Pharmacology 4th year

Neuroleptic drugs:-

The neuroleptic drugs (also called antipsychotic drugs, or major tranquilizers) are used primarily to treat schizophrenia, but they are also effective in other psychotic states, such as manic state s with psychotic symptoms such as grandiosity or paranoia and hallucinations, and delirium.

FIRST-GENERATION ANTIPSYCHOTIC (low potency)
Chlorpromazine THORAZINE
Prochlorperazine COMPAZINE
Thioridazine MELLARIL
FIRST-GENERATION ANTIPSYCHOTIC (high potency)
Fluphenazine PROLIXIN
Haloperidol HALDOL
Pimozide ORAP
Thiothixene NAVANE
SECOND GENERATION ANTIPSYCHOTIC
Aripiprazole ABILIFY
Asenapine SAPHRIS
Clozapine CLOZARIL
Iloperidone FANAPT
Lurasidone LATUDA
Olanzapine ZYPREXA
Quetiapine SEROQUEL
Paliperidone INVEGA
Risperidone RISPERDAL
Ziprasidone GEODON

1- All currently available antipsychotic drugs that alleviate symptoms of schizophrenia decrease dopaminergic and/or serotonergic neurotransmission.

2- The traditional or typical neuroleptic drugs (also called conventional or first-generation antipsychotics) are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blocking of dopamine receptors. These drugs vary in potency. For example, chlorpromazine is a low-potency drug, and fluphenazine is a high-potency agent . No one drug is clinically more effective than another.

3- the newer antipsychotic drugs are referred to as atypical (or second-generation antipsychotics), **because they have fewer extrapyramidal adverse effects than the older, traditional agents.**

4- These drugs appear to owe their unique activity to blockade of both serotonin and dopamine (and, perhaps, other) receptors.

5- Current antipsychotic therapy commonly employs the use of the atypical agents to minimize the risk of debilitating movement disorders associated with the typical drugs that act primarily at the D_2 dopamine receptor.

6- All of the atypical antipsychotics exhibit an efficacy that is equivalent to, or occasionally exceeds, that of the typical neuroleptic agents.

7- Neuroleptic drugs are not curative and do not eliminate the fundamental and chronic thought disorder, but they often decrease the intensity of hallucinations and delusions and permit the person with schizophrenia to function in a supportive environment.

Schizophrenia:-

Schizophrenia is a particular type of psychosis that is, a mental disorder caused by some inherent dysfunction of the brain. It is characterized by delusions, hallucinations (often in the form of voices), and thinking or speech disturbances. The illness often initially affects people during late adolescence or early adulthood and is a chronic and disabling disorder. Schizophrenia has a strong genetic component and probably reflects some fundamental biochemical abnormality, possibly a dysfunction of the mesolimbic or mesocortical dopaminergic neurons.

Neuroleptic Drugs:-

The tricyclic phenothiazine derivative, chlorpromazine , was the first neuroleptic drug used to treat schizophrenia. Antipsychotic drugs developed subsequently, such as **haloperidol** , are

more than 100-fold as potent as chlorpromazine but have an increased ability to induce parkinson-like and other extrapyramidal effects.

Mechanism of action:-

Dopamine receptor blocking activity in the brain: All of the older and most of the newer neuroleptic drugs block dopamine receptors in the brain and the periphery . Five types of dopamine receptors have been identified. D_1 and D_5 receptors activate adenylyl cyclase, often exciting neurons, whereas D_2, D_3 and D_4 receptors inhibit adenylyl cyclase, or mediate membrane K^+ channel opening leading to neuronal hyperpolarization. The neuroleptic drugs bind to these receptors to varying degrees. The actions of the neuroleptic drugs are antagonized by agents that raise synaptic dopamine concentrations for example, **levodopa** and **amphetamines** or mimic dopamine at post-synaptic binding sites for example, **bromocriptine.**

Serotonin receptor:-blocking activity in the brain: Most of the newer atypical agents appear to exert part of their unique action through inhibition of serotonin receptors (5-HT), particularly 5-HT_{2A} receptors. Thus,

- **clozapine** has high affinity for D_1, D_4, 5-HT_2, muscarinic, and α-adrenergic receptors.

