

# ANTIPSYCHOTICS (NEUROLEPTICS/MAJOR TRANQUILLIZERS):

## Overview:

- Primarily used in schizophrenia and manic states with psychotic symptoms
- Typical neuroleptics (1<sup>st</sup> gen):
  - Competitive dopamine receptor inhibitors
- Atypical (2<sup>nd</sup> gen):
  - Block both 5-Ht and dopamine receptors
  - Less extrapyramidal side effects
- Not curative, but:
  - Decrease intensity of hallucinations and delusions
  - Permit functioning in supportive environment
- Classification
  - Typical neuroleptics (low potency)
    - Chlorpromazine
    - Prochlorperazine
    - Thioridazine
  - Typical neuroleptics (high potency):
    - Fluphenazine
    - Haloperidol
    - Pimozide
    - Thiothixene
  - Atypical neuroleptics:
    - Aripiprazole

- Clozapine
- Olanzapine
- Quetiapine
- Paliperidone
- Risperidone
- Ziprasidone
- Chlorpromazine was first drug
- Haloperidol is 100X more potent; increased extrapyramidal effect

#### MOA of dopamine receptor blockers:

- All of older, most of newer block dopamine receptors in brain
- 5 types of dopamine receptors (D<sub>1</sub>-D<sub>5</sub>)
  - D<sub>5</sub>, D<sub>1</sub> activate adenylyl cyclase (levodopa)
  - D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub> inhibit adenylyl cyclase
- Clinical efficacy:
  - Ability to block D<sub>2</sub> is mesolimbic system
- Actions antagonized by high dopamine conc

#### MOA of 5-HT receptor blockers:

- Most of newer inhibit 5-HT<sub>2A</sub>

#### Effects:

- Antipsychotic:
  - Blockade at dopamine, serotonin receptors
  - Also block cholinergic, adrenergic and histaminergic receptors, causing side effects
  - Reduce hallucinations, delusions
  - Partial response to negative symptoms (anhedonia, apathy)

- Calming effect
- Do not depress intellectual function
- Minimal motor incoordination
- Effect occur several days to weeks later.
- Extrapiramidal:
  - Dystonia (sustained muscular contraction), causing distorted posture
  - Parkinsonian symptoms
  - Akathisia (motor restlessness)
  - Tardive restlessness (involuntary movements of tongue, lips, neck, trunk and limbs)
- Antiemetic:
  - Blocking of D<sub>2</sub> at chemoreceptor trigger zone (except aripiprazole, thioridazine)
  - Promethazine used especially in children
  - Atypical antipsychotics not used
- Antimuscarinic:
  - Produced by:
    - Thioridazine
    - Chlorpromazine
    - Clozapine
    - Olanzapine
  - Include:
    - Blurred vision
    - Dry mouth (except clozapine, which increases salivation)
    - Confusion

- Constipation, urinary retention
  - Assist in reducing risk of extrapyramidal symptoms
- Others:
  - Orthostatic hypotension (block alpha adrenergic receptors)
  - Poikilothermia
  - Hyperprolactinemia by blocking D<sub>2</sub> in pituitary
  - Sedation (block H<sub>1</sub>-receptor – chlorpromazine, olanzapine, quetiapine, clozapine)
  - Sexual dysfunction

### Therapeutic uses:

- Schizophrenia:
  - Only treatment for schizophrenia
  - Traditional neuroleptics most effective for positive symptoms
  - 5-HT<sub>2A</sub> receptors effective for negative symptoms
  - Clozapine reserved for refractory states associated with blood dyscrasias.
- Others:
  - Tranquilizers
  - Analgesics
  - Intractable hiccups
  - Pruritus
  - Tourette's tics

### P'kinetics:

- Absorption of ziprasidone, paliperidone increased with food
- Readily pass into brain
- Large Vd.

- o Bind well to plasma proteins
  - o Metabolized by CYP450
  - o Some tolerance but little physical dependence.
  - o Slow release preps:
    - o Fluphenazine decanoate, haloperidol decanoate, risperidone microspheres
    - o Given deep IM
    - o For non-compliant patients
    - o Low risk of EPS
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## ADRs:

- Occur in all patients
- High therapeutic index
- Tremor, Postural hypotension, constipation, sexual dysfunction and confusion
- Extrapyrarnidal symptoms:
  - Inhibitory effects of dopaminergic neurons are balanced by excitatory actions of cholinergic neurons
  - Blocking dopamine receptors causes relative excess of cholinergic influence, causing extrapyramidal action.
  - Time- and dose-dependent:
    - Dystonia in hours to days
    - Akathisia in days to weeks
    - Parkinsonian-like symptoms in weeks to months
    - Tardive dyskinesia (irreversible – months to years)
  - Minimized by blocking anticholinergic activity to restore balance
  - Give anticholinergic drugs e.g. benztropine
  - Thioridazine has strong anticholinergic activity (less EPS)
  - Haloperidol and fluphenazine have low anticholinergic activity (less EPS)
  - Atypical antipsychotics have lower EPS due to 5-HT<sub>2A</sub> blockade
  - Risperidone:
    - 1<sup>st</sup> line
    - Metabolized to paliperidone
  - Clozapine:

- Refractory period
  - Bone marrow suppression
- Tardive dyskinesia:
  - o Long-term treatment
  - o Involuntary movements
  - o Prolonged drug holiday may reduce symptoms
- Neuroleptic malignant syndrome:
  - o Fatal:
    - Muscle rigidity
    - Fever
    - Altered mental status
    - Unstable BP
    - Myoglobinemia
  - o Discontinue treatment and offer supportive therapy
  - o Dantrolene/bromocriptine may be useful.
- Others:
  - o Drowsiness – CNS depression, antihistaminic effects
  - o Confusion
  - o Antimuscarinic effects
  - o Alpha adrenergic blockade may cause orthostatic hypotension
  - o Thermoregulation due to hypothalamic depression
  - o Amenorrhea, galactorrhea, gynecomastia, infertility, impotence
  - o Weight gain causes non-compliance
  - o Glucose intolerance, hyperlipidemia (atypical agents) – monitor

**Caution and contraindications:**

- Aggravates alcoholic withdrawal syndrome
- Lower seizure threshold:
  - CI: chlorpromazine, clozapine
  - Aggravate preexisting epilepsy
- Atypical agents have increased mortality in elderly patients with dementia