors in the nigrostriatal pathway probably causes these unwanted movement symptoms. The atypical neuroleptics exhibit a lower incidence of these symptoms.

Antiemetic effects:

- With the exceptions of aripiprazole and thioridazine , most of the neuroleptic drugs have antiemetic effects that are mediated by blocking D2-dopaminergic receptors of the chemoreceptor trigger zone of the medulla.

- [Note: The atypical antipsychotic drugs are not used as antiemetics.]

Antimuscarinic effects:

- particularly **thioridazine**, **chlorpromazine**, **clozapine**, and **olanzapine**, produce anticholinergic effects

- including blurred vision, dry mouth , confusion, and 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.

Therapeutic uses

- Treatment of schizophrenia
- Prevention of severe nausea and vomiting
  The older neuroleptics (most commonly prochlorperazine) are useful in the treatment of drug-induced nausea
- Other uses

Adverse effects

- Extrapyramidal side effects
- Effect of anticholinergic drugs
- Tardive dyskinesia
- **Neuroleptic malignant syndrome** : fatal reaction to neuroleptic drugs is characterized by muscle rigidity, fever, altered mental status and stupor, unstable blood pressure, and myoglobinemia. Treatment necessitates discontinuation of the neuroleptic and supportive therapy. Administration of dantrolene or bromocriptine may be helpful.

Cautions and contraindications

- Acute agitation accompanying withdrawal from alcohol or other drugs
- epilepsy.
- The high incidence of agranulocytosis with clozapine may limit its
- elderly patients with dementia-related behavioral disturbances and psychosis.

Antipsychotics in schizophrenia

- Selection of typical antipsychotics
  - Equally efficacious
  - Chosen by side effect profile
- Atypical antipsychotics may be appropriate if
  - Adverse effect is a particular concern
  - Additional benefits for negative and cognitive symptoms required
- Clozapine
  - 2nd line treatment when other agents are ineffective or not tolerated

Antipsychotics in schizophrenia

- Depot antipsychotic preparations
  - Useful for noncompliant patients with poor insight
- Antidepressents and mood stabilisers
  - In schizoaffective disorders
  - Patients with secondary mood symptoms or aggressivity
- Differentiate between adverse effects and signs of disease progression
  - E.g. Parkinsonism vs. psychotic hysteria, Akathisia vs. exacerbation of psychosis

Antipsychotics in schizophrenia

- Treatment response
  - First 7 days
    - Decreased agitation, hostility, combativeness, anxiety, tension and aggression
    - Normalization of sleep and eating habits
  - First 2-3 weeks
    - Increased socialization, improvement in self-care
  - 6-8 weeks
    - Improvement in formal thought disorder

Antipsychotics in schizophrenia

- Acute phase
  - Initiate therapy
  - Titrate as tolerated to average effective dose
- Stabilization phase
  - Dose titration within the therapeutic range
- Maintenance phase
  - Good treatment responders should be treated for at least 5 years
  - Continuous lifetime maintenance required in the majority of patients to prevent relapse
    - Lowest effective and tolerable dose