Typical Antipsychotics - Dr Mithunjith K K (15.04.2024)

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Describe the mechanisms of action, types, doses, side effects, indications and contraindications of the drugs which act on CNS (including anxiolytics, sedatives and hypnotics, antipsychotic, antidepressant drugs, antimanics, opioid agonists and antagonists, drugs used for neurodegenerative disorders, antiepileptic drugs).

Introduction

Antipsychotics, previously known as neuroleptics and major tranquilizers, form a crucial class of psychotropic medications. Their primary purpose is to manage psychosis, which includes symptoms like delusions, hallucinations, paranoia, and disordered thinking. While their primary application lies in treating schizophrenia, antipsychotics are also essential for other psychotic disorders. Additionally, they play a pivotal role alongside mood stabilizers in managing bipolar disorder. Furthermore, they serve as adjuncts in the treatment of treatment-resistant major depressive disorder

History

-Rauwolfia serpentina 1931
-ECT1937
-Chlorpromazine 1950

First-Generation Antipsychotics (Typical Antipsychotics):

These medications emerged in the 1950s, with chlorpromazine being the pioneer. French psychiatrists Pierre Deniker and Jean Delay introduced chlorpromazine, marking a significant breakthrough in psychiatric treatment.
Other first-generation antipsychotics followed suit until the early 1970s.
Mechanism: These drugs primarily block dopamine receptors in the brain.
Notable examples include chlorpromazine, haloperidol, and fluphenazine.

Second-Generation Antipsychotics (Atypical Antipsychotics):
The 1960s witnessed the advent of second-generation antipsychotics.
Clozapine was the trailblazer, introducing a new era of antipsychotic therapy.
Mechanism: Atypical antipsychotics not only block dopamine receptors but also target serotonin receptors.
Examples include risperidone, olanzapine, and aripiprazole.

Third-Generation Antipsychotics:
Introduced in the 2000s, these medications offer a novel approach.
Instead of complete blockade, they provide partial agonism at dopamine receptors.
This generation aims for improved efficacy and fewer side effects.
Examples include aripiprazole and brexpiprazole.

Classification of psychiatric conditions

Psychiatric conditions, also known as mental disorders, are classified into various categories based on their symptoms, causes, and treatment methods. The two most widely used psychiatric classification systems are:

International Classification of Diseases, 10th edition (ICD-10), produced by the World Health Organization (WHO).
Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), produced by the American Psychiatric Association (APA).
Here are some of the major categories of disorders described in these systems:

Organic, including symptomatic, mental disorders: These are disorders of mental function that are attributable to diseases of the brain, and involve disturbances of consciousness, cognition, mood, perception, and behavior.

Mental and behavioral disorders due to psychoactive substance use: These disorders are characterized by behavioral and other psychological changes that are a direct consequence of the use of psychoactive substances.

Schizophrenia, schizotypal and delusional disorders: These are characterized by distortions in thinking, perception, and emotions, poor rapport with others, and eccentric behavior.

Mood [affective] disorders: These involve disturbances in the spectrum of mood, ranging from elation to depression.

Neurotic, stress-related and somatoform disorders: These disorders are characterized by the presence of distressing and disabling psychological symptoms, such as anxiety or depression, but where serious physical pathology, if present, does not account for the severity and duration of the symptoms.

Behavioral syndromes associated with physiological disturbances and physical factors: These are conditions in which the physical symptoms or physical consequences of a general medical condition have a direct and major impact on the individual's personal, social, or occupational functioning.

Disorders of adult personality and behavior: These are deeply ingrained and enduring behavior patterns, manifesting as inflexible responses to a broad range of personal and social situations.

Schizophrenia: Pathophysiology

Schizophrenia is a complex psychiatric disorder characterized by a range of cognitive, behavioral, and emotional dysfunctions. The exact pathophysiology remains poorly understood, but several theories have been proposed.

