ANTIPSYCHOTICS / MAJOR TRANQUILLIZERS NEUROLEPTICS

OR
ANTI-SCHIZOPHRENIC DRUGS

Learning objective
- After completion of the lecture the student should be able to
- List three different classes of antipsychotic drugs and describe the main pharmacological effects they produce
- Describe the common adverse effects and specific neurological conditions caused by antipsychotic drugs
- Explain the mechanism of action and uses of antipsychotic drugs
- List the adverse effects associated with antipsychotic drugs.
- Describe the pharmacology of drugs used to treat some forms of mental illness.
- explains how antipsychotic drugs suppress the symptoms of schizophrenic and other psychotic conditions, and explains the numerous adverse effects that these drugs produce.

TYPES OF PSYCHOSIS
- schizophrenia
- affective disorders (depression/mania)
- organic psychoses (caused by head injury, alcoholism, others)

PSYCHOSIS
Psychosis is a thought disorder characterized by disturbances of reality and perception, impaired cognitive functioning, and inappropriate or diminished affect (mood).

Psychosis denotes many mental disorders.

SCHIZOPHRENIA
Schizophrenia is a particular kind of psychosis characterized mainly by a clear sensorium but a marked thinking disturbance.

THE NATURE OF SCHIZOPHRENIA
- 1% population, begins at an early age, with strong hereditary factor
- SEX: Equally prevalent in men and women
- AGE: MEN-between 15 and 25
  WOMEN-between 25 and 35

POSITIVE SYMPTOMS
- Delusions
- Hallucinations
- Thought disorder
  Disorganized behavior
  Disorganized speech/thinking
  Catatonic behaviors
NEGATIVE SYMPTOMS

- Withdrawal from social contacts
- Flattening of emotional responses
- Alogia, Avolition-Apathy, Anhedonia-Asociality
- Attention

Diagnostic Criteria for Schizophrenia

**DSM-IV**

A. **Two or more of the following** (one-month period)
   - delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior and negative symptoms.

B. **Social/occupational dysfunction**: one or more major areas of functioning such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset.

C. **Continuous signs of the disturbance** persist for at least SIX months.

Etiology of Schizophrenia

Idiopathic

**Biological Correlates**

1. Genetic Factors
2. Neurodevelopmental abnormalities.
3. Environmental stressors.

**Dopamine Theory of Schizophrenia**

- increased activity of the dopaminergic system as being critical in the symptomatology of schizophrenia.

**Dopaminergic system**

There are 4 major pathways for the dopaminergic system in the brain:

- The mesolimbic pathway
- from substantia nigra to limbic system, functions of memory, emotion, arousal, and pleasure
- The mesocortical pathway
- from substantia nigra to neocortex, cognition, social behavior, planning, problem solving, motivation, and reinforcement in learning

- The nigro striatal pathway
- from the substantia nigra to the striatum, coordination of involuntary movement
- The tubero infundibular pathway
  from the hypothalamus to the pituitary gland, secretion of certain hormones (prolactin)
Dopamine receptors

- D₁, D₅ dopamine receptors - cAMP by activation of adenylyl cyclase
  - D₁ – putamen, nucleus accumbens
  - D₅ – hypothalamus, hippocampus
- D₂, D₃, D₄ dopamine receptors - cAMP by inhibition of adenylyl cyclase, inhibits Ca²⁺ channels and open K⁺ channels
  - D₂ – caudate–putamen, nucleus accumbens
  - D₃ – frontal cortex, medulla, midbrain

The dopamine hypothesis (1):
- Most antipsychotic drugs strongly block postsynaptic D₂ receptors in the CNS (mesolimbic system)
- Drugs that increase dopaminergic activity aggravate schizophrenia and produce psychosis de novo
- Increased dopamine receptor density has been found post mortem in brains of schizophrenics

