Antipsychotics

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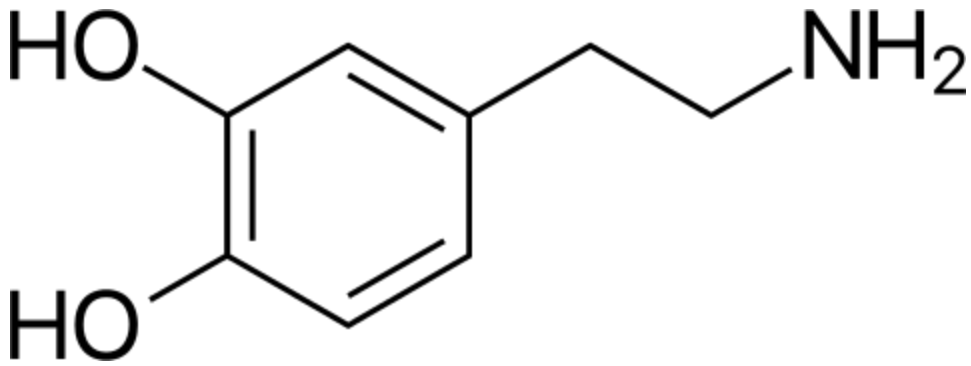
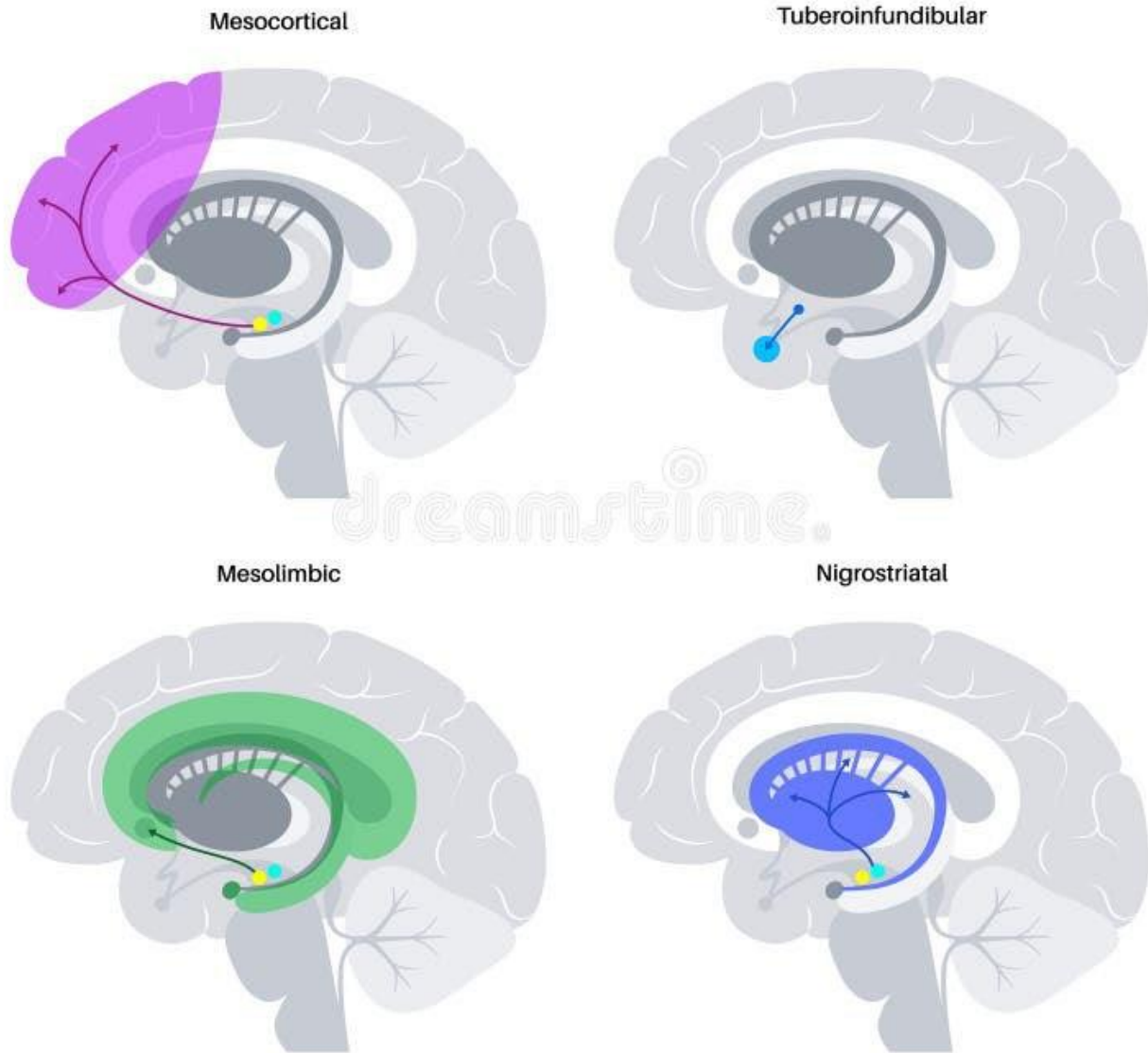
Dopamine

- 1950s: **chlorpromazine** found to improve psychosis
- Also found to block CNS **dopamine** receptors
- Dopamine hypothesis



Dopamine

DOPAMIN PATHWAYS



Dopamine Pathways

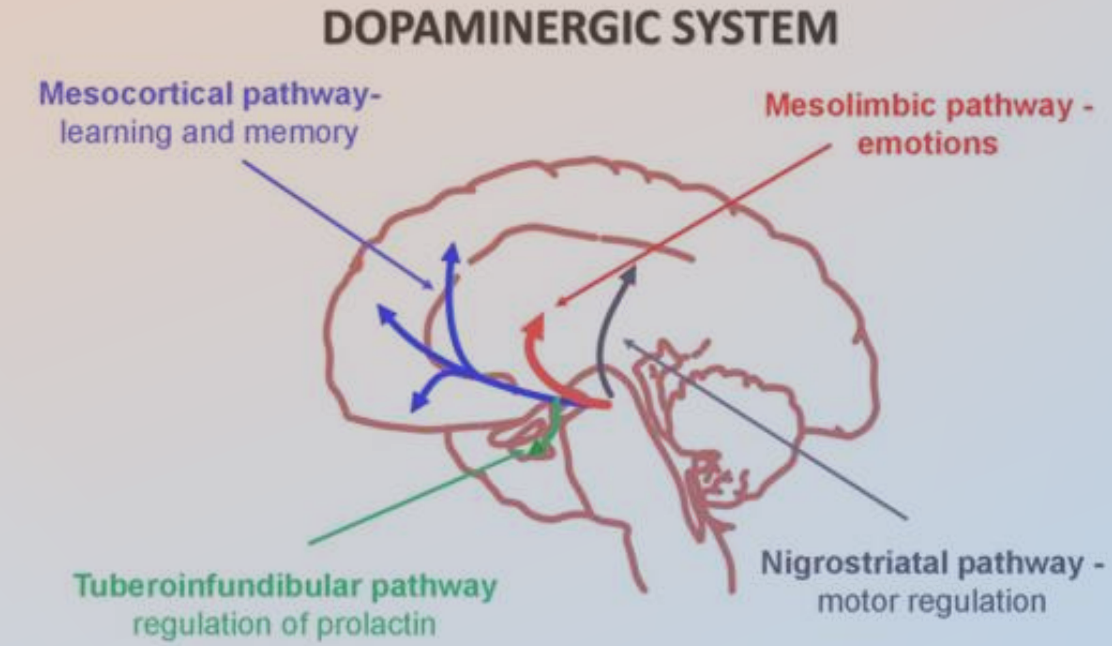
Prefrontal cortical

Responsible for negative symptoms

Tuberoinfundibular

Blocked by neuroleptics, causing Hyperprolactinemia (gynecomastia, galactorrhea, and menstrual irregularities)

Ural Federal University



Stahl SM. Essential Psychopharmacology of antipsychotics and mood stabilizers; 1st ed. Cambridge: Cambridge University Press; 2002

Mesolimbic

Excessive dopaminergic activity responsible for positive symptoms

Nigrostriatal

Blocked by neuroleptics, causing extrapyramidal side effects such as tremor, akathisia, dystonia.

Parkinson's Disease

- Motor dysfunction
- Tremors, rigidity
- Associated with **↓ CNS dopamine activity**

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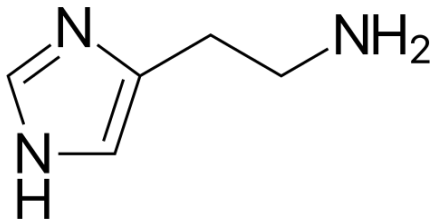
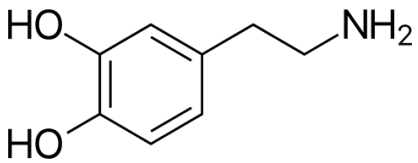
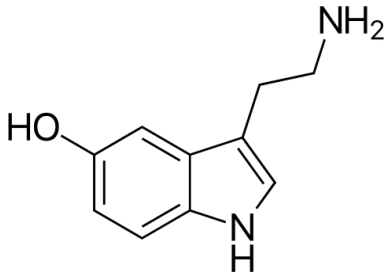
Neurotransmitters



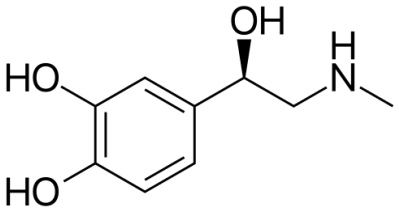
Histamine



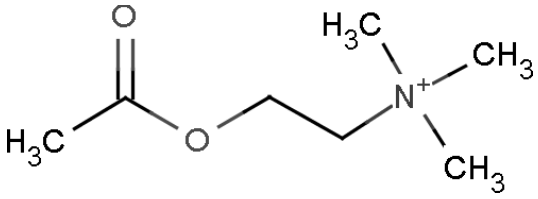
Dopamine



Serotonin
5-HT



Epinephrine



Acetylcholine
(Muscarinic)

Antipsychotics

- First Generation or Typical (old)
- Second Generation or Atypical (new)

Antipsychotics

First Generation or Typical

- Haloperidol
- Pimozide
- Fluphenazine
- Trifluoperazine
- Chlorpromazine
- Thioridazine

- Primary antipsychotic effect: **D2 receptor blockade**

Antipsychotics

First Generation or Typical

- **High potency agents**
  - Haloperidol, fluphenazine, pimozide
- Lower dose required to achieve effect
- Example: haloperidol 1mg
- Little effect on histamine and muscarinic receptors
  - Less sedation (histamine) or dry mouth (muscarinic)
- **Extrapyramidal side effects**

Chlorpromazine: α1=5HT> D2
Haloperidol: D2 > α1 > 5HT > H1

Antipsychotics

First Generation or Typical

- **Low potency agents**
  - Thioridazine, chlorpromazine
  - Example: Thioridazine 50-100mg
- Less extrapyramidal side effects
- **More non-neurologic side effects**
  - Sedating ("sedatives")
  - Dry mouth

Chlorpromazine: α1=5HT> D2
Haloperidol: D2 > α1 > 5HT > H1

Antipsychotics

First Generation or Typical

- Dopamine blockade
- Serotonin blockade
- Histamine blockade
- Acetylcholine (muscarinic) blockade
- Epinephrine (alpha-1) blockade

Chlorpromazine: α1=5HT> D2
Haloperidol: D2 > α1 > 5HT > H1

Antipsychotics

First Generation or Typical

Low Potency
Thioridazine
Chlorpromazine

High Potency
Haloperidol
Trifluoperazine
Fluphenazine

Non-EPS Effects
Sedation
Dry mouth

EPS Effects
Movement symptoms

Antipsychotics

First Generation or Typical

- Dopamine blockade
    - Parkinsonian effects (extrapyramidal)
    - Hyperprolactinemia
    - Gynecomastia
    - Galactorrhea
    - Amenorrhea

Anti-emetic (Prochlorperazine/Chlorpromazine)

Antipsychotics

First Generation or Typical

- ACh muscarinic receptor blockade
  - Dry mouth
  - Constipation
  - Urinary retention
  - Tachycardia
  - Sexual dysfunction
- α1 receptor blockade
  - Hypotension
- Histamine receptor blockade
  - Sedation
  - Seratonin
  - Weight gain

Xerostomia
(Dry Mouth)

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Pyramidal vs. Extrapyramidal

- Pyramidal system
  - Corticospinal tract
  - Run in pyramids of medulla
  - Damage → weakness

- Extrapyramidal system
  - Basal ganglia nuclei and associated tracts
  - controlling and coordinating involuntary movements, posture, and muscle tone.
  - Damage → movement disorders

Wikipedia/Public Domain

EPS

Extrapyramidal Symptoms

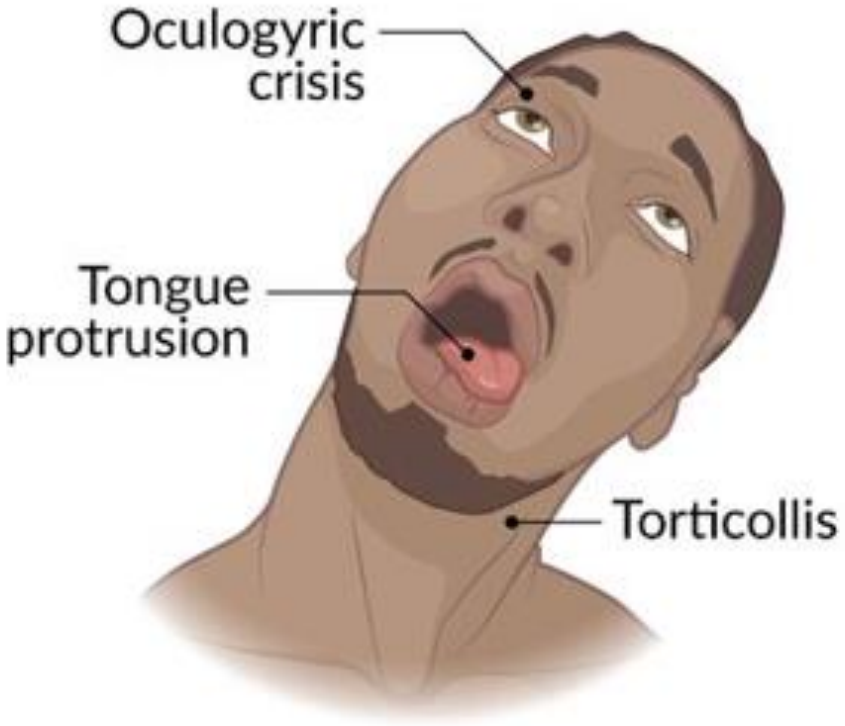
- Response to dopamine receptor blockade
- **Movement** side effects
- Dystonia
- Akathisia
- Bradykinesia
- Tardive dyskinesia

Dystonia

Extrapyramidal Symptoms

- Acute side effect
- Occurs within hours/days
- Involuntary contraction of muscles
- Spasms, stiffness

- Treatments:
  - **Benztropine (anticholinergic)**
  - **Diphenhydramine (antihistamine)**
  - Improves dystonia



Akathisia

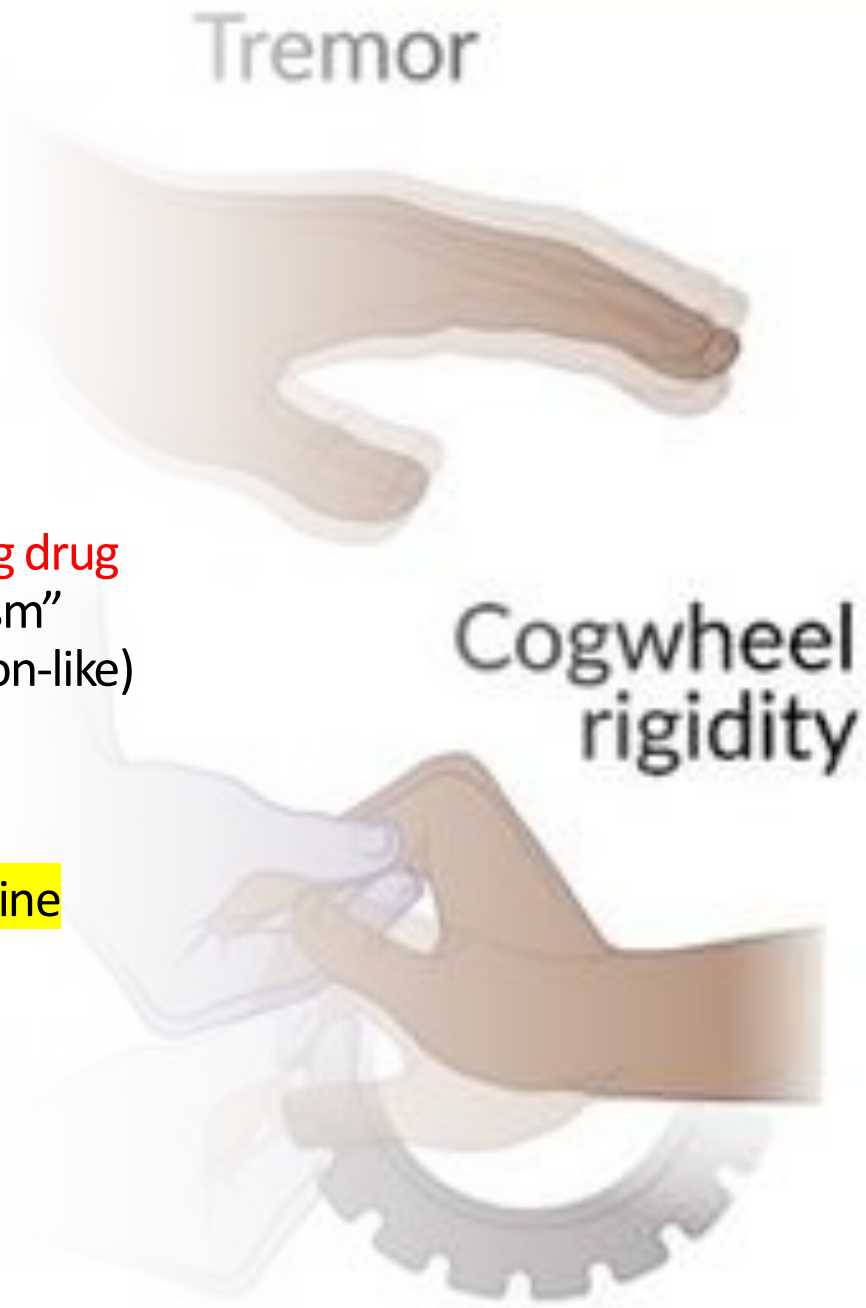
- Extrapyramidal Symptoms
  - Occurs within days
  - Most common EPS adverse effect
  - Restlessness, urge to move
  - Sometimes misdiagnosed as worsening agitation

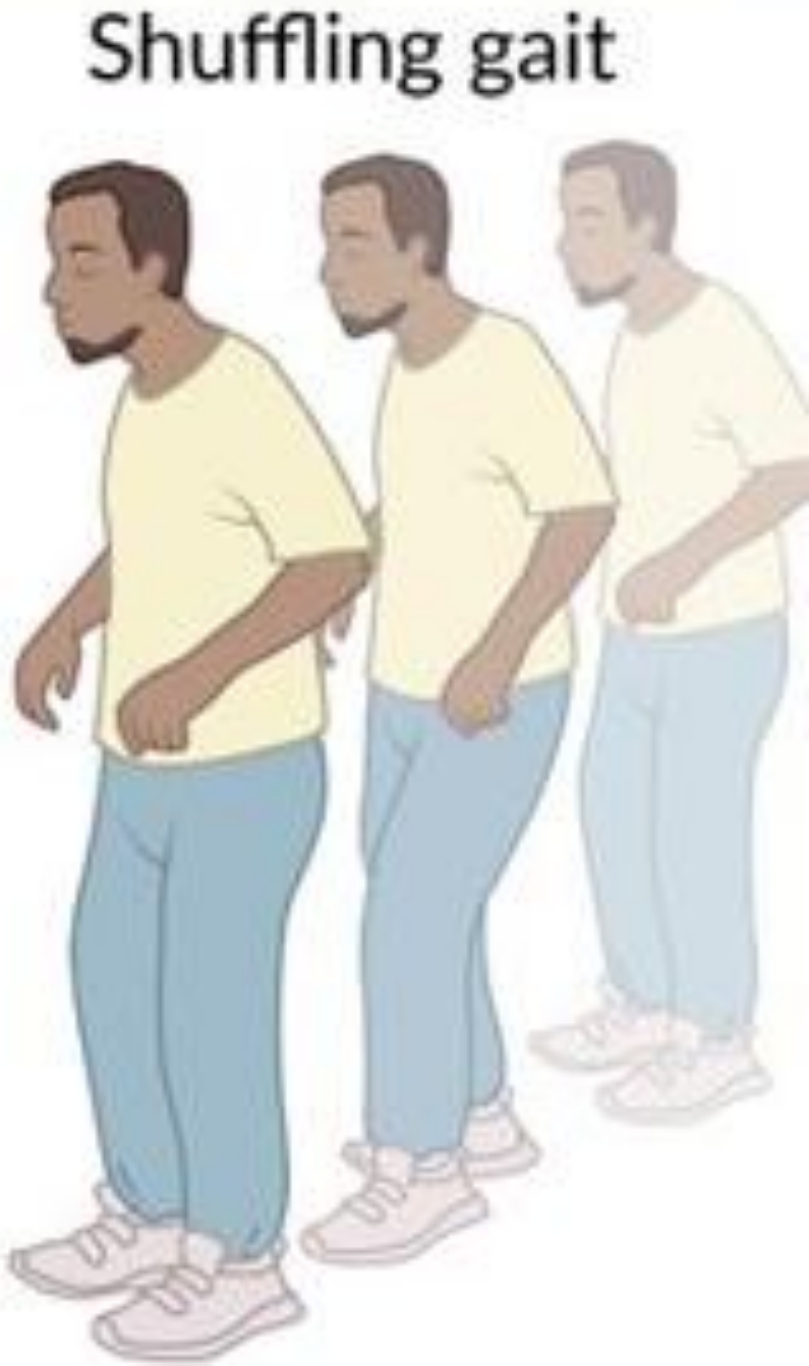
  - Treatments:
    - Lower dose
    - Benzodiazepines
    - Propranolol

Bradykinesia

- Extrapyramidal Symptoms
  - Occurs weeks after starting drug
  - “Drug-induced Parkinsonism”
  - Slow movements (Parkinson-like)

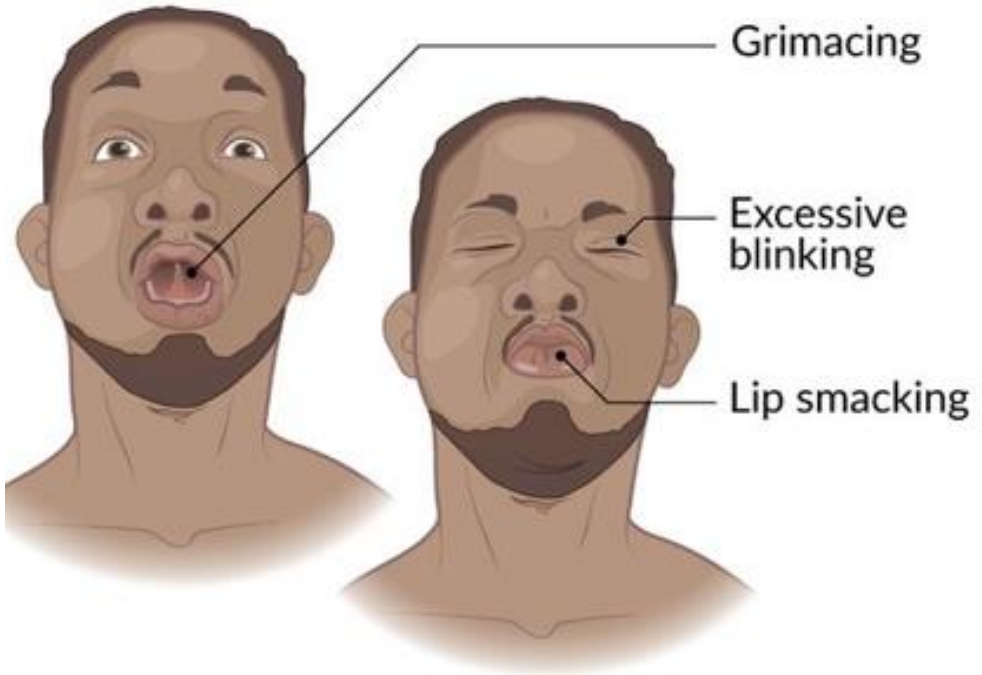
  - Treatment:
  - **benztropine**
    - Second line: amantadine





Tardive Dyskinesia

- Extrapyramidal Symptoms
  - Occurs months or years after starting drug
  - **Choreoathetosis**
    - Chorea: irregular migrating contractions
    - Athetosis: twisting and writhing
- Mouth, tongue, face, limbs
  - Smacking lips, grimacing
  - **Often irreversible**
    - Stopping drug doesn't help



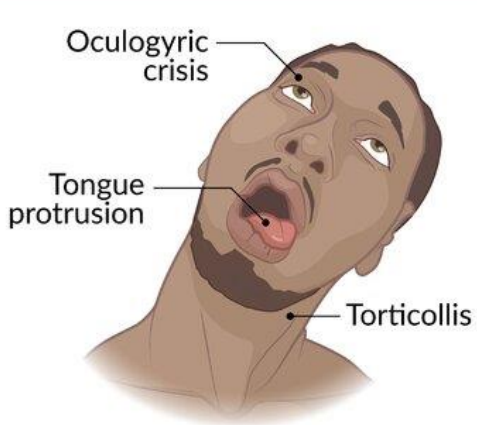
Initiation of treatment

Hours to days

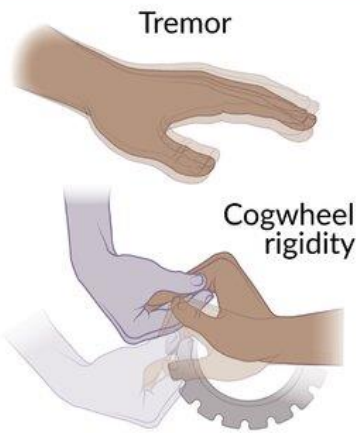
Days to weeks

Months to years

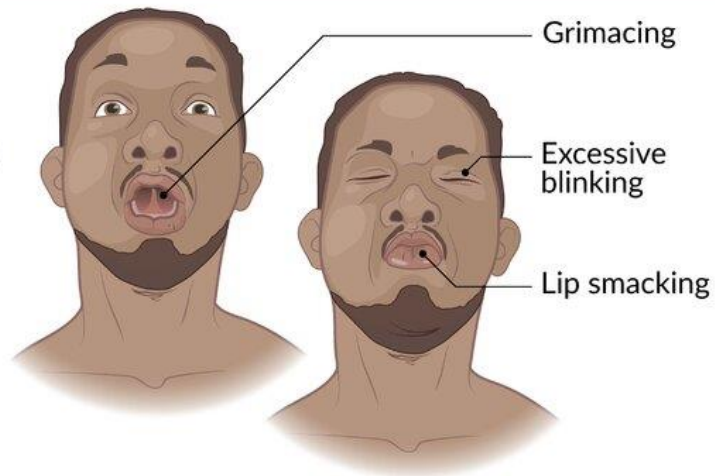
Acute dystonia



Pseudoparkinsonism



Tardive dyskinesia



Akathisia

NMS

Neuroleptic Malignant Syndrome

- Rare, dangerous reaction to neuroleptics
- Usually high-potency first-generation drugs
  - Haloperidol, fluphenazine
- Usually 7-10 days after treatment started
- **Fever and rigid muscles**
- Mental status changes (encephalopathy)
- Elevated creatine kinase (muscle damage)
- Myoglobinuria → acute renal failure (rhabdomyolysis)

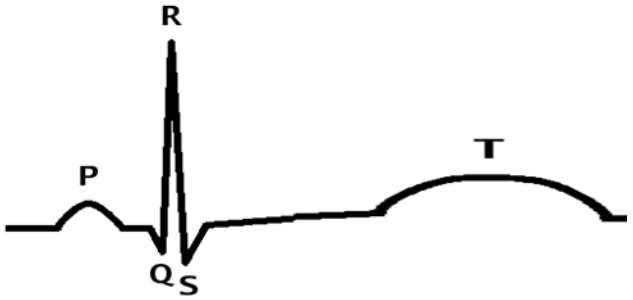
NMS

Treatment

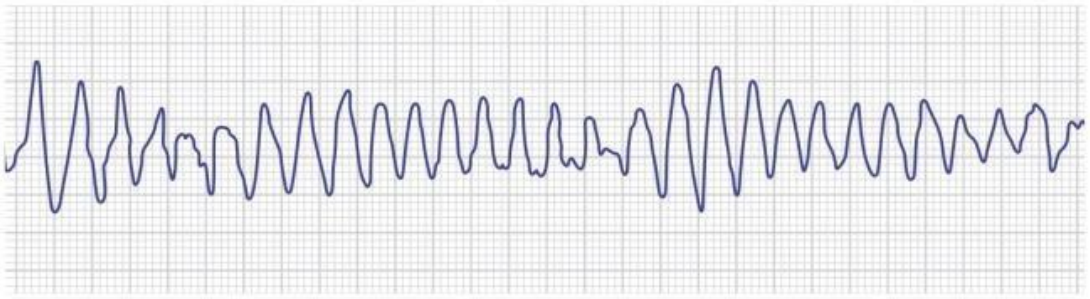
- Dantrolene (muscle relaxant)
- Bromocriptine (dopamine agonist)
- Similar to malignant hyperthermia
  - Reaction to halothane, succinylcholine
  - Same treatment: dantrolene (muscle relaxant)

QT interval

- May block cardiac potassium channels
- Prolongs QT interval
- Strongest association with IV haloperidol



Prolonged QT



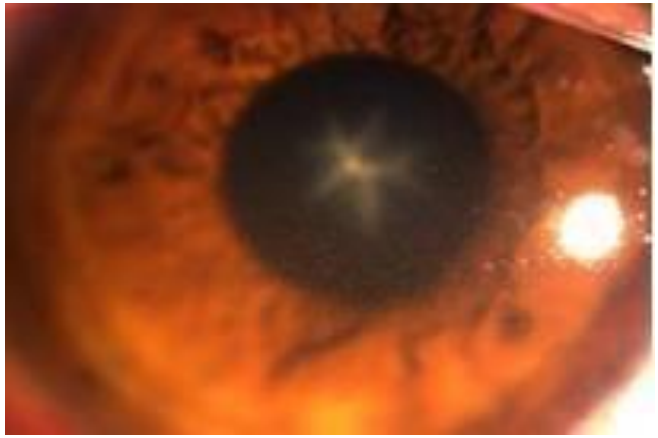
Torsade de Pointes

Thioridazine and Chlorpromazine

- **Retinal deposits**
  - "browning" of vision

Christian Hamel

- **Corneal deposits**
  - May accelerate aging of lens
  - Possibly associated with cataracts



Sushil et a.. Ophth Res 4(4) 108-111

Chlorpromazine

- **Skin effects**
  - Occurs in sun-exposed areas
  - Photosensitivity
  - Skin pigmentation (blue-gray)

- **Cholestatic jaundice**
  - Occurs in 1 to 2 percent of patients

International journal of dermatology 2016
Chlorpromazine-induced severe skin pigmentation and corneal opacities in a patient with schizophrenia.
Ana María Molina-Ruiz, Águeda Pulpillo, R. M. Molina-Ruíz, Teresa Sagrario, Luis Requena

Antipsychotics

Second Generation or Atypical

- Clozapine
- Olanzapine
- Quetiapine
- Asenapine
- Iloperidone
- Paliperidone
- Risperidone
- Lurasidone
- Ziprasidone

Pines
Lowest EPS risk
Metabolic symptoms

Dones
Highest EPS risk
Qt symptoms

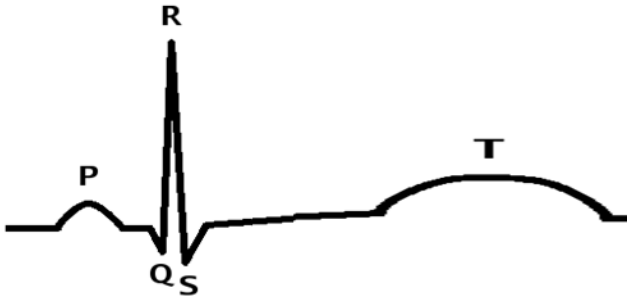
- **Defining feature: Less EPS adverse effects**

Metabolic Syndrome

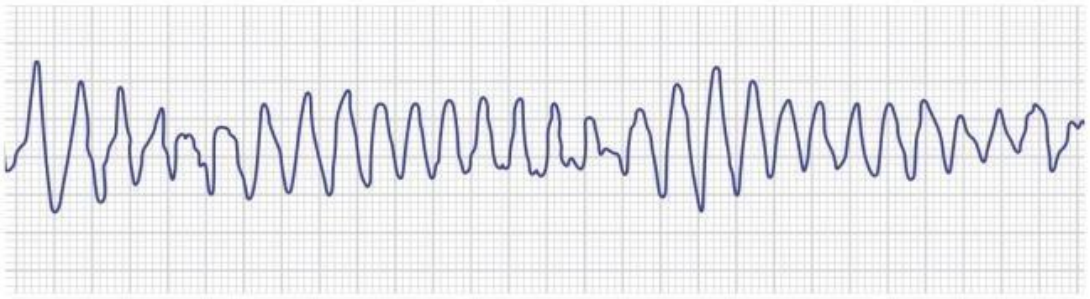
- May occur with any antipsychotic
- Common with “pines” – especially **clozapine** and **olanzapine**
- Weight gain
- Hyperglycemia
- Hyperlipidemia

QT interval

- Prolongation also can occur with atypical drugs
- More risk with “dones”
- Highest risk: **ziprasidone**



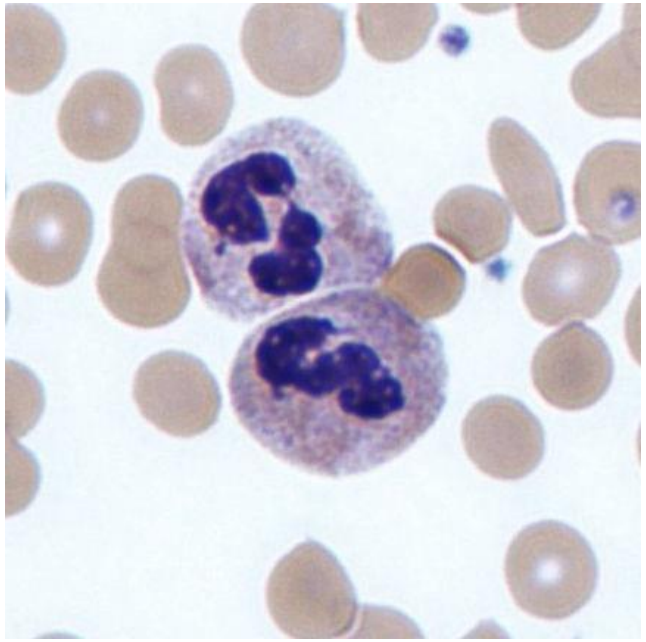
Prolonged QT



Torsade de Pointes

Clozapine

- Highly effective but not first line due to adverse effects
  - Used in refractory cases
- May cause **agranulocytosis** (1-2% of patients)
- Must monitor WBCs during therapy
  - Weekly at start
  - Every few weeks to monthly thereafter
  - Stop if neutrophil counts < 1500
- Reversible when drug stopped
- May also cause **seizures** (2-5% of patients)
  - Dose related
- Rarely associated with myocarditis



Dr Graham Beards

Aripiprazole

- **D2 partial agonist**
  - Some blockade, some agonist effects

- Associated with **loss of impulse control**
  - Pathologic gambling
  - Binge eating
  - Shopping sprees

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Atypical Antipsychotics

Drug	Key Adverse Effects
“pines”	Metabolic syndrome
Clozapine	Agranulocytosis
Quetiapine	Lowest risk of EPS (Quetiapine is quiet) Use in patients with movement disorders (Parkinson’s)
“dones”	Highest risk of QT prolongation
“dones”	Highest risk of EPS
Aripiprazole	Loss of impulse control

Case scenario

Ms. B is a 28-year-old, overweight female . Police found
her in a local shopping mall, talking to herself and telling a passer by that
the devil had “stolen her soul.”
the hospitalization, you found that she was diagnosed with schizophrenia.
However, during her last appointment with her primary care doctor,
she was told she had an elevated fasting glucose of 115 and triglycerides of
180, and that she had gained 12 pounds in the past 3 months with a waist
circumference of 36 inches. Her blood pressure was normal, but she
reported
a family history of diabetes and high blood pressure.
What is the drug that she take for schizophrania ?

Metabolic Syndrome

- May occur with any antipsychotic
- Common with “pines” – especially **clozapine** and **olanzapine**
- Weight gain
- Hyperglycemia
- Hyperlipidemia

Condition	Acute Use	Chronic Use	First-Line Therapy
Schizophrenia	Manage acute psychotic episodes (e.g., hallucinations, delusions)	Maintenance therapy to prevent relapses	Second-generation antipsychotics (SGAs)
Bipolar Disorder	Acute manic or mixed episodes	Maintenance to prevent relapses	SGAs (e.g., quetiapine, olanzapine)
Major Depressive Disorder with Psychotic Features	Adjunct to antidepressants in severe cases	-	SGAs (e.g., aripiprazole)
Schizoaffective Disorder	Acute psychotic episodes with mood disorder	Long-term management combining antipsychotics and mood stabilizers	SGAs (e.g., risperidone, quetiapine)
Delirium	Control acute agitation and psychotic symptoms	-	Low-potency typical antipsychotics (e.g., haloperidol)
Dementia-related Psychosis	Manage acute behavioral disturbances	Long-term management of psychosis	SGAs (e.g., risperidone, olanzapine)

Notes

- Schizophrenia (typical antipsychotics primarily treat positive symptoms; atypical antipsychotics treat both positive and negative symptoms) .
- Other uses : Tourette syndrome, OCD, Huntington disease.
- Clozapine is used for treatment resistant psychotic disorders or those with persistent suicidality (cloze to the edge)

YES/NO important question

- Are antipsychotics addictive?

- NO

- Are antipsychotics save in pregnancy?

YES

Not : during pregnancy the first line is 1st generation , but in ppp the first line is 2nd generation

- نَسِيرُ للمَوْتِ كَأَنَّا في طَرَب
- وَقَدْ صَحِبْنَاهُ وَطَالَ المُصْطَحَب
- حَتَّى عَرَفْنَا مَا قَلَى وَمَا أَحَب
- مُعَوَّذٌ عَلَى الجَلالِ وَالرَّهَب
- فَإِنْ رَآكَ لَم تَخَفْ مِنْهُ اضْطَرَب
- وَنَحنُ مِنَّا كُلُّ مَعروفِ النَّسَب