Dopamine Hypothesis

The dopamine hypothesis is one of the most enduring theories. It suggests that schizophrenia is associated with an overactivity of dopamine in the brain. This is supported by the observation that drugs which increase dopamine activity can induce a

schizophrenic-like psychosis, while antipsychotic medications used in the treatment of schizophrenia often work by blocking dopamine receptors.

Glutamate Hypothesis

The glutamate hypothesis proposes that schizophrenia is caused by reduced activity of glutamate, a major excitatory neurotransmitter in the brain. This theory is supported by the finding that drugs which block the NMDA subtype of glutamate receptor can reproduce many of the symptoms, cognitive deficits, and neurophysiological abnormalities of schizophrenia.

GABAergic, Cholinergic, and Other Neurotransmitter Systems

There is also strong evidence to support roles for other neurotransmitter systems in the pathophysiology of schizophrenia. These include the GABAergic, cholinergic, and other systems. Dysregulation of these systems and their interactions may contribute to the complex symptomatology of schizophrenia.

Genetic and Environmental Factors

Schizophrenia is known to have a strong genetic component, but environmental factors also play a significant role. These may include prenatal exposure to infections or malnutrition, psychosocial factors, and drug abuse.

Symptoms and Clinical Presentation

Schizophrenia is characterized by a range of symptoms, which can be broadly categorized into positive symptoms (hallucinations, delusions, thought disorders), negative symptoms (blunted affect, anhedonia, reduced social drive), and cognitive symptoms (impaired memory, attention, and executive function).

Classification

1st generation

Chemical Classification:
Phenothiazines: Examples include chlorpromazine, fluphenazine, perphenazine, prochlorperazine, and trifluoperazine.
Butyrophenones: The primary example is haloperidol.
Diphenylbutylpiperidines: Examples include pimozide, penfluridol, and fluspirilene.
Thioxanthenes: Examples include flupenthixol, zuclopenthixol, and thiothixene.
Others: Includes loxapine and other tricyclic antipsychotics.

Potency-Based Classification:
High Potency: Includes haloperidol, fluphenazine, perphenazine, and pimozide.
Medium Potency: Includes loxapine and zuclopenthixol.
Low Potency: These are less commonly used due to higher rates of side effects

2nd generation

Amisulpride
Aripiprazole
Asenapine
Olanzapine
Paliperidone
Quetiapine
Risperidone

3rd generation

Aripiprazole
Brexpiprazole
Cariprazine

Mechanism of action of antipsychotics

First-Generation Antipsychotics (FGAs)

FGAs, also known as typical antipsychotics, function by binding to the dopaminergic dopamine D2 receptor. There is a relationship between the drug's therapeutic effect and its D2 receptor binding action2. They anatomically stop depolarization in dopamine cells in the mesolimbic, corticolimbic, and nigrostriatal systems of the brain. These medications are also associated with extrapyramidal side effects because of their ability to block D2 receptors.

Second-Generation Antipsychotics (SGAs)

SGAs, also known as atypical antipsychotics, work by inhibiting the reuptake of serotonin as do some antidepressants which

makes them more effective in treating the depressive aspects of schizophrenia. They also block dopamine receptors, but unlike FGAs, they have a higher affinity for serotonin receptors. This difference in receptor affinity is thought to result in fewer extrapyramidal side effects and greater efficacy in treating the negative symptoms of schizophrenia1.

Third-Generation Antipsychotics (TGAs)

TGAs offer partial agonism, rather than blockade, of dopamine receptors1. They can both activate and block dopamine receptors depending on the local concentration of dopamine1. This unique mechanism of action is thought to provide a more balanced and targeted approach to treating psychotic disorders.

Chlorpromazine: The Prototypical Antipsychotic

Chlorpromazine, a phenothiazine derivative, stands as the cornerstone of antipsychotic medication. Its discovery in the 1950s revolutionized the treatment of schizophrenia and marked the dawn of the typical antipsychotic era.

Mechanism of Action:

The precise mechanism by which chlorpromazine exerts its antipsychotic effect remains elusive. However, its therapeutic action is believed to be primarily related to its antagonism of dopamine D2 receptors in the mesolimbic pathway. This pathway is implicated in reward processing and thought to be hyperactive in schizophrenia. By blocking these receptors, chlorpromazine

disrupts the dopaminergic overactivity, leading to a reduction in positive symptoms like hallucinations and delusions.
Limbic area- antipsychotic
Pituitary- prolactin release
Basal ganglia- EPS
CTZ- antiemetic

Beyond Dopamine:

Chlorpromazine is a pharmacological chameleon, interacting with a multitude of receptor systems. It possesses potent antihistaminic (H1) and anticholinergic (muscarinic) properties. H1 antagonism contributes to its sedative effects, while muscarinic antagonism is responsible for a range of peripheral side effects like dry mouth, constipation, and urinary retention. Additionally, chlorpromazine exhibits alpha-adrenergic blocking activity, leading to postural hypotension (dizziness upon standing). This complex interplay of receptor interactions contributes to both the therapeutic and adverse effects of chlorpromazine.
Muscarinic receptor- anticholinergic
Alpha1 adrenergic receptor- nasal stuffiness, hypotension
H1 histamine receptor- sedation, antihistaminic effects

Pharmacokinetics:

Chlorpromazine is well absorbed orally but undergoes significant first-pass metabolism in the liver, resulting in a variable bioavailability. It is highly lipophilic, readily distributed to the central nervous system (CNS) and accumulating in fat tissues. This extensive tissue distribution contributes to its long elimination

half-life (ranging from 30 to 100 hours), necessitating divided daily dosing. Chlorpromazine undergoes extensive metabolism in the liver by CYP2C19, a polymorphic enzyme. This can lead to inter-individual variability in drug clearance, necessitating dose adjustments in certain patient populations. The metabolites are primarily excreted in the urine and feces.

Clinical Effects:

Chlorpromazine's primary therapeutic effect is the reduction of positive symptoms of schizophrenia. Additionally, its sedative properties can be beneficial in managing agitation and aggression. However, its broad spectrum of receptor antagonism comes at a cost. The anticholinergic and alpha-adrenergic blocking effects contribute to a significant side effect profile, including dry mouth, constipation, blurred vision, dizziness, and postural hypotension. Extrapyramidal symptoms (EPS), a movement disorder mimicking Parkinson's disease, are another major drawback, limiting the tolerability of chlorpromazine in some patients.

Adverse effects:

Common Side Effects:

Drowsiness: This is one of the most frequently reported side effects.
Dry Mouth or Stuffy Nose: These are typical anticholinergic side effects.
Blurred Vision: Another anticholinergic side effect.

Constipation: This can occur due to the anticholinergic effects of the drug.
Impotence, Trouble Having an Orgasm: These are potential sexual side effects of the medication.

Severe Side Effects:

Extrapyramidal Symptoms: These include Parkinson-like symptoms, dystonia, akathisia, and tardive dyskinesia. These movement disorders are a significant concern with chlorpromazine and other first-generation antipsychotics.
Neuroleptic Malignant Syndrome: This is a rare but potentially life-threatening condition characterized by fever, altered mental status, muscle rigidity, and autonomic dysfunction.
Agranulocytosis: This is a serious condition where the body does not have enough white blood cells, which can lead to severe infections.
Jaundice: This can occur due to liver damage.
Seizures: Chlorpromazine can lower the seizure threshold, leading to an increased risk of seizures.

Indications

Psychotic Disorders: Chlorpromazine is used to treat psychotic disorders such as schizophrenia or manic-depression in adults.
Severe Behavioral Problems in Children: In children ages 1 through 12 years, chlorpromazine is used to treat severe behavioral problems such as combative or explosive behavior or hyperactivity with excessive motor activity.

Nausea and Vomiting: Chlorpromazine is also used in adults to treat nausea and vomiting.
Preoperative Anxiety: It is used to alleviate anxiety before surgery.
Chronic Hiccups: Chlorpromazine is used to relieve hiccups that have lasted one month or longer.
Acute Intermittent Porphyria: It is used in the treatment of acute intermittent porphyria, a group of rare genetic disorders that affect the nervous system.
Symptoms of Tetanus: Chlorpromazine is used as an adjunct in the treatment of tetanus.

Contraindications

Hypersensitivity: Chlorpromazine is contraindicated in patients with known hypersensitivity to chlorpromazine or other phenothiazines.
Comatose States: Chlorpromazine should not be used in comatose states or in the presence of large amounts of central nervous system depressants like alcohol, barbiturates, and narcotics.
Circulatory Depression: Chlorpromazine is contraindicated in patients with severe circulatory depression.
CNS Depression: It should not be used in patients with severe central nervous system depression.
Bone Marrow Suppression: Chlorpromazine is contraindicated in patients with bone marrow suppression.
Pheochromocytoma: It should not be used in patients with pheochromocytoma, a rare tumor of the adrenal glands.
Hepatic Failure: Chlorpromazine is contraindicated in patients with hepatic failure.

Fluphenazine

Fluphenazine is a high-potency typical antipsychotic used in the treatment of chronic psychoses such as schizophrenia. It works by blocking postsynaptic mesolimbic dopaminergic D1 and D2 receptors in the brain. It also depresses the release of hypothalamic and hypophyseal hormones and is believed to depress the reticular activating system, thus affecting basal metabolism, body temperature, wakefulness, vasomotor tone, and emesis. It has limited activity on histaminergic, muscarinic, and alpha receptors.

While both fluphenazine and chlorpromazine block dopamine receptors, fluphenazine is considered a high-potency antipsychotic, while chlorpromazine is considered a low-potency antipsychotic. This means that fluphenazine generally requires lower doses to achieve the same therapeutic effect as chlorpromazine. However, high-potency antipsychotics like fluphenazine are often associated with a higher risk of extrapyramidal side effects.

Prochlorperazine

Prochlorperazine is a propyl piperazine derivative of phenothiazine. It exerts its antipsychotic effects by blocking dopamine receptors. Prochlorperazine is also known to block histaminergic, cholinergic, and noradrenergic receptors. It is primarily used for the symptomatic treatment of severe nausea and vomiting, and for the management of manifestations of

psychotic disorders, such as schizophrenia and generalized non-psychotic anxiety.

While both prochlorperazine and chlorpromazine block dopamine receptors, they have different affinities for other receptor types. Prochlorperazine is known to block histaminergic, cholinergic, and noradrenergic receptors, while chlorpromazine has strong anticholinergic and sedative effects and exhibits anti-serotonergic and antihistaminergic properties.

In terms of clinical use, prochlorperazine is primarily used for the symptomatic treatment of severe nausea and vomiting, and for the management of manifestations of psychotic disorders.

Trifluoperazine

Trifluoperazine is a high-potency typical antipsychotic used in the treatment of chronic psychoses such as schizophrenia. It works by blocking postsynaptic mesolimbic dopaminergic D1 and D2 receptors in the brain. It also depresses the release of hypothalamic and hypophyseal hormones and is believed to depress the reticular activating system thus affecting basal metabolism, body temperature, wakefulness, vasomotor tone, and emesis.

While both trifluoperazine and chlorpromazine block dopamine receptors, they have different affinities for other receptor types. Trifluoperazine is known to block histaminergic, cholinergic, and noradrenergic receptors, while chlorpromazine has strong

anticholinergic and sedative effects and exhibits anti-serotonergic and antihistaminergic properties.

In terms of clinical use, trifluoperazine is primarily used for the symptomatic treatment of severe nausea and vomiting, and for the management of manifestations of psychotic disorders.

Haloperidol

Butyrophenone. High potency typical antipsychotic. Acts on D1 and D2 receptors. Lesser incidence of cholinergic side effects. Hence preferred in older patients. Lesser epileptogenic property. Longer half life. Used in acute schizophrenia, Tourette’s syndrome, Huntington's disease.

Trifluperidol

Butyrophenone. More potent than haloperidol

Penfluridol

Butyrophenone. Once a week dose.

Flupenthixol

Thioxanthine. Additional antidepressant effect. Depot preparation available.