  **The dopamine hypothesis (2):**
  - PET has shown increased dopamine receptor density in schizophrenics
  - Successful treatment of schizophrenics changes the amount of homovanilinic acid – metabolite of dopamine in cerebrospinal fluid, plasma and urine.
**SCHIZOPHRENIA**

- Dysfunction of DA-ergic system:
  - Hyperactivity of DA system
  - (mesolimbic pathway)
  - Hypo-activity in frontal cortex (mesocortical pathway)

- Dysfunction of 5-HT, GABA and glutamate–ergic systems

**CLASSIFICATION OF ANTIPSYCHOTIC DRUGS**

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**TYPICAL ANTIPSYCHOTICS:**

**A. PHENOTHIAZENE DERIVATIVE**

- ALIPHATIC DERIVATIVE:
- CHLORPROMAZINE
- TRIFLUPROMAZINE

**B. PIPERIDINE DERIVATIVE:**

- THIORIDAZINE
- MESORIDAZINE
- PIPERACETAZINE

- Decrease incidence of EPS side effects due to ↑ antimuscarinic activity

**C. PIPERAZINE DERIVATIVE:**

- FLUPHENAZINE
- PERPHENAZINE
- TRIFLUOPERAZINE

- Most potent phenothiazene & thioxanthene antipsychotic compound
  - ↑ EPS but ↓ tendency to produce sedation or autonomic side effects

**B. THIOXANTHENE DERIVATIVES:**

**ALIPHATIC DERIVATIVE:**

**CHLORPROTHIXENE**
PIPERAZINE DERIVATIVE:
CHLOPENTHIXOL
FLUPENTIXOL
THIOTHIXENE

C. BUTYROPHENONE:
- HALOPERIDOL

CLASSIFICATION OF ANTI-PSYCHOTIC DRUGS

2. ATYPICAL ANTI-PSYCHOTICS
- CLOZAPINE
- LOXAPINE
- RISPERIDONE
- MOLINDONE
- SERTINDOLE
- ZIPRASIDONE
- OLANZAPINE
- QUETIAPINE
- PIMOZIDE

Typical neuroleptics – mechanism of action

MECHANISM OF ACTION OF ANTIPSYCHOTICS
- Blockade of the dopamine receptors in the mesolimbic and mesocortical areas in the brain.
- Blocking of the serotonin receptors: clozapine
- The mechanism of the main adverse effects is blockade of the dopamine receptors in the tuberoinfundibular, nigrostriatal areas.
What is the clinical difference between older and newer drugs?

- New antipsychotic drugs has been shown to be more effective than older ones for treating negative symptoms

**DIFFERENCES AMONG ANTI-PSYCHOTIC DRUGS**

- **CHLORPROMAZINE**  \( \alpha_1 = 5HT > D_2 > D_1 \)
- **HALOPERIDOL**  \( D_2 = D_1 = D_4 > \alpha_1 > 5HT_2 \)
- **CLOZAPINE**  \( D_4 = \alpha_1 > 5HT > D_2 = D_1 \)
- **RISPERIDONE**  \( D_2 = 5HT_2 \)
- **OLANZAPINE**  \( 5HT_2 \geq D_1, D_2, \alpha_2 \)

**Pharmacological Actions of neuroleptic drugs (1)**

- **Dopamine receptor**
  - all, particularly: haloperidol, fluphenazine, thiothixene
- **Muscarinic receptor**
  - thioridazine, chlorpromazine
- **\( \beta \) - Adrenergic receptor**
  - chlorpromazine
- **Serotonin receptor**
  - risperidone, clozapine
- **H1 - Histamine receptor**
  - promethazine, chlorpromazine

**Pharmacological Actions of neuroleptic drugs (2)**

- **Antipsychotic actions:**
  - reduce the hallucinations
  - reduce spontaneous physical movement
- **Occur after 4 – 6 weeks of treatment**
- **Extrapyramidal effects:**
  - Parkinsonian symptoms
  - akathisia
- tardive dyskinesia

**Pharmacological Actions of neuroleptic drugs (3)**
- Antiemetic effect (except thioridazine)
- Antimuscarinic effect:
  - blurred vision, dry mouth, sedation, confusion, inhibition of GI and urinary smooth muscle
- Other effects:
  - hypotension, lightheadness

- Neuroleptic drugs are not curative and do not eliminate the fundamental thinking disorder, but often do permit the psychotic patient to function in a supportive environment

**PHARMACOKINETICS**
- NEUROLEPTICS ARE ABSORBED AFTER ORAL ADMINISTRATION
- PASS THROUGH BLOOD – BRAIN BARRIER
- BIND WELL TO PLASMA PROTEINS, HIGHLY LIPID-SOLUBLE
- ARE METABOLIZED IN LIVER BY P-450 SYSTEM
- READILY BUT INCOMPLETELY ABSORBED
- FIRST PASS METABOLISM
- HIGHLY LIPID SOLUBLE
- LARGE VOLUME OF DISTRIBUTION
- PROTEIN BOUND
- COMPLETELY METABOLIZED
- EXCEPT MESORIDAZINE (MAJOR METABOLITES OF THIORIDAZINE)
- LITTLE EXCRETED UNCHANGED
- T ½ IS 10-24 HOURS

**CLINICAL INDICATIONS**
- PSYCHIATRY INDICATIONS
- SCHIZOPHRENIA
- SCHIZO-AFFECTIVE DISORDERS
- MANIC EPISODES IN BIPOLAR DISORDERS
- GILLES DE LA TOURETTE SYNDROME
- SENILE DEMENTIA
- NON-PSYCHIATRIC INDICATIONS
- ANTI-EMETIC EFFECT
- ANTI-PRURITIC EFFECT
- PRE-OPERATIVE ANESTHESIA
- NEUROLEPTIC ANESTHESIA
THERAPEUTIC USES

- Schizophrenia
- Other psychosis
- Schizoaffective disorders
- Delirium
- Prevention of severe nausea and vomiting (vertigo, motion sickness, cancer chemo- and radiotherapy)
- Tranquilizers
- In combination with narcotic analgesics for treatment of chronic pain with severe anxiety
- Intractable hiccups

SIDE EFFECTS OF NEUROLEPTIC DRUGS

A. NEUROLOGIC EFFECTS
   1. ACUTE DYSTONIA: spasm of muscles (tongue, face, neck, back), may mimic seizures
      During the first 1-5 days of Rx
      Mechanism unknown
      Rx: anti-parkinson’s agents
   2. AKATHISIA: motor restlessness
      5-60 days
      Mechanism unknown
      Rx with diphenhydramine
   3. PARKINSONISM
      bradykinesia, rigidity, tremor, mask facies, shuffling gait seen in 5-30 days
      Mechanism: antagonism of dopamine
      Rx: anti-parkinson’s agents
   4. NEUROLEPTIC MALIGNANT SYNDROME
      catatonia, stupor, fever, unstable BP, myoglobulinemia after weeks of treatment
      Mechanism: antagonism of dopamine
      Rx: Stop neuroleptic immediately; dandrolene; bromocriptine, Anti-parkinsons - not effective
   5. TARDIVE DYSKINESIA
      Supersensivity of D receptors (cholinergic def)
      oral-facial dyskinesia, choreoathetosis, dystonia
      After months or years of RX
      Worse on withdrawal
      Mechanism: excess function of dopamine
      Rx: prevention crucial
      Rx: unsatisfactory
ADVERSE EFFECTS

B. BEHAVIORAL EFFECTS
Pseudo-depression; toxic confusional state

C. AUTONOMIC NERVOUS SYSTEM EFFECTS
urinary retention, dry mouth, loss of accommodation, constipation

(MUSCARINIC CHOLINERGIC BLOCKADE)
orthostatic hypotension, impotence, failure to ejaculate

(ALPHA ADRENORECEPTOR BLOCKADE)
ADVERSE EFFECTS

D. METABOLIC & ENDOCRINE EFFECTS
Weight gain, hyperglycemia, hyperprolactinemia, amenorrhea-galactorrhea syndrome, infertility, impotence in males

E. TOXIC OR ALLERGIC REACTIONS
Agranulocytosis (clozapine), cholestatic jaundice, skin eruptions

F. CARDIAC TOXICITY
Ventricular arrythmias (thioridazine)

G. OCULAR COMPLICATIONS:
“browning of vision”

Adverse effects (1)

Acute
- Acute dystonia

Medium-term
- Akathisia
- Parkinsonism

Chronic
- Tardive dyskinesia
- Tardive dystonia

Acute dystonia
- Fixed muscle postures with spasm:
  - clenched jaw muscles
  - protruding tongue
  - opisthotonos
  - torticollis
  - oculogyric crisis
  - (mouth open, head back, eyes staring upwards)

➢ In the beginning of treatment
➢ Common in young males
➢ Treatment with anticholinergic drugs (procyclidine 5-10mg or benztropine i.m or i.v)
**Akathisia**
- motor restlessness
- affect lower limb
- very distressing to the patient
- **Treatment** – reduction of the drug dose.

**Parkinsonism**
- induced by blockade of D2 receptors in the striatum !!!
- appear after a few days to weeks
- **Treatment:**
  - anticholinergic drugs (e.g. procyclidine)
  - reduction of dose
  - switching to an atypical antipsychotic
- **Tardive dyskinesia** orofacial dyskinesia - lip smacking and tongue rotating.
- **Tardive dystonia** specific movements of the head, neck and trunk.
- Appear after months to years of drug treatment
- Clozapine and Risperidone have a low potential for causing extrapyramidal symptoms and lower risk of tardive dyskinesia
- There is no effective treatment !!! They are irreversible.

**Adverse effects (2):**
- Anticholinergic effects due to muscarinic blockade:
  - loss of accommodation, dry mouth, blurred vision, constipation, urinary retention
- Orthostatic hypotension due to α-adrenergic blockade
- Neuroendocrine adverse effects due to D2 blockade in the tuberoinfundibular pathway:
  - Amenorrhea-galactorrhoea
  - Infertility
  - Impotence, Failure to ejaculate
- Drowsiness
- Weight gain,
- Urticaria, dermatitis, rashes, dermal photosensitivity

**Adverse effects of clozapine**
- Bone marrow suppression
- Cardiovascular side effects
- Diabetes

**Adverse effects of chlorpromazine**
- Cholestatic jaundice

**Neuroleptic Malignant Syndrome**
- Precise pathophysiology unknown – deranged dopaminergic function?
• It is an idiosyncratic reaction that appears from a few days to weeks after beginning treatment, but can occur anytime.
• The mortality – 20% in untreated (bromocriptine – D1/D2 agonist; dantrolene – skeletal muscle relaxant; supportive treatment)

**Neuroleptic Malignant Syndrome (NMS)**
• Hyperthermia
• Muscle rigidity
• Autonomic instability
• Fluctuating consciousness
• Mortality due to renal failure caused by rhabdomyolysis.

**Interactions of neuroleptics**
• Additive effects:
  - sedatives
  - β - adrenoreceptor – blocking drugs
  - anticholinergic drugs
  - quinidine-like action (*thioridazine, ziprasidone*)

**Contraindications**
• Alcohol abuse
• Seizure disorders (*Chlorpromazine*)
• Epilepsy
• Agranulocytosis (*Clozapine*)

**Dosage of neuroleptic drugs**
• Antipsychotics may be given in divided daily doses initially while effective dosage level is being sought.
• 2 or more episodes of schizophrenia – therapy for 5 years
• *Fluphenazine* and *haloperidol* i.m. ⇒ slow release drugs (up to 3 weeks)

THANK YOU