-**Risperidone** blocks 5-HT_{2A} receptors to a greater extent than it does D_2 receptors, as does **olanzapine**.

-**aripiprazole** is a blocker of 5-HT_{2A} receptors.

-**Quetiapine** blocks D_2 receptors more potently than $5HT_{2A}$ receptors .

Actions:-

The antipsychotic actions of neuroleptic drugs appear to reflect a blockade at dopamine and/or serotonin receptors. However, many of these agents also block cholinergic, adrenergic, and histaminergic receptors .

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.

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 D_2-dopaminergic

receptors of the chemoreceptor trigger zone of the medulla. [Note: The atypical antipsychotic drugs are not used as antiemetics.]

Antimuscarinic effects: Some of the neuroleptics, particularly **thioridazine, chlorpromazine, clozapine, and olanzapine** , produce anticholinergic effects, including blurred vision, dry mouth (exception: clozapine increase salivation), confusion, and inhibition of gastrointestinal and urinary tract smooth muscle, leading to constipation and urinary retention..

Other effects:

1- Blockade of α-adrenergic receptors causes orthostatic hypotension and light-headedness.
2- The neuroleptics also alter temperature-regulating mechanisms and can produce poikilothermia (body temperature varies with the environment).
3- In the pituitary, neuroleptics block D_2 receptors, leading to an increase in prolactin release.
4- Atypical neuroleptics are less likely to produce prolactin elevations.
5- Sedation occurs with those drugs that are potent antagonists of the H_1-histamine receptor, including chlorpromazine, olanzapine, quetiapine, and clozapine.
6- Sexual dysfunction may also occur with the antipsychotics due to various receptor-binding characteristics.

Treatment of schizophrenia: The neuroleptics are considered to be the only efficacious treatment for schizophrenia. Not all patients respond, and complete normalization of behavior is seldom achieved. The traditional neuroleptics are most effective in treating positive symptoms of schizophrenia (delusions, hallucinations, thought processing, and agitation).

The newer agents with 5-HT_{2A} receptor blocking activity may be effective in many patients who are resistant to the traditional agents, especially in treating the negative symptoms of schizophrenia (social withdrawal, blunted emotions, ambivalence, and reduced ability to relate to people).

[Note: **Clozapine** is reserved for the treatment of individuals who are unresponsive to other neuroleptics, because its use is associated with blood dyscrasias and other severe adverse effects].

Prevention of severe nausea and vomiting: The older neuroleptics (most commonly **prochlorperazine**) are useful in the treatment of drug-induced nausea . Nausea arising from motion should be treated with sedatives, antihistamines, and anticholinergics, however, rather than with the powerful neuroleptic drugs. [Note: **Transdermal scopolamine** is a drug of choice for treatment of motion sickness.]

Other uses:

1- The neuroleptic drugs can be used as tranquilizers to manage agitated and disruptive behavior secondary to other disorders.
2- Neuroleptics are used in combination with narcotic analgesics for treatment of chronic pain with severe anxiety.
3- **Chlorpromazine** is used to treat intractable hiccups.

4- Promethazine is not a good antipsychotic drug; however, this agent is used in treating pruritus because of its antihistaminic properties.
5- **Pimozide** is primarily indicated for treatment of the motor and phonic tics of Tourette's disorder.
6- **risperidone and haloperidol** are also commonly prescribed for this tic disorder.

Absorption and metabolism:-

1-After oral administration, the neuroleptics show variable absorption that is unaffected by food (except for ziprasidone and paliperidone, the absorption of which is increased with food).
2- These agents readily pass into the brain, have a large volume of distribution, bind well to plasma proteins, and are metabolized to many different substances, usually by the cytochrome P450 system in the liver, Some metabolites are active.

Adverse effects:-

Adverse effects of the neuroleptic drugs can occur in practically all patients and are significant in about 80 percent . Although antipsychotic drugs have an array of adverse effects, their therapeutic index is high.

Extrapyramidal side effects: The inhibitory effects of dopaminergic neurons are normally balanced by the excitatory actions of cholinergic neurons in the striatum. Blocking dopamine receptors alters this balance, causing a relative excess of cholinergic influence, which results in extrapyramidal motor effects. The maximal risk of appearance of the movement disorders is time and dose dependent, with dystonias occurring within a few hours to days of treatment, followed by akathisias (the inability to remain seated due to motor restlessness) occurring within days to weeks. Parkinson-like symptoms of bradykinesia, rigidity, and tremor usually occur within weeks to months of initiating treatment. Tardive dyskinesia, which can be irreversible, may occur after months or years of treatment.

Effect of anticholinergic drugs: If cholinergic activity is also blocked, a new, more nearly normal balance is restored, and extrapyramidal effects are minimized. This can be achieved by administration of an anticholinergic drug, such as **benztropine**. Those drugs that exhibit strong anticholinergic activity, such as thioridazine, show fewer extrapyramidal disturbances, because the cholinergic activity is strongly dampened.

Atypical antipsychotics (clozapine and risperidone): These drugs exhibit a lower potential for causing extrapyramidal symptoms and lower risk of tardive dyskinesia, which has been

attributed to their blockade of 5-HT_{2A} receptors. These two drugs appear to be superior to **haloperidol and chlorpromazine** in treating some of the symptoms of schizophrenia, especially the negative symptoms. **Risperidone should be included among the first-line antipsychotic drugs, whereas clozapine should be reserved for severely schizophrenic patients who are refractory to traditional therapy.** Clozapine can produce bone marrow suppression, seizures, and cardiovascular side effects. **Paliperidone**, the major active metabolite of risperidone, exhibits neuroleptic activity similar to that of the parent drug. The other atypical antipsychotics **(olanzapine, quetiapine, ziprasidone, and aripiprazole)** have proven efficacy in treating psychotic symptoms, but their efficacy is not considered to be consistently superior to that of the older neurolepitcs. However, their lower incidence of EPS commonly places these newer agents ahead of the older neuroleptics when treating patients with schizophrenia.

Tardive dyskinesia: Long-term treatment with neuroleptics can cause this motor disorder. Patients display involuntary movements, including lateral jaw movements and fly-catching motions of the tongue. A prolonged holiday from neuroleptics may cause the symptoms to diminish or disappear within a few months. However, in many individuals, tardive dyskinesia is irreversible and persists after discontinuation of therapy.

Neuroleptic malignant syndrome: This potentially 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 **bromocriptine** may be helpful.

Other effects: Drowsiness occurs due to CNS depression and antihistaminic effects, usually during the first few weeks of treatment. Confusion is sometimes encountered. Those neuroleptics with potent antimuscarinic activity often produce dry mouth, urinary retention, constipation, and loss of accommodation. Others may block α-adrenergic receptors, resulting in lowered blood pressure and orthostatic hypotension. The neuroleptics depress the hypothalamus and causing amenorrhea, galactorrhea, gynecomastia, infertility, and impotence

Maintenance treatment:-
Patients who have had two or more psychotic episodes secondary to schizophrenia should receive maintenance therapy for at least 5 years, and some experts prefer indefinite therapy.

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Fluphenazine decanoate, *is* long-acting injectable (LAI) formulations of antipsychotics that are administered via deep gluteal intramuscular injection
or deltoid injection. These formulation has a therapeutic duration of
action of up to 2 to 4 weeks and, therefore, is often used to treat outpatients
and individuals who are noncompliant with oral medications.
However, patients may still develop EPS, but the risk of EPS is lower with
this LAI formulation compared to their respective oral formulations.
The antipsychotic drugs produce some tolerance but little physical
dependence.

Fluphenazine Oral formulation has a high potential for EPS; low potential for weight gain, sedation, and orthostasis; low tomoderate potential for anti-muscarinic ,ects; common use is in the LAI formulation administered every 2-3 weeks
in patients with schizophrenia and a history of non-compliance with oral antipsychotic regimens.

Asenapine
Low potential for EPS; low potential for weight gain; low to moderate potential for sedation; low potential for
orthostasis; also approved for the treatment of bipolar disorder; available as a sublingual formulation.

palpiredone
Low to moderate potential for EPS; low potential for weight gain; low potential for sedation; available as a LAI formulation administered every 4 weeks; also approved for use in schizophrenic disorder.