ANTIPSYCHOTICS

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LEARNING OUTCOMES

By the end of the lecture, students will be able to…

1. recall the biochemical basis of psychotic illnesses
2. classify the antipsychotic drugs (with examples)
3. describe the mechanism of action, pharmacokinetics, adverse drug effects of antipsychotic drugs
4. list the clinical uses of antipsychotic drugs
A. Definition-Psychosis
B. Dopamine hypothesis
C. Classification of Antipsychotics
D. Pharmacological Profile of Each Category
E. Clinical Usage
PSYCHOSIS

- A symptom of mental illnesses
- Characterized by a distorted or non-existent sense of reality
  - Hallucinations
  - Delusions
  - Disorganized speech
  - Disorganized or agitated behaviour
PSYCHOSIS

- Mood disorders (major depression or mania) with psychotic features
- Substance-induced psychosis
- Dementia with psychotic features
- Delirium with psychotic features
- Schizophrenia
DOPAMINE HYPOTHESIS

- Put forward by Arvid Carlsson

“The clinical features of schizophrenia (sometimes extended to psychosis in general) is related to over activity of dopaminergic function within the brain.”
CLASSIFICATION

A. Typical/First Generation Antipsychotics
   I. Phenothiazines e.g. chlorpromazine
   II. Butyraphenones e.g. haloperidol
   III. Thioxanthenes e.g. flupentixol

B. Atypical/Second Generation Antipsychotics
   e.g. clozapine, risperidone, olanzapine
       quetiapine, aripiprazole
FIRST GENERATION ANTIPSYCHOTICS

- **Mode of Action:**
  - Predominantly act as antagonists at brain dopamine D$_2$ receptors
  - Also blocks
    - Muscarinic acetylcholine receptors
    - Antihistamine receptors
    - α adrenoceptors
PHARMACOKINETICS

- High rapid oral absorption
- Highly lipophilic with high apparent volumes of distribution
- Undergo extensive phase 1 metabolism by CYPs and subsequent phase 2 conjugations
- Excreted in the urine and to some extent in the bile
ADVERSE DRUG REACTIONS

- Extrapyrformal Motor Effects
  
  Due to dopamine $D_2$ receptor blockade in the nigrostriatal pathway (except tardive dyskinesia)
  
  a) Acute dystonia
  b) Akathisia
  c) Parkinsonism
  d) Tardive Dyskinesia
ACUTE DYSTONIA

- Spasm of muscles of tongue, face, neck, back
- High risk in- first few weeks, young, antipsychotic naive
TARDIVE DYSKINESIA

- Develops after months or years
- In 20-40% of patients treated with first-generation antipsychotic drugs
- Often irreversible, often gets worse when antipsychotic therapy is stopped
- Elderly at 5-fold greater risk
ADVERSE DRUG REACTIONS

Endocrine effects

Due to blockage of dopamine $D_2$ receptors in tuberohypophyseal pathway → Increased prolactin

a) Gynaecomastia
b) Galactorrhoea
c) amenorrhea in women
d) sexual dysfunction or infertility in men
ADVERSE DRUG REACTIONS

- Central antagonism of H$_1$ receptors
  a) sedation
  b) weight gain via appetite stimulation
- Muscarinic antagonism - anticholinergic effects
- $\alpha_1$ Adrenergic antagonism - orthostatic hypotension
ADVERSE DRUG REACTIONS

● Adverse Cardiac Effects

Blockage of cardiac $K^+$ channels

Prolong QT in ECG

Ventricular arrhythmia & sudden cardiac death
ADVERSE DRUG REACTIONS

- Increased risk for cerebrovascular events and all-cause mortality in dementia patients
- Lowers seizure threshold
- Increased triglycerides
- Hyperglycaemia
NEUROLEPTIC MALIGNANT SYNDROME

- A fatal idiosyncratic ADR of antipsychotics
- Characterized by,
  1. Mental status changes
  2. Muscle rigidity
  3. Hyperthermia
  4. Autonomic dysfunction
CLASSIFICATION

A. Typical/First Generation Antipsychotics
   I. Phenothiazines e.g. **chlorpromazine**
   II. Butyraphenones e.g. **haloperidol**
   III. Thioxanthenes e.g. **flupentixol**

B. Atypical/Second Generation Antipsychotics
   e.g. **clozapine, risperidone, olanzapine**
   quetiapine, aripiprazole
SECOND GENERATION ANTIPSYCHOTICS

- Mode of Action:
  
  Predominant antagonism of 5-HT\textsubscript{2A} receptors with a lesser degree antagonism of dopamine D\textsubscript{2} receptors

- Has efficacy against negative symptoms esp. clozapine
ADVERSE DRUG REACTIONS

- **Extrapyramidal Motor Effects**
  - Considerably less compared to typical antipsychotics
  - Blockage of 5-HT$_{2A}$ receptors increase dopamine in striatum preventing extrapyramidal effects

- **Cardiotoxicity**
  - Less associated with QT prolongation at therapeutic doses
ADVERSE DRUG REACTIONS

- High risk of new onset diabetes and diabetes ketoacidosis esp. with clozapine and olanzapine

- Agranulocytosis common with clozapine esp. in first 6 months

∴ regular FBC monitoring essential
OTHER CLINICAL USES

- Treatment of Anxiety Disorders
- Treatment of autism
- As an antiemetic
- Treatment of refractory hiccups
SUMMARY

A. Definition-Psychosis
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C. Classification of Antipsychotics
D. Pharmacological Profile of Each Category
E. Clinical